2022 ASCO®
ANNUAL MEETING

MEETING ABSTRACTS

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2022 Annual Meeting Abstracts

(a supplement to *Journal of Clinical Oncology*)

Editor: Pamela Kunz, MD
Associate Editor: Ryan Gentzler, MD

Managing Editor: Lindsay Pickell, MFA
Production Manager: Catherine Forrest

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2022 ASCO ANNUAL MEETING PROCEEDINGS ABSTRACTS

Letter From the Editors

The 2022 *ASCO Annual Meeting Abstracts* (a supplement to *Journal of Clinical Oncology*) is an enduring record of the more than 2,400 abstracts selected by the ASCO Scientific Program Committee for presentation as part of the ASCO Annual Meeting.

Publication-only abstracts are included in the online supplement to the June 1 issue of *Journal of Clinical Oncology* at JCO.org. Abstracts can be also accessed online through the ASCO Meeting Experience (meetings.asco.org). Online abstracts include the full list of abstract authors and their disclosure information. All abstracts carry *Journal of Clinical Oncology* citations, for example:

J Clin Oncol 40:16s, 2022 (suppl; abstr 500)

We are also excited to share a new initiative to increase awareness of abstract publication through social media, specifically to increase awareness of less publicized, yet important, research. We will partner with *JCO* to curate abstract collections for publication on JCO.org and promote collections via Twitter. We will launch this initiative with the 2022 ASCO Annual Meeting and themes will include: diversity, equity and inclusion, global health, merit awardees, and health economics. Follow us on Twitter @JCO_ASCO, @ASCO, #ASCO22!

Should you have any questions or comments about this publication, we encourage you to provide feedback by contacting us at abstracts@asco.org.

Sincerely,

Pamela L. Kunz, MD
Consultant Editor for Meeting Abstracts, Journal of Clinical Oncology

Ryan D. Gentzler, MD, MS
Associate Consultant Editor for Meeting Abstracts, Journal of Clinical Oncology

ASCO Abstracts Policy

Public Release of Abstracts

The 2022 ASCO Annual Meeting Abstracts were publicly released by ASCO at 5:00 PM EDT on Thursday, May 26, 2022. Abstracts are publicly available online at meetings.asco.org. Late-Breaking Abstracts, which include all Plenary Abstracts, will be publicly released according to the following schedule:

- Late-Breaking Abstracts presented in a scientific presentation on Friday, June 3, will be publicly released Friday, June 3, at 8:00 AM EDT.
- Late-Breaking Abstracts presented in a scientific presentation on Saturday, June 4, will be publicly released Saturday, June 4, at 8:00 AM EDT.
- Late-Breaking Abstracts presented in a scientific presentation on Sunday, June 5, will be publicly released Sunday, June 5, at 8:00 AM EDT.
- Late-Breaking Abstracts presented in a scientific presentation on Monday, June 6, will be publicly released Monday, June 6, at 8:00 AM EDT.
- Late-Breaking Abstracts presented in a scientific presentation on Tuesday, June 7, will be publicly released Tuesday, June 7, at 8:00 AM EDT.

In the unlikely event that ASCO publicly releases an abstract in advance of the scheduled time, the release will be publicly announced on https://conferences.asco.org/am/abstract-policies-embargoes-exceptions.

Conflict of Interest Disclosure

All financial relationships reported by contributors to this activity are provided to learners prior to the start of the activity. During planning and development of the activity, relevant financial relationships were mitigated for all contributors. Relationships are considered self-held and compensated unless otherwise noted (I = Immediate family member; Inst = My Institution). Disclosures are submitted per the ASCO Policy for Relationships with Companies.

Please email coi@asco.org with specific questions or concerns.

LBA1 **Plenary Session**

Panitumumab (PAN) plus mFOLFOX6 versus bevacizumab (BEV) plus mFOLFOX6 as first-line treatment in patients with *RAS* wild-type (WT) metastatic colorectal cancer (mCRC): Results from the phase 3 PARADIGM trial. *First Author: Takayuki Yoshino, National Cancer Center Hospital East, Kashiwa, Japan*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

LBA2 **Plenary Session**

Phase III assessment of topotecan and cyclophosphamide and high-dose ifosfamide in rEECur: An international randomized controlled trial of chemotherapy for the treatment of recurrent and primary refractory Ewing sarcoma (RR-ES). *First Author: Martin McCabe, University of Manchester, Manchester, United Kingdom*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

LBA3 **Plenary Session**

Trastuzumab deruxtecan (T-DXd) versus treatment of physician's choice (TPC) in patients (pts) with HER2-low unresectable and/or metastatic breast cancer (mBC): Results of DESTINY-Breast04, a randomized, phase 3 study. *First Author: Shanu Modi, Memorial Sloan Kettering Cancer Center, New York, NY*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

LBA4 **Plenary Session**

Lenalidomide, bortezomib, and dexamethasone (RVd) ± autologous stem cell transplantation (ASCT) and R maintenance to progression for newly diagnosed multiple myeloma (NDMM): The phase 3 DETERMINATION trial. *First Author: Paul G. Richardson, Department of Medical Oncology, Dana-Farber Cancer Institute, Jerome Lipper Center for Multiple Myeloma Research, Harvard Medical School, Boston, MA*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

LBA100 **Clinical Science Symposium**

Adjuvant chemotherapy guided by circulating tumor DNA analysis in stage II colon cancer: The randomized DYNAMIC Trial. *First Author: Jeanne Tie, Peter MacCallum Cancer Centre, University of Melbourne, Walter and Eliza Hall Institute, Melbourne, VIC, Australia*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

101 **Clinical Science Symposium**

Circulating tumor DNA (ctDNA) analyses of the phase III VOYAGER trial: KIT mutational landscape and outcomes in patients with advanced gastrointestinal stromal tumor (GIST). *First Author: Cesar Serrano, Vall d'Hebron Institute of Oncology, Vall d' Hebron University Hospital, Barcelona, Spain*

Background: The genotype of primary mutations predicts imatinib response in untreated metastatic GIST. However, the sequence of salvage treatments in metastatic GIST is based solely on the chronological order of registration trials. ctDNA sequencing offers a powerful diagnostic tool to detect resistance mutations in GIST but has not been shown to correlate with outcomes in clinical trials of pretreated patients (pts). We analyzed ctDNA samples collected at baseline in the phase III VOYAGER trial (NCT03465722) to describe the landscape of KIT alterations and its association with outcomes of pts treated with avapritinib or regorafenib. **Methods**: In VOYAGER, 476 pts with advanced KIT-mutant GIST were randomly assigned to avapritinib (240 pts) or regorafenib (236 pts) in 3rd-4th line. Baseline plasma was collected and ctDNA analyzed with the Guardant 360 (G360), 74-gene panel. KIT molecular subgroups were determined and correlated with outcomes. PDGFRA-mutant GISTs were excluded from outcomes analysis. **Results**: Baseline ctDNA analysis was performed in 386/476 pts (81%). ctDNA was detected in 333 pts (86%), with 250 and 18 pts showing at least one KIT (75%) or PDGFRA (5%) variant, respectively. KIT primary mutations were detected in 71% pts (exon 11, 56%; exon 9, 14%; exon 13, 1%) and KIT secondary mutations in 55% of pts. Activation loop (AL, exons 17 and 18) was more commonly affected (44%) than the ATP-binding pocket (ABP, exons 13 and 14; 23%). Among KIT-mutant tumors, multiple KIT mutations were commonly detected within individual tumors (mean, 2.56; range, 1-14). Notably, 17% of pts had > 3 mutations (mean, 6.07; range, 4 to 14). Median PFS and OS were shorter for patients whose ctDNA was positive for V654A or T670I (ABP hot spots) when treated with avapritinib vs. regorafenib: mPFS, 1.9 mo vs. 7.4 mo; log-rank p < .001; mOS, 8.3 mo vs. 11.7 mo; log rank p = .0651. mPFS was shorter for patients with ctDNA positive for KIT exon 17 mutation if concurrently KIT V654A/T670I was absent when treated with avapritinib, with no difference in OS: mPFS, 4.7 mo vs. 6.7 mo; log-rank p = .03; mOS, 19.2 mo vs. NR; log-rank p = .628. mPFS on avapritinib was longer when ABP mutations were absent when compared to those with ABP present (5.6 vs. 1.9 mo; log-rank p < .001). There were no differences considering AL mutations vs. no AL mutations (3.8 vs. 3.9 mo; log-rank p = .622) when treated with avapritinib. Regorafenib showed similar activity regardless of KIT mutational status and the location of KIT mutation. **Conclusions**: Hybrid capture-based plasma sequencing detects ctDNA in the majority of patients with advanced TKI-resistant GIST, including heterogeneity of KIT mutations. This study is the first to show that ctDNA sequencing correlates with outcomes in pretreated GIST. Identification of ABP (exon13/14) KIT mutations negatively correlates with avapritinib activity. Research Sponsor: Blueprint Medicines, Other Foundation.

102 **Clinical Science Symposium**

Largest evaluation of acquired resistance to sotorasib in *KRAS* p.G12C-mutated non–small cell lung cancer (NSCLC) and colorectal cancer (CRC): Plasma biomarker analysis of CodeBreaK100. *First Author: Bob T. Li, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Sotorasib, a specific, irreversible $KRAS^{G12C}$ inhibitor, has been approved in multiple countries for adults with *KRAS* p.G12C-mutated locally advanced or metastatic NSCLC who received prior systemic therapy based on the global phase 1/2 CodeBreaK100 trial. Here we describe putative mechanisms of acquired resistance to sotorasib from the largest single dataset evaluated to-date. **Methods:** Patients with advanced *KRAS* p.G12C-mutated NSCLC or CRC from the CodeBreaK100 Ph1/2 trial who received sotorasib monotherapy at 960 mg once daily were analyzed for efficacy. Primary endpoint was objective response rate (ORR) assessed by central review. To investigate biomarkers of resistance to sotorasib, an exploratory endpoint was defined to examine acquired genomic alterations at disease progression. Plasma samples collected at baseline and progression were analyzed for genomic alterations with the 23-gene Resolution Bioscience ctDx Lung test for NSCLC and the 74-gene Guardant 360 ctDNA test for CRC. Acquired genomic alterations were defined by their absence at baseline and presence at progression. **Results:** In 174 pts with NSCLC and 91 pts with CRC-treated with sotorasib, the ORR were 41% and 12% respectively. Median progression-free survival and median overall survival were 6.3 months (mos) and 12.5 mos for NSCLC pts and 4.2 mos and 13.4 mos for CRC pts (median follow-up: 22.5 mos NSCLC; 12.5 mos CRC). A total of 67 NSCLC pts and 45 CRC pts had a plasma sample sequenced both at baseline and at progression. At least one new acquired genomic alteration at progression was detected in 19 (28%) NSCLC pts and in 33 (73%) CRC pts (Table). The acquired genomic alterations were heterogeneous in both NSCLC and CRC, with variants detected across multiple genes and pathways. The most prevalent putative pathway of resistance in both NSCLC and CRC was the receptor tyrosine kinase (RTK) pathway. Secondary *RAS* alterations occurred more frequently in CRC versus NSCLC pts (16% vs. 3%). **Conclusions:** Based on the largest descriptive dataset to-date, diverse mechanisms of acquired resistance occur in *KRAS* p.G12C-mutated NSCLC and CRC pts treated with sotorasib. New RTK pathway alterations frequently emerged at progression, highlighting the potential role for combining sotorasib with upstream inhibitors of RTK, such as SHP2 or EGFR inhibitors. Serial plasma DNA analysis revealed acquired resistance patterns that support the development of $KRAS^{G12C}$ inhibitor combination therapies. Clinical trial information: NCT03600883. Research Sponsor: Amgen Inc.

Patients, n (%)	NSCLC (N = 67)	CRC (N = 45)
Acquired genomic alteration at progression	19 (28)	33 (73)
RTK pathway alteration	16 (24)	12 (27)
EGFR	6 (9)	7 (16)
2° *RAS* alteration	2 (3)	7 (16)
>1 alteration	8 (12)	27 (60)

103 **Clinical Science Symposium**

Circulating tumor DNA (ctDNA) and late recurrence in high-risk, hormone receptor–positive, HER2-negative breast cancer (CHiRP). *First Author: Marla Lipsyc-Sharf, Dana-Farber Cancer Institute, Boston, MA*

Background: Hormone receptor–positive breast cancer (HR+ BC) is the most common cause of BC-related death. Over half of metastatic recurrences occur ≥ 5 years (y) from diagnosis. Detection of minimal residual disease (MRD) via circulating tumor DNA (ctDNA) can identify cancer recurrence months to years in advance and may be an important tool to guide therapy. Little is known about ctDNA in the late adjuvant setting. We investigated ctDNA dynamics and clinical outcomes in pts ≥ 5 y from diagnosis of high-risk early-stage HR+ BC. **Methods:** Patients with high-risk HR+ BC (T3-4 or N2-3 or T1 with 3+ lymph nodes, or T2N1 [and Oncotype RS ≥ 26; grade 3; or Ki-67 ≥ 20%]) with no evidence of recurrence 5 y after diagnosis were prospectively identified and consented. Plasma samples were collected at time of consent and at routine visits every 6-12 mos. Whole-exome sequencing (WES) was performed on primary tumor tissue to identify somatic mutations and design for each patient a RaDaR assay, a tumor-informed liquid biopsy test to detect plasma ctDNA. Per current practice standards, pts did not undergo regular surveillance imaging. All pts were followed for development of local and/or distant metastatic recurrence, as determined by their clinical provider. **Results:** Of 103 pts enrolled, 85 had sufficient tumor tissue, and 83 pts had successful WES. Personalized RaDaR assays were designed targeting 12-51 variants (median, 36), and used to test 219 plasma samples from 83 pts. The number of plasma samples per patient ranged from 1-7 (median, 2). 57 pts (68.7%) had stage 3 disease, and most (75, 90.4%) received curative-intent chemotherapy. All pts received endocrine therapy (ET). 39 (47%) remained on adjuvant ET at time of last follow up. Of 44 pts who completed adjuvant ET, 41 (93.2%) received > 5 y of treatment. Time from diagnosis to first sample ranged from 4.9-20 y (median, 8.4 y). Median (range) follow up was 10.2 (6.7-22.3) y from diagnosis and 1.8 (0-3.6) y from first sample. 5 pts (6%) developed distant metastatic recurrence and 2 pts (2.4%) had locoregional recurrence. 4/83 (5%) pts were MRD+ at study entry and 8/83 (10%) pts were MRD+ at any time point. 5/5 (100%) pts with metastatic recurrence were MRD+, with ctDNA lead times up to 37.6 mos. ctDNA was detected at tumor fractions of 0.0027-26.84% (median, 0.396%). 2/8 (25%) MRD+ pts had not had clinical recurrence at latest follow up, one with no follow up since detection and one 15.4 mos from ctDNA detection (with ctDNA levels 0.045% and 26.84%). **Conclusions:** Here we report—to our knowledge—the first data on ctDNA detection in late adjuvant HR+ BC. 10% of pts had MRD at ≥ 5 y from diagnosis. ctDNA analysis identified MRD in all cases of distant recurrence. ctDNA was detected in 2 pts who have not yet experienced recurrence. Longer follow up is necessary for these pts at high risk. Additional studies will determine if ctDNA-guided intervention can alter clinical outcomes. Research Sponsor: AstraZeneca and Susan G. Komen Career Catalyst Research Grant to Dr. Heather Parsons (1K08CA252639-01A1), Inivata; Dana-Farber/Harvard Cancer Center (DF/HCC) Breast Cancer Specialized Program of Research Excellence (SPORE) grant (Grant 1P50CA168504), Susan G. Komen Leadership Grant to Dr. Eric Winer (SAB190001).

104 **Clinical Science Symposium**

Updated overall survival (OS) data from the phase 1b study of tebentafusp (tebe) as monotherapy or combination therapy with durvalumab (durva) and/or tremelimumab (treme) in metastatic cutaneous melanoma (mCM). *First Author: Mark R. Middleton, University of Oxford, Oxford, United Kingdom*

Background: Tebe is a T-cell receptor bispecific (gp100 x CD3) against gp100 peptide-HLA-A2 complexes that are overexpressed in uveal (UM)/cutaneous melanoma (CM). Tebe is the only therapy to show an OS benefit (HR 0.51) in a phase (Ph) 3 trial in previously untreated metastatic UM. In a prior Ph 1 trial, tebe demonstrated monotherapy activity in anti-PD1 naïve mCM (1-yr OS, approx. 74%). The safety and initial activity of tebe with dose escalation of durva and/or treme in previously treated mCM has been reported. Here, we present updated OS in the subset of mCM patients (pts) relapsed or refractory to prior anti-PD1, a population where recent reports suggest a benchmark 1-yr OS of approximately 55% and median OS of approximately 14 months (mos). **Methods:** Patients with HLA-A2+, pre-treated mCM received weekly tebe (IV) monotherapy in Arm 4a or in combination with dose escalation of durva and/or treme (IV) on day 15 of each cycle (Arms 1-3). Primary objective was RP2D, secondary objectives were safety and efficacy. Subgroup analyses were performed for durva doses ≥10 mg/kg, a threshold previously defined by Bavarel et al, 2018. Analysis performed on data cut-off 04 January 2022 with median follow up for 14.3 mos. [NCT02535078] **Results:** 112 pts were treated with median age 59, 23% were ECOG = 1, 37% were BRAFm (73% received prior BRAFi/MEKi), 55% had LDH > ULN. 92% of pts were 2L+ and 74% 3L+; median 3 prior lines. The safety profile of all therapy arms within this study therapy remains very favorable with no new safety signals identified. 97 of 112 pts were documented as relapsed or refractory to prior anti-PD1 (80% also received ipilimumab). Of these 97 pts, 32 received tebe + durva (Arm 1), 13 received tebe + treme (Arm 2), 26 received triplet therapy (Arm 3), and 20 received tebe monotherapy (Arm 4a). 33 of 97 pts in any arm received durva ≥ 10 mg/kg with 1-yr OS of 79%, 2-yr OS of 34%, and median OS of 20 mos. 64 of 97 pts received durva < 10 mg/kg with 1-yr OS of 53%, 2-yr OS of 24%, and median OS of 13 mos. Tebe + durva doublet therapy had similar OS to triplet therapy with tebe + durva + treme: 1-yr OS of 74% vs. 76%, and 2-yr OS of 32% vs. 27%, respectively. **Conclusions:** Promising OS is seen in mCM similar to mUM, with both tumor types overexpressing gp100. In mCM relapsed or refractory to prior anti-PD1, tebe with anti–PD-L1 continues to demonstrate promising OS (1-yr, approx. 75%) compared to recent benchmarks (1-yr, approx. 55%). These data provide rationale for a randomized study of tebe with anti-PD(L)1 in mCM. Clinical trial information: NCT02535078. Research Sponsor: Immunocore.

105 **Clinical Science Symposium**

Efficacy and safety of zenocutuzumab, a HER2 x HER3 bispecific antibody, across advanced NRG1 fusion (NRG1+) cancers. *First Author: Alison M. Schram, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: NRG1 fusions are rare oncogenic drivers that have been identified in a variety of solid tumors. These proteins bind HER3, leading to HER2/HER3 heterodimerization and oncogenic transformation. Zenocutuzumab (MCLA-128; Zeno) is a Biclonics antibody that overcomes HER3 mediated NRG1 (or NRG1 fusion) signaling in tumor cells. Zeno docks on HER2, then binds to and blocks the NRG1 fusion-HER3 interaction and HER3 heterodimerization with HER2. Zeno is being evaluated in patients (pts) with NRG1+ cancer in the ongoing pivotal phase 2 part of the eNRGy study and early access program (EAP). **Methods:** Pts with NRG1+ solid tumors previously treated with or not candidates for standard therapy, aged ≥ 18 years, with ECOG PS ≤ 2, and measurable (RECIST 1.1) or evaluable disease, were enrolled. *NRG1* fusions were determined by next generation sequencing (NGS) before enrollment. Zeno (750 mg IV Q2W) was administered until disease progression or unacceptable toxicity. Tumor imaging was conducted every 8 weeks. The primary endpoint is investigator (INV)-assessed objective response rate (ORR) and secondary endpoints include duration of response (DOR) and safety. **Results:** As of 12 Jan 2022, 99 pts with NRG1+ cancer (85 eNRGy, 14 EAP) were enrolled. Efficacy was assessed in 73 pts who received ≥ 1 dose of Zeno and who were enrolled as of 12 Jul 2021 to allow for the opportunity to have ≥ 6 months (mo) follow-up and met the criteria for the primary efficacy population. Median age was 59 y (range 22–84), 58% were female, 47%/53% pts had ECOG PS 0/1. Tumor types were non-small cell lung cancer (NSCLC; 41 pts), pancreas cancer (18 pts), breast cancer (5 pts), cholangiocarcinoma (3 pts), colorectal cancer (2 pts), and 4 other tumor types (1 pt each), with a median 2 prior systemic therapies (range 0-9). The most frequent fusion partners were CD74 (27%), SLC3A2 (18%), and ATP1B1 (15%). Among the 71 pts with measurable disease, the INV-assessed confirmed ORR was 34% (90% CI, 25;44), including responses in NSCLC (35%; 14/40 pts), pancreas cancer (39%; 7/18 pts), breast cancer (2/4 pts), and cholangiocarcinoma (1/3 pts). Responses occurred at the first tumor assessment in 20/24 responders, and are ongoing in 13 pts. Treatment is ongoing in 22 pts (13 NSCLC, 6 pancreas, 3 other solid tumors). Median DOR was 9.1 mo (95% CI, 5.2-12.0). Kaplan-Meier estimate of DOR rate at 6 mo was 70%. Among the 208 pts treated with Zeno monotherapy across all dosing schedules in the phase 2 setting, for individual adverse events irrespective of causality, grade ≥ 3 events were reported in <5% of pts. **Conclusions:** Zeno demonstrated robust and durable efficacy in pts with advanced NRG1+ cancer regardless of tumor histology. A well tolerated safety profile of Zeno was observed. Clinical trial information: NCT02912949. Research Sponsor: Merus NV.

106 **Clinical Science Symposium**

A study of AK104 (an anti-PD1 and anti-CTLA4 bispecific antibody) combined with standard therapy for the first-line treatment of persistent, recurrent, or metastatic cervical cancer (R/M CC). *First Author: Jing Wang, Hunan Cancer Hospital, Changsha, China*

Background: Current first-line standard therapy (SOC) for R/M CC is platinum-based chemotherapy +/- bevacizumab (bev). AK104 monotherapy has shown promising efficacy and tolerable toxicity in pretreated R/M CC (NCT04380805). In this study, we report the efficacy and safety of AK104 combined with SOC for the first-line treatment of R/M CC (NCT04868708). **Methods:** The multicenter, open-label, phase II study enrolled R/M CC pts without previous systemic therapy. Eligible pathological types were squamous cell carcinoma, adenocarcinoma, or adenosquamous cell carcinoma. Pts were assigned to 3 cohorts (A-15/A-10: AK104 15/10 mg/kg + PTX 175mg/m^2 + DDP 50 mg/m^2/CBP AUC 5, q3w; B-10: AK104 10 mg/kg + PTX 175 mg/m^2 + DDP 50 mg/m^2/CBP AUC 5 + bev 15 mg/kg, q3w). All pts received AK104 until PD or unacceptable toxicity. The primary endpoint was safety. Secondary endpoints included ORR, PFS per RECIST1.1, and OS, etc. **Results:** 45 pts were enrolled at 6 centers from Jun 3, 2021, to Nov 5, 2021. As of Jan 10, 2022, we assessed safety in all pts and efficacy in pts with at least one tumor assessment result. TRAEs of any grade occurred in 43 (95.6%) pts. Grade ≥3 TRAEs occurred in 23 (51.1%) pts. The most common TRAEs were anemia (55.6%), white blood cell count decreased (46.7%), rash (24.4%), and hypoesthesia (24.4%). The most common grade ≥ 3 TRAEs were anemia (15.6%), white blood cell count decreased (11.1%), neutrophil count decreased (8.9%), and platelet count decreased (8.9%). TRSAE occurred in 17 (37.8%) pts. IrAEs of any grade, assessed by INV, occurred in 24 (53.3%) pts. Grade ≥ 3 irAE occurred in 8 (17.8%) pts. One death due to hemorrhagic shock occurred in cohort B-10 and was judged as treatment-related. ORR were 73.3% (11/15) for A-15, 68.8% (11/16) for A-10, 92.3% (12/13) for B-10, respectively. The response to the treatment was favorable regardless of CPS (Table). PFS or OS data are not mature by cut-off date. **Conclusions:** AK104 combined with standard therapy was well tolerated, with encouraging antitumor activity in pts with R/M CC. Meanwhile, long-term safety evaluation still needs following up. A phase III trial is ongoing to evaluate the efficacy of AK104 plus standard therapy in first-line treatment for R/M CC (NCT04982237). Clinical trial information: NCT04868708. Research Sponsor: Akeso.

Summary of best overall response per investigator by CPS.

	Cohort A-15	Cohort A-15	Cohort A-10	Cohort A-10	Cohort B-10	Cohort B-10
	CPS>= 1 (N = 10)	Total (N = 15)	CPS>=1 (N = 8)	Total (N = 16)	CPS>= 1 (N = 9)	Total (N = 13)
ORR, n (%)	7 (70.0)	11 (73.3)	6 (75.0)	11 (68.8)	8 (88.9)	12 (92.3)
95% CI	[34.8, 93.3]	[44.9, 92.2]	[34.9, 96.8]	[41.3, 89.0]	[51.8, 99.7]	[64.0, 99.8]
CR, n (%)	3 (30.0)	4 (26.7)	0 (0.0)	1 (6.3)	1 (11.1)	1 (7.7)
95% CI	[6.7, 65.2]	[7.8, 55.1]	[0.0, 36.9]	[0.2, 30.2]	[0.3, 48.2]	[0.2, 36.0]
PR, n (%)	4 (40.0)	7 (46.7)	6 (75.0)	10 (62.5)	7 (77.8)	11 (84.6)
95% CI	[12.2, 73.8]	[21.3, 73.4]	[34.9, 96.8]	[35.4, 84.8]	[40.0, 97.2]	[54.6, 98.1]

107 **Clinical Science Symposium**

Safety and clinical activity of MEDI5752, a PD-1/CTLA-4 bispecific checkpoint inhibitor, as monotherapy in patients (pts) with advanced renal cell carcinoma (RCC): Preliminary results from an FTIH trial. *First Author: Laurence Albiges, Institut Gustave Roussy, Villejuif, France*

Background: MEDI5752 is a monovalent bispecific antibody targeting PD-1 and CTLA-4. A phase I, open-label study (NCT03530397) of MEDI5752 monotherapy 2.25–2500 mg IV Q3W showed encouraging antitumor activity in advanced solid tumors. Maximum tolerated dose was not reached; doses <1500 mg were better tolerated than doses ≥1500 mg. Here we present preliminary results in pts with advanced RCC in the escalation (ESC) and expansion (EXP) cohorts. **Methods:** Eligible pts were ≥18 yrs old (ECOG PS 0–1). In ESC and EXP, pts could be treatment-naïve (1L) or refractory. Eligible EXP pts had clear cell component (ccRCC), were immunotherapy-naïve (IO-naïve) and limited to ≤2 prior lines of therapy. Pts were treated until progression or unacceptable toxicity. Primary objectives were safety and tolerability (ESC), and antitumor activity by objective response per RECIST v1.1 (EXP). **Results:** Overall, 46 RCC pts were treated: 19 ESC, 27 EXP. In ESC, pts (all IO-naïve, 73.7% prior nephrectomy, 26.3% 1L, 89.5% clear cell histology) were treated across 3 dose levels: 750 mg (n=1), 2000 mg (n=16) and 2500 mg (n=2). Seven pts (36.8%) had objective responses (all PRs); 4 of these were 1L, including 1 each with papillary and sarcomatoid histology. In EXP, pts (all IO-naïve, 63.0% prior nephrectomy, 48.1% 1L [of whom 69.2% had IMDC intermediate/poor risk], 96.3% clear cell histology) received MEDI5752 1500 mg IV Q3W. Ten (38.5%) had objective responses (2 CRs, 8 PRs). In 1L EXP pts, 58.3% had objective responses (1 CR and 6 PRs); disease control rate (DCR) was 91.7% (Table). Grade 3/4 treatment-related adverse events (TRAEs) were seen in 68.4% of ESC and 74.1% of EXP pts. In EXP, treatment-emergent AEs (TEAEs), particularly hepatotoxicity, were the most common cause of treatment discontinuation (D/C). At a median duration of follow-up of 14.6 mo, median duration of response (DOR; including in those who discontinued MEDI5752 due to AEs), median PFS and OS were NR in 1L EXP pts. **Conclusions:** MEDI5752 monotherapy showed deep and durable antitumor activity in pts with advanced RCC, despite high rates of treatment D/C, particularly in the 1L setting. To better characterize the risk-benefit profile, MEDI5752 is now being explored at doses <1500 mg in 1L ccRCC expansion cohorts. Clinical trial information: NCT03530397. Research Sponsor: AstraZeneca.

	ESC	EXP total	EXP 1L ccRCC
Efficacy (modified response-evaluable population)	**n = 19**	**n = 26**	**n = 12**
Objective response rate, % (95% CI)	36.8 (16.3–61.6)	38.5 (20.2–59.4)	58.3 (27.7–84.8)
Median DOR, months (range)	13.8 (2.5–19.4)	NR (4.1–14.1)	NR (4.1–14.1)
DCR (CR + PR + SD), % (95% CI)	63.2 (38.4–83.7)	73.1 (52.2–88.4)	91.7 (61.5–99.8)
Safety (safety analysis set)	**n = 19**	**n = 27**	**n = 13**
TRAEs, n (%)	19 (100)	26 (96.3)	13 (100)
Grade 3/4 TRAEs, n (%)	13 (68.4)	20 (74.1)	7 (53.8)
Grade 5 TRAEs, n (%)	1 (5.3)	1 (3.7)	0
TEAEs leading to D/C, n (%)	11 (57.9)	19 (70.4)	9 (69.2)

108 **Clinical Science Symposium**

Prostate cancer risk in African American men evaluated via digital histopathology multi-modal deep learning models developed on NRG Oncology phase III clinical trials. *First Author: Mack Roach, University of California San Francisco, San Francisco, CA*

Background: Artificial intelligence (AI) tools can display racial bias as a result of existing systemic health inequities and biased datasets. We have previously developed multi-modal AI (MMAI) prognostic models based on digital pathology images from five phase III randomized radiotherapy prostate cancer trials that outperform NCCN risk groups for prediction of distant metastasis (DM), biochemical failure (BF), prostate cancer-specific mortality (PCSM) and all-cause mortality (OS). In this study, we assessed the algorithmic fairness of the locked MMAI models between African American (AA) and non-AA populations in the five randomized trials. **Methods**: Patients enrolled in NRG/RTOG 9202, 9408, 9413, 9910, and 0126 with digitized biopsy histopathology slides were included in this study. The locked MMAI models were applied, and subgroup analyses were conducted by comparing distributions of clinical variables and MMAI scores (medians for continuous variables and proportions for categorical variables reported), and evaluating MMAI models' prognostic ability among AA and non-AA men. The performance of the models were compared using DM as the primary endpoint and secondary endpoints of BF, PCSM, OS (death without an event as a competing risk) with Fine-Gray or Cox Proportional Hazards models. Either Kaplan Meier or cumulative incidence estimates were computed and compared using log-rank or Gray's test. **Results:** This study included 5,624 men: 932 (17%) AA, 4503 (80%) white, and 189 (3%) other races. AA had younger median age (69 vs 71 year [yr]), higher median baseline PSA (12 vs 10 ng/mL), more T1-T2a (62% vs 57%), more Gleason < 7 (42% vs 36%) and 8-10 (15% vs 12%), and more NCCN low and high risk (12% vs 10% and 41% vs 33%). AA and non-AA had estimated 5-yr BF rates 27% and 27%, 5-yr DM rates 5% and 5%, 10-yr PCSM 5% and 7%, and 10-yr OS 58% and 60%, respectively. The median (interquartile range) score of the model optimizing for 5-yr DM (5-yr DM MMAI) was 0.044 (0.037–0.059) in AA and 0.043 (0.036–0.057) in non-AA. Similarly, all other MMAI models had differences in the medians between AA and non-AA ranging from 0.001 to 0.02. For all endpoints, the 5-yr DM MMAI model showed strong prognostic signal (hazard ratio [HR] per one standard deviation increase: 1.6 for DM, 1.4 for BF, 1.6 for PCSM and 1.3 for OS, all p-values < 0.001) and had comparable trends within AA vs. non-AA in the entire cohort (e.g., HR for DM 1.4 vs 1.6). Similar results were observed for the MMAI model optimizing for 10-yr PCSM. **Conclusions**: To our knowledge, this represents the first comparative analyses of a digital pathology AI prognostic model in AA vs. non-AA prostate cancer patients. The prognostic performance of the AI models was found to be comparable between subgroups. Our data supports the use of these models across racial groups, though further validation in AA cohorts is ongoing. Research Sponsor: U.S. National Institutes of Health, Artera, Inc.

109 **Clinical Science Symposium**

Long-term effect of machine learning–triggered behavioral nudges on serious illness communication and end-of-life outcomes among patients with cancer: A randomized clinical trial. *First Author: Ravi Bharat Parikh, University of Pennsylvania, Philadelphia, PA*

Background: Early serious illness conversations (SICs) between oncology clinicians and patients are associated with improved mood, quality of life, and quality of end-of-life (EOL) care. Yet, most patients with cancer die without a documented SIC. We report on pre-specified 40-week SIC and EOL outcomes from a stepped-wedge randomized clinical trial (NCT03984773) testing the impact of clinician-directed behavioral nudges to prompt SICs among patients with cancer at high risk of mortality based on a machine learning algorithm. **Methods:** Our sample consisted of patients with cancer receiving care at one of 9 tertiary or community-based medical oncology clinics between June 2019 and April 2020. We identified high-risk patients using a prospectively validated electronic health record machine learning algorithm to predict 6-month mortality. The intervention consisted of: (1) Weekly emails comparing individual oncologists' SIC rate relative to peers; (2) Weekly lists of forthcoming encounters with high-risk patients; and (3) Opt-out text messages to prompt SICs before high-risk patient encounters. Clinics were randomized in stepped-wedge fashion to receive the intervention in 4-week intervals through week 16, when all clinics received the intervention. Patients were followed through week 40. The primary outcome was SIC rates for all and high-risk patients. EOL outcomes among decedents were based on ASCO/NQF guidelines and included death in the hospital, intensive care unit admission within 30 days of death, receipt of systemic therapy within 14 days of death, hospice enrollment prior to death, and hospice length of stay. Intention-to-treat analyses were adjusted for clinic and wedge fixed effects and clustered at the oncologist-level. **Results:** The sample consisted of 20,506 patients and 41,021 encounters. 1,324 (6.5%) patients died by the end of follow-up. Among high-risk patients, the unadjusted SIC rate was 3.4% (59/1754) in the control period and 13.5% (510/3765) in the intervention period and remained >12% throughout follow-up. In adjusted analyses, the intervention was associated with an increase in SICs (adjusted odds ratio 2.09, 95% CI 1.53-2.87, p<0.001) and a decrease in systemic therapy at the end of life, relative to control (6.8% [72/1066]) vs 9.3% [24/258], adjusted odds ratio 0.27, 95% CI 0.12-0.63, p=0.002). There were no differences between control and intervention patients in hospice enrollment or length of stay, inpatient death, or EOL ICU utilization. **Conclusions:** In this randomized trial, a machine learning-based behavioral intervention led to a sustained increase in serious illness communication and reduction in EOL systemic therapy among outpatients with cancer. Machine learning and behavioral nudges can lead to long-lasting improvements in cancer care delivery. Clinical trial information: NCT03984773. Research Sponsor: U.S. National Institutes of Health, Penn Center for Precision Medicine.

110 **Clinical Science Symposium**

Sarcopenia identified by computed tomography (CT) imaging using a machine learning–based convolutional neural network (CNN) algorithm impacts survival in patients with newly diagnosed multiple myeloma (NDMM). *First Author: Bharat Nayar Nandakumar, Division of Hematology, Mayo Clinic, Rochester, MN*

Background: Sarcopenia or a loss of muscle mass increases with aging and is associated with increased overall mortality in patients with cancer. Recent advances in machine learning–based CNN algorithms have allowed for the rapid processing of digital images to produce image classifications of body composition. Since incidence of MM is highly associated with aging, we sought to determine if the presence of sarcopenia, as determined by utilizing this machine learning–based CNN algorithm on CT images, had prognostic value in patients with NDMM. **Methods:** We identified all patients with NDMM from January 2003 to July 2019 who had a standard-dose CT scan that included the L3 vertebral level performed within 6 months of diagnosis. Using a machine learning–based CNN-algorithm, abdominal CT images were analyzed to measure muscle area. These measurements were normalized by dividing the area values by the height of the patient squared (m^2) to obtain skeletal muscle index (SMI) values. Patients were categorized as sarcopenic according to international gender-specific consensus cutoffs for SMI (male: < 55 cm^2/m^2 and female: < 39 cm^2/m^2). Patients with the following FISH cytogenetics were considered high risk (HR): t(4;14), t(14;16), t(14;20), and deletion 17p/monosomy 17 whereas the remainder were standard risk (SR). Survival analysis was performed using the Kaplan-Meier method and compared via the log-rank method. **Results:** The study cohort consisted of 344 patients. 68 (20%) were categorized as HR based on FISH cytogenetics.187 (54%) patients were sarcopenic based on their peri-diagnosis standard-dose CT scan. Sarcopenic patients were more likely to have ISS-3 disease (45% vs. 30%; p = .023), be male (73% vs. 48%; p < .001), and be ≥ age 75 (27% vs. 14%; p = .002) compared to non-sarcopenic patients. The median OS for patients with HR FISH and ISS 2 / 3 disease was 40 months and 57 months respectively compared to 90 months and 119 months for those with SR FISH and ISS-1 disease respectively (FISH: p < .004; ISS: p < .001). The median OS for sarcopenic patients was 44 months compared to 90 months for those not sarcopenic (p < .001). The time to next therapy (TTNT) for sarcopenic patients was 39 months compared to 45 months for those not sarcopenic (p = .05). In a multivariable model, the presence of sarcopenia (HR 1.64, 95% CI, 1.05–2.56; p = .03) retained significance in the presence of HR FISH, ISS 2 / 3 disease, and age ≥ 75. **Conclusions:** Gender-specific sarcopenia identified by a machine learning–based CNN algorithm significantly affects OS in patients with NDMM and is independent of age, ISS stage, and cytogenetic status. Future studies utilizing this machine learning–based methodology of assessing sarcopenia in larger prospective clinical trials are required to validate these findings. Research Sponsor: U.S. National Institutes of Health.

LBA5 **Clinical Science Symposium**

Single agent PD-1 blockade as curative-intent treatment in mismatch repair deficient locally advanced rectal cancer. *First Author: Andrea Cercek, Memorial Sloan Kettering Cancer Center, New York, NY*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

500 **Oral Abstract Session**

Final results from a phase III randomized clinical trial of adjuvant endocrine therapy ± chemotherapy in women ≥ 70 years old with ER+ HER2- breast cancer and a high genomic grade index: The Unicancer ASTER 70s trial. *First Author: Etienne Brain, Institut Curie, Saint-Cloud, France*

Background: Benefit of adjuvant chemotherapy (CT) in addition to endocrine therapy (ET) remains controversial for patients (pts) aged ≥ 70 years with oestrogen receptors-positive (ER+) HER2-negative (HER2-) breast cancer (BC). In a large prospective trial, we first assessed the tumour genomic grade index (GGI) in all pts, and second, randomized pts with a high GGI between CT + ET vs. ET alone. **Methods:** Eligible pts were women ≥ 70 years with ER+ HER2- primary BC or isolated local relapse, irrespective of other characteristics, for whom adjuvant systemic treatment was considered. G8 score, Charlson comorbidity index (CCI) and 4-year mortality Lee score were collected at baseline. GGI was centrally performed by RT-PCR on FFPE samples. Pts with low GGI were not recommended to receive CT and were followed in an observational cohort. Pts with high (+ equivocal) GGI were randomized 1:1 to CT + ET vs. ET alone, using G8, pN and centre for stratification. Investigators chose between 3 CT regimens: 4 cycles of doxorubicin/cyclophosphamide, non-pegylated liposomal doxorubicin/cyclophosphamide or docetaxel/cyclophosphamide, given q3w with G-CSF. Standard ET consisted of 5 years of aromatase inhibitor, tamoxifen or a sequence based on tolerance. Based on CALGB 49907 results, the primary objective was to demonstrate an overall survival (OS) benefit for CT (4-year assumptions 87.5 vs 80%, HR=0.60) in the intent to treat (ITT) population. With 171 events, the trial had 90% power to demonstrate a difference with a bilateral test α=0.05. Secondary objectives included BC specific survival (BCSS), invasive disease-free survival (iDFS), event-free survival (EFS), competing events, cost-effectiveness and Q-TWiST analysis, geriatric dimensions, willingness and quality of life. **Results:** Between 04/2012 and 05/2016, 1,969 pts from 61 French and 12 Belgian centres were enrolled. Of them, 1,089 (55%) were randomized between CT + ET and ET alone. Median follow-up was 5.8 years at the data cut-off (17/12/2021) with 180 OS events observed. Median age was 75 (70-92), G8 score, CCI and Lee score being >14, ≤ 2, and ≤ 8 in 60%, 62% and 84% of pts, respectively. Tumours were ≥ pT2, pN+, isolated local relapses, with histological grade III, in 56%, 46%, 11% and 39% of cases, respectively. No significant OS difference was observed between arms (HR 0.85 [0.64-1.13], p=0.2538); 4-year OS was 90.5% in the CT + ET arm and 89.7% in the ET alone arm. The forest plot could not identify any subgroup deriving significant benefit from CT. ITT and per protocol analysis of secondary objectives (BCSS, iDFS, EFS) showed similar results. **Conclusions:** In this large phase III trial, we did not find a statistically significant OS benefit with the addition of CT to ET after surgery for ER+ HER2- BC with a high GGI. Analysis of the other outcome measures will be presented. Clinical trial information: NCT0156405. Research Sponsor: PHRC 2011, Pharmaceutical/Biotech Company, LIGUE CONTRE LE CANCER, ARCS (AIDE A LA RECHERCHE CANCEROLOGIQUE DE SAINT-CLOUD).

LBA501 **Oral Abstract Session**

LUMINA: A prospective trial omitting radiotherapy (RT) following breast conserving surgery (BCS) in T_1N_0 luminal A breast cancer (BC). *First Author: Timothy Joseph Whelan, McMaster University, Hamilton, ON, Canada*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

502 **Oral Abstract Session**

Assessing the benefit of adjuvant endocrine therapy in patients following breast-conserving surgery with or without radiation stratified by a 7-gene predictive DCIS biosignature. *First Author: Pat W. Whitworth, Nashville Breast Center, Nashville, TN*

Background: Breast conserving surgery (BCS) followed by radiotherapy (RT) has been the mainstay for DCIS treatment. Adjuvant endocrine therapy (ET) has often been recommended based on multiple randomized clinical trials (RCT). However, these studies have failed to identify subsets of patients who did or did not benefit from adjuvant RT/ET therapy after BCS. We evaluated the association of a 7-gene predictive DCIS biosignature (PreludeDx, Laguna Hills, CA) to assess the impact of ET on 10-yr ipsilateral breast recurrence (IBR) risk after BCS alone or with RT. **Methods:** DCISionRT with integrated Residual Risk subtype (RRt) reported a decision score (DS) and three risk groups, a) Low Risk (DS≤2.8), b) Elevated Risk (DS > 2.8 without RRt) and c) Residual Risk (DS > 2.8 with RRt). DCISionRT/RRt was evaluated in 926 patients from 4 cohorts who were treated with BCS alone or with RT/ET. The three risk groups were assessed for 10-yr total (invasive and in situ) IBR risk by Kaplan Meier and Cox proportional hazards survival analysis. **Results:** DCISionRT/RRt classified 338 (37%) women as Low Risk, 399 (43%) as Elevated Risk, and 189 (20%) as Residual Risk. Overall, patients treated with ET had a significantly lower 10-yr IBR risk in multivariable analysis independent of RT (HR = 0.55, p = 0.033). In the Low Risk group treated with BCS without RT, the average 10-yr IBR risk was 5.6% (95% CI 2.5-12.1%, n = 124) and was not significantly different with vs without ET (p = 0.33). The 10-yr IBR risk after BCS alone was 22.6% in the Elevated Risk group and 50.3% in the Residual Risk group. Compared to BCS alone, the 10-year IBR risk tended to be lower in patients prescribed ET without RT in the Elevated (11.6%, 95% CI 3.9-32%) and Residual (15.4%, 95% CI 4.1-49%) Risk groups. 10-yr IBR risk was not significantly reduced by RT within the Low Risk group (p = 0.7) but was significantly reduced to 6.3% (95% CI 3.4-12%) by RT within the Elevated Risk (HR = 0.2, p < 0.001) and to 12.5% (95% CI 6.4-23%) within the Residual Risk (HR = 0.2, p < 0.001) groups. 10-yr IBR risk was significantly higher after RT in the Residual (HR = 2.5, p = 0.013) vs. Elevated Risk groups. After BCS and RT, there was no significant reduction in 10-yr IBR risk for those treated with vs without ET in the Elevated (p = 0.22) and Residual (p = 0.87) risk groups. **Conclusions:** The DCISionRT/RRt biosignature demonstrated prognostic and predictive RT response in Elevated and Residual Risk patients. Consistent with prior RCT data, ET was associated with lower 10-yr IBR risk overall, and within the DCISionRT Elevated and Residual Risk groups without RT. However, neither ET nor RT were asssociated with significant risk reduction in the Low Risk group. There was no added benefit of ET in the Elevated and Residual Risk groups after BCS+RT; the Residual Risk group patients still had a high IBR risk after RT. Research Sponsor: PreludeDx.

503 **Oral Abstract Session**

Event-free survival by residual cancer burden after neoadjuvant pembrolizumab + chemotherapy versus placebo + chemotherapy for early TNBC: Exploratory analysis from KEYNOTE-522. *First Author: Lajos Pusztai, Yale School of Medicine, Yale Cancer Center, New Haven, CT*

Background: KEYNOTE-522 (NCT03036488) tested the benefit from adding pembrolizumab (pembro) to chemotherapy (chemo) in patients (pts) with early TNBC. The primary results showed statistically significant and clinically meaningful improvements in pCR and EFS with pembro.Prior studies have shown the prognostic value of the residual cancer burden (RCB) method to quantify the extent of residual disease after neoadjuvant chemo. In this exploratory analysis, we assessed EFS by RCB in KEYNOTE-522. **Methods:** 1174 pts with previously untreated, nonmetastatic, stage T1c/N1-2 or T2-4/N0-2 TNBC were randomized 2:1 to pembro 200 mg Q3W or placebo (pbo) given with 4 cycles of paclitaxel + carboplatin, then 4 cycles of doxorubicin or epirubicin + cyclophosphamide. After definitive surgery, pts received pembro or pbo for 9 cycles or until recurrence or unacceptable toxicity. Dual primary endpoints are pCR and EFS. RCB was assessed by the local pathologist at the time of surgery. The association between RCB categories (RCB-0, -1, -2, -3, corresponding to increasingly larger residual cancer) and EFS was assessed based on a Cox regression model with treatment as a covariate. **Results:** Median follow-up was 39.1 months at data cutoff (23 MAR 2021). Pembro shifted RCB to lower categories across the entire spectrum (Table). The HRs (95% CI) for EFS were 0.70 (0.38 - 1.31) for RCB-0 (equivalent to pCR), 0.92 (0.39 - 2.20) for RCB-1, 0.52 (0.32 - 0.82) for RCB-2, and 1.24 (0.69 - 2.23) for RCB-3. The most common EFS event in both arms was distant recurrence, which occurred in fewer pts in the pembro arm in all RCB categories. **Conclusions:** Increased RCB score was associated with worse EFS. Pts with residual disease had lower RCB values in the pembro arm, including fewer pts with RCB-3. Pembro + chemo prolonged EFS vs chemo alone in the RCB-0, -1, and -2 categories; the small sample size limits interpretation in the RCB-3 category. The small subset of pts with extensive residual disease (RCB-3) in both arms, 5.1% and 6.7%, respectively, had a poor prognosis. These results highlight the importance of neoadjuvant treatment with pembro for improving survival in pts with early TNBC, and identified a subset of pts for whom additional therapies will be needed. Clinical trial information: NCT03036488. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

	RCB-0 Pembro	RCB-0 Pbo	RCB-1 Pembro	RCB-1 Pbo	RCB-2 Pembro	RCB-2 Pbo	RCB-3 Pembro	RCB-3 Pbo
Frequency, n/N (%)	497/784 (63.4)	219/390 (56.2)	69/784 (8.8)	45/390 (11.5)	145/784 (18.5)	79/390 (20.3)	40/784 (5.1)	26/390 (6.7)
Any EFS event, n/N (%)	26/497 (5.2)	16/219 (7.3)	12/69 (17.4)	9/45 (20.0)	37/145 (25.5)	35/79 (44.3)	29/40 (72.5)	18/26 (69.2)
Distant recurrence, n (%)	16 (3.2)	12 (5.5)	6 (8.7)	4 (8.9)	22 (15.2)	18 (22.8)	14 (35.0)	14 (53.8)
36-mo EFS, % (95% CI)	94.7 (92.2 - 96.4)	92.6 (88.2 - 95.4)	83.8 (72.6 - 90.7)	84.4 (70.1 - 92.3)	75.7 (67.8 - 81.9)	55.9 (44.1 - 66.2)	26.2 (13.5 - 41.0)	34.6 (17.5 - 52.5)

504 **Oral Abstract Session**

Pathologic complete response (pCR) rates for HR+/HER2- breast cancer by molecular subtype in the I-SPY2 Trial. *First Author: Laura Ann Huppert, UCSF Helen Diller Comprehensive Cancer Center, San Francisco, CA*

Background: Hormone receptor positive (HR+), HER2- breast cancer (BC) is a heterogenous disease. We hypothesized that molecular subtypes capturing luminal, basal, and immune biology could predict response for patients (pts) with HR+/HER2- disease in the I-SPY2 trial. **Methods:** I-SPY2 trial is a phase II, randomized, adaptive study evaluating multiple investigational agents as neoadjuvant BC therapy; the primary endpoint is estimated pCR rate. Investigational agents are given with control weekly paclitaxel x 12, followed by AC x 4. Regimens graduate when the predicted pCR rate in any signature meets the pre-specified threshold of 85% probability of success in a hypothetical 300 pt randomized, phase 3 trial. We analyzed estimated pCR rates for the 1st 7 investigational agents in the HR+/HER- subset, analyzed by clinical/molecular features: BluePrint (BP) Luminal vs. Basal, Mammaprint High1 [MP1] vs. Mammaprint High2 [MP2], MP2 is < -0.57, Responsive Predictive Subtype-5 (RPS-5) (classification based on HR, HER2, immune, DNA-repair, and basal/luminal markers), histology, and stage/nodal status. **Results:** 38% (379/987) of pts had HR+/HER2- disease. Only pembrolizumab met the pre-specified graduation criteria for HR+/HER2- BC. pCR rates by treatment arm and molecular subtype are described in the Table. 28% were MP2; 72% were MP1. Overall, pCR rates were higher in pts with MP2 vs MP1 disease (30% vs 11%) including with pembrolizumab (55% vs. 21%). 29% were BP Basal, 71% were BP Luminal; BP Basal was more likely to be MP2 than BP Luminal (77% vs 8%). In all arms except MK2206, HR+/HER2- BP Basal pts were more likely to achieve pCR than BP Luminal pts. For MK2206, BP Luminal pts were more likely to achieve pCR. Immune+ by RPS-5 (39% of HR+/HER2-) predicted pCR to pembrolizumab irrespective of BP Basal or Luminal status (11 pCR/16 pts). Results by histology and stage/nodal status will also be reported. **Conclusions:** Our data suggest that MP2 and BP Basal signatures identify a subset of HR+/HER2- BC more likely to respond to neoadjuvant therapy; and that an immune signature can identify pts more likely to respond to pembrolizumab. These findings will aid in guiding prioritization of targeted agents with the goal to optimize pCR for all pts. Clinical trial information: NCT01042379. Research Sponsor: U.S. National Institutes of Health, Other Foundation, Pharmaceutical/Biotech Company.

	HR+HER2-		pCR rate (N)				
	N	pCR rate	MP1	MP2	Basal	Luminal	Immune+
Control	94	0.15	0.10 (71)	0.30 (23)	0.28 (25)	0.10 (68)	0.24 (34)
Veliparib/carboplatin	32	0.16	0.04 (23)	0.44 (9)	0.50 (10)	0 (22)	0.25 (12)
Neratinib	17	0.18	0 (10)	0.43 (7)	0.33 (9)	0 (7)	0.22 (9)
MK2206	28	0.18	0.21 (19)	0.11 (9)	0.10 (10)	0.22 (18)	0.31 (13)
AMG386	62	0.16	0.1 (48)	0.36 (14)	0.47 (15)	0.06 (47)	0.43 (21)
Ganitumab	58	0.14	0.09 (44)	0.29 (14)	0.47 (13)	0.10 (42)	0.23 (22)
Ganetespib	48	0.13	0.13 (30)	0.11 (18)	0.18 (17)	0.10 (31)	0.19 (21)
Pembrolizumab	40	0.30	0.21 (29)	0.55 (11)	0.67 (9)	0.19 (31)	0.69 (16)
All arms	**379**	**0.17**	**0.11 (274)**	**0.3 (105)**	**0.33 (108)**	**0.1 (266)**	**0.31 (148)**

505 **Oral Abstract Session**

Measurement of endocrine activity (SET2,3) related to prognosis and prediction of benefit from dose-dense (DD) chemotherapy in estrogen receptor-positive (ER+) cancer: CALGB 9741 (Alliance). *First Author: Otto Metzger, Dana-Farber Cancer Institute, Alliance for Clinical Trials in Oncology, Boston, MA*

Background: We investigated the clinical utility of SET2,3, a novel biomarker designed to measure to endocrine sensitivity. SET2,3 measures nonproliferative hormone receptor-related transcription (SETER/PR) adjusted for a baseline prognosis index derived from tumor size, nodes involved and a 4-gene molecular subtype (RNA4). CALGB 9471 is a seminal phase III study that showed improved DFS and OS from 2-weekly dose-dense (DD) vs 3-weekly chemotherapy in ER-negative cancers. Risk of recurrence (ROR-PT) score (intrinsic subtype, proliferation score and tumor size) measured by Nanostring assay was reported to be prognostic in CALGB 9741, but did not predict benefit from DD chemotherapy. **Methods:** SET2,3 was performed using an aliquot of 200-300 ng RNA (residual from prior ROR-PT testing) from 682 ER+ tumor samples and tested using the QuantiGene Plex bead-based hybridization assay (ThermoFisher, Luminex). We report results for the primary and two secondary objectives of the NCI/CTEP-approved correlative science proposal CSC0154) to evaluate SET2,3 in CALGB 9741 for prognosis (primary endpoint: 95%CI for 5-year (yr) DFS > 75% for High SET2,3 using the predefined prognostic cutpoint 2.10), SET2,3 prognostic independence from ROR-PT, and prediction of outcome according to chemotherapy regimen. We used Cox models to estimate hazard ratios (HR) for prognosis and comparison with ROR-PT results (using c-indices) and for prediction according to chemotherapy schedule using an interaction term (prespecified significance level for interaction: $p < 0.10$). **Results:** The study met its primary endpoint with a 5-yr DFS of 85.6% (95%CI 81.3-90.2) in the High-SET subset (244/613, 40%). High-SET vs Low-SET was significantly associated with favorable outcomes at 5 yr (DFS 85.6% vs 69%, $p < .0001$; OS 95.3% vs 84.6%, $p < .0001$) and 10 yr (DFS 77.7% vs 58.2%, $p < .0001$; OS 86.9% vs 65.9%, $p < .0001$). PAM50 ROR-PT and SET classification were available for 596 tumors. In multivariate models for DFS and OS, SET2,3 remained an independent prognostic variable for DFS (SET high vs low HR = 0.46, 95% CI, 0.34 – 0.63, $p < 0.0001$; PAM50 ROR-PT high vs low HR = 1.22, 95% CI, 0.91 – 1.64, $p = 0.18$) and for OS (SET high vs low HR = 0.36, 95% CI, 0.25 – 0.53, $p < 0.0001$; PAM50 ROR-PT high vs low HR = 1.26, 95% CI, 0.91 – 1.75, $p = 0.16$). Similar observations were seen in models including SET and PAM50 ROR-PT as continuous variables. Lower SET2,3 values predicted improved outcomes from DD vs 3-weekly chemotherapy (interaction p=0.0998 for DFS, 0.042 for RFS and 0.027 for OS). This was unrelated to menopausal status and lower SET2,3 values favored DD concurrent treatments. **Conclusions:** SET2,3 index was strongly prognostic, independent of ROR-PT, and predicted survival benefit from DD chemotherapy in pre- and postmenopausal women with ER+ cancer. Clinical trial information: NCT00003088. Research Sponsor: https://acknowledgments.alliancefound.org Breast Cancer Research Foundation (BCRF-158), U10CA180821, U10CA180882, U24CA196171.

506 **Oral Abstract Session**

Adding ovarian function suppression to tamoxifen in young women with hormone-sensitive breast cancer who remain premenopausal or resume menstruation after chemotherapy: 8-year follow-up of the randomized ASTRRA trial. *First Author: Soo Yeon Baek, Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea*

Background: Addition of Ovarian Suppression to Tamoxifen in Young Women With Hormone-Sensitive Breast Cancer Who Remain Premenopausal or Regain Vaginal Bleeding After Chemotherapy (ASTRRA) trial, at 63 months median follow-up, showed that the addition of 2 years of ovarian function suppression (OFS) to Tamoxifen (TAM) significantly improved disease-free survival (DFS) compared with TAM alone in patients with hormone receptor–positive breast cancer who remain in a premenopausal state or resume ovarian function after chemotherapy. We report updated long-term outcomes from ASTRRA trial with 106.4 months median follow-up. **Methods:** This study is a post-trial follow-up of the ASTRRA trial, which randomly assigned 1,298 patients with breast cancer in a 1:1 ratio to receive TAM only (n = 647) or TAM + OFS (n = 635). The primary endpoint was DFS and secondary endpoint was overall survival (OS). We used Kaplan-Meier estimates for time to event endpoints and hazard ratios (HR) with 95% confidence interval (CI) from Cox-regression model. **Results:** At 106.4 months of median follow-up, there continues to be a statistically significant reduction in DFS event rate in favor of the TAM+OFS group. The estimated 8-year DFS rate was 85.4% in the TAM + OFS group and 80.2% in the TAM-only group (HR 0.67; 95% CI, 0.51 to 0.87). There were no significant differences in OS between two groups. The estimated 8-year OS rate was 96.5% in the TAM + OFS group and 95.3% in the TAM-only group (HR, 0.78; 95% CI, 0.49 to 1.25). The results of DFS and OS between the two groups defined from the time of random assignment to the time of events were also similar. **Conclusions:** These data demonstrate consistent survival advantages of adding OFS 2 years to TAM treatment over time, with the long-term follow-up reported to date. This study finding suggest that adding OFS to TAM should be considered for those who remain in a premenopausal state or resume ovarian function after chemotherapy. Longer follow-up is needed to fully evaluate the OS benefit. Research Sponsor: This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number : HI19C0481, HC19C0147).

507 **Oral Abstract Session**

Long-term outcomes of adjuvant denosumab in breast cancer: Fracture reduction and survival results from 3,425 patients in the randomised, double-blind, placebo-controlled ABCSG-18 trial. *First Author: Michael Gnant, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria*

Background: State-of-the-art adjuvant endocrine therapy with aromatase inhibitors (AI) compromises bone health in postmenopausal patients with hormone receptor-positive (HR+) breast cancer, increasing fracture incidence. Adjuvant treatment with the anti-RANK ligand denosumab (Dmab) counteracts these side effects and may improve outcomes. We here report the final long-term outcomes of the ABCSG-18 trial (ClinicalTrials.gov NCT00556374). **Methods:** In this prospective, double-blind, placebo-controlled, phase 3 trial, 3,425 postmenopausal patients with early HR+ breast cancer on AI therapy were randomised in 58 trial centers between 2006 and 2013 to receive either Dmab 60 mg or placebo s.c. every 6 months (q6m). The primary endpoint was time to first clinical fracture, secondary disease outcome-related endpoints were disease-free survival (DFS), bone-metastasis free survival (BMFS), and overall survival (OS). In addition to the main endpoint analyses reported previously, exploratory long-term follow-up was conducted in ABCSG-18. Main time-to-event analyses were based on stratified Cox models. Sensitivity analyses accounting for treatment cross-over associated with a late Dmab open-label phase, as well as for receiving any anti-resorptive agents were performed. **Results:** For this final protocol-defined analysis, median follow-up is 8 years (Q1,3: 6, 9.6), and all patients had ended their randomly assigned double-blind treatment (Dmab 60mg s.c. q6m n = 1711; placebo s.c. q6m n = 1709) for a median of 5 years. DFS was improved in the Dmab group versus the placebo group (309 versus 368 DFS events, hazard ratio (HR) 0.83, 95% CI 0.71-0.97, p = 0.016), resulting in an absolute 9-year DFS difference of 3.5% (79.4% vs 75.9%, respectively). When censoring for late cross-over and use of anti-resorptive agents, the DFS difference was confirmed (HR 0.82, p = 0.010). BMFS was improved by 19 per cent (HR 0.81, 95% CI 0.65-1.00, p = 0.047) in the Dmab group, and OS was improved by 20 per cent in the uncensored analysis (127 versus 158 OS events, HR 0.80, 95% CI 0.64-1.01, p = 0.065), and 26 per cent after censoring (HR 0.74, 95% CI 0.58-0.94, p = 0.013). The previously reported marked reduction in clinical fractures persisted even long-term, with 201 fractures in the Dmab and 255 fractures in the placebo group (HR 0.76, 95% CI 0.63-0.92, p = 0.004). No new toxicities for this (low) bone-protective dose of adjuvant Dmab were reported, particularly no ONJ occured.. **Conclusions:** Adjuvant Dmab 60mg every 6 months during AI therapy is safe, and markedly reduces treatment-induced clinical fractures even in the long-term. DFS, BMFS, and OS are improved in this descriptive final long-term analysis of ABCSG-18. Adjuvant denosumab should be considered for routine clinical use in postmenopausal patients with HR+ breast cancer. Clinical trial information: NCT00556374. Research Sponsor: Amgen.

508 **Oral Abstract Session**

Historical early treatment effects of adjuvant endocrine therapy for breast cancer in high-risk subgroups: Reanalysis of BIG 1-98, SOFT and TEXT. *First Author: Meredith M. Regan, Dana-Farber Cancer Institute and International Breast Cancer Study Group, Boston, MA*

Background: Clinical trials testing adjuvant endocrine therapy (ET) have not historically limited enrollment to patients with clinically high-risk breast cancer (BC), nor estimated treatment (trt) effects prior to 5 yrs. In light of recent trial results for adjuvant CDK4/6 inhibitors, we estimated early relative and absolute trt effects of aromatase inhibitor (AI) vs tamoxifen (T), with ovarian suppression (OFS) if premenopausal, in high risk subgroups. **Methods:** From pts enrolled in adjuvant phase 3 randomized clinical trials BIG 1-98 (postmenopausal, 5yr AI v T), TEXT (5yr AI+OFS v T+OFS) and SOFT (5yr AI+OFS v T+OFS v T), we identified subgroups with HR+/HER2- BC and high risk features (≥4 pLN; or 1-3 pLN with grade 3, pT≥5 cm and/or Ki-67≥20% [retrospectively centrally assessed]). TEXT randomized at start of adjuvant trt; BIG 1-98 and SOFT after chemotherapy. Disease-free survival (DFS) was defined from randomization to invasive recurrence at local, regional, distant or contralateral breast, second non-breast malignancy or death. We estimated trt effects as differences in 2, 3 and 5yr DFS Kaplan-Meier estimates (KM diffs at *t* yrs) and hazard ratios over time intervals of 0-2, 0-3 and 0-5 yrs (HRs over 0 to *t* yrs) to approximate the maturity of trial results with increasing follow-up. **Results:** The high-risk HR+/HER2- subgroups were 695/4922, 707/2660 and 526/3047 pts in BIG 1-98, TEXT and SOFT with 202, 122, 142 DFS events observed by 5 yrs since randomization. 60%, 46% and 44% of pts had ≥4 pLNs; 42%, 90% and 92% had chemotherapy. The table summarizes results. **Conclusions:** In re-analysis of clinical high risk HR+/HER2- subgroups of 3 trials each ~700 pts, 5 yrs AI vs T had similar magnitude of early trt effects after 2-3 yrs follow-up of all pts vs trt effects observed after 27 mos median follow-up in monarchE trial (HR=0.70; KM diffs 2.7% at 2 yrs, 5.4% at 3 yrs; n=5637). Relative and absolute trt effects sometimes diminished when estimated over 5 yrs rather than over 2 yrs, but meaningful absolute differences remained at 5 yrs in contrast to Penelope-B trial results. Design and interpretation of high risk HR+/HER2- early BC trials may depend on timing of randomization and selection of backbone adjuvant trts; follow-up >5 yrs must remain standard. Research Sponsor: None.

Comparison	DFS Trt Effect	t=2 yr	t=3 yr	t=5 yr
BIG 1-98 AI v T	HRs over 0 to *t* yrs	0.68 (0.42-1.08)	0.67 (0.47-0.95)	0.73 (0.56-0.97)
	KM diffs at t yr	4.1% (-0.4 – 8.6)	7.0% (1.2 – 12.8)	7.7% (0.9 – 14.4)
TEXT AI+OFS v T+OFS	HRs over 0 to t yrs	0.72 (0.38-1.37)	0.75 (0.47-1.21)	0.68 (0.48-0.97)
	KM diffs at t yr	1.7% (-1.7 – 5.1)	2.6% (-1.9 – 7.1)	6.4% (0.6 – 12.2)
SOFT AI+OFS v T	HRs over 0 to t yrs	0.70 (0.39-1.24)	0.86 (0.53-1.39)	0.82 (0.54-1.24)
	KM diffs at t yr	4.5% (-3.2 – 12.3)	1.7% (-7.2 – 10.7)	4.0% (-6.0 – 14.0)
SOFT T+OFS v T	HRs over 0 to t yrs	0.68 (0.39-1.17)	0.72 (0.45-1.16)	0.86 (0.58-1.26)
	KM diffs at t yr	4.9% (-2.4 – 12.3)	5.3% (-2.9 – 13.4)	2.8% (-6.8 – 12.3)

509 **Poster Discussion Session**

Prognostic and predictive implications of the intrinsic subtypes and gene expression signatures in early-stage HER2+ breast cancer: A pooled analysis of CALGB 40601, NeoALTTO, and NSABP B-41 trials. *First Author: Aranzazu Fernandez-Martinez, Lineberger Comprehensive Cancer Center, Department of Genetics, University of North Carolina, Chapel Hill, NC*

Background: Several biologic features are implicated in the differences in response and survival to dual (trastuzumab and lapatinib [HL]) vs. single (trastuzumab [H]) HER2-blockade across neoadjuvant trials in early-stage HER2+ breast cancer. We evaluated the association of intrinsic subtypes and gene expression signatures with pathologic complete response (pCR) and event-free survival (EFS) in a pooled analysis of three independent phase III neoadjuvant studies with similar designs: CALGB 40601 (Alliance), NeoALTTO, and NSABP B-41. **Methods:** Gene expression profiling by RNA sequencing was assessed on 761 pre-treatment samples (264 from CALGB 40601, 249 from NeoALTTO, 248 from NSABP B-41). Intrinsic subtypes and 759 gene expression signatures were calculated. We studied the association of pCR and the benefit of dual (HL) vs. single (H) HER2-blockade by tumor intrinsic subtype in the pooled set. The ability of multiple gene expression signatures to predict pCR and EFS across the three studies was also tested by logistic and Cox regression analyses. **Results:** pCR status was associated with EFS only in HER2-Enriched (HR 0.45, 95% CI 0.29-0.71, p-value < 0.001) and Basal-like (HR 0.19, 95% CI 0.04-0.86, p-value 0.031) intrinsic subtypes, but not in Luminal and/or ER+ tumors. The EFS benefit of dual vs. single HER2-blockade was limited to HER2-Enriched tumors (HR 0.47, 95% CI 0.27-0.81, p-value 0.007). When evaluating the three clinical trials separately, we found 89/759 (11.7%) gene expression signatures in common for the prediction of pCR across the three clinical trials, including HER2-amplicon and immune activation signatures. Luminal-related signatures were associated with lower pCR rates but better EFS outcomes, especially in patients with residual disease. Stratified Cox regression models by study showed a significant and strong association of NK, B and plasma cells, as well as Ig-related signatures with a better EFS outcome, while vascular, proliferation, and metastasis signatures were associated with poor EFS. **Conclusions:** In early-stage HER2+ breast cancer, the relationship between pCR and EFS differs by tumor intrinsic subtype, and the benefit of dual vs. single HER2-blockade seems to be limited to HER2-Enriched subtype tumors. Immune signatures were associated with higher pCR rates and better EFS, luminal signatures were associated with lower pCR rates but good EFS outcomes, and vascular/proliferation/metastasis signatures were associated with poor EFS across the three clinical trials. Clinical trial identification: CALGB 40601: NCT00770809. (CALGB is part of the Alliance for Clinical Trials in Oncology). NeoALTTO: NCT00553358 NSABP B-41: NCT00486668 Research Sponsor: CALGB 40601: BCRF, Susan G Komen, NCI SPORE (P50-CA58823), R01-CA229409, and Alliance U10CA180821, U24CA196171(LAC, CMP); https://acknowledgments.alliancefound.org. Fundacion SEOM, Becas FSEOM para Formacion en Investigacion en Centros de Referencia en.

510 **Poster Discussion Session**

Molecular subtype to predict pathologic complete response in HER2-positive breast cancer in the I-SPY2 trial. *First Author: Alexandra Thomas, Wake Forest Comprehensive Cancer Center, Winston-Salem, NC*

Background: HER2-positive breast cancer (bc) is a very heterogenous disease. We hypothesized that molecular subtype may predict disease response to investigational agents in HER2+ bc. Here, we report the pathologic complete response (pCR) rate in the first six agents tested in HER2+ bc in the I-SPY 2 trial for the full HER2+ cohort, by molecular subtype, and by disease receptor status. **Methods:** Women with HER2+ tumors which were > 2.5 cm were eligible. The I-SPY2 platform trial tests novel agents given neoadjuvantly with a backbone of taxol (T) and trastuzumab (H) followed by doxorubicin and cyclophosphamide. Agents investigated in HER2+ bc were TH (control), MK2206, AMG386, pertuzumab (P), neratinib (N (given in place of H), and TDM1+P (given in place of TH). An investigational arm graduated if there was >85% chance of success compared to control in a 300-person phase 3 neoadjuvant trial. Further details of the I-SPY2 methods have been previously published. Molecular subtyping based on gene expression was utilized to categorize tumors into 5 response predictive subtypes (RPS) (HER2-/Immune-/DRD (DNA repair deficiency)-, HER2-/Immune+, HER2-/Immune-/DRD+, HER2+/Her2_or_-Basal and HER2+/Luminal). **Results:** For the full HER2+ cohort (N=245) pCR rate was higher in all investigational arms than control (Table). By tumor receptor status, HER2+/HR- tumors (N=89) had a higher pCR rate than HER2+/HR+ tumors (N=156; 63% vs 37%, p = 0.0001). In HER2+/HR- tumors N, MK2206, P and TDM1/P graduated. In HER2+/HR+ tumors P and TDM1/P graduated. 76% (185/245) of I-SPY 2 HER2+ patients were classified as HER2+/Her2_or_Basal and 24% (60/245) were HER2+Luminal. pCR rate was significantly higher in the HER2+/Her2_or_Basal group than in the HER2+/Luminal group (57% vs 15%, p < 0.0001). All agents, except for MK2206, where numbers were small, showed greater efficacy in the HER2+/Her2_or_Basal group than in the HER2+/Luminal group. HER2+/Luminal appeared to be more sensitive to the AKT inhibitor MK2206 than to targeted HER2 agents, though numbers are small. **Conclusions:** pCR rates for patients with HER2+ bc treated with investigational agents, particularly dual HER2-blockade, were promising. Molecular response predictive subtype classification provides insight on how to better target therapy. The HER2+/Luminal group had low pCR rates with dual HER2-blockade but may have higher pCR rate with the addition of an AKT inhibitor and identifies a subgroup of HER2+ tumors in need of novel approaches. AKT inhibition for HER2/Luminal is being tested in I-SPY 2.2. Clinical trial information: NCT01042379. Research Sponsor: U.S. National Institutes of Health, Other Foundation, Pharmaceutical/Biotech Company.

	Full HER2+ cohort		Genomic Subtype				Tumor Receptors			
			HER2+/Her2_or_Basal		HER2+/Luminal		HER2+/HR-		HER2+/HR+	
	N	pCR %	N	pCR %	N	pCR %	N	pCR %	N	pCR %
TH	31	26	18	39	13	8	12	42	19	16
N	65	40	56	46	9	0	23	57	42	31
MK2206	34	50	29	48	5	60	18	67	16	31
AMG386	19	37	15	40	4	25	4	50	15	33
THP	44	59	32	78	12	8	15	80	29	48
TDM1/P	52	58	35	77	17	18	17	71	35	51
Total	**245**	**47**	**185**	**57**	**60**	**15**	**89**	**63**	**156**	**37**

LBA511 **Poster Discussion Session**

TX05-03e: Adjuvant treatment following neoadjuvant treatment and surgical resection in TX05-03, a trial comparing the safety, efficacy, and immunogenicity of trastuzumab biosimilar candidate (TX05) with originator trastuzumab in HER2+ EBC. *First Author: Petr Krivorotko, Federal State Budget Institution "National Medical Research Center of Oncology na N.N. Petrov" Ministry of Healthcare of Russian Federation, Saint-Petersburg, Russian Federation*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

512 **Poster Discussion Session**

Phase 2 study of response-guided neoadjuvant sacituzumab govitecan (IMMU-132) in patients with localized triple-negative breast cancer: Results from the NeoSTAR trial.

First Author: Laura Spring, Massachusetts General Hospital Cancer Center, Boston, MA

Background: Sacituzumab govitecan (SG), a novel antibody-drug conjugate in which the topoisomerase 1 inhibitor SN-38 (active metabolite of irinotecan) is linked to a humanized monoclonal antibody targeting the tumor antigen Trop2, is currently approved for treatment of patients (pts) with pre-treated metastatic triple negative breast cancer (TNBC). We conducted a phase 2 study evaluating neoadjuvant (NA) SG as upfront therapy for pts with localized TNBC (NCT04230109). The primary objective was to assess pathological complete response (pCR) rate in breast and lymph nodes (ypT0/isN0) with SG. Secondary objectives included assessment of radiological response rate, evaluation of the safety and tolerability (CTCAE v5.0) and event-free survival (EFS). **Methods:** Patients with localized TNBC (tumor size ≥1cm, or any size if node positive) with no prior treatment were eligible. SG was administered IV on Days 1, 8 of each 21-day cycle at a starting dose of 10 mg/kg for 4 cycles. After 4 cycles, patients with biopsy-proven residual disease, considered as no pCR for primary endpoint, had the option to receive additional NA therapy at the discretion of the treating physician. Radiologic response (US or MRI) was defined by RECIST version 1.1 using a composite response of CR & PR. Standard descriptive statistics were utilized, including 95% binomial confidence intervals for all rates estimated. **Results:** From 7/14/20 – 8/31/21, 50 pts were enrolled (median age = 48.5; 11 stage I disease, 24 stage II, 11 stage III, 4 unknown; 62% node negative). The majority (98%; n = 49) of pts completed 4 cycles of SG. Overall, the radiological response rate with SG alone was 62% (n = 31, 95% CI 48%, 77%). 26 pts proceeded directly to surgery after SG. Overall, the pCR rate with SG alone was 30% (n = 15/50, 95% CI 18%, 45%). The other 11 pts had RCB-1 (n = 3), RCB-2 (n = 5), and RCB-3 (n = 3) disease, respectively. Of the 24 pts who received additional NA therapy, 6 had a pCR (3 received anthracycline-based regimen, 2 carboplatin/taxane, and 1 docetaxel/cyclophosphamide). Among pts with a germline BRCA mutation (n = 8), 7 proceeded directly to surgery after SG and 6 had a pCR (86%, 95% CI 42%, 99%). The most common AEs with SG were nausea (82%, n = 41), fatigue (78%, n = 39), alopecia (76%, n = 38), neutropenia (58%, n = 29), anemia (36%, n = 18), and rash (48%, n = 24). 6% of pts required dose-reduction. No pts discontinued SG therapy due to disease progression or AEs; 1 discontinued due to minimal response per investigator preference. At the time of data cut-off (1/18/22), no pts experienced disease recurrence. Updated biomarker and EFS results will be presented at the meeting. **Conclusions:** In the first neoadjuvant trial in TNBC with an ADC, SG demonstrated single agent efficacy in localized TNBC. Further research on optimal duration of SG as well as NA combination strategies, including immunotherapy, are needed. Clinical trial information: NCT04230109. Research Sponsor: Immunomedics.

513 **Poster Discussion Session**

Clinical and biomarker results of neoadjuvant phase II study of pembrolizumab and carboplatin plus docetaxel in triple-negative breast cancer (TNBC) (NeoPACT).

First Author: Priyanka Sharma, University of Kansas Medical Center, Westwood, KS

Background: Addition of pembrolizumab to anthracycline-taxane-platinum chemotherapy improves pathologic complete response (pCR) and event free survival (EFS) in TNBC. Aim of this study was to assess the efficacy of the anthracycline free neoadjuvant regimen of pembrolizumab plus carboplatin plus docetaxel (Cb+D) in TNBC. **Methods:** In this multicenter study, eligible patients with stage I-III TNBC received carboplatin (AUC 6) + docetaxel (75 mg/m^2) + pembrolizumab (200 mg) every 21 days x 6 cycles. The primary endpoint was pCR (no evidence of invasive tumor in breast and axilla). Secondary endpoints were residual cancer burden (RCB), EFS, toxicity, and immune response biomarkers. RNA isolated from pretreatment tumor tissue was subjected to next generation sequencing. Samples were classified as DNA Damage Immune Response (DDIR) signature and DetermaIO signature positive/negative using predefined cutoffs. Evaluation of stromal tumor infiltrating lymphocytes (sTILs) was performed using standard criteria. **Results:** 117 patients were enrolled from September 2018 to January 2022. 18% were African American, 39% had node positive disease, 88% had stage II/III disease and 15% had ER/PR 1-10%. Pathologic response information is available for 105 patients. pCR and RCB 0+1 rates were 60% (95% CI 51%-70%) and 71% (95% CI 62%-80%), respectively. Treatment related adverse events led to discontinuation of any trial drug in 12% of patients. Immune adverse events were observed in 28% of patients (Grade ≥3=6%). 47% of patients had sTILs ≥30%, 48% were DetermaIO positive, and 61% DDIR positive. The table describes the impact of these biomarkers on pCR and RCB. The areas under the prediction curve (AUC) for pCR were 0.660, 0.709, and 0.719 for DDIR, sTILs, and DetermaIO respectively. At a median follow up of 21 months, 2-year EFS is 88% in all patients; 98% in pCR group and 82% in no pCR group. **Conclusions:** Neoadjuvant pembrolizumab plus Cb+D regimen yields pCR of 60% and 2-year EFS of 88% in the absence of adjuvant pembrolizumab. The regimen was well tolerated, and no new toxicity signals were noted. Immune enrichment identified by sTILs or DetermaIO signature was associated with high pCR rates approaching or exceeding 80%. PD-L1 and additional biomarker analyses are ongoing. Clinical trial information: NCT03639948. Research Sponsor: Merck & Co, Inc.

	pCR			RCB 0+1		
Variable	**Frequency**	**OR (95% CI)**	**p**	**Frequency**	**OR (95% CI)**	**p**
ER/PR						
<1%	53/87 (61%)	1		62/86 (72%)	1	
1-10%	10/18 (56%)	0.71 (0.25-2.01)	0.518	12/18 (67%)	0.70 (0.23-2.10)	0.523
sTILs						
< 30%	19/42 (45%)	1		26/41 (63%)	1	
≥ 30%	29/37 (78%)	4.39 (1.63-11.82)	0.003	30/37 (81%)	2.47 (0.87-6.99)	0.088
DDIR						
Negative	16/35 (46%)	1		20/34 (58%)	1	
Positive	39/55 (71%)	2.90 (1.20-7.00)	0.018	44/55 (80%)	2.80 (1.08-7.24)	0.034
DetermaIO						
Negative	20/47 (43%)	1		27/46 (59%)	1	
Positive	35/43 (81%)	5.91 (2.26-15.45)	<0.001	37/43 (86%)	4.34 (1.53-12.32)	0.006

sTILs available for n=79
DDIR and DetermaIO available for n=90

514 **Poster Discussion Session**

The ImPrint immune signature to identify patients with high-risk early breast cancer who may benefit from PD1 checkpoint inhibition in I-SPY2.

First Author: Lorenza Mittempergher, Research and Development, Agendia NV, Amsterdam, Netherlands

Background: The remarkable increase of novel Immuno-Oncology drugs in many malignancies has led to the need for biomarkers to identify who would benefit. Various predictive biomarkers have been developed (PD-1/PD-L1 expression, mutations in mismatch repair genes and microsatellite instability, tumor mutational burden and immune infiltration), none have consistently predicted efficacy. The I-SPY2 consortium qualified several expression-based immune biology related signatures that predict response to PD1 checkpoint inhibition. Here we assessed whole transcriptome data of high-risk early-breast cancer (EBC) patients who received Pembrolizumab within the neoadjuvant biomarker-rich I-SPY2 trial (NCT01042379), aiming to migrate the I-SPY2 research findings to a robust clinical grade platform signature to predict sensitivity to PD1 checkpoint inhibition. **Methods**: Whole transcriptome microarray data were available from pre-treatment biopsies of 69 HER2- patients enrolled in the Pembrolizumab (4 cycles) arm of the I-SPY2 trial. All patients had a High-Risk 70-gene MammaPrint profile. Pathologic complete response (pCR) was defined as no residual invasive cancer in breast or nodes at the time of surgery. Of the 69 patients, 31 had a pCR (12 HR (hormonal receptor)+HER2-, 19 Triple Negative (TN)), while 38 (28 HR+HER2-, 10 TN) had residual disease (RD). To identify the most predictive genes associated with pCR, gene selection was performed comparing pCR and RD groups by iteratively splitting the dataset in training and test, balancing for HR status. Due to limited sample size, leave one out cross validation was used for performance assessment. Genes with effect size > 0.45 were considered significant. **Results**: A signature of 53 genes, named ImPrint, was identified with overall sensitivity and specificity > 90% and > 80% for predicting pCR to pembrolizumab in all patients. Sensitivity and specificity in TN were > 95% and ≥70%, and in HR+HER2- > 80% and > 85%, respectively. The Positive Predictive Value (PPV) is 77% for the HR+HER2- subgroup. Biological annotation of the 53 genes showed that over 90% of the genes have known immune system related functions, of which 63% were previously known to be involved in immune response (including genes coding PD-L1 and PD-1, as well as those identified in I-SPY2). **Conclusions**: In the signature development phase, ImPrint predicts pCR to Pembrolizumab in a set of 69 high risk EBC with high sensitivity and specificity. The signature features genes with immune-related functions known to be involved in immune response indicating that it might aid identifying patients with an immune-active phenotype. Importantly, ImPrint appears effective in identifying a subset of HR+HER2- patients who could benefit from immunotherapy. External validation in independent dataset(s) is ongoing and will be presented at the time of the meeting. Research Sponsor: None.

515 **Poster Discussion Session**

Racial/ethnic disparities in locoregional recurrence in hormone-receptor positive node-negative breast cancer patients enrolled in the TAILORx trial.

First Author: Olga Kantor, Dana-Farber Brigham Cancer Center, Boston, MA

Background: Whether racial/ethnic disparities in locoregional recurrence (LRR) exist in patients (pts) with similar access to care treated on clinical trials is uncertain. We examined racial/ethnic differences in LRR in hormone-receptor positive HER2-negative (HR+HER2-) node-negative pts enrolled in the TAILORx trial. **Methods:** 10,273 pts age 18-75 were enrolled in TAILORx, which assigned pts with an OncotypeDx Recurrence Score (RS) <11 to endocrine therapy (ET) alone, those with RS >25 to chemotherapy + ET (CET), and randomized pts with RS 11-25 to ET or CET. Pts with unknown race/ethnicity (n=323) or incomplete treatment adherence information (n=1,168) were excluded from this analysis. Race/ethnicity was self-reported. LRR was defined as ipsilateral invasive in-breast, chest wall, or regional nodal recurrence without distant recurrence. Kaplan-Meier curves were used to estimate 8-year LRR. Cox proportional hazards analysis adjusted for clinical and treatment factors was used to determine factors associated with LRR. **Results:** 8,782 pts with T1-2N0 HR+HER2- breast cancer were included. Race/ethnicity was non-Hispanic White (NHW) in 6,932 (78.9%), non-Hispanic Black (NHB) in 629 (7.2%), Hispanic in 818 (9.3%), and Asian in 403 (4.6%). Treatment adherence was high across groups over time, with a 9.1% crossover in treatment arms. Average duration of ET was 63.8 +/- 0.3 months. Radiation therapy was planned in 96.0% of pts after breast conservation and 12.7% after mastectomy. At a median follow-up of 8 years, LRR rates were 1.9% in NHW, 4.2% in in NHB, 3.2% in Hispanic, and 3.9% in Asian pts (p<0.01). LRR rates broken down by RS are shown in the Table. On adjusted analyses, NHB and Asian (vs. NHW) pts were more likely to have LRR (HR 1.94 for NHB, HR 2.04 for Asian, p<0.05 for both). Additional statistically significant factors associated with LRR included age <50 (HR 1.85), T2 tumors (HR 1.43), higher grade (HR 2.30 for grade 3), and high RS (HR 3.13 for RS>25). Treatment receipt (chemotherapy, ET duration, and radiation) was not associated with LRR in this population. **Conclusions:** Racial/ethnic differences in LRR were seen in T1-2N0 HR+HER2- breast cancer pts enrolled in the TAILORx trial despite high rates of treatment adherence in this clinical trial population, with highest LRR rates in NHB and Asian pts. Further study in needed to understand racial/ethnic patterns in LRR by breast cancer subtype and if failure to rescue after LRR may contribute to differences in breast cancer mortality. Research Sponsor: None.

8-year LRR by race/ethnicity and Recurrence Score						
	Overall	**NHW**	**NHB**	**Hispanic**	**Asian**	**P-value**
Overall	2.2%	1.9%	4.2%	3.2%	3.9%	<0.01
RS <11	2.0%	1.6%	0%	2.5%	1.2%	0.96
RS 11-25	2.1%	1.7%	5.4%	2.9%	3.6%	<0.01
RS >25	3.7%	3.2%	2.6%	5.3%	11.1%	0.03

516 **Poster Discussion Session**

Clinical outcomes and immune markers by race in a phase I/II clinical trial of durvalumab concomitant with neoadjuvant chemotherapy in early-stage TNBC. *First Author: Julia Foldi, Yale School of Medicine, New Haven, CT*

Background: The incidence of triple negative breast cancer (TNBC) is higher among Black or African American (AA) women, yet AA patients (pts) are underrepresented in clinical trials, exemplifying racial disparity in oncology. We conducted a phase I/II trial to assess the safety and efficacy of durvalumab concurrent with weekly nab-paclitaxel and dose dense doxorubicin/cyclophosphamide (ddAC) neoadjuvant therapy for stage I-III TNBC. The primary efficacy endpoint was pathologic complete response (pCR; ypT0/is,N0) rate. Given the unclear efficacy and safety of immunotherapy in AA pts with breast cancer, we extended our accrual to recruit AA pts, with the goal of evaluating the association between racial groups and PD-L1 expression, stromal tumor infiltrating lymphocytes (sTILs), toxicities, treatment response and survival. **Methods:** Our study population included 67 pts. PD-L1 immunohistochemistry results and sTIL counts were available on 59 and 60 pts, respectively. Chi-Squared test was used to evaluate associations between race and baseline characteristics. Cox proportional hazards model was used to assess association between AA race and overall survival (OS) and event free survival (EFS), adjusting for age, comorbidities and pCR status. Multivariate logistic regression analyses were used to evaluate the association between race and pCR, development of immune-related adverse events (irAEs) and breast cancer recurrence. **Results:** Twenty-one pts (31%) self-identified as AA. No significant associations between AA race and baseline body mass index (BMI; p=0.075), Charlson comorbidity index (p=0.32), tumor stage (p=0.40), grade (p=0.54), PD-L1 status (0.92) and sTIL count (p=0.57) were observed. pCR rates did not significantly differ between AA and non-AA pts: 9/21 (43%) AA vs. 22/48 (48%) non-AA (p=0.71). 3-yr OS was 87% in the non-AA versus 81% in the AA cohort (HR 1.72, 95% CI 0.481-6.136; p=0.405); 3 yr EFS were 78.3% and 71.4% in non-AA and AA pts respectively. (HR 1.451, 95% CI 0.524-4.017; p=0.474). Pts with pCR were more likely to remain event-free at 3 yrs, irrespective of race (HR 0.234, 95% CI 0.066-0.829; p=0.024). In multivariate logistic regression analyses, lack of pathologic response (OR for pCR 0.17, 95% CI 0.03-0.7; p=0.02) and node positive status (OR 4.13, 95% CI 1.05-19.88; p=0.05) were associated with recurrence. The incidence of irAEs was similar between AA and non-AA pts and no significant associations were found between irAEs and pathologic response. **Conclusions:** pCR rates after neoadjuvant immunotherapy and chemotherapy were similar in AA and non-AA pts. Stromal TILs, PD-L1 status, 3yr OS and EFS, and the frequency of irAEs were also similar. These results suggest that when patients receive identical treatment and are monitored closely, disparities in outcomes can be mitigated or abolished. Clinical trial information: NCT02489448. Research Sponsor: AstraZeneca.

517 **Poster Discussion Session**

Whole transcriptomic analysis of HR+ breast cancer in Black women classified as basal-type by BluePrint. *First Author: Sonya A. Reid, Vanderbilt University Medical Center, Nahsville, TN*

Background: Breast cancer is the leading cause of cancer-associated death among Black women, and they are 41% more likely to die from breast cancer compared to White women. Few studies have evaluated if tumor biology differences contribute to this disparity in outcomes. Similar to triple negative breast cancer (TNBC), hormone receptor-positive (HR+) tumors classified as Basal-Type with BluePrint genomic analysis (HR+/Basal) are more aggressive, higher grade, are over-represented among young Black women and have worse clinical outcomes. TNBC is associated with low ACKR1 expression, which encodes the Duffy antigen and correlates with worse breast cancer outcomes. Given the over-representation and worse outcomes among Black women with HR+/Basal tumors, we compared differentially expressed genes (DEGs) by race and subtype. **Methods:** This study includes 2657 women with Stage I-III breast cancer who received BluePrint testing and are participants of the ongoing BEST study (5R01CA204819) at Vanderbilt University Medical Center or FLEX study (NCT03053193). Of 455 Black women, 315 had Luminal (HR+/Luminal) and 140 had Basal tumors (66 HR+/Basal and 74 HR-/Basal). White women within FLEX (n = 2202) were included as a reference group with HR+/Luminal (n = 1825), HR+/Basal (n = 158), or HR-/Basal (n = 219) tumors. Two-tailed proportional z-test was used to assess differences in subtype proportion by race. Limma R package was used to perform differential gene expression analysis (DGEA) of whole transcriptome data. Significant DEGs had an adjusted p-value < 0.05 and absolute log2 fold change > 1. **Results:** Black women had a significantly higher proportion of HR+/Basal (15%; p < 0.001) and HR-/Basal (16%; p < 0.001) tumors compared to White women (7% and 10%, respectively). In a multidimensional scaling analysis, HR+/Basal tumors cluster with TNBC rather than with HR+/Luminal tumors. While a DGEA comparing HR+/Basal with HR+/Luminal tumors resulted in over 700 DEGs within Black women, no DEGs were identified when comparing HR+/Basal tumors with TNBC. ACKR1 expression in HR+/Basal tumors was comparable to TNBC in Black women (p = 0.81) and White women (p = 0.46). In contrast, HR+/Basal tumors had significantly lower ACKR1 expression than HR+/Luminal tumors in Black (p < 0.01) and White women (p < 0.01). **Conclusions:** In this racially diverse cohort, transcriptomic analyses suggest that HR+/Basal tumors are biologically analogous to TNBC, independent of race. Molecular profiling identified racial disparities in the proportion of HR+/Basal tumors and underscores the need for diverse representation in clinical trials. With an over-representation of HR+/Basal tumors in Black women and evidence of worse outcomes, these data suggest that patients with HR+/Basal tumors should not be treated uniformly with HR+/Luminal tumors and highlight the importance of further genomic classification for patients with HR+ tumors. Clinical trial information: NCT03053193. Research Sponsor: Agendia Inc. , U.S. National Institutes of Health.

518 **Poster Discussion Session**

Impact of body mass index on treatment and outcomes in patients with early hormone receptor-positive breast cancer receiving endocrine therapy with or without palbociclib in the PALLAS trial. *First Author: Georg Pfeiler, Department of Obstetrics and Gynecology and Center for Breast Health, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria*

Background: Body Mass Index (BMI) impacts breast cancer risk and prognosis. Conflicting results have been published regarding BMI as a predictive factor for endocrine therapy benefit. CDK4/6 inhibitors (CDK4/6i) in combination with endocrine treatment (ET) are standard-of-care treatments for metastatic hormone receptor-positive breast cancer. In contrast to cytotoxic chemotherapy, CDK4/6i are given at a fixed dose irrespective of BMI or weight. The PALLAS trial compared the combination of the CDK4/6i palbociclib and adjuvant ET to ET alone in the early breast cancer setting. This analysis investigates the impact of BMI on the efficacy and the side effect profile of palbociclib (P) in the PALLAS trial. **Methods:** In this pre-planned analysis, patients (pts) enrolled in PALLAS were categorized according to BMI as underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5-24.9 kg/m^2), overweight (BMI 25-29.9 kg/m^2) and obese (^{3}30 kg/m^2), respectively. Adverse event differences were assessed with Chi-squared tests. Time to early discontinuation of P was analyzed with Fine and Gray competing risk models. Cox models were used to investigate the association between BMI category and time to invasive disease-free survival (iDFS). **Results:** Of a total of 5698 pts included in this analysis, 68 (1.2%) were underweight, 2082 (36.5%) normal weight, 1818 (31.9%) overweight and 1730 (30.4%) obese at baseline. Significantly different rates of all grade neutropenia were observed in normal weight, overweight and obese pts with regard to total (88.5%, 85.7% and 74.7%), as well as grade 3 (64.1%, 62.0% and 43.9%) and grade 4 neutropenia (7.0%, 3.6% and 2.0%), respectively. The lower frequency and severity of neutropenia observed in overweight and obese pts was associated with a significant lower treatment discontinuation rate over time when compared to normal weight patients (overweight vs normal weight: HR 0.73 CI 0.63-0.84, p<0.0001, and obese vs normal weight: HR 0.65 CI 0.56-0.75, p<0.0001). In pts treated with P, neutropenia was the primary toxicity leading to treatment discontinuation in 21.1% of normal weight pts, 14.0% of overweight pts and 5.9% obese pts, respectively. Despite these observations, there was no statistically significant improvement in iDFS with the addition of P to ET in any weight category (normal weight HR 0.84 CI 0.63-1.12, overweight HR 1.10 CI 0.82-1.49 and obese HR 0.95 CI 0.69-1.30). **Conclusions:** This pre-planned analysis of outcomes by BMI in the PALLAS trial demonstrates significantly less frequent and less severe neutropenia in overweight and obese pts compared to those with normal weight, leading to significant lower treatment discontinuation rates. However, no difference in iDFS outcomes by BMI was observed. Additional long-term follow-up will further evaluate whether BMI ultimately impacts outcome. Clinical trial information: NCT02513394. Research Sponsor: Pfizer Inc.

519 **Poster Discussion Session**

A randomized presurgical trial of alternative dosing of exemestane in postmenopausal women with early-stage ER-positive breast cancer. *First Author: Andrea De Censi, EO Ospedali Galliera, Genoa, Italy*

Background: Successful therapeutic cancer prevention requires definition of the minimal effective dose of the proposed agent. Aromatase inhibitors substantially decreased breast cancer incidence in high risk postmenopausal women in phase III trials but their clinical use in prevention and adherence in adjuvant setting is limited by adverse events. We conducted a randomized presurgical phase IIb trial to evaluate two alternative doses of exemestane. **Methods:** We conducted a multi-center, pre-surgical, double-blind, 3-arm, non-inferiority phase IIb study in postmenopausal women with histologically confirmed estrogen receptor (ER)-positive breast cancer. Patients were randomized to receive either exemestane 25 mg/day (QD), or 25 mg/three times/week (TIW), or 25 mg once a week (QW) for 4-6 weeks before surgery. Blood and tissue biomarkers were collected at baseline and final visit. The primary aim was a non-inferiority percent change of circulating estradiol relative to the standard dose. Secondary endpoints were the change in Ki-67 and PgR expression in cancer tissue, blood sex hormones, lipid profile, toxicity and menopausal symptoms. For the power calculation we assumed a non-inferiority difference of 6% in the percentage change of estradiol among arms, using a one-sided, two-sample t-test. Assuming a 10% drop-out rate, a total sample size of 180 participants (60 per arm) had 80% power to detect a 6% margin of equivalence. The significance level for the main endpoint was 0.025 to account for multiple comparisons and 0.05 for secondary endpoints. **Results:** A total of 230 women were screened, 180 agreed to participate and 173 were evaluable for response. The median percent change of estradiol was -98%, -98%, and -70% for exemestane QD (n = 56), TIW (n = 57), and QW (n = 60), respectively, showing no significant difference between QD and TIW arms (p = 0.9). Similarly, no differences were observed for estrone, total estrone and estrone sulfate between QD and TIW arms. The QW arm showed some modulation in all hormones, even though less significantly so. Among the secondary endpoints, Ki-67 and PgR were reduced in all arms, with a median change of -5% vs -7.5% for Ki-67(p = 0.124), and -9 vs -17 for PgR (p = 0.246) in the TIW vs QD arms, respectively. SHBG and HDL-cholesterol had a more favorable profile with the TIW dose compared to the daily dose. Adverse events, measured according to the CTCAE (v4), and menopausal symptoms according to MENQOL were similar in all arms, but the short treatment time may not be representative. **Conclusions:** Exemestane 25 mg TIW retains a comparable activity than 25 mg QD. This activity was similar in both arms throughout the primary and the main secondary endpoints. This new schedule should be further assessed in prevention studies and in women on adjuvant treatment who do not tolerate the daily dose. Clinical trial information: NCT02598557. Research Sponsor: U.S. National Institutes of Health, Other Foundation, Other Government Agency.

520 **Poster Session**

Chemotherapy refusal and subsequent survival in older women with high genomic risk, estrogen receptor–positive breast cancer. *First Author: McKenzie White, University of Minnesota, Minneapolis, MN*

Background: Patients with estrogen receptor (ER)- positive breast cancer and high-risk 21-gene recurrence score (RS) assay results benefit from chemotherapy, however some patients choose to decline chemotherapy. We evaluated factors associated with chemotherapy refusal by older women with high RS breast cancer and investigated the association of chemotherapy refusal with mortality. **Methods:** We used the National Cancer Database (2010-2017) to retrospectively identify women aged ≥65 years with ER-positive, HER2-negative, high RS (≥26) breast cancer. Women with Charlson Comorbidity Index ≥1, stage III or IV disease, or any unknown variables were excluded. Women with high RS who refused chemotherapy were compared to women with high RS who received chemotherapy. Refusal trends were analyzed using the Cochrane Armitage test. Factors associated with chemotherapy refusal were evaluated with a multivariable regression model. Overall survival (OS) by age and by treatment were evaluated with Kaplan-Meier and Cox proportional hazards modeling. **Results:** 6827 women met study criteria; 5449 (80%) received chemotherapy and 1378 (20%) refused. Relative to those who received chemotherapy, those who refused chemotherapy were older (median age 71 vs 69 years; $p < 0.05$), more often insured with Medicare (83% vs 80%; $p = 0.05$), were diagnosed more recently (2014-2017 vs 2010-2013, 67% vs 61%; $p < 0.05$), had lower grade tumors (grade 1 or 2 vs grade 3, 57% vs 48%; $p < 0.05$), more frequently had progesterone receptor-positive tumors (68% vs 63%; $p < 0.05$), and received radiation less frequently (67% vs 71%; $p < 0.05$). Chemotherapy refusal was significantly associated with increasing age (age 75-79 vs 65-74 OR 1.61, CI 1.4-1.85; age ≥80 vs 65-74 OR 3.24, CI 2.76-3.79) and more recent year of diagnosis (2014-2017 vs 2010-2013; OR 1.3 CI 1.14-1.48). Chemotherapy refusal was significantly associated with decreased 5-year OS for patients aged 65-74 years (92% vs 95%; $p < 0.05$) and patients aged 75-79 years (85% vs 92%; $p < 0.05$), but not for those aged ≥80 years (84% vs 91%; $p = 0.07$). Overall, when controlling for patient factors, hazard of death with chemotherapy refusal was significantly increased (HR 1.12, CI 1.04-1.2), but was not increased for women aged ≥80 years when stratified by age. **Conclusions:** Among healthy women aged ≥65 with high genomic risk ER-positive breast cancer, chemotherapy refusal increased with increasing age. Chemotherapy refusal was significantly associated with decreased OS in women aged 65-79, but did not impact OS in women aged ≥80. Lower use of chemotherapy in women ≥80 may demonstrate pragmatic decision-making between physicians and patients. Furthermore, the routine use of genomic assays may not be appropriate in this age group. More research is needed to determine why women aged 65-79 refuse chemotherapy, and whether patients remain satisfied with these choices. Research Sponsor: None.

521 **Poster Session**

Physician perspectives on extrapolating data from trials testing less-intense treatment to underrepresented populations. *First Author: Gabrielle Betty Rocque, University of Alabama at Birmingham, Birmingham, AL*

Background: Clinical trials provide the foundation for evidence-based practices, yet trial participants are often not representative of all patients. Historically, clinical trials involved adding novel agents to standard of care to improve survival. There has been a shift to an individualized approach with testing less intense treatment, yet vulnerable patient groups are at risk for underrepresentation. Little is known about physician perspectives on implementing less intense treatment approaches for patients who are not represented in sufficient number to draw conclusions on subpopulations. **Methods:** Open-ended, individual qualitative interviews with medical oncologists from different cancer centers exploring their perspectives on trials that test less intense treatment for patients with cancer. Interviews were audio-recorded and transcribed. Four independent coders utilized a content analysis approach to analyze transcripts using NVivo. Major themes and exemplary quotes were extracted. **Results:** Of the 39 participating physicians, 61.5% felt comfortable extrapolating, 30.8% were hesitant, and 7.7% would not feel comfortable extrapolating trial outcomes to underrepresented populations. One physician noted, "We've been extrapolating for as long as I can remember and certainly that I've been in practice; so we do need to do better there, but extrapolation is only natural with what we have." Facilitators of comfort included sentiment that "biology is biology", such that the cancer characteristics were what mattered; the strength of the evidence from the trial overall; inclusion of subset analysis on underrepresented populations; and prior experience making decisions with limited data. Barriers to extrapolation included the potential harm over the patient's lifetime; concerns about groups that had minimal participants; application specifically to younger patients; and extending findings to racially and ethnically diverse populations. Oncologists highlighted the need for shared decision-making when applying study results to underrepresented populations. They also expressed concerns about study findings being applied to patients who would have been ineligible in the original trials. Universally, broader inclusion in trials testing lowering chemotherapy is desired. **Conclusions:** The majority (92%) of physicians report that they would extrapolate clinical trial results to patients poorly represented in de-escalation trials, while expressing concerns about applicability to specific subpopulations based on tumor characteristics (e.g. stage, biology) and patient demographics (e.g. age, race). Further work is needed to increase clinical trial representation of diverse populations to safely and effectively optimize treatment for patients with cancer. Research Sponsor: Komen.

522 **Poster Session**

Effect of mevalonate pathway inhibitors on outcomes of patients (pts) with HER2-positive early breast cancer (BC) in the ALTTO trial. *First Author: Carmine De Angelis, Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy*

Background: Our preclinical findings suggest a role for the mevalonate pathway (MVA) in treatment resistance in HER2+ BC by providing alternative growth and survival signaling to bypass potent HER2 blockade, which could be overcome by the MVA inhibitors statins and nitrogen-containing bisphosphonates (NBs). Here we explored the effect of MVA inhibitors' use on pts' outcomes in the ALTTO trial (BIG2-06; NCT00490139). **Methods**: In the ALTTO trial, 8381 pts with HER2+ BC were randomized to 1 year of adjuvant lapatinib (L), trastuzumab (T), L+T, or T→L. All pts with documented treatment start with statins or NBs < 1 year after randomization were considered as MVA inhibitors users. Survival curves, with a median follow-up of 6.9 years, for disease-free survival (DFS), distant relapse-free interval (DRFI), BC-specific survival (BCSS), and overall survival (OS) according to MVA inhibitors use were estimated by the Kaplan Meier method and Log-rank test. All multivariate survival analyses employed a Cox proportional hazards regression model, adjusting for tumor size, nodal status, hormonal receptor (HoR), menopausal status, BMI, timing of chemo, and randomization arm. We considered interactions terms in Cox's model between MVA inhibitors use and randomization arm, hormonal status, and BMI group. **Results**: Among the 8381 pts included in this study, 493 and 299 were statins or NBs users, respectively. Table 1 summarizes the significant differences in pts' characteristics according to MVA inhibitors use ($P < .005$). In multivariate survival analyses, only NBs use was associated independently with better BCSS (HR, 0.44; 95% CI, 0.23 - 0.84; $P = 0.014$). Statin use was not independently associated with prognosis but only in interaction with pts characteristics: worse DFS, BCSS and OS in pts treated with L+T, worse DRFI and OS in pts treated with HoR+ BC (respective interaction P-values <0.05 in the Cox's model). **Conclusions**: NBs independently predicted improved BC-specific outcome in pts with HER2+ BC treated with adjuvant anti-HER2 therapy. Statin use was associated with an inferior outcome in pts with HoR+ disease and/or those treated with L+T. Whether this inferior association in statin users may reflect the underlying predisposition factors that can weaken the efficacy of anti-HER2 treatments and whether this effect was observed only in the L+T arm due to the more potent inhibition of the HER2 signaling pathway remain open questions. Further clinical investigations on the impact of MVA inhibitors on the outcome of pts with HER2+ BC are warranted. Research Sponsor: U.S. National Institutes of Health.

	Statin		NB	
	Yes	No	Yes	No
Age (median, yrs)*	60	51	57	51
BMI (median, kg/m²)*	28.0	25.2	24.3	25.4
Tumor size (median, mm)*			20	22
HoR+ (%)¶			70.2	56.9
Grade 3 (%)¶	65.3	56.6		
Postmenopausal status (%)¶	89.9	54.5	77.3	55.8
Concurrent chemo (%)¶	56.0	44.3	54.9	44.6

*Wilcoxon test, ¶chi-square test.

523 **Poster Session**

Socioeconomic disparities in supportive therapy use and tolerance of aromatase inhibitors in patients with early-stage, hormone-positive breast cancer. *First Author: Melanie Wain Kier, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: Socioeconomic disparities impact breast cancer survival with significantly higher mortality among women of lower socioeconomic status. Little is known about how disparities affect patients with early-stage hormone receptor positive (HR+) breast cancer (BC) and patients' tolerance and adherence to standard of care adjuvant aromatase inhibitor (AI) therapy. AI-related adverse effects are common and can cause therapy intolerance and early discontinuation. Supportive therapies have been shown to improve symptom tolerability when utilized by patients. This study assessed socioeconomic disparities in utilization of supportive therapies and adherence to initial AI therapy. **Methods:** We performed a retrospective chart review of all female patients at our academic institution with early-stage, HR+, BC who were initiated on adjuvant AI between 2011-2020. We collected information on side effects, duration of first AI and use of supportive therapies. We linked median family income with zip codes based on national census data and sorted them based on the Pew Research Center categorization. Primary endpoints were the rate of discontinuation of AI at 1-year and utilization of supportive therapies in relation to income, insurance coverage and primary language. The Fisher's exact test, Pearson's Chi-squared test, and Wald test methods were used to compare rates of discontinuation of front-line AI therapy and use of supportive therapies for each group. **Results:** We identified 1006 patients of whom 95% (n = 954) had AI related side effects yet only 31% (n = 311) received supportive therapies in the first year of AI treatment. The majority (59%) of patients were in the middle-income range ($52,200-$156,000), followed by upper (24%) and lower (17%) income. Upper-income was associated with higher use of supportive therapies (OR 1.46, $p = 0.031$) but was not associated with lower 1-year discontinuation rate. Medicare was the most common insurance coverage (45%), followed by Commercial (32%) and Medicaid (23%). English was the primary language for 86% of patients. Neither insurance coverage nor primary language was associated with either endpoint. In evaluating race, Black patients had the least use of supportive therapies ($p < 0.001$), yet this group had the lowest 1-year discontinuation rate ($p = 0.005$). **Conclusions:** Our results demonstrate that income and race were associated with use of crucial supportive therapies that are proven to help patients mitigate AI toxicities. The etiology of these disparities is likely multifactorial and requires further study to ensure equitable care and access for all patients. Research Sponsor: None.

524 **Poster Session**

Estradiol (E2) levels in premenopausal women with hormone receptor-positive (HR+) breast cancer (BC) on ovarian function suppression (OFS) with gonadotropin-releasing hormone agonists (GnRHa).

First Author: Megan Elizabeth Tesch, Dana-Farber Cancer Institute, Boston, MA

Background: OFS is an important treatment component for premenopausal women with early and advanced HR+ BC and optimal efficacy may depend on complete E2 suppression with GnRHa, especially when combined with aromatase inhibitors (AI). However, standard assays lack sensitivity and accuracy at very low E2 concentrations, rendering detection of breakthrough ovarian function challenging. More informative data regarding endocrine effects of GnRHa are needed, particularly in young women who derive the most benefit from OFS yet more frequently had breakthrough E2 levels in the SOFT trial substudy, SOFT-EST. **Methods:** Using a prospective cohort study of women with BC diagnosed at age ≤ 40 years, we identified participants with stage I-IV HR+ BC on OFS treatment with leuprolide, goserelin or triptorelin and blood collected 1 year after diagnosis. Clinical data were obtained through surveys and medical records. Plasma estrogens were measured by liquid chromatography-tandem mass spectrometry, with a limit of detection of 0.2 pg/mL compared to 10 pg/mL with standard assays. We assessed the proportion of women on OFS with E2 > 2.72 pg/mL (10 pmol/L) and > 10 pg/mL. Patient characteristics, estrone (E1) and FSH levels, and disease-free (DFS) and overall survival (OS) were compared between those with and without elevated E2 using Fischer's exact, Wilcoxon rank sum and log rank tests, respectively. **Results:** Of 84 patients who met inclusion criteria, 72 (86%) had stage I-III and 12 (14%) had stage IV BC; 25 were on OFS plus AI and 59 were on OFS plus tamoxifen (TAM). Median E2 was 3.1 pg/mL (range 0.2-30.9). 46 patients (55%) had E2 > 2.72 pg/mL, including 8 on AI and 38 on TAM; 4 (5%) had E2 > 10 pg/mL, including 1 on AI and 3 on TAM. Factors associated with E2 > 2.72 pg/mL were no prior chemotherapy, TAM and high E1 ($P \leq .05$), but not age, BMI or GnRHa schedule (Table). After a median follow-up of 7 years, DFS events were seen in 6 patients with E2 > 2.72 pg/mL and 5 without ($P = .232$); OS events were seen in 7 patients with E2 > 2.72 pg/mL and 5 without ($P = .608$). **Conclusions:** More than half of young women with ER+ BC had E2 > 2.72 pg/mL on OFS, 91% of whom would not have been detected by standard assays. This may be an area amenable to intervention to improve outcomes in young women. However, larger studies are needed to elucidate the optimal E2 target on OFS and clinical implications of incomplete E2 suppression on ultrasensitive assays. Research Sponsor: Susan G. Komen, Breast Cancer Research Foundation.

	E2 ≤ 2.72 pg/mL (n = 38)	E2 > 2.72 pg/mL (n = 46)	*P*
Age, median (range)	35 (26-40)	36 (17-40)	.808
BMI, median (range)	23 (16-45)	24 (19-35)	.211
Prior chemotherapy, n (%)	27 (71)	22 (48)	.045
GnRHa monthly, n (%)*	23 (61)	24 (52)	.485
trimonthly	13 (34)	21 (46)	
Concurrent AI, n (%)	17 (45)	8 (17)	.009
TAM	21 (55)	38 (83)	
E1 (pg/mL), median (range)	5.1 (0.2-29)	14.0 (0.2-43.4)	<.001
FSH (IU/L), median (range)	4.1 (1.5-85.4)	3.0 (1.2-87.7)	.321

*n = 3 missing data

525 **Poster Session**

Exploring homologous recombination deficiency thresholds for predicting response to platinum-based treatment in triple negative breast cancer.

First Author: Kirsten Timms, Myriad Genetics Inc., Salt Lake City, UT

Background: Homologous recombination deficiency (HRD) status can be used to identify patients who are eligible for treatment with DNA damaging agents. Using a 3-biomarker Genomic Instability Score (GIS) threshold of ≥42, studies have previously examined the association between HRD status and outcomes in patients with triple negative breast cancer (TNBC). However, evidence suggests that a GIS threshold of ≥33 may be more appropriate. Here, we conducted an exploratory analysis evaluating the ability of ≥33 and ≥42 GIS thresholds to predict response to platinum-based treatment in patients with TNBC. **Methods:** Patients across 5 cohorts (TBCRC030[1], TBCRC008[2], NCT01372579[3], PrECOG 0105[4], combined cisplatin cohort[4]) were included in this analysis if they had a primary TNBC diagnosis, received neoadjuvant platinum-based treatment, had a valid GIS, and had known pathologic complete response (pCR) status. GIS was determined by a combination of loss of heterozygosity, telomeric-allelic imbalance, and large-scale state transitions.[4,5] BRCA mutation status was defined by loss of function resulting from a pathogenic variant in *BRCA1* or *BRCA2*. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), were calculated by comparing binary threshold status and binary pCR status. **Results:** A total of 204 tumors (158 BRCAwt; 33 BRCAm; 13 unknown) were included; pCR to platinum-based treatment occurred in 55 cases (39 BRCAwt; 14 BRCAm; 2 unknown). Sensitivity, specificity, PPV, and NPV were comparable between the ≥33 and ≥42 GIS thresholds, with the ≥33 threshold producing higher sensitivity values. This was true when thresholds were applied to all samples and to BRCAwt samples only (Table). Among patients who achieved pCR in response to platinum-based treatment, 5.5% of patients in the full cohort and 7.7% of those in the BRCAwt cohort had a GIS between 33-41. **Conclusions:** To ensure that the majority of patients likely to benefit from treatment are identified, a GIS of ≥33 may be the most appropriate threshold to predict response to platinum-based treatment in patients with TNBC; however, a prospective trial will be needed to confirm these findings. Additional studies will be important to determine whether this threshold may be appropriate to determine eligibility for other DNA-damaging agents such as PARP inhibitors. 1. Ann Oncol. 2020;31(11):1518-25 2. J Nucl Med. 2015;56(1):31-7. 3. Breast Cancer Res Treat. 2015;151(3):629-38. 4. Clin Cancer Res. 2016;22(15):3764-73. 5. Breast Cancer Res Treat. 2014;16(6):1-9. Research Sponsor: Myriad Genetics, Inc., Other Foundation, Pharmaceutical/Biotech Company, U.S. National Institutes of Health, QVC; Fashion Footwear Association of New York.

Sensitivity, specificity, and predictive values for pCR to platinum-based treatment by GIS threshold.

	Sensitivity	Specificity	PPV	NPV
All (N=204)				
GIS ≥33 (N=141)	0.945	0.403	0.369	0.952
GIS ≥42 (N=123)	0.891	0.503	0.398	0.926
BRCAwt (N=158)				
GIS ≥33 (N = 100)	0.923	0.462	0.360	0.948
GIS ≥42 (N = 84)	0.846	0.571	0.393	0.919

526 **Poster Session**

Metformin, placebo, and endocrine therapy discontinuation among participants in a randomized double-blind trial of metformin versus placebo in hormone receptor–positive early-stage breast cancer (CCTG MA32).

First Author: Dawn L. Hershman, Columbia University College of Physicians and Surgeons, New York, NY

Background: The MA32 study (NCT01101438) investigated whether 5-years of metformin improves invasive disease-free survival in early-stage breast cancer (BC). Non-adherence to endocrine therapy (ET) and medications for chronic conditions is common, and increases with drug toxicity and polypharmacy. This secondary analysis evaluates rates and predictors of early discontinuation of metformin, placebo, and ET among participants with HR positive BC. **Methods:** Patients with high-risk non-metastatic BC were randomized to 60 months of metformin (850 mg BID) or placebo. Patients were administered bottles of metformin/placebo every 180 days. Metformin/placebo compliance was defined as a bottle dispensed at month 48 or later (i.e., medication supplied for 54 months). The ET compliance analysis included patients with HR positive BC who received adjuvant ET with start and stop date reported and was defined as > 48 months of use. Associations of baseline covariates with drug compliance and with ET adherence were examined using multivariable models. **Results:** Among the 2,521 HR-positive BC patients, 32.9% were non-compliant to study drug. Non-compliance was higher among patients on metformin vs. placebo (37.1% vs. 28.7%, p<0.001). Reassuringly, compliance to ET was similar between treatment arms (28.4% vs 28.0%, p=0.86). Patients who were non-compliant to endocrine therapy, were more likely to be non-compliant to study therapy (38.8% vs. 30.1%, p<0.0001). In a multivariable analysis, study drug non-compliance was increased with metformin vs. placebo (OR=1.43, 95% CI, 1.21-1.70; p<0.0001); grade 1 or greater GI toxicity during the first year (70.9% vs. 53.2%; OR=1.20, 95% CI, 1.01-1.44; p=0.044); lower age (age < 50 OR = 1.44, 95% CI, 1.21 – 1.71; p<0.01) and higher body mass index (BMI > 30, OR=1.49, 95% CI, 1.25 - 1.77; p<0.0001). Study drug non-compliance was decreased with prior receipt of chemotherapy (OR = 0.68, 95% CI, 0.50–0.84; p<0.001). Non-compliance with endocrine therapy was associated with increased non-compliance to study drug (OR: 1.47, 95% CI, 1.20, 1.70, p < 0.0001). Study drug (metformin vs placebo) non-compliance was not associated with endocrine therapy non-compliance (OR=0.97, 95% CI, 0.80-1.17; p=0.74). **Conclusions:** While non-compliance was higher among patients on metformin, it was still considerable among patients on placebo. Among other factors, development of GI toxicity and non-adherence to ET were associated with non-adherence to study drug. Many BC patients on ET are prescribed metformin and other oral medications for the treatment of chronic conditions. Reassuringly, non-adherence to study drug did not impact endocrine therapy adherence. Attention to global medication adherence is needed to improve BC and cardiovascular outcomes in cancer survivors. Clinical trial information: NCT0110143. Research Sponsor: U.S. National Institutes of Health.

527 **Poster Session**

Adjuvant abemaciclib for high-risk early breast cancer (EBC): Factors increasing the rate of treatment discontinuations in monarchE.

First Author: Sara M. Tolaney, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

Background: Adjuvant abemaciclib plus endocrine therapy (ET) demonstrated clinically meaningful improvement in reducing the risk of recurrence in patients (pts) with HR+, HER2– high risk EBC. In monarchE, 25.6% pts discontinued abemaciclib before completing the 2-year treatment period due to reasons other than recurrence. This exploratory analysis evaluates the impact of baseline factors on time to discontinuation for abemaciclib-treated patients with an aim to identify pts at higher risk of discontinuation. **Methods:** Time to discontinuation (TTD) was defined as time from first dose to the discontinuation of abemaciclib or all treatment due to reasons other than recurrence. These exploratory analyses evaluated the association between TTD and baseline demographics, disease characteristics, and the extent of pre-existing medical comorbidities. Factors with p-value <0.05 in the univariate Cox model were considered as potentially associated with TTD and then fitted into a multivariate Cox model with stepwise variable selection, with entry and retaining p-value threshold of 0.05. Discontinuation rates at selected timepoints (6-month, 12-month, 18-month, 24-month) within each subgroup were estimated using the Kaplan-Meier method. **Results:** The following variables were significantly associated with higher risk of discontinuation in the multivariate model: Age ≥65 yr, enrolled in North America or EU, ECOG PS=1, post-menopausal, 1-3 positive nodes, or 4 or more pre-existing comorbidities. The majority of discontinuations occurred within the first 6 months of the treatment period; thus, this timepoint was selected to estimate discontinuation rates for factors independently associated with TTD (Table). Complete results on discontinuation rates at other timepoints will be reported in the presentation. **Conclusions:** This exploratory analysis identified several factors associated with a greater risk of discontinuation. These results illustrate the importance of close monitoring and dose adjustments early on, particularly for patients with an increased risk of discontinuation prior to completing the 2-yr treatment period of abemaciclib. Clinical trial information: NCT03155997. Research Sponsor: Eli Lilly and Company.

Factors		N	Discontinuation rate [6 months], % (95% CI)	p-value [multivariate model]
Geographic region	North America/ EU	1458	16.5 (14.7, 18.5)	<0.0001
	Asia	573	10.3 (8.0, 13.0)	
	Other	760	12.1 (9.8, 14.5)	
Menopausal status	Premenopausal	1217	9.3 (7.8, 11.0)	<0.0001
	Postmenopausal	1574	17.7 (15.8, 19.6)	
Age group	<65 years	2361	11.6 (10.3, 12.9)	<0.0001
	>=65 years	430	27.6 (23.4, 31.9)	
Baseline ECOG PS	0	2392	13.7 (12.4, 15.2)	0.022
	1	399	15.8 (12.4, 19.6)	
Number of positive nodes	1 to 3	1115	16.1 (14.0, 18.3)	<0.0001
	4 to 9	1096	13.2 (11.3, 15.3)	
	10 or more	573	11.6 (9.1, 14.4)	
Number of unique pre-existing comorbidities	0	466	9.7 (7.2, 12.6)	0.0007
	1 to 3	1370	12.8 (11.1, 14.6)	
	4 or more	955	18.0 (15.6, 20.5)	

528 **Poster Session**

AMEERA-4: A preoperative window-of-opportunity (WOO) study to assess the pharmacodynamic (PD) activity of amcenestrant or letrozole in postmenopausal patients with ER+/HER2− primary breast cancer. *First Author: Mario Campone, Institut de Cancérologie de l'Ouest, René Gauducheau, St Herblain, France*

Background: Amcenestrant is an optimized oral selective ER degrader (SERD) that antagonizes and degrades the ER and has demonstrated favorable preliminary safety and antitumor activity as monotherapy and in combination with palbociclib in postmenopausal patients with ER+/HER2− advanced breast cancer, irrespective of baseline (BL) *ESR1* mutation status. Here we present the final results of AMEERA-4 (NCT04191382), a Phase 2 preoperative WOO study that evaluated the PD activity of two dose levels of amcenestrant or letrozole using paired biopsies assessed for biomarkers. **Methods:** Postmenopausal women with operable stage I–III (tumor size ≥ 10 mm by ultrasound) ER+/HER2− breast cancer and Ki67 levels ≥ 15% by local assessment were randomized 1:1:1 to amcenestrant 400 mg once daily (QD), amcenestrant 200 mg QD or letrozole 2.5 mg QD for 14 days before surgery. Antiproliferative activity, as measured centrally by change from BL in Ki67 using paired biopsies before and after a 14-day treatment with 2 different doses of amcenestrant vs letrozole, was the planned primary endpoint. Main secondary endpoints included ER target engagement, assessed through the change in ER expression measured by change from BL in H-Score, and safety. **Results:** Trial enrollment was voluntarily stopped early, as informative data supporting adjuvant development became available; therefore, no formal statistical comparisons were conducted. Among 105 randomized patients (amcenestrant 400 mg: n = 34, amcenestrant 200 mg: n = 36, letrozole: n = 35), 95 were treated and had available pre- and post-treatment Ki67 per central review (modified ITT population). No major imbalances in BL patient and tumor characteristics were observed. The geometric least squares means (LSM) estimate (95% CI) of Ki67 reduction was 75.9% (67.9, 81.9) for amcenestrant 400 mg, 68.2% (58.4, 75.7) for amcenestrant 200 mg and 77.7% (70.0, 83.4) for letrozole. The LSM estimate (95% CI) of absolute change from BL in ER H-score was –176.7 (–201.4, –152.0) for amcenestrant 400 mg, –202.9 (–226.1, –179.7) for amcenestrant 200 mg and –32.5 (–57.2, –7.7) for letrozole, with median relative changes of –65.3%, –68.3% and –9.5%, respectively. The incidence of treatment-related adverse events (TRAEs) was 21.2% for amcenestrant 400 mg, 22.2% for amcenestrant 200 mg and 25.7% for letrozole. No Grade ≥ 3 TRAEs occurred in any treatment arm. **Conclusions:** Both doses of amcenestrant demonstrated robust Ki67 reductions, strongly engaged the ER target, and continued to show a favorable safety profile in an early breast cancer population, consistent with previous published reports. Based on PD activity and safety, and emerging results from other ongoing amcenestrant trials, the 200 mg QD dose of amcenestrant was selected for our ongoing study in the adjuvant setting; AMEERA-6 (NCT05128773). Clinical trial information: NCT04191382. Research Sponsor: The study was sponsored by Sanofi. Editorial support was provided by Amanda Sheldon, PhD, CMPP, of inScience Communications (Philadelphia, PA, USA), funded by Sanofi.

529 **Poster Session**

Association of progesterone receptor status with 21-gene recurrence score and survival among patients with estrogen receptor-positive breast cancer. *First Author: Sung Jun Ma, Roswell Park Comprehensive Cancer Center, Buffalo, NY*

Background: Among patients with estrogen receptor (ER)-positive breast cancer, progesterone receptor (PR)-negative tumors were shown to have worse prognosis than PR-positive tumors. However, PR-negative tumors were underrepresented in trials such as TAILORx and RxPONDER, and the role of PR status in the setting of 21-gene recurrence score (RS) remains unclear. We performed an observational cohort study to evaluate the association of PR status with RS and the magnitude of chemotherapy benefits on survival. **Methods:** The National Cancer Database (NCDB) was queried for women diagnosed between 2010 and 2017 with ER-positive, human epidermal growth factor receptor 2 (HER2)-negative, pT1-3N0-1a breast cancer who underwent surgery and endocrine therapy. Logistic and Cox multivariable analyses (MVA) were used to identify variables associated with high RS (> 25) and overall survival (OS), respectively. Interaction test was performed among PR status, chemotherapy, and nodal staging. Propensity score matching was performed to reduce selection bias. Sensitivity analysis was performed after excluding those with postdiagnosis survival of less than 6 months to reduce immortal time bias. **Results:** A total of 143,828 patients met our criteria (n = 110,421 for PR-positive/pN0, n = 11,897 for PR-negative/pN0, n = 19,928 for PR-positive/pN1a, n = 1,582 for PR-negative/pN1a). Median follow up was 51.5 months (interquartile range 34.8-71.9). On logistic MVA, PR-negative tumors were more likely to have high RS (adjusted odds ratio [aOR] 6.68, 95% confidence interval [CI] 6.40-6.97, p < 0.001). On Cox MVA, PR-negative tumors were associated with worse OS (adjusted hazards ratio [aHR] 1.20, 95% CI 1.10-1.31, p < 0.001). Interaction among PR status, chemotherapy, and nodal staging was statistically significant (interaction p = 0.049). On subgroup analyses, the magnitude of chemotherapy benefit for OS was comparable among pN0 tumors (PR-positive: aHR 0.74, 95% CI 0.66-0.82; PR-negative: aHR 0.63, 95% CI 0.51-0.77) and was greater for PR-negative status among pN1a tumors (PR-positive: aHR 0.57, 95% CI 0.47-0.67; PR-negative: aHR 0.31, 95% CI 0.20-0.47). Similar findings were noted in 9,979, 1,822, 4,196, and 354 matched pairs for PR-positive/pN0 (HR 0.43, 95% CI 0.37-0.50), PR-negative/pN0 (HR 0.53, 95% CI 0.41-0.69), PR-positive/pN1a (HR 0.55, 95% CI 0.45-0.67), and PR-negative/pN1a (HR 0.25, 95% CI 0.14-0.45) tumors, respectively. On sensitivity analysis, our findings were consistent in Cox MVA using interaction and subgroup analyses. **Conclusions:** To our knowledge, this is the largest study using a nationwide oncology database suggesting that PR-negative status is an independent, adverse prognostic factor for survival associated with high RS, with greater chemotherapy benefits compared to PR-positive status among pN1a tumors even after adjusting for RS. Research Sponsor: None.

530 **Poster Session**

A prognostic model for distant recurrence-free survival in triple-negative breast cancer (TNBC) and the outcomes of initiation of adjuvant chemotherapy in the risk of relapse. *First Author: Zaida Morante, Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru*

Background: TNBC is a highly complex, heterogenous disease associated with poor outcomes, high incidence of distant metastases, and limited treatment options. With the purpose of identify patients at different risk of distant recurrence, we developed a prognostic model using clinicopathological characteristics that contribute to the risk of recurrence in TNBC patients and also evaluate its influence in the time of beginning of adjuvant therapy. **Methods:** We retrospectively analyzed 687 TNBC patients who received adjuvant chemotherapy between January 2000 to December 2014 at the Instituto Nacional de Enfermedades Neoplasicas (Lima, Peru). The database was randomly divided into two groups to create a discovery set (n = 344) and a validation set (n = 343). Univariate and multivariate Cox regression analysis was conducted to identify prognostic factors for distant recurrence-free survival (DRFS). We developed a linear risk score based on clinicopathologic characteristics. Under STEPP methodology we classified patients at high, intermediate or low-risk of distant recurrence and the absolute treatment effects of time to initiation of chemotherapy (TTC, ≤ 30 vs > 30 days) through risk subgroups was estimated. **Results:** The median of follow-up was 9.90 years. In total, 31.0% (n = 213/687) relapses were registered. Variables associated with DRFS in the multivariate analysis were: age, T-staging, and N-staging. A tumor staging of T3-T4 vs. T1/T2 (HR = 2.92, 95%CI: 1.39 - 6.17), followed by the number of positive lymph nodes (N2-N3 vs N0/N1; HR = 2.78, 95%CI: 1.74 - 4.45) and an older age (≥ 60 years vs. ≤ 40/41-59, HR = 2.66, 95%CI: 1.46 - 4.88) were the clinicopathologic characteristics contributing to a higher risk score according to the 3-variable model. Also, 3 risk groups were identified and corroborated in the validation group. In the discovery set, patients with a TTC > 30 days experienced an overall decreased of 17.5% (95%CI: 6.7 - 28.3) in 10-year DFRS vs. those who initiated adjuvant therapy before 30 days. The impact of TTC > 30 days was higher in patients classified as high-risk (Decreased 10-year DFRS: 53.3 ± 28.8 %), similar findings were found in the validation set. **Conclusions:** A prognostic model based in clinicopathological characteristics (age, pT and pN), was able to classify TNBC patients' candidates to adjuvant chemotherapy in 3 prognostics groups. We identified a subgroup of patients in which delaying of adjuvant chemotherapy (> 30 days) confers very high-risk of relapse. Research Sponsor: Own resources.

531 **Poster Session**

Breast density reduction as a predictor for prognosis in premenopausal women with hormone receptor–positive breast cancer: A retrospective analysis of the ASTRRA study. *First Author: Soong June Bae, Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea*

Background: While the relationship between mammographic breast density (MD) decline and anti-hormone therapy efficacy has been reported in estrogen-receptor (ER)-positive breast cancer, it is still unclear in premenopausal women and in the case of adding ovarian function suppression (OFS) to anti-hormone therapy. We aimed to investigate the MD reduction (MDR) rate and impact of MDR on prognosis stratified by treatment from the updated result of the ASTRRA trial. **Methods:** ASTRRA trial, a randomized phase 3 study, showed that adding ovarian function suppression (OFS) to tamoxifen (TAM) improved survival in premenopausal women with ER+ breast cancer after chemotherapy. We updated survival outcomes with a median follow-up of 108 months. We assessed mammography taken before treatment and the follow-up mammography taken annually for up to five years after initiation of treatment. MD was classified into four categories based on the Breast Imaging Reporting and Data System. MDR positivity was defined as a downgrade in MD among follow-up mammography up to two years after randomization, with the pretreatment MD grade as a reference. **Results:** Among the 1,293 patients from ASTRRA trial, we successfully evaluated MDR in 947 patients, of which 796 (83.4%) belong to high MD (grade C or D). The patient characteristics were similar between the entire ASTRRA trial and the subgroup with available MDR. There was no difference in MDR-positive rate between two treatment groups (106 of 477 [22.2%] in TAM-only group vs. 87 of 470 [18.5%] in TAM + OFS group, $P = .156$). MDR-positivity was significantly associated with better disease-free survival (DFS) in TAM + OFS group (estimated 8-year DFS: 92.9% in MDR-positive vs. 82.2% in MDR-negative, $P = .013$), but did not in TAM-only group (estimated 8-year DFS: 80.3% in MDR-positive vs. 80.2% in MDR-negative, $P = .927$; $P_{interaction} = .025$). Simialr trends were observed in terms of recurrence-free survival, distant metastasis-free survival (DMFS), locoregional-free survival, and overall survival. In addition, MDR-positivity was an independent factor for favorable DFS (adjusted hazard ratio [HR], 0.37; 95% CI, 0.16 to 0.86; $P = .021$) and DMFS (adjusted HR, 0.35; 95% CI, 0.13 to 0.98; $P = .045$) in TAM + OFS group. **Conclusions:** Although the proportion of patients with MDR-positive was comparable between the two treatment groups, MDR-positive was independently associated with favorable outcomes only in TAM + OFS group. Future work is warranted to verify the mechanism by which the association between MDR and clinical benefit differs according to the treatment group. Clinical trial information: NCT00912548. Research Sponsor: This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI19C0481, HC19C0147).

532 **Poster Session**

The survival benefit of anti-HER2 treatment in the management of small (T1mic, T1a, T1b, T1c), node-negative HER2+ breast cancer. *First Author: Kai Conrad Cecil Johnson, Ohio State University - James Cancer Center, Columbus, OH*

Background: Limited compelling prospective and retrospective data regarding the added benefit of anti-HER2 therapy in the management of small, node-negative HER2-positive breast cancer (HER2+BC) exists, in part due to differences in outcome reporting, unmatched analyses, and a lack of head-to-head comparisons. As a result, national guideline committees find themselves unable to confidently recommend anti-HER2 therapy and clinicians are left to exercise clinical judgement on whether the use of anti-HER2 therapy should be considered for such patients. **Methods:** Our team performed a multi-institutional retrospective analysis using the ASCO CancerLinQ database, with a focus on clinical data from small, node-negative HER2+BC patients diagnosed between 2010 to 2021. We compared clinical outcomes between those who received adjuvant trastuzumab therapy, with or without chemotherapy, to those who did not, with our primary outcomes being invasive disease-free survival (iDFS) and overall survival (OS). We performed both a univariate and multivariate analysis, using a Cox proportional hazard model to control for factors including age, ethnicity, body mass index, hormone status, tumor grade, histology type, BRCA status, region, and smoking history. Additionally, a three-arm univariate analysis was performed comparing untreated patients to trastuzumab alone versus combination therapy. **Results:** In total, 1206 patients met inclusion criteria, including 779 patients who received trastuzumab with or without chemotherapy. We found a statistically significant improvement in both iDFS (HR 0.73, p = 0.01) and OS (HR 0.63, p = 0.027) on univariate analysis for those receiving anti-HER2 therapy. Similarly on multivariate analysis, iDFS (HR 0.75, p = 0.030) and OS (HR 0.61, p = 0.029) were improved in those who received therapy, regardless of tumor size. Our three-arm univariate analysis involving no treatment (n = 427), trastuzumab monotherapy (n = 169), and combination therapy (n = 578) found that iDFS was significantly improved for both treatment arms compared to observation alone (p = 0.006), whereas OS trended towards significance in the treatment arms but did not reach this target (p = 0.061). No significant difference was noted between treatment arms. **Conclusions:** Our analysis found a statistically significant improvement in iDFS and OS when patients with small, node negative, HER2+BC received adjuvant anti-HER2 therapy with or without chemotherapy as compared to observation. From our univariate three-arm comparison, it appears that trastuzumab provides the majority of benefit to patients in terms of DFS, but this result is exploratory. Further investigation is warranted, including meta-analyses to better characterize the degree of benefit seen with anti-HER2 treatment. For now, this data adds to evidence suggesting added benefit with therapy over observation. Research Sponsor: None.

533 **Poster Session**

Outcomes of patients with T1a,b N0 Her2-positive breast cancer treated with adjuvant trastuzumab in a prospective registry in Ontario, Canada. *First Author: Andrea Eisen, University of Toronto, Toronto, ON, Canada*

Background: Multiple randomized trials of chemo +/- tras in early stage, Her 2 positive BrCa demonstrated improvement in survival, but patients (pts) with T1a,b N0 disease were mostly excluded. Given the uncertainty of benefit in this group and the toxicities of chemo + tras, treatment in Ontario was funded for these patients conditional upon data collection for toxicity and survival endpoints. We report the outcomes for 483 patients enrolled in this Evidence Building Program (EBP). **Methods**: Between 2011 and 2018, 483 eligible pts with Her 2 pos disease and adequate cardiac function were treated with chemo + tras in the EBP. Cardiac toxicity, febrile neutropenia (FN), event-free (EFS), and overall survival (OS) were determined for this cohort from administrative datasets, and compared retrospectively to controls of similar stage selected from the Ontario Cancer Registry who did not receive tras and/or chemo. For the EBP cohort, clinicians also reported changes in left ventricular ejection fraction (LVEF). **Results**: Pt characteristics are shown in the Table. EBP patients had improved OS when compared to controls who received no chemo or tras. The 3-year OS in the EBP pts was 99.1%, versus 96.9% in the controls [adjusted HR 0.59 (95% CI 0.29-1.20)]. Patients receiving EBP tras had a significantly longer EFS than controls with or without chemo [adjusted HR 0.54 (0.36-0.83), p=0.005]. Use of chemo + tras in EBP pts was associated with an increased risk of clinical congestive heart disease (CHD) and febrile neutropenia (FN). About 3.5% of pts experienced CHD during treatment with chemo + tras. About 6% of pts had an absolute reduction of LVEF >10% or reached LVEF <50%. In an adjusted analysis, the risk of CHD was higher in older pts [HR 1.06 (1.03-1.08) per 1-yr increase in age, p<0.0001) and for pts who received anthracyclines [HR 5.00 (1.71-14.7). In a matched analysis, the crude frequency of FN during treatment was 20% in EBP pts vs. 3% among controls who did not receive chemo or tras (p<0.001). **Conclusions:** Analysis of the Ontario EBP for pts with, T1a,b N0 HER2 pos BrCa revealed that the prognosis is excellent and is improved with the use of chemo + tras. The safety profile was expected and tolerable, especially when non anthracycline chemo was used. These results led to a funding policy change where prospective data collection has been discontinued and chemo + tras is now routinely funded in this population. Research Sponsor: Ontario Ministry of Health.

	EBP tras pts (n=483)	Control pts (n=13,296)*
Age at diagnosis (y)	57.6 (SD 10.0)	63.2 (SD 11.3)
T size		
1 to 9.9 mm	393 (81%)	10,917 (82%)
10 mm	90 (19%)	2,379 (18%)
HER2/ER/PR status		
HR+, HER2+	315 (65%)	1,009 (8%)
HR+, HER2-	0 (0%)	9,535 (72%)
HR-, HER2+	168 (35%)	455 (3%)
HR-, HER2-	0 (0%)	683 (5%)
Missing	0 (0%)	1,614 (12%)

*Analyses restricted to Her2+N0 subgroups.

534 **Poster Session**

Safety and tolerability of olaparib combined with breast radiotherapy in patients with triple-negative breast cancer: Final results of the RADIOPARP phase 1 trial. *First Author: Pierre Loap, Institute Curie, Department of Radiation Oncology, Paris, France*

Background: Preclinical studies have demonstrated that triple-negative breast cancer (TNBC) cells were sensitive to PARP inhibitors when used as radiosensitizers. Combining PARP-inhibitors with radiotherapy may consequently enhance the biological effectiveness of the irradiation, leading to improved locoregional control in TNBC patients. We aimed to establish the appropriate dosing and the safety profile of Olaparib used as a radiosensitizer in combination with radiotherapy in TNBC patients with residual disease after neoadjuvant chemotherapy. **Methods:** RADIOPARP (NCT03109080) was a prospective phase I dose-escalation trial establishing the tolerance profile of Olaparib combined with breast radiotherapy in high-risk early TNBC patients. Inclusion criteria were resected TNBC with non-complete pathological response after neoadjuvant chemotherapy, or unresectable TNBC despite prior neoadjuvant chemotherapy. Olaparib was started seven days before irradiation and continued during radiotherapy. A time-to-event continual reassessment method was used to increase Olaparib through four increasing dose levels (50mg, 100mg, 150mg or 200mg twice a day) with a 25% maximum probability rate of dose-limiting toxicities (DLT). Radiotherapy delivered 50 Gy to the breast or to the chest wall, with or without lymph node irradiation. Toxicities were graded according to CTCAE (version 4.03). Homologous recombination (HR) proficiency status was genetically determined based on shallow whole genome sequencing. **Results:** Twenty-four TNBC patients were enrolled between 09/2017 and 11/2019. Olaparib was escalated to 200 mg twice a day without DLT and the MTD was not reached. With a median follow-up of 34 months, no late treatment-related grade $\geq$ 3 toxicity was observed, and the maximum observed toxicities were limited to grade 2 breast pain (n=2), fibrosis (n=2), deformity (n=1) and telangiectasia (n=1). Three-year OS and EFS were 83% [95% CI: 70%-100%] and 65% [51%-91%], respectively. HR proficiency status was not associated with OS and EFS. **Conclusions:** Olaparib used as a radiosensitizer in combination with radiotherapy in TNBC patients was well-tolerated. The MTD was not reached, and no significant late toxicity was reported. For future trials evaluating the anti-tumor efficacy of this combination, an Olaparib dose of 200 mg twice a day should be considered. Clinical trial information: NCT03109080. Research Sponsor: AstraZaneca.

535 **Poster Session**

Efficacy and safety of initial five years of adjuvant endocrine therapy in postmenopausal hormone receptor-positive breast cancer: A systematic review and network meta-analysis. *First Author: Hao Liao, Peking University Cancer Hospital, Beijing, China*

Background: Endocrine therapy has greatly improved the clinical outcomes of hormone receptor-positive breast cancer patients. However, there was an unmet need to identify the potentially best regimen of initial adjuvant endocrine therapy. Therefore, in this network meta-analysis, we synthesized the latest evidence to indirectly compare the efficacy and safety among different 5 years of regimens of initial adjuvant endocrine therapy. **Methods:** We conducted a systematic search of the PubMed, Web of Science, and EMBASE in January 2022. Randomized clinical trials assessing the efficacy and safety of initial 5 years of adjuvant endocrine therapy were included. The primary outcomes were disease-free survival (DFS) and overall survival (OS) and the secondary outcome was severe adverse effects (SAEs). A Bayesian network meta-analysis was carried out to indirectly compare all regimens and the SUCRA values were used to obtain rankings. **Results:** Eleven studies with 49,987 subjects were included. For DFS, exemestane (EXE) (hazard ratio [HR] 0.91, 95% confidence interval [95%CI] 0.87-0.96), anastrozole (ANA) (0.94, 0.90-0.97), letrozole (LET) (0.93, 0.89-0.97), tamoxifen (TAM) followed by EXE (0.91, 0.87-0.96), and TAM followed by ANA (0.92, 0.87-0.98) were more favorable than TAM, with TAM followed by EXE ranking as the first of SUCRA. For OS, only TAM followed by ANA showed significant superiority than TAM (HR 0.91, 95%CI 0.86-0.97) and ranked as the first of SUCRA. For SAEs, EXE (HR 1.72, 95%CI 1.04-2.98), ANA (1.58, 1.03-2.43), and LET (1.63, 1.02-2.57) showed greater associations with bone fracture than TAM. However, no significant difference in the incidences of cardiac events, thromboembolic events, and cerebrovascular events was found among all comparisons. **Conclusions:** The sequential use of aromatase inhibitors may be the optimal treatment mode for hormone receptor-positive postmenopausal early breast cancer patients. In addition, the three kinds of aromatase inhibitors achieved roughly equal efficacy, but caused different types of SAEs. Research Sponsor: None.

536 **Poster Session**

Concordance and clinical impact of ER, PR, HER2 expression by local and central immunohistochemistry versus RT-PCR in HR+/HER2- early breast cancer (EBC): Results from the ADAPT trial. *First Author: Oleg Gluz, West German Study Group and Ev. Hospital Bethesda, Breast Center Niederrhein, Moenchengladbach, Germany and University Hospital Cologne, Cologne, Germany*

Background: We evaluated concordance of ER, PR and HER2 status between local, central, and RT-PCR/mRNA assessments and its clinical impact in the ADAPT trial collective in HR+ HER2- EBC (NCT01779206). Particularly, validity of borderline ER-positivity (expression level 1-10%) has great clinical relevance as treatment concepts between luminal-like and triple negative (TNBC) EBC differ substantially. **Methods**: Patients (pts) with clinically high-risk HR+/ HER2- EBC (ER and/or PR >1%) were initially treated by 3 (+/-1) weeks of endocrine therapy (ET) before surgery or sequential core biopsy (CB) and then allocated to an ET-alone or chemotherapy (ET) trial, depending on risk and endocrine response. OncotypeDX (incl. RT-PCR for ER, PR, HER2) and central IHC for ER, PR, HER2 were performed on the initial 1.CB. ER-low cohort was defined as 1-10% expression by local OR central lab (ASCO-CAP). Cox models were used to estimate hazard ratios. **Results**: In ADAPT, 5149 pts from 81 centers in Germany with locally ER and/or PR positive (known quantitative levels) EBC were screened 2012-2018. Median follow-up was 59 months. For ER (positive vs. negative), overall concordance measured as agreement (κ) was high between all three assessments: Local vs. central IHC: 99.3% (κ = 0.45), RT-PCR vs. central IHC: 99% (κ = 0.48). Concordance was lower for PR: RT-PCR vs. central IHC: 90.5% (κ = 0.58), local vs. central IHC: 93.1% (κ = 0.56). 3% were centrally found as HER2+ in 1.CB (73% of them were negative by RT-PCR) and/or 2. Sample. Regarding HER2-low status (1+ or 2+ but ISH negative), concordance between local and central IHC was only 53.8% (κ = 0.09). Of all pts, only 2% (n=109; n=85 with both measurements available) had low ER expression (1-10%) by either local or central pathology. Only 9 of them were concordantly identified as ER-low (11%); 8/58 (14%) ER-low by local lab had TNBC by central lab. 17/47 ER-low cases (36.2%) with known post-endocrine Ki67post had Ki67post <10% vs. 59.7% in ER>10%. 41.8% of ER-low cases had RS<25 vs. 76.7% in ER>10%. All cases with ER <10% by both assessments and those with Ki-67≥40% had RS >25. We observed worse iDFS (HR 1.91, p=0.034) in the ER-low group vs. ER>10%. **Conclusions**: Although we have confirmed high agreement between local and central IHC and RT-PCR for ER, PR, HER2 assessment in locally HR+/HER2- EBC, there are still a few clinically relevant discordances. Regarding HER2-low status, standardization and quality assurance are needed if this becomes clinically relevant. Treatment of the heterogeneous ER-low group as TNBC appears reasonable only if "ER-low" is confirmed by a second assessment and in cases with Ki-67>40%. Preoperative ET response assessment may be helpful if an endocrine-based therapy concept is intended. Clinical trial information: NCT01779206. Research Sponsor: Roche, Exact Sciences.

537 **Poster Session**

Adherence to EndoPredict test scores for extended endocrine therapy management in the prospective EndoPredict Extended Endocrine Trial (EXET). *First Author: Adam Brufsky, University of Pittsburgh Medical Center, Pittsburgh, PA*

Background: Current guidelines advise that individuals with estrogen receptor-positive (ER+) breast cancer (BC) undergo 5 years of endocrine therapy with consideration of up to 10 years of extended endocrine therapy (EET). The relative benefit of EET beyond 5 years is minimal for many patients, yet a significant group of patients at higher risk of late recurrence may benefit. EndoPredict is a gene expression assay to stratify those with high versus low BC recurrence risk and is validated to predict early and late distant metastasis up to 15 years using an EPclin score. In the prospective EXET study we evaluated adherence to EndoPredict test results when making decisions regarding EET. **Methods:** Patients with prior ER+, human epidermal growth factor 2 negative (HER2-) BC diagnosis and 4-6.5 years of endocrine therapy underwent EndoPredict testing. To evaluate the impact on decision making for EET, chart review was performed at or after test results were clinically disclosed. Univariable analysis was used for EPclin risk classification (high, low), multivariable analysis was used to evaluate the EPclin score with clinical variables and Firth logistic regression was used to assess the association of a given variable with the therapy decision. **Results:** The cohort consisted of 411 patients with an average age of 62 years (range 27, 90), 107 received adjuvant chemotherapy (26%), and 71 were lymph node positive (17.3%). The rate of EET was significantly different for those with low-risk scores (EPclin Score ≤ 3.3) compared to high-risk scores (EPclin Score > 3.3; OR 8.5×10^{-4} [95% CI 6.8×10^{-6}, 6.0×10^{-3}], p-value 5.7×10^{-68}). All patients with high-risk scores received EET. Within the low-risk group, those treated with adjuvant chemotherapy and those who were lymph node positive chose to extend endocrine therapy at higher rates. The EPclin score provided significant information in predicting EET status, even when accounting for clinical variables such as node status, tumor grade, age at diagnosis, adjuvant chemotherapy status and tumor stage (EPclin Score OR 20.2 [10.1, 44.0]; p-value=3.1×10^{-25}). **Conclusions:** Even after adjusting for other clinical factors, EndoPredict is a significant predictor of clinical decision on EET. High adherence to EndoPredict test results in EET decision making was noted in our study. Clinical trial information: NCT04016935. Research Sponsor: Myriad Genetics.

Rate of medical decision to extend endocrine therapy.

	N	EPclin High Risk (95% CI)	EPclin Low Risk (95% CI)	p-value
All patients	411	166/166, 100% (97.8%, 100%)	54/245, 22% (17.0%, 27.8%)	5.7×10^{-68}
With adjuvant chemotherapy	107	80/80, 100% (95.5%, 100%)	17/27, 63% (42.4%, 80.6%)	1.5×10^{-13}
Without adjuvant chemotherapy	304	86/86, 100% (95.8%, 100%)	44/218, 20.2% (15.2%, 26.1%)	2.4×10^{-43}
Lymph node negative	340	112/112, 100% (96.8%, 100%)	46/228 20.2% (15.2%, 26.0%)	5.1×10^{-53}
Lymph node positive	71	54/54, 100% (93.4%, 100%)	8/17, 47.1% (23.0%, 72.2%)	1.4×10^{-7}

538 **Poster Session**

The real-world experience of adjuvant docetaxel and cyclophosphamide (TC) chemotherapy in HER-2 negative breast cancer. *First Author: Danilo Giffoni M. M. Mata, Sunnybrook Health Sciences Centre, Toronto, ON, Canada*

Background: Adjuvant chemotherapy in breast cancer (BC) substantially improves overall survival (OS) and the risk of recurrence. The short and long-term side effects of anthracycline, and its modest benefits in the adjuvant setting, led to controversy about its role in comparison with TC. We aim to compare the OS of TC with anthracycline-based regimens in Ontario, the most populous province in Canada. **Methods**: We conducted a retrospective population-based cohort study using the Institute for Clinical Evaluative Sciences (ICES) database, involving females with stage I-III BC HER2-negative. Patients were treated with adjuvant chemotherapy between January 2009 to December 2017. The anthracycline regimens for comparison were as follows, FEC-D: Fluorouracil, Epirubicin, Cyclophosphamide, followed by Docetaxel; and ACT: Doxorubicin, Cyclophosphamide, followed by Docetaxel or Paclitaxel. Exclusion criteria included missing baseline characteristics, a prior history of malignancy or chemotherapy starting more than 120 days from breast surgery. The end of follow-up was March 31st, 2018. Adjusted analyses to compare OS by positive axillary lymph nodes (LN) and chemotherapy regimens were conducted with Cox proportional hazards models. **Results**: Of a total 10634 female patients with BC, 60% were ≥ 50 years-old, with 19.6% stage I, 61.1% stage II, and 19.3% stage III and 7130 (67%) women were classified as ER+ and 2379 (22.4%) as ER-. Among 5764 (54.2%) patients with positive LN, 4300 (40.4%) had LN 1-3 and 1464 (13.8%) had LN ≥ 4. There were 4945 (46.5%) high-grade cases. There were 2487 (23.5%) patients treated with TC, 2981 (28%) with ACT, and 5166 (48.5%) with FEC-D. With a median follow-up of 5.5 years, the OS comparison for the entire study population showed hazard ratio (HR) of TC vs ACT was 1.47 (95% CI 1.14 – 1.90), p = 0.0027 and TC vs FEC-D HR was 1.48 (95% CI 1.18 – 1.86), p = 0.0007. For ER+ patients treated with TC, the OS comparison of LN 1-3 and LN ≥ 4 vs. LN 0 showed HR 1.34 (95% CI 0.81 – 2.21), p = 0.26, and HR 4.29 (95% CI 2.09 – 8.79), p < 0.0001, respectively. For ER+ LN 0 patients, the OS HR of TC vs. ACT was 1.15 (95% CI 0.58 – 2.35), p = 0.67, and TC vs. FEC-D HR was 1.38 (95% CI 0.81 – 2.33), p = 0.23. For ER- patients treated with TC, the OS comparison of LN 1-3 and LN ≥ 4 vs. LN 0 showed HR 1.12 (95% CI 0.42 – 3.01), p = 0.82 and HR 4.41 (95% CI 1.33 – 14.59), p = 0.015, respectively. For ER- LN 0 patients, the OS HR for TC vs. ACT was 2.04 (95% CI 1.09 – 3.81), p = 0.025, and TC vs. FEC-D HR was 2.05 (95% CI 1.08 – 3.90), p = 0.028. **Conclusions**: Patients treated with adjuvant TC who had four or more axillary LN had significantly lower OS when compared to patients with LN 0. For women with ER- disease, TC demonstrated a significant unfavourable survival outcome when compared to anthracycline-based treatments. Research Sponsor: The Department of Breast Cancer of Sunnybrook Health Sciences Centre, Odette Cancer Centre.

539 **Poster Session**

Ovarian function suppression is not indispensable in patients with early breast cancer who are older than age 40. *First Author: Jianqiao Xian, Sun Yat-Sen University Cancer Center, Guangzhou, China*

Background: Based on SOFT/TEXT studies, ovarian function suppression (OFS) has become the standard treatment for pre-menopausal breast cancer patients. However, a few studies reported more than 80% pre-menopausal breast cancer patients over 40 years old experienced permanent chemotherapy-induced amenorrhea (CIA) after chemotherapy, suggesting that these patients may not benefit from OFS. The purpose of this study was to evaluate the application value of OFS in early pre-menopausal hormonal receptor (HR)-positive breast cancer patients who experienced chemotherapy after 40 years old. **Methods:** 1386 pre-menopausal patients over 40 years of age with early HR-positive breast cancer underwent chemotherapy from 2010 to 2017 at the Sun Yat-Sen University Cancer Center. Serum hormone levels were used to define pre-menopausal status. OFS only referred to gonadotropin-releasing hormone agonist (GnRHa). Propensity score matching (PSM) was performed to reduce the selection bias between patients administrated with OFS and those without OFS. The prognostic value of OFS was determined using Kaplan-Meier and Cox proportional hazards analysis. **Results:** A total of 1386 patients (median age, 46 years; rang, 40-55 years) were enrolled in this study, 258 patients were treated with OFS and 1128 patients did not receive OFS treatment. After PSM, there were 258 patients allocated in Non-OFS group and 258 patients in OFS group. There had no statistically significant difference in terms of overall survival (OS) (p=0.5) and disease-free survival (DFS) (p=0.62) between Non-OFS group and OFS group. In Non-OFS group, 100 patients (8.86%) resumed menstruation after chemotherapy, and 1028 patients (91.14%) experienced permanent CIA. There also had no statistically significant difference in either OS (p=0.35) or DFS (p=0.79) between menstrual recovery group and permanent CIA group. In terms of the menstrual recovery duration time of the 100 patients who resumed menstruation, 37 patients (37%) were ≤ 6 months, 18 patients (18%) were 7 ~ 12 months, and 45 patients (45%) were > 12 months. In terms of the intervals from last time of chemotherapy to the beginning of menstrual recovery, 29 patients (29%) were ≤ 6 months, 16 patients (16%) were 7 ~ 12 months, and 55 patients (55%) were > 12 months. Finally, we analyzed the survival difference of different menstrual recovery durations and different intervals. We found that there still had no statistically significant difference in different recovery durations (OS, p=0.15; DFS, p=0.19) and different intervals (OS, p=0.11; DFS, p=0.24). **Conclusions:** In this study, early pre-menopausal HR-positive breast cancer patients who experienced chemotherapy after 40 years old did not benefit from OFS treatment in DFS and OS. These results suggest that OFS is not indispensable in early HR-positive breast cancer patients aged over 40 years. Research Sponsor: The National Natural Science Foundation of China (82172722).

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Adjuvant chemotherapy is associated with an overall survival benefit regardless of age in patients with ER+/HER2-breast cancer with 1-3 positive nodes and Oncotype DX recurrence score 20 to 25: A National Cancer Database analysis. *First Author: Lifen Cao, University Hospitals at Cleveland Medical Center, Cleveland, OH*

Background: Based on the results of the RxPonder trial, post-menopausal women over age 50 with estrogen receptor (ER)+ breast cancer, 1-3+ nodes, and a 21-gene Oncotype DX recurrence score (RS) score of <25, did not benefit from receiving adjuvant chemotherapy. By contrast, adjuvant chemotherapy was beneficial in premenopausal women. We aimed to replicate the RxPonder trial using a larger sample sizes with real world data to determine whether a threshold with RS exists where adjuvant chemoendocrine therapy (CET) is beneficial regardless of age. **Methods:** The National Cancer Database (NCDB) was queried for women with ER+, human epidermal growth factor receptor 2 (HER2) negative breast cancer, 1-3 positive axillary nodes, and RS <25 who received endocrine therapy (ET) only or CET. Interaction was explored between CET and age as a surrogate for menopausal status in the Cox regression models. **Results:** The final analytic cohort included 28,427 eligible women: 7,487 (26.3%) received adjuvant CET and 20,940 (73.7%) ET. In the entire cohort, RS had a normal distribution, with a median score of 14. After correcting for demographic and clinical variables, a threshold effect was observed with RS >20 being associated with a significantly inferior overall survival (OS) (P value range: < 0.001-0.019). In women with RS of 20-25, CET was associated with a significant improvement in OS compared to ET alone, regardless of age (age < = 50: HR = 0.334, P = 0.002; age > 50: HR = 0.521, P = 0.019). **Conclusions:** Among women with ER+/HER2- breast cancer with 1–3 positive nodes, and RS of 20-25, in contrast to the RxPonder trial we observed that CET was associated with an OS benefit in women regardless of age. Research Sponsor: Institutional Fund.

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Predictive value of ectopic *HORMAD1* tumor expression for high-dose platinum-based chemotherapy benefit in patients with high-risk HER2-negative breast cancer. *First Author: Leonora Wijnandina De Boo, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: The meiotic DNA break regulator *HORMAD1* is aberrantly expressed in many cancers and is associated with increased genomic instability. The susceptibility of *HORMAD1* expressing tumors to agents targeting DNA damage repair (DDR) pathways is poorly understood since clinical data within the context of a randomized clinical trial (RCT) is lacking. Here, we retrospectively studied *HORMAD1* expression as a putative predictive biomarker in an RCT for benefit of adjuvant high-dose platinum-based chemotherapy (HDCT) with autologous stem cell support in patients with high-risk HER2-negative early breast cancer (BC). **Methods:** Patients with stage III BC participated in an RCT comparing HDCT to conventional chemotherapy (CDCT; Rodenhuis et all, NEJM, 2003; Steenbruggen et all, JAMA Oncol, 2020). We studied the subgroup with HER2-negative BC for whom tumor *BRCA1*-like classification was previously determined using a validated DNA comparative genomic hybridization algorithm (Vollebergh et all, BCR, 2014). Tumor *HORMAD1* expression was determined on FFPE samples using RNAscope, an RNA in situ hybridization method, and classified as negative (no expression) or positive (any expression detected). **Results:** For 195/246 (79.3%) HER2-negative patients treated according to protocol, *HORMAD1* RNAscope status was available; dropout was due to absence or insufficient quality of tumor specimens. *HORMAD1* positivity was enriched in triple-negative breast cancer (TNBC) (23/47; 48.9%). Furthermore, in all HER2-negative BCs, *HORMAD1* positivity (45/195; 23.1%) was associated with age ≤40 years, histological grade III, <10 positive lymph nodes, breast-conserving surgery, *BRCA1*-like profile, and tumor-infiltrating lymphocytes (TILs) >10%. Such association, although not significant, was also observed within TNBC. During a median follow-up of 20.3 years, 124 (63.6%) recurrences and 115 deaths (59.0%) occurred. The prognostic effect of *HORMAD1* positivity on overall survival (OS) varied with follow-up time and was borderline significant at 10 years and significant thereafter (10-year: adjusted (adj.) HR 0.47, 95% CI 0.21-1.04; 15-year: adj. HR 0.25, 95% CI 0.07-0.91). Benefit on RFS from HDCT over CDCT was stronger in patients with *HORMAD1*-positive tumors (adj. HR 0.18, 95% CI 0.06-0.54) than in patients with *HORMAD1*-negative tumors (adj. HR 0.69, 95% CI 0.46-1.02) (P-interaction = 0.02). Similar results were observed for OS. **Conclusions:** In this retrospective sub study of 195 patients with high-risk HER2-negative BC participating in an RCT, tumor *HORMAD1* expression is predictive for benefit of high-dose platinum-based chemotherapy. Our observations are consistent with the prior observations that *HORMAD1* expression is associated with genomic instability and impaired DDR pathways. Further research is warranted to validate our findings. Clinical trial information: NCT03087409. Research Sponsor: A Sister's Hope.

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Adherence to adjuvant endocrine therapy assessed by data from prescription renewals and medical records from tamoxifen in Swedish patients with cytochrome P450 2D6 (CYP2D6) genotyped early breast cancer. *First Author: Linda Thoren, Department of Clinical Science and Education at Sodersjukhuset, Karolinska Institutet, Department of Oncology, Sodersjukhuset, Stockholm, Sweden*

Background: Suboptimal adherence to adjuvant endocrine treatment (AET) is an important clinical concern. A correlation between CYP2D6 activity and tamoxifen discontinuation has been suggested. The main aim of this study was to investigate the consistency between prescription refill data and reports from medical records on adherence to AET in early breast cancer. We also studied if there was an association between menopausal status, CYP2D6 activity, estimated risk for recurrence and adherence to AET. **Methods:** 1235 pre-and postmenopausal Swedish breast cancer patients operated 2006 – 2014, genotyped for CYP2D6, who initiated adjuvant tamoxifen treatment, were included in the study. Information on AET was retrospectively collected from both medical records and the Swedish Prescribed Drug Registry. Consistency was defined as dispensed doses of AET divided by AET intake documented in medical records. Adherence was calculated for patients with at least 4.5 years of follow up and was defined as Medical Possession Rate (MPR) ≥ 80 %. Subgroup analyses were performed based on menopausal status, recurrence-risk and CYP2D6 activity. **Results:** In 84% of the patients the consistency of AET between the sources of information was within 80-125%. Consistency < 80% was most frequent in premenopausal/high risk patients and CYP2D6 Poor Metabolizers (PM). Among 899 patients with at least 4.5 years follow up, adherence to tamoxifen was 72% according to prescription refill data, compared to 77% as reported by medical records. When including aromatase inhibitors adherence increased to 82% and 88%. Adherence did not differ by menopausal status or risk for recurrence. CYP2D6 PM had poorer adherence (54%) to tamoxifen compared to patients with the highest CYP2D6 activity (83%). **Conclusions:** Consistency between medical records and dispensing data on adherence was better than anticipated. Adherence to AET was good, 82% when including switch to aromatase inhibitors. Surprisingly, CYP2D6 PMs had low adherence to tamoxifen, despite a reduced risk of side effects according to previous studies. Further work is needed to clarify the impact of CYP2D6 activity on adherence to tamoxifen. Research Sponsor: SM received grants from The Cancer Society in Stockholm, the Percy Falk Foundation for research on Prostate Cancer and Breast Cancer, the Swedish Breast Cancer Association, the Stockholm County Council (ALF20180419), EE received grants from CIMED, the Stockholm County Council (ALF20190536). The study was also supported by grants from Jonas Bergh's research group which is supported by grants from the Swedish Cancer Society (19 0292 PJ 01 H and 19 0189 US01 H), The Research Funds at Radiumhemmet (164003), Karolinska Institutet, Stockholm County Council (ALF2017-1341), FOU (Karolinska University Hospital account number 907515).

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Estimating survival benefit of adjuvant chemotherapy in postmenopausal women with pT1-2N0 early-stage breast cancer and Oncotype DX recurrence score > 26: A National Cancer Database (NCDB) analysis. *First Author: Lifen Cao, University Hospitals at Cleveland Medical Center, Cleveland, OH*

Background: Early validation studies using the Oncotype DX recurrence score (RS) in NSABP B20 demonstrated that women with node negative breast cancer and RS >31 had significant survival benefit from the addition of adjuvant chemotherapy to endocrine therapy (CET). Consequently, in the prospective TAILORx trial, node negative women with RS >26 received CET. These studies did not clearly delineate the magnitude of benefit of adjuvant chemotherapy for post-menopausal node negative women. A recently published well-designed adjuvant trial (RxPONDER) demonstrated that adjuvant chemotherapy was not beneficial in post-menopausal pts with ER+/HER2- breast cancer, 1-3 positive nodes, and RS <25. We hypothesized that CET would be associated with a modest but statistically significant overall survival (OS) in women with hormone receptor positive ER+/HER2- node negative breast cancer with RS >26 compared to endocrine therapy (ET) alone, given that CET is more beneficial in women <50 years of age. **Methods:** The National Cancer Database (NCDB) was queried to analyze women age > 50 with ER+/HER2- pT1-2N0M0 breast cancer with RS >26, to assess real world utilization. We separated women into two groups based on adjuvant treatment: ET alone or CET. Chi-square and logistic regression analysis determined difference between different systemic treatment groups. OS was analyzed using a multivariable Cox model. **Results:** A total of 16,745 eligible women who underwent surgery and received ET were identified in the NCDB—4,740 (28.3%) received ET alone and 12,005 (71.7%) received CET. We observed that CET use increased over time. Women were more likely to receive CET if their tumors were moderately differentiated (OR = 1.853, p < 0.001), poorly/undifferentiated tumors (OR = 3.875, p < 0.001), or associated with lymph-vascular invasion (OR = 1.206, p = 0.001). After accounting for demographic and oncologic factors, 5-year OS rates in this cohort were significantly superior in women receiving CET compared to ET alone (95.4% vs 92.0%, Hazard Ratio = 0.680, p < 0.001). **Conclusions:** Utilizing the NCDB to represent real world outcomes, we observed that women > 50 years with pT1-2N0M0 ER+/HER2- breast cancer, and RS > 26 had a significantly superior 5-year OS when receiving adjuvant chemotherapy provides a measurable OS benefit for post-menopausal women in this setting and should be discussed with patients. Research Sponsor: Institutional Fund.

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Comparison of predicted benefit using RS clin versus observed benefit in a U.S. registry of stage I ER-positive HER2-negative high oncotype DX RS breast cancer.

First Author: Christopher David Walden, Gundersen Lutheran Health System Inc., La Crosse, WI

Background: The 21-gene recurrence score assesses the risk of distant breast cancer recurrence and predicts the benefit of adjuvant chemotherapy in ER positive early-stage breast cancer. However, clinicopathologic risk factors continue to impact absolute benefit of adjuvant chemotherapy. Absolute benefit of adjuvant chemotherapy in low clinicopathologic risk Stage I ER positive breast cancer with high Oncotype RS is an important clinical component of shared decision making. The RSClin clinical tool, which integrates the 21-gene recurrence score (RS) and clinicopathologic features, was found to be more prognostic than RS result alone. We assessed RS Clin predicted benefit and compared to absolute benefit in low clinicopathologic risk Stage I ER positive breast cancer with high Oncotype RS as observed in the NCDB. **Methods:** Using the National Cancer Data Base (NCDB), we identified female patients age 18-75, ER positive and Her 2 negative, 21 gene signature high risk > 25 with negatives surgical margins, <2cm, lymph node negative breast cancers, who had received endocrine therapy with either Tam or AI diagnosed during 2010 - 2017. Clinicopathologic factors and RS were entered into the RSClin calculator, and a predicted benefit of chemotherapy was calculated for each patient. Using NCDB data, Cox proportional hazards regression models were used to project absolute survival benefit at 10 years from diagnosis for those who did vs those who did not receive chemotherapy. NCDB-derived absolute benefit of chemotherapy was compared to estimated absolute benefit as predicted by the RSClin tool. **Results:** 18,226 patients were identified. Stages T1a = 670(4%), T1b = 4,289(23%), and T1c = 13,267(73%). Median age 59 years (21-75). Race white 84% (15,365), black 10% (1840), and other 1021(6%). AI use 80% (14,711) was greater than Tam use 20% (3515). Chemotherapy was administered in 75% (13,827) of patients. Most patients had high or intermediate grade disease, G3 45% (8225), G2 46% (8328), and G1 9% (1672). Median duration of follow up was 57 months (2-160). Probability of death T1b at 10yrs with chemotherapy was 8.5%, and without chemotherapy was 15.1% with an absolute benefit of 6.6%. Predicted benefit in T1b using RS Clin at 10yrs was 10.8%. Probability of death for T1c at 10yrs with chemotherapy was 15.1%, and without chemotherapy was 23.5% with an absolute benefit of 8.4%. Predicted benefit in T1c using RS Clin at 10yrs was 14%. **Conclusions:** Patients with stage IB and IC hormone receptor positive HER2 negative breast cancers with high RS had a lower absolute benefit than predicted by RS Clin. The RSClin tool overestimated benefit of therapy in both IB and IC stages requiring caution when using this tool in patients with the lowest clinicopathologic risks. Research Sponsor: Gundersen Medical Foundation.

545 **Poster Session**

Predictive performance of breast cancer index (BCI) and clinical treatment score post-5 years (CTS5) in the IDEAL study.

First Author: Gerrit-Jan Liefers, Leiden University Medical Center, Leiden, Netherlands

Background: The Breast Cancer Index (BCI) is a gene expression–based signature that stratifies patients based on the risk of overall (0-10y) and late (post-5y) distant recurrence (DR) and predicted the likelihood of benefit from extended endocrine therapy in MA.17, Trans-aTTom, IDEAL, and B-42 trials. The Clinical Treatment Score post-5 years (CTS5) is an algorithm incorporating four clinicopathologic variables (nodes, age, tumor size and grade), which has been shown to be prognostic for late DR. Previous analysis of CTS5 in IDEAL showed that CTS5 was not predictive of extended endocrine therapy benefit. The current analysis compared the predictive performance of BCI (H/I) and CTS5 for the benefit of extended endocrine therapy in the same subset of patients from the IDEAL study. **Methods:** 818 patients from the IDEAL trial who remained recurrence free 2.5y after randomization and had both BCI (H/I) and CTS5 results available were included in this study. The primary endpoint was recurrence-free interval (RFI). Absolute benefit was measured as the difference in 10-year risk of recurrences between the two treatment arms. The likelihood ratio test from Cox regression models was used to test for interaction. **Results:** 818 IDEAL patients (68% ≥50y at surgery; 48% T2; 47% G2; 73% N+) were included in the analysis. CTS5 stratified 167, 346 and 305 patients into Low-, Intermediate-, and High-risk groups. The analysis revealed that no group derived significant benefit with CTS5-Low showing 6.4% absolute benefit (HR = 0.61, 95% CI: 0.20-1.86, P = 0.377), CTS5-Intermediate showing 6.7% absolute benefit (HR = 0.55, 95% CI: 0.27-1.09, P = 0.080), and CTS5-High showing 2.1% absolute benefit (HR = 0.80, 95% CI: 0.42-1.51, P = 0.482). BCI (H/I) stratified 428 and 390 patients into BCI (H/I)-Low and BCI (H/I)-High groups. Only BCI (H/I)-High patients derived a significant absolute benefit of 10.5% (HR = 0.38, 95% CI: 0.18-0.79, P = 0.007), while BCI (H/I)-Low patients did not show any absolute benefit (HR = 0.94, 95% CI: 0.55-1.60, P = 0.817). The treatment by biomarker interaction was significant for BCI (H/I) (P = 0.045), but not for CTS5 (P = 0.731). When re-stratifying CTS5 categories by BCI (H/I) or vice versa, only BCI (H/I)-High patients showed consistent absolute benefit regardless of CTS5 category (19.4%, 8.1% and 8.8% in CTS5-Low, -Intermediate and -High, respectively). In contrast, CTS5-High patients did not show any benefit (-4.4%) in the BCI (H/I)-Low group. **Conclusions:** These results demonstrate that CTS5 does not provide predictive information to support extended endocrine therapy decision-making. Only BCI (H/I) was a predictive biomarker of benefit from extended endocrine therapy. This study further highlights the clinical utility of BCI as an endocrine response biomarker and emphasizes that prognostic information does not equate to predictive information in guiding duration of endocrine therapy. Clinical trial information: NTR3077; BOOG 2006-05; Eudra-CT 2006-003958-16. Research Sponsor: Biotheranostics, A Hologic Company, Leiden University Medical Center Institutional Grant; Novartis.

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Clinical utility of genomic recurrence risk stratification in early, hormone receptor–positive, human epidermal growth factor receptor 2–negative breast cancer.

First Author: Khalil Choucair, University of Kansas School of Medicine, Wichita, KS

Background: RNA-based genomic assessment of recurrence risk is used to estimate chemotherapy benefit in patients with hormone-receptor positive (HR+)/Human Epidermal Growth Factor 2-negative (*ERBB2*-) breast cancer (BC). While originally validated in patients who met established clinicopathologic guidelines for consideration of adjuvant chemotherapy, it is virtually used in all patients with early HR+/*ERBB2*- BC regardless of clinical recurrence risk. **Methods:** We conducted a retrospective chart review of adult patients with early-stage (T1-3; N0; M0) HR+/*ERBB2*- BC who underwent genomic risk assessment of recurrence using the Oncotype DX (Exact Sciences) 21-genes assay, between January 2015 and December 2020. Clinicopathologic features were collected to assess the clinical recurrence risk. A low clinical risk score (CRS) was defined as a tumor size ≤ 3 cm in diameter with histologic grade 1, or ≤ 2 cm with grade 2 or ≤ 1 cm with grade 3. A composite risk score of distant recurrent (RRS), derived from a COX model using data from the SOFT and TEXT trials (https://rconnect.dfci.harvard.edu/CompositeRiskSTEPP/), was also computed for 374 patients for whom clinical data was available. RRS > 1.42 was defined as high. High genomic risk of recurrence was defined as a score (GRS) ≥25. The data was collected under IRB approval. **Results:** A total of 517 patients with early-stage disease were referred for genomic testing, and clinical data was available for 501 of them. Median age was 69 years (IQR=13), median tumor size 1.03 cm (IQR=0.9), and grade 2 histology (57.49%) was the most common. Results of recurrence risk, using the 3 prognostication methods, are summarized in Table. Within patients with low CRS (n=349), 9.17% had a high GRS, compared to 8.93% in patients with low RRS (n=280). In patients with grade 1 histology (n=130), 3.85% had a high GRS and 68.46% had tumors > 1cm, of whom only 4.49% had a high GRS. Tumor size > 1cm did not associate with a high GRS (Fisher's Exact test; *P=1.00*). **Conclusions:** In patients with early HR+/*ERBB2*- BC, <10% of patients with low clinical risk, and <5% of patients with grade 1 tumors, had a high genomic recurrence risk, respectively. Given current NCCN recommendation for testing, our findings raise the question of whether genomic testing for patients with grade 1 tumors can be safely omitted, irrespective of size, and call for a better understanding of the need for routine genomic testing in patients with low grade/low clinical risk of recurrence. Research Sponsor: None.

	GRS low/intermediate	*GRS high*	Total	Association (χ^2)	Overall concordance (%)
CRS low	317	32	349	CRS *vs.* GRS	CRS *vs.* GRS
CRS high	101	51	152	*P < 0.001*	73.45
Total	418	83	**501**		
RRS low	225	25	280	RRS *vs.* GRS	RRS *vs.* GRS
RRS high	56	38	94	*P < 0.001*	70.32
Total	311	63	**374**		

547 **Poster Session**

Type of endocrine therapy and DFS in patients with early HER2+/HR+ BC: Analysis from the phase III randomized ShortHER trial.

First Author: Maria Vittoria Dieci, University of Padova, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy

Background: Optimal adjuvant endocrine therapy for HER2+/HR+ patients treated with chemotherapy and trastuzumab is still unclear. We evaluated the impact of the type of endocrine therapy on DFS in patients with HER2+/HR+ breast cancer enrolled in the phase III ShortHER trial. **Methods:** The Short-HER study randomized 1254 patients with HER2+ early breast cancer to receive 9 weeks vs 1 year of adjuvant trastuzumab combined with anthracycline-taxane chemotherapy. The type of adjuvant endocrine was collected every 6 months during the first 5 years of follow-up and was classified as: aromatase inhibitor (AI), tamoxifen and aromatase inhibitor (TAM-AI, in case of both drugs were administered for at least 1 year each), or tamoxifen (TAM). For premenopausal patients, the use of GnRH analogue was also collected. DFS was calculated from randomization to disease recurrence (locoregional or metastatic), second primary invasive cancer, or death. **Results:** 853 patients with HR+ BC (ER and/or PgR >10%) were included: 60% postmenopausal, 40% premenopausal. The pattern of endocrine therapy was: 55% AI, 22% TAM, 15% TAM-AI (8% missing data). Among premenopausal patients, 51% received GnRH. At a median follow up of 8.7 years (IQR 7.6-9.0), patients who received AI had a significantly better DFS as compared to patients who received TAM or TAM-AI: 7-yr DFS 87.3% vs 81.7%, log-rank P=0.017 (HR 1.46, 95%CI 1.05-2.03). In multivariate analysis including menopausal status, stage, and treatment arm, the type of endocrine therapy maintained a significant association with DFS (Table). In the subgroup of premenopausal patients, the use of GnRH was associated with numerically improved DFS: 86.6% vs 81.6%, log-rank P=0.168 (HR=0.70, 95%CI 0.43-1.16). **Conclusions:** In this post-hoc analysis of the ShortHER trial, adjuvant treatment with aromatase inhibitor was independently associated with improved DFS. Subgroup analysis in premenopausal patients suggests potential benefit with ovarian suppression. Clinical trial information: NCT00629278. Research Sponsor: ShortHER trial.

Multivariate analysis	HR	95%CI	P
TAM-AI or TAM vs AI	1.56	1.02-2.40	0.042
Stage I	Ref		
Stage II	1.49	1.00-2.22	0.051
Stage III	4.54	1.80-4.42	<0.001
Postmenopausal vs premenopausal	1.11	0.72-1.71	0.630
Short vs long treatment arm	1.10	0.79-1.54	0.564

548 **Poster Session**

Molecular diagnostics to reduce inequity in breast cancer diagnosis. *First Author: Clement Adebayo Adebamowo, Department of Epidemiology and Public Health and Greenebaum Comprehensive Cancer Center, University of Maryland School of Medicine, Baltimore, MD*

Background: Modern management of breast cancer requires proper subtyping of the breast tumor to guide appropriate treatment and prognostication. However, there are barriers to availability of this resource in low- and middle-income countries (LMIC) which contributes to global inequalities in breast cancer management and outcomes. The non-availability is due to high cost, and lack of personnel and infrastructure required for immunohistochemistry (IHC), the current gold standard for subtyping. IHC results are affected by pre-analytic and analytic handling and are subjective. Alternative methods that are more objective, cost less and require less infrastructure and skilled personnel will improve access and reduce disparities. **Methods:** In the AFBRECANE Project, we compared the results of ER and PR subtyping of 1,000 breast cancer tumors from patients recruited from 5 clinical sites in Nigeria using IHC and Cepheid GeneXpert RNA STRAT4 biomarker assay at ACCME Lab in Nigeria and University of Maryland. **Results:** For ER, the sensitivities, specificities, and agreement between IHC and STRAT4 ranged from 50.0%, 71.4% and 59.4% to 77.1%, 80.0% and 78.5% while for PR, they ranged from 58.1%, 66.7% and 62.5% to 84.6%, 84.2% and 84.4%. **Conclusions:** The wide range of sensitivities, specificities, and agreement between IHC and STRAT4 in this study confirms the challenges of molecular subtyping of breast cancer in LMICs like Nigeria. Sustainable objective methods are sorely needed to improve diagnosis, treatment and prognostication, and reduce global disparities. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

549 **Poster Session**

Establishment of a novel BRCAness score that predicts response to PARP inhibitors. *First Author: Masanori Oshi, Roswell Park Comprehensive Cancer Center, Buffalo, NY*

Background: BRCAness is a generic term used to describe characteristic features of homologous recombination deficiency (HRD) mimicking mutations in BRCA genes. Although clinical genetic testing has increased the detection of mutations in BRCA1 and BRCA2, we hypothesized that a measure to quantify BRCAness will identify the responders to PARP inhibitors that cause synthetic lethality in BRCA mutation tumors. **Methods:** The BRCAness score was established by using gene set variation analysis (GSVA) algorithm on 34 BRCA-mutation related genes. We investigated the clinical relevance of the score by performing silico analyses of 6245 breast cancer patients using multiple independent large cohorts in this study. **Results:** A score to quantify BRCAness was generated using gene set variation analysis algorithm on 34 BRCA1-mutation related genes selected by high AUC levels in ROC curve between BRCA1 mutation and wildtype breast cancer. The score was significantly associated with BRCA1 mutation, high overall mutation load and intratumoral heterogeneity as well as high HRD, DNA repair and MKI67 expression regardless of mutation in BRCA gene. High score tumor enriched not only DNA repair, but also five cell proliferation-related gene sets (E2F targets, G2M checkpoint, MYC targets v1 and v2, and MITOTIC signaling) in Hallmark collection (all false discovery rate < 0.10). Breast cancers with high score were significantly associated with higher infiltration of anti-cancerous immune cells and higher cytolytic activity. Not all breast cancer cell lines with BRCA-mutation showed high score and the other cells in human breast cancer tumor microenvironment were contributing to the score. We found that the BRCAness score was the highest in triple-negative among subtypes consistently in all cohorts (all $p < 0.001$). Finally, BRCAness was associated with response to chemotherapy and correlated strongly with response to PARP inhibitor in both triple-negative (AUC = 0.815) and ER-positive/HER2-negative breast cancer (AUC = 0.715). **Conclusions:** We established a novel BRCAness score using mRNA expression of BRCA-mutation-related genes and found that it associates with DNA repair and response to PARP inhibitor regardless of BRCA mutation. Research Sponsor: U.S. National Institutes of Health.

LBA550 **Poster Session**

Evaluation of booster injections in maintaining peak immunity in a phase IIb study evaluating HER2/neu peptide GP2 (GLSI-100) versus GM-CSF alone after adjuvant trastuzumab in women with HER2-positive breast cancer. *First Author: Snehal Patel, Greenwich LifeSciences, Stafford, TX*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

551 **Poster Session**

Predominance of BRCA2 mutation and estrogen receptor-positive breast cancer among BRCA1/2 mutation carriers. *First Author: Pascal Pujol, CREEC, UMR IRD 224-CNRS 5290 Université Montpellier, Montpellier, France*

Background: PARP inhibitor (PARPi) agents can improve progression-free survival of patients with breast cancer (BC) who carry a germline *BRCA1* or *BRCA2* pathogenic or likely pathogenic variant (gBRCA1/2) in both the metastatic and adjuvant setting. Therefore, we need to redefine the criteria of women and tumor phenotype that should be tested for gBRCA1/2. **Methods:** We studied the relative distribution of gBRCA1 and gBRCA2 in unselected populations of women with BC and in unaffected individuals. We also analyzed the proportion of estrogen receptor (ER)-positive (ER+) tumors in unselected BC patients with gBRCA1/2.We performed a meta-analysis of studies of unselected BC that analyzed the relative contribution of gBRCA1 versus gBRCA2 and ER+ tumors among gBRCA1/2 carriers. We then performed a meta-analysis of gBRCA1/2 carriage in unaffected individuals, from genome-wide population studies, the gnomAD databank, and case–control studies. **Results:** The *BRCA2* gene was involved in 54% of BC in unselected patients with gBRCA1/2 (n=108,699) and 59% of unaffected individuals (n=238,973) as compared with 38% of gBRCA1/2 family cohorts (n=29,700). The meta-analysis showed that 1.66% (95% CI 1.08-2.54) and 1.71% (95% CI 1.33-2.2) of unselected BC patients carried a gBRCA1 and gBRCA2, respectively. In unaffected individuals, the frequency of heterozygosity for gBRCA1 and gBRCA2 was estimated at 1/434 and 1/288, respectively. Nearly 0.5% of unaffected individuals in the studied populations carried a gBRCA1/2. Carriage of a gBRCA was 2.5% for patients with ER+ tumors (95% CI 1.5-4.1) and 5.7% (95% CI 5.1-6.2) for those with ER- tumors. Overall, 58% of breast tumors occurring in women carrying a gBRCA1/2 were ER+ (n=86,870). **Conclusions:** This meta-analysis showed that gBRCA2 carriage is predominant in unselected BC and in unaffected individuals. ER+ tumors among women with gBRCA1/2-related BC is predominant and has been underestimated. Because PARPi agents improve progression-free survival with ER+ gBRCA1/2 BC in both the adjuvant and metastatic setting, BC should be considered regardless of ER status for BRCA1/2 screening for therapeutic purposes. Research Sponsor: None.

552 **Poster Session**

Low baseline vitamin D levels correlate with adverse pathological features and clinical outcomes among patients with breast cancer. *First Author: Dina Barakat, Faculty of Medicine, Assiut University, Egypt, Assiut, Egypt*

Background: Serum vitamin D levels have been linked to breast cancer development; however, the impact on breast cancer features and outcomes remains unclear. The present study aimed at investigating the prognostic value of baseline vitamin D level among non-metastatic breast cancer patients. **Methods:** In this study; we prospectively assessed female patients presenting to our department with non-metastatic breast cancer during the period from October 2018 to December 2019 for their baseline serum vitamin D levels measured by ELISA test before starting systemic therapy, in addition to other clinicopathological factors. Low Vit-D was defined as Vit-D level less than 30 ng /l. Chi-square test (Fisher's exact test) was used to examine the relation between qualitative variables. Survival analysis was done using Kaplan-Meier method and comparison between two survival curves was done using log-rank test. Multivariate analysis was done using Cox-regression hazard model for the significant factors affecting survival on univariate analysis. **Results:** We enrolled 221 patients with non-metastatic breast cancer as they matched our eligibility criteria. Median age at diagnosis was (50.7± 10.9). About two thirds of the patients (64.7%) were post menopause. Median vitamin D level was (23.1 ng/l) with a range of (4-62.46 ng/liter). Around half of the patients (56.5%) had vitamin D level lower than 30 ng/liter, with higher numbers of low vitamin D levels among HER2 positive and triple negative (TNBC) patients compared to hormonal receptor positive (HR+ve) patients (P=<0.001). There was a significant negative correlation between vitamin D levels and tumor size, lymph node positivity and stage at diagnosis (the lower the vitamin D level, the larger the tumor size, and the higher the number of positive lymph nodes and the stage; r= -0.414, r= -0.586, r= -0.674; respectively; p<0.001). On follow up, the number of local recurrences, bone metastases and liver metastases were significantly higher among the low vitamin D level group, however; there was no significant difference between the two groups in terms of development of brain and lung metastases. Disease free survival (DFS) and overall survival (OS) was significantly worse among the low vitamin D level group (p<0.001). **Conclusions:** Low serum vitamin D in breast cancer patients negatively correlates with tumor size, lymph node positivity and stage at diagnosis. It is linked to HER-2 positive and TNBC, and is significantly associated with worse DFS and OS. Research Sponsor: None.

553 **Poster Session**

Correlation of Ki67 working group prognostic risk categories with oncotype DX recurrence score (RS) in early breast cancer (EBC). *First Author: Rima Patel, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: The 21-gene RS (Oncotype DX) provides prognostic information for distant recurrence risk and is predictive of adjuvant chemotherapy benefit in hormone receptor (HR)-positive, HER-2 negative EBC. Ki67 protein expression is a proliferation marker that is determined by immunohistochemistry (IHC). The International Ki67 Working Group (IKWG) has provided guidelines for clinical use of Ki67 for prognostic classification (PMID: 33369635). The objectives of this study were to determine the correlation between IHC-measured Ki67 with the 21-gene RS, and evaluate their association with other anatomic and biologic tumor features. **Methods:** We performed a retrospective chart review of women with HR-positive, HER-2 negative EBC with 0-3 positive lymph nodes who had both Ki67 (via IHC using MIB-1 antibody on surgical specimen at our institutional pathology CLIA laboratory) and 21-gene RS between 2013 to 2021. Patients were categorized into Ki67 low (≤ 5%), intermediate (6-29%), and high (≥30%) based on IKWG recommendations. Overall and risk stratified agreement between Ki67 and RS were assessed using the proportion of agreement and Kappa statistic. Linear regression was used to test for associations between tumor features of ER%, PR%, and tumor size and log transformed Ki67 and RS. A t-test was used to compare average log transformed Ki67 and RS by tumor differentiation and nodal status. **Results:** We identified 461 patients with HR-positive BC of whom 26.7% were ≤ 50 years at diagnosis, 30% pre-menopausal and 10% node-positive. Overall, 29% (n = 137) of patients had low Ki67, 49% (n = 227) intermediate, and 21% (n = 97) high Ki67. 18% (n = 85) had RS 0-10, 67% (n = 311) had RS 11-25 and 14% (n = 65) had RS ≥ 26. There was no significant agreement (kappa < 0) between Ki67 and RS (Kappa = -0.0035, p = 0.5406) in the overall population and fair agreement (kappa 0.21-0.40) between high Ki67 and RS (Kappa = 0.2510, p < 0.0001). Higher ER% was significantly associated with lower RS (p < 0.0001) and lower Ki67 (p = 0.0042). High tumor grade was associated with higher RS and higher Ki67 (p < 0.0001). Higher PR% was associated with lower RS (p > 0.0001) but not lower Ki67. Positive nodal status and larger tumor size were associated with higher Ki67 (p = 0.0081, p < 0.0001) but not RS. Among the 49% of patients with intermediate Ki67 of 6-29%, the distribution of low, intermediate, and high RS was 24%, 65%, and 11%, respectively. **Conclusions:** In this group of patients selected to have a 21-gene RS, there was no correlation between Ki67 and RS in the overall population, and fair agreement between high Ki67 and high RS. Among the approximately one-half with an intermediate Ki67 of 6-29%, 89% would be spared chemotherapy based on a low-intermediate RS. In patients with high Ki67, 68% might be spared chemotherapy based on the RS. In the low Ki67 group, 6% had a high RS. Ki67 has limited utility in identifying patients with high or low RS. Research Sponsor: None.

554 **Poster Session**

Detection of early-stage breast cancer in women by plasma lipidomic profiling. *First Author: Cheka Kehelpannala, BCAL Dx, Sydney, NSW, Australia*

Background: Early detection of breast cancer provides the best opportunity for cure. Mammography is the benchmark for screening, but suffers technical, logistic, and diagnostic limitations. An effective and accurate blood test to detect early stages of the disease should increase the screening detection rate for breast cancer. We conducted a series of lipidomic studies in early-stage breast cancer patients and combined the datasets via a machine learning driven analysis to test if plasma lipidomic profiles can detect breast cancer. **Methods:** Blood samples were collected from women with stage 0-IV breast cancer (4 separate cohorts) with age and BMI matched breast cancer-free controls. Lipids from plasma enriched extracellular vesicles were extracted and analysed by high resolution accurate mass LC-MS. A commercially available software was used to annotate and quantify >400 manually curated lipid species. Following variable selection, a lipid signature was identified capable of distinguishing breast cancer samples from control. **Results:** Plasma samples from women with breast cancer were distinguished from controls with an average cross-validated accuracy of 0.81, and average AUC of 0.84 across 4 cohorts (Table 1). An optimised cross-cohort subset of early-stage IDC, DCIS and ILC were differentiated from controls with a cross-validated AUC of 0.90, sensitivity of 0.88 and specificity of 0.82 (201 early-stage breast cancer, 199 controls) (Table 1). For this optimised cohort our test achieved a sensitivity of 0.71 at a prescribed specificity of 0.90, or equivalently a sensitivity of 0.89 at a prescribed specificity of 0.80. **Conclusions:** Our study demonstrates the high sensitivity and specificity of a lipid biomarker signature with potential for early detection of breast cancer. Ongoing studies will prospectively compare the lipid-biomarker based test against mammographic and pathological diagnosis. Research Sponsor: BCAL Diagnostics.

Performance of plasma lipidomic profiling across cohorts.

	Cohort 1 Stage I-IV IDC (n=44) Control (n=44)	Cohort 2 Stage I-II IDC (n=100) Control (n=101)	Cohort 3 Stage I-II IDC (n=100) Control (n=101)	Cohort 4 Stage 0 DCIS (n=51) Stage I-II ILC (n=48) Control (n=100)	Average performance of the model across cohorts 1-4	Optimised combined cohort performance (n=201 early stages of IDC, DCIS and ILC)
Accuracy	0.81	0.83	0.82	0.79	0.81	0.85
Sensitivity	0.86	0.81	0.81	0.72	0.80	0.88
Specificity	0.75	0.84	0.82	0.86	0.82	0.82
PPV	0.78	0.84	0.82	0.83	0.82	0.83
NPV	0.85	0.81	0.81	0.76	0.81	0.88
AUC	0.77	0.88	0.85	0.86	0.84	0.90

555 **Poster Session**

Risk of contralateral breast and other cancers in patients with invasive lobular breast cancer. *First Author: Grace Mei Yee Choong, Mayo Clinic, Rochester, MN*

Background: Women with early-stage breast cancer (BCa) are living longer, and survivorship issues including second primary cancers (SPCs) are therefore increasingly important. This study seeks to determine the risk of SPCs, including contralateral breast cancer (CBCa), in women with early-stage invasive lobular carcinoma (ILC). **Methods:** The study population consisted of women with BCa diagnosis between 2000-2018 within the NCI Surveillance, Epidemiology, and End Results (SEER v 3.2.9) registry and between 2000-2021 in the Mayo Clinic Cancer Registry. In the SEER registry, the standardized incidence ratios (SIR) for SPCs were estimated for adult women with histologically confirmed early stage (I-III) ILC compared to the development of any primary cancer in the general population. For reference, SIRs for SPCs for a similar patient population with invasive ductal carcinoma (IDC) of the breast were also estimated. For comparison of CBCa between ILC and IDC, follow up records from the Mayo Clinic Cancer Registry were evaluated among adult women who underwent lumpectomy or unilateral mastectomy for early stage ILC or IDC. A multivariable Cox proportional hazards regression was performed to compare the risk of CBCa between ILC and IDC while adjusting for the age at diagnosis, race/ethnicity and estrogen receptor status of the primary tumor. **Results:** An increased incidence (p<0.05) of any SPCs and second BCa was noted for both ILC and IDC compared to the expected rate of primary cancer in the general population (Table). Interestingly, women with ILC were observed to have a significantly increased incidence of subsequent gastric cancer which was not seen for women with IDC. An SIR >1.5 was noted for subsequent risk of sarcoma, myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) for both ILC and IDC (Table). In the Mayo Clinic Cancer Registry of 2,218 women with ILC and 14,629 women with IDC meeting the inclusion criteria, the 5-year risk of CBCa was 2.6% and 1.5% (log rank statistic p-value =0.001) for ILC and IDC respectively. A significantly increased risk of CBCa was noted in women with ILC (Hazard Ratio 1.82, 95% CI 1.34-2.47, p<0.001) compared to women with IDC in the multivariable analysis. **Conclusions:** Women with ILC may have an increased risk of SPC and second BCa compared to the risk of any primary cancer in the general population. The increased incidence of gastric cancer and the higher risk of CBCa in ILC survivors compared to women with IDC is intriguing and needs to be investigated further including evaluation of the role of germline genetic factors. Research Sponsor: Mayo Clinic Breast Cancer Spore.

SIR for SPC in IDC and ILC in the SEER dataset.

	ILC SIR (95% CI)	IDC SIR (95% CI)
All cancers	1.09 (1.07-1.12)*	1.16 (1.15-1.17)*
Breast	1.36 (1.31-1.42)*	1.39 (1.37-1.41)*
Gastric	1.67 (1.40-1.99)*	1.03 (0.95-1.11)
Sarcoma	1.64 (1.22-2.15)*	1.60 (1.45-1.76)*
MDS	1.84 (1.54-2.18)*	1.82 (1.71-1.91)*
AML	1.97 (1.59-2.41)*	2.08 (1.94-2.24)*

*p value < 0.05

556 **Poster Session**

Whole transcriptome analysis of tumors with discordant oncotype and MammaPrint results in the FLEX trial. *First Author: Matei P. Socoteanu, Texas Oncology-Longview Cancer Center, US Oncology, Longview, TX*

Background: Genomic tests, such as MammaPrint (MP) and Oncotype DX Breast Recurrence Score (RS), assess risk of recurrence in patients with early breast cancer (EBC). Using both assays may yield discordant results which leads to uncertainty in treatment recommendations. The assays differ in technology and genes analyzed. RS relies on RT-PCR to query 16 cancer-related genes and 5 controls. MP uses a microarray to query 70 cancer-related genes and 465 normalization controls. Here we explore the genetic basis for discordance by using the FLEX whole transcriptome database to examine differentially expressed genes among patients who received discordant RS and MP results. **Methods:** Patients with EBC enrolled in the FLEX study (NCT03053193) undergo standard of care MP and BluePrint (BP) tests, and consent to clinically annotated whole transcriptome data collection. MP stratifies risk of recurrence as Low risk and High. RS classifies patients as Low Risk (RS 0-10), Intermediate (RS 11-25), and High Risk (RS 26-100). Due to low representation of BP Basal and BP HER2-type tumors in this data set, we only examined BP Luminal-type tumors (N = 705). We used full genome transcriptomes to compare gene expression among discordant cases. Gene expression data were quantile normalized and analyzed using R package 'limma'. Genes were considered differentially expressed at a fold change of at least 1.7 and an adjusted p-value of lower than 0.05. To keep the analysis as unbiased as possible, comparisons between RS categories only included tumors within the same MP score range and similarly comparisons of MP categories only contained tumors within the same RS score range. **Results:** The comparisons between discordant cases, their numbers and the amount of differentially expressed genes (DEGs) are shown below. Sample sizes are shown in parentheses. Of the 49 DEGs found in the RS Intermediate group, several are associated with increased proliferation or increased metastatic potential. SCUBE2 and MMP9 were among the 49 genes and are among the 70-genes assayed by MP. **Conclusions:** The comparisons highlight the genomic diversity of the RS Intermediate (RS11-25) group, as seen with the high number of DEGs. MP separates cases into more genomically distinct categories, as reflected by fewer DEGs. Clinical trial information: NCT03053193. Research Sponsor: Agendia.

RS Intermediate (458)	MP High (213) vs MP Low (245)	49 DEGs
MP High (297)	RS High (85) vs RS Intermediate (212)	7 DEGs
MP Low (354)	RS Intermediate (245) vs RS Low (109)	12 DEGs

557 **Poster Session**

A breast cancer (BC) risk model incorporating Tyrer-Cuzick version 8 (TCv8) and a polygenic risk score (PRS) for diverse ancestries. *First Author: Elisha Hughes, Myriad Genetics, Inc., Salt Lake City, UT*

Background: BC risk assessment is important for guiding personalized screening and risk-reducing interventions. TCv8 is used to estimate BC risk based on age, breast density, family cancer history and other clinical factors. Accuracy may be improved by combining TCv8 with a PRS. We developed and validated a PRS for diverse ancestries based on 149 common genetic variants (PRS-149) comprised of 56 ancestry-informative and 93 BC-associated variants. Here, we describe a BC risk model that combines PRS-149 with TCv8. **Methods:** Subjects had multigene panel testing for hereditary cancer and were negative for pathogenic variants in known BC susceptibility genes. A combined risk score (CRS), incorporating PRS-149 and TCv8, was developed based on 189,230 women, including 43,444 (23%) with a history of BC. Breast Imaging Reporting and Data System (BI-RADS) breast density measurements were available for 12,363 women. We used multivariable logistic regression to test breast density and PRS-149 for association with risk of BC. An independent test cohort of 6,030 BC-unaffected women with BI-RADS assessment was used to evaluate the effect of PRS-149 on risk stratification. Relative contributions of family history, breast density, other clinical factors in TCv8 and PRS-149 were examined by adding terms sequentially to an ANOVA model. We compared differences in classification of women as high (20%) or low/moderate (20%) remaining lifetime risk according to TCv8 versus CRS. **Results:** In the development cohort, increased breast density was significantly associated with higher risk of BC ($p=3.0x10^{-6}$) with an effect size consistent with TCv8. PRS-149 improved BC risk prediction over age, breast density and family history (OR per unit standard deviation: 1.41, 95% CI: 1.37 – 1.46; p: $1.8x10^{-105}$). PRS-149 was weakly but significantly correlated with both family history (r=0.09) and breast density (r=0.01). After adjusting for multiple testing, no other factors were correlated with PRS-149. In the independent test cohort, PRS-149 explained 27% of CRS variability after accounting for family history, breast density and other clinical factors. Adding PRS-149 to TCv8 significantly altered risk estimates, with 16.3% (983/6,030) of patients classified differently by CRS versus TCv8. By TCv8 alone, 38.0% (2,289/6,030) of patients were classified as high-risk. Among patients who were high-risk by TCv8, 25.2% (576/2,289) were downgraded by CRS. **Conclusions:** This is the first BC risk model that includes breast density, family history, and a PRS based on genetically determined ancestry that is validated for diverse populations. Addition of PRS-149 improved risk prediction and substantially modified risk stratification compared to TCv8 alone. Implementation of CRS may therefore lead to improved identification of women who are likely to benefit from increased surveillance and preventive medications. Research Sponsor: Myriad Genetics, Inc.

558 **Poster Session**

Real-world clinical outcomes in patients with local/regional HER2-low breast cancer: An NCDB analysis. *First Author: Changchuan Jiang, Roswell Park Cancer Center, Buffalo, NY*

Background: The development of novel anti-HER2 drugs opens new treatment options, including women with lower expression of HER2. This study aimed to compare local/regional HER2-low and HER2-0 breast cancer outcomes in the real world. **Methods:** Women diagnosed between 2010 and 2017 with clinical stage I-III breast cancers with low HER2 expression or HER2-zero (0) expression were identified in the National Cancer Database (NCDB), a nationwide oncology outcomes database in the United States. HER2-Low was defined as IHC1+ or 2+/ISH negative, whereas HER2-zero was IHC-0. The primary outcome was overall survival (OS). We performed a multivariable Cox regression model to estimate hazard ratios and adjusted for the following factors: age, race/ethnicity, education, insurance, comorbidities, grade, stage, lymph nodes, type of surgery, the type of cancer center, and if any chemotherapy, any hormonal therapy, and any adjuvant radiation in the first treatment course. Stratification factors were hormone receptor status. Subgroup analyses for those who received neoadjuvant (NAC), adjuvant (AC), and no chemotherapy were performed, and the pathologic complete response (pCR) rates in NAC groups were estimated. **Results:** 376,199 (68%) women with HER2-low tumors and 177,298 (32%) with HER2-0 tumors were analyzed. 336,147 (89%) of the HER2-low tumors and 141,528 (79%) of the HER2-0 tumors were HR-positive. Low HER2 expression was associated with longer OS in both HR-positive (adjusted Hazard Ratio (aHR): 0.94, 95%CI 0.93-0.96, p<0.001) and HR-negative diseases (aHR: 0.88, 95%CI 0.85-0.91, p<0.001). HR-positive, HER2-low tumors had statistically significantly better survival than HR-positive, HER2-0 tumors in NAC (aHR 0.84, 95%CI 0.79-0.90, p<0.001) and AC (aHR 0.90, 95%CI 0.85-0.94, p<0.001) groups, but not in the no-chemo group (aHR 1.02, 95%CI 1.00-1.05, p=0.09, p interaction<0.001). In contrast, HR negative, HER2-low tumors had better OS than HR negative, HER2-0 tumors in all subgroups, regardless of receipt or timing of chemotherapy (NAC aHR 0.88, 95%CI 0.83-0.94, p<0.001, AC aHR 0.86, 95%CI 0.81-0.92, p<0.001, No chemo aHR 0.93, 95%CI 0.87-0.99, p=0.03, p interaction=0.06). In NAC groups, HER2-low expression was linked to lower pCR rates in both HR-positive (8.9% vs. 11.2%, p<0.001) and HR-negative (31.2% vs. 34.1%, p<0.001). **Conclusions:** Local/regional HER2-low breast cancer has better survival than HER2-0 breast cancer, irrespective of its hormone receptor status. The survival advantage was observed in HR-negative disease and only with receipt of chemotherapy in HR-positive breast cancer. Specific therapies, such as trastuzumab deruxtecan, have activity in HER2-low breast cancers, and other therapeutics for HER-2 low diseases should be sought. Research Sponsor: None.

559 **Poster Session**

Investigation of a genomic signature for transcription factor MAF gene amplification and lack of bisphosphonate benefit in early breast cancer. *First Author: Azadeh Nasrazadani, UPMC Hillman Cancer Center, Pittsburgh, PA*

Background: MAF amplification has been associated with increased bone metastases in breast cancer (BC). On the contrary, patients without MAF amplification in the primary tumor are more likely to benefit from adjuvant bisphosphonates as shown in a retrospective analysis of the AZURE trial and confirmed with a subset of NSABP-B34 specimens. A genomic signature could identify patients that lack MAF amplification as candidates for adjuvant bisphosphonates. Here we investigated the genes that could predict MAF amplification status. As MAF amplification is associated with high risk of bone metastases, 70-gene risk of distant recurrence signature (MammaPrint/MP) and 80-gene molecular subtyping signature (BluePrint/BP) were used to stratify the patient groups. **Methods:** A total of 166 BC patients from the UPMC were included in this pilot cohort. Fluorescence in situ hybridization was performed to detect MAF copy number. Signal-to-nucleus ratio (SNR) of ≥2.5 was used as the MAF-amplified (MAF+) cut-off. Differential gene expression analysis was performed with R limma using whole genome microarray data. MAF+ and MAF- (SNR<2.5) were compared within all patients and within patients matched by MP/BP to balance high risk groups. Differentially expressed genes (DEGs) were defined as absolute fold change ≥2 and adjusted p-value <0.05. Prediction of MAF amplification based on gene expression was performed using a correlation-based metric with training set, as well as with 1179 stage I-III BC patients from the FLEX Study (NCT03053193), which includes MP/BP testing and whole transcriptome data collection. **Results:** Of the 166 patients, 12% were MAF+ and 88% were MAF-. Among the MAF+ patients, 95% were MP High Risk, as expected from the association of MAF amplification and bone metastasis, as opposed to 29% of MAF- patients. Notably, there was no significant correlation between amplification and gene expression of MAF, which emphasizes the importance of utilizing other genes to predict MAF amplification. Comparing whole transcriptome of MAF+ and MAF- patients, 48 DEGs were found. From the MP/BP matched comparisons, genes ≥2-fold change were included in the final set of 57 genes, where C-X-C motif chemokine ligand and S100 calcium binding protein encoding genes were enriched. The 57-gene classifier of MAF status yielded 92% accuracy, 94% specificity, and 75% sensitivity on the training set. Interestingly, when the classifier was applied on the FLEX cohort, 12% MAF+ cases were identified, similar to the training set. **Conclusions:** Whole transcriptome analysis showed that BC tumors with MAF amplification are transcriptionally different than those without. Here we provide a set of 57 genes that could potentially predict MAF amplification status. Future work will expand the dataset and further explore the predictive value of such genomic signature in response to bisphosphonates. Clinical trial information: NCT03053193. Research Sponsor: University of Pittsburgh support, Pharmaceutical/Biotech Company.

560 **Poster Session**

Clinical implications for patients with discordant oncotype and MammaPrint results. *First Author: Matei P. Socoteanu, Texas Oncology-Longview Cancer Center, US Oncology, Longview, TX*

Background: Genomic tests provide critical information regarding risk of recurrence and inform treatment plans by identifying those patients who may safely forgo chemotherapy (CT) or shorten endocrine therapy (ET) duration. The IMPACT trial demonstrated that the 70 -gene risk of recurrence assay MammaPrint (MP) and 80-gene subtyping assay BluePrint (BP) inform treatment planning and increase physician confidence. However, not all genomic tests yield the same results. To examine consistency among genomic tests, we analyzed therapy implications for patients who received results from both MP/BP and Recurrence Score (RS). **Methods:** Using the FLEX cohort (NCT03053193), we examined 723 patients who received both MP/BP, and RS genomic assays. We assessed the potential clinical impact by examining the standardized reports of RS and MP/BP results. MP classified tumors as either ultralow, low, or high risk and BP further classified them as luminal, basal, or HER2. RS classified tumors as low (RS0-10), intermediate (RS11-25), or high (RS26-100). Clinical impact was defined as discordant genomic resulting in different treatment recommendations. Undertreatment indicates patients who may not have received CT based on RS but may have based on MP/BP and overtreatment those patients who would have received CT based on RS, but not based on MP/BP. ET duration too long is indicative of those patients that are ultralow risk by MP, regardless of RS classification, as those patients may have safely reduced the duration of their ET. Although outcomes are not available, treatment impacts are presuming a patient received both tests, but the treating physician opted to guide therapy according to the RS results rather than MP/BP. **Results:** We observed discordant results with a clinical impact in 49% (354) of patients, with 34% (244) who may be undertreated, 2% (11) potentially overtreated, and 14% (99) who may not be given the option to decrease ET to two years based on ultralow MP genomic risk. Of 114 concordant High-Risk tumors, 14% (16) were genomically Basal, and likely to require more aggressive CT than typically used in ER+ cancers. The table below summarizes the results. **Conclusions:** More than half of the patients in this cohort were at potential risk for undertreatment or overtreatment. The risk to patients is far more significant in the event of undertreatment, as this may result in incurable metastatic recurrence. Discordance between RS and MP/BP most often results in potential undertreatment if RS is used for treatment decision-making. Clinical trial information: NCT03053193. Research Sponsor: None.

561 **Poster Session**

Molecular characteristics and clinical outcomes of breast cancer with *HRAS* mutations. *First Author: Samuel Kareff, University of Miami/Jackson Memorial Hospital, Miami, FL*

Background: The RAS pathway regulates tumorigenesis and cell proliferation. HRAS is a RAS family member that activates via farnesylation. Indirectly targeting mutant HRAS with tipifarnib, a farnesyltransferase inhibitor (FTI), recently demonstrated efficacy in head and neck tumors. We aimed to investigate the molecular characteristics and clinical outcomes of HRAS mutations (HRASmut) for any potential role as a prognostic and therapeutic biomarker in breast cancer (BC). **Methods:** A total of 14,013 BC tissue samples had molecular profiling, including next generation DNA (592 Gene Panel, NextSeq, or WES, NovaSeq) or RNA sequencing (NovaSeq, WTS), and immunohistochemistry analyses, at Caris Life Sciences. MAP kinase (MAPK) activation and likelihood of a tumor's response to anti-PD1 therapy were evaluated via MAPK Pathway Activity Score (MAPS) and interferon (IFN) score, respectively. Wilcoxon, Fisher's exact, or Dunnett's tests were used to determine statistical significance. Overall survival (OS) was calculated from date of tissue collection to insurance claims last contact using the Kaplan-Meier method. HRAS mutations (HRASmut) were compared to the general BC cohort (GC). **Results:** HRASmut were significantly enriched in older patients (median 69 vs 60 yrs; $q<.0001$), and in primary compared to metastatic BC tumor samples (55.9% vs 41.9%, $p<.05$). There were 70 total HRASmut (0.5%): Q61 was the most frequent (41.4%), followed by G12 (28.6%) and G13 (24.3%). Patients with Q61 HRASmut had significantly worse OS compared to GC (HR 1.86, 95% CI [1.10-3.13]; $p<0.05$). HRASmut had significantly higher MPAS compared to GC (1.26, all; 1.31, Q61; 1.7, G12; -.39, GC, $q<.01$). HRASmut were found in HR+/HER2- (22.6%) and TNBC (77.4%) tumors, but no HR-/HER2+ BC. TNBC samples with HRASmut displayed more PIK3CA (62.5% VS. 18.9%, $q<.05$) but less TP53 mutations (50% vs 84.9%, $q<.05$), higher expression of PD-L1 (41.2% vs 10.8%, $p<.05$) and androgen receptor (AR, 45.8% vs 24.4%, $p<.05$), and more frequent ARv7 fusions (20.7% vs 4.3%, $p<.05$) compared to HR+/HER2- (Table 1). Q61 HRASmut had the highest MPAS (2.39 vs -0.28, p<.01) in TNBC, whereas G12 HRASmut displayed the highest MPAS (2.01 VS -0.47, $p<.05$) in HR+/HER2- BC. Conversely, Q61 had the lowest IFN score (-0.45 vs -0.3) in HR+/HER2- but the highest (-0.18 vs -0.3) in TNBC. **Conclusions:** HRASmut were mutually exclusive with HER2+ BC. The association of Q61 HRASmut with worse survival highlights the oncogenic role of these mutations and supports therapeutic investigation using FTI. PIK3CA was significantly co-mutated in HRASmut, highlighting a potential benefit of combining PIK3CA inhibitors with tipifarnib. Overall, HRASmut displayed a subtype-specific distinct genomic landscape and may represent a key therapeutic target in BC. Research Sponsor: None.

Percentage of co-alterations in HR+/HER2- BC.

	HRASmut	GC
PIK3CA	71.4	41.2
PTCH1	20	0.3
EPHA2	16.7	0.1
TERT	16.7	0.4
MSH3	16.7	0.5
CLTC	42.9	3.5
DDX5	28.6	2.5

562 **Poster Session**

Serial postoperative ctDNA monitoring of breast cancer recurrence. *First Author: Jacqueline A. Shaw, University of Leicester, Leicester, United Kingdom*

Background: Up to 30% of patients with breast cancer relapse after primary treatment. There are no sensitive or reliable tests to monitor these patients and detect distant metastases before overt recurrence. Here, we demonstrate the use of personalized circulating tumour DNA (ctDNA) profiling performed postoperatively, postadjuvantly, and serially for detection of recurrence in breast cancer. **Methods:** Patients with primary breast cancer (n=188) were recruited following surgery and adjuvant therapy and were followed-up for up to 10 years with semi-annual blood sampling for ctDNA analysis. Patients (n=29) with insufficient residual tumour for whole exome sequencing (WES) were excluded from the analysis. Tumour WES profiles were generated for 159 patients; samples from 2 patients failed WES QC requirements and a personalised ctDNA panel could not be generated for 1 patient. In 156 patients, plasma samples (n=1141) were retrospectively tested for the presence of ctDNA using personalized Signatera assays (mPCR-NGS) targeting up to 16 somatic single nucleotide variants selected from primary tumour WES. **Results:** Plasma ctDNA was detected ahead of clinical or radiologic relapse in 30 of the 34 relapsed patients (sensitivity of 88%). Metastatic relapse was predicted with a lead interval of up to 2 years (median: 10 months, range: 0-39 months); median lead intervals for HR+/HER2- were 15 (2 - 39); for HR-/HER2+ 6 (0.5 – 12) for HR+/HER2+ 8 (5 – 14) and 9 (0-20) for TNBC. Patients with a positive ctDNA test had poorer relapse-free-survival (RFS) (HR=47.5; 95% CI 18.5-161.4; p <0.001) from surgery and all four breast cancer subgroups showed a similarly reduced RFS. Overall survival was also significantly reduced for patients who were ctDNA positive (HR=84.15; 95%CI 16.43-1538; p <0.001). The number of variants, mean VAF and MTM/mL varied between patients, with significantly higher values at the time closest to relapse than in the first ctDNA positive sample (p =0.0002). Among the 4 relapsed patients not detected in the study all were HR+/HER2-, 1 had a local recurrence, 2 had bone recurrence (1 with axillary LN involvement) and 1 had cancer cells in pleural fluid. Of the remaining 122 patients, only 5 developed ctDNA-positivity, all with low VAF, none of them have relapsed by the follow-up census date (31 December 2021). However, follow-up for some of these patients limits definitive assessment. Lastly, 4 patients developed a second primary cancer (2 breast, 2 lung) all of whom were ctDNA-negative. **Conclusions:** This study demonstrates that serial post-operative ctDNA analysis has strong prognostic value. More importantly, earlier detection of metastatic disease provides a possible window for therapeutic intervention, while repeated negative ctDNA tests can provide reassurance to patients. Future interventional studies may assess the clinical utility of ctDNA-based risk-stratification. Research Sponsor: Cancer Research UK, Astrazeneca.

563 **Poster Session**

Associations of a breast cancer polygenic risk score with tumor characteristics and survival. *First Author: Josephine Lopes Cardozo, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: A polygenic risk score (PRS) consisting of 313 single nucleotide polymorphisms (PRS_{313}) is associated with risk of breast cancer and contralateral breast cancer. One of the most promising clinical applications for the use of PRS is to provide a personalized risk assessment to individualize breast cancer screening programs. This study aimed to evaluate the association of the PRS_{313} with clinical-pathological characteristics and survival of breast cancer. **Methods:** Women of European ancestry with invasive breast cancer were included, 98,397 women from the Breast Cancer Association Consortium (BCAC) and 683 women from the MINDACT trial. Associations between PRS_{313} (continuous, per SD) and clinical-pathological characteristics, including the 70-gene signature for patients included in MINDACT, were evaluated with logistic regression analyses. Associations of PRS_{313} with overall survival (OS), breast cancer-specific survival (BCSS) and distant metastasis-free interval (DMFI) were evaluated with Cox regression analyses, adjusted for clinical-pathological characteristics and treatment. **Results:** The PRS_{313} was associated with favorable tumor characteristics. In BCAC, increasing PRS_{313} was mostly associated with lower grade, hormone receptor-positive tumors, and with smaller tumor size. In MINDACT, PRS_{313} was associated with a low risk 70-gene signature, but the association was attenuated after adjustment for clinical-pathological characteristics. In BCAC, univariable analyses showed an association of PRS_{313} with better survival, hazard ratio (HR) per unit SD increase of PRS_{313} for OS: 0.96 (95% confidence interval (CI): 0.94-0.97), for BCSS HR: 0.96 (95% CI: 0.94-0.98) and for DMFI HR: 0.98 (95% CI: 0.96-1.00). The association in the unadjusted analysis was explained by differences in clinical-pathological characteristics (and treatment) and disappeared after adjustment: OS HR: 1.01 (95% CI: 0.98-1.05), BCSS HR: 1.02 (95% CI: 0.98-1.07) and DMFI HR: 1.03 (95% CI: 0.99-1.07). **Conclusions:** An increased PRS_{313} is associated with favorable tumor characteristics but was not independently associated with prognosis. This information is crucial input for modelling effective stratified screening programs, especially in the current era of optimized (systemic) treatments. Given the significant increase in breast cancer risk associated with increasing PRS_{313}, absolute breast cancer mortality will still be higher for women with higher PRS_{313}. Research Sponsor: European Union's Horizon 2020 Research and Innovation Programme (grant numbers 634935 and 633784 for BRIDGES and B-CAST respectively), and the PERSPECTIVE I&I project, funded by the Government of Canada through Genome Canada and the Canadian Institutes of, Additional funding for BCAC is provided via the Confluence project which is funded with intramural funds from the National Cancer Institute Intramural Research Program, National Institutes of Health.

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Is there a role for the oncotype DX breast recurrence score genomic assay in estrogen receptor-low positive breast cancer? *First Author: Julia Giordano, Dana-Farber Brigham Cancer Center, Boston, MA*

Background: The Oncotype DX Breast Recurrence Score assay is widely used in estrogen receptor (ER)-positive breast cancer patients to help determine the potential benefit of chemotherapy. However, little is known about the value of the test in breast cancer patients who have ER-low positive (1-10%) cancers. The purpose of this study was to determine the potential utility of the Oncotype test for these patients by describing the range of Recurrence Score (RS) results and patient outcomes. **Methods**: Patients treated between 8/2011-8/2020 for primary non-metastatic breast cancer that was ER-low positive (10%) and HER2-negative in whom tissue from their surgical excision specimen was available to perform the Oncotype DX assay were identified. Clinicopathologic characteristics were abstracted from patient charts, and the RS result was determined. **Results**: 38 women with ER-low positive breast cancer and available tissue were identified. The median age was 56.5 (range 36-94); 34 patients were Caucasian, 2 Black, 1 Asian and 1 Hispanic. Thirty-seven patients underwent surgery as their initial intervention and 1 received neoadjuvant chemotherapy. The final pathologic anatomic stage was IA in 26 (68.4%), IB in 10 (26.3%) and IIA in 2 (5.3%); the pathologic nodal status was pN0 in 24 (63.2%), pN0i+ in 3 (7.9%), pN1mi in 1 (2.6%), pN1 in 6 (15.8%) and pNx in 4 (10.5%). The average and median RS was 49 with a range of 23-72; only 2 patients had a RS 25. One patient with RS = 24 was a 64yo with pT1cN0 disease who received chemotherapy + endocrine therapy therefore could potentially have been spared chemotherapy based on the RS result and the TAILORx trial data. Six patients had previously had a RS determined on their diagnostic core biopsy (RS = 46, 58, 45, 47, 51 and 52); the RS on their surgical specimen was concordant (RS = 45, 54, 47, 48, 47, and 50). The ER status as determined by the Oncotype DX assay was positive for 8 (21%) patients. Adjuvant therapy included: chemotherapy and endocrine therapy in 13 (34.2%), chemotherapy alone in 13 (34.2%) and endocrine therapy alone in 4 (10.5%). 8 (21.1%) received no adjuvant therapy. After a median follow-up of 40 months (range 3-106), 3 patients have experienced a recurrence; all 3 had received chemotherapy. The 3-year recurrence free survival rate was 97.0% (95% CI: 96.9-97.1%). All 3 of these patients had a local recurrence; 2 also had a distant recurrence which they ultimately succumbed to. The 3-year disease-specific survival rate was also 97.0% (95% CI: 96.9-97.1%). **Conclusions**: The majority of the patients with low ER+/HER2- breast cancer had RS > 25 suggesting these tumors are high-risk, more similar to ER- disease. The RS result is of limited utility in ER-low positive patients, as these data indicate that most would benefit from chemotherapy. Research Sponsor: Exact Sciences, Rob and Karen Hale Distinguished Chair - Philanthropy.

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Recurrence Score (RS) results, clinicopathologic characteristics, treatments, and outcomes in primary versus subsequent breast cancer (BC): Exploratory analysis of the Clalit Health Services (CHS) registry. *First Author: Shlomit Strulov Shachar, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel*

Background: In this exploratory analysis of the CHS registry we investigated differences in RS results and clinicopathologic characteristics between a primary and subsequent BC as well as the association with treatments received (after the first BC) and clinical outcomes. **Methods:** The analysis included all ER+ HER2-negative BC pts who were RS-tested through CHS between 1/2006 and 12/2020, had ≤3 positive lymph nodes in their first BC, and ≥2 RS results > 1 yr apart. **Results:** The analysis included 60 pts (all had second BC, 2 also had a third BC). All were female; the median age at diagnosis of the first BC was 56 (IQR, 44-62) yrs and at the subsequent diagnosis, 61 (50-67) yrs. In the first diagnosis, 46/14 pts (77%/23%) were N0/node-positive; in the subsequent BC, it was 50/9 pts (81%/15%), (missing data for 3 pts [5%]). Of the 46 N0 pts at the first BC, 37 (80%) were N0 in the subsequent BC. Tumor characteristics were similar between the first and the subsequent BC tumors. No statistically significant differences were observed between the first and subsequent tumors with respect to tumor size, grade, histology, and the proportion of N0 vs N1/N1mi pts. The RS results were statistically significantly higher in the subsequent BC vs the first (mean [SD] of 24 [12]) vs 19 [10]; $P = .00062$, Mann-Whitney test). In the first BC, 7 (12%), 44 (73%), and 9 (15%) had RS 0-10, 11-25, and 26-100, respectively. In the subsequent BC, the distribution shifted with more pts in the higher RS category (5 [8%], 32 [52%], and 25 [40%], respectively; $P = .0072$, χ^2-test). The differences in the RS between the first and subsequent BC varied considerably between pts (median difference, 6; IQR, -0.25 to 11.0; range, -50 to 56). Of the 46 pts with N0 at the first BC, 36 (78%) received endocrine therapy (ET), 34 (74%) received radiation therapy (RT), and 5 (11%) received CT after the first BC diagnosis; of the 14 N1mi/N1 pts, 12 (86%) received ET, 12 (86%) RT, and 4 (29%) CT after the first BC diagnosis. In 45 N0 pts with available information, higher RS in the subsequent BC was observed more often in irradiated breasts (pts who received RT to the breast that was subsequently diagnosed with second/third BC, n = 23) vs non-irradiated breast (pts with no RT or pts with subsequent BC in the opposite breast, n = 22): 83% vs 55%, $P = .042$; χ^2-test. No other statistically significant associations were observed between treatments received after the first diagnosis and RS differences between the first and subsequent BC diagnoses. With a median (IQR) follow up of 4.2 (1.6-8.2) yrs from the latest diagnosis, 5 distant recurrences were reported: 2 in pts with RS≤25 in their second BC (of whom one had N1 BC), and 3 in pts with RS > 25 in their second BC. **Conclusions:** In ER+ HER2-negative BC pts, the RS in a second/third BC is generally higher than the first, particularly if the breast involved was irradiated. Research Sponsor: Rhenium-Oncotest.

566 **Poster Session**

Immune landscape of breast tumors with low and intermediate estrogen receptor (ER) expression. *First Author: Leonie Voorwerk, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: Immune checkpoint blockade (ICB) is currently only approved for patients with triple-negative breast cancer (TNBC). However, the cut-off used for ER expression (<1% and in some countries <10%) has been developed as a biomarker for endocrine treatment response and not for selection for likelihood of response to ICB. While stromal tumor-infiltrating lymphocytes (sTILs) and PD-L1 expression are higher in TNBC compared to ER-positive tumors, the distribution of these and other key immune parameters in tumors with very low (1-9%), low (10-50%), intermediate (51-99%) and high (100%) ER levels is unknown. **Methods:** We collected a consecutive series of treatment-naïve tumor blocks of ER+/HER2- breast tumors diagnosed between 2010 and 2019. All available tumor blocks were used from the groups with ER expression between 1-9% and 10-50%. For the other groups, we randomly selected tumor blocks aiming for similar group sizes. This resulted in the following subgroups: ER 0% (n=46), 1-9% (n=17), 10-50% (n=22), 51-99% (n=37) and 100% (n=51). sTILs were scored using H&E slides. Immunohistochemistry was performed for CD8 and PD-L1 (22C3, scored on immune cells, cut-off ≥1%). Gene expression analysis was performed using the NanoString nCounter Breast Cancer 360 panel. **Results:** We found the highest levels of sTILs and stromal CD8+ cells in tumors with ER0% with comparable levels in tumors with ER1-9% and ER10-50% (Table). The proportion of PD-L1 positive tumors was 86% in tumors with ER0%, 81% in tumors with ER1-9%, 76% in tumors with ER 10-50% and 59% and 50% in tumors with ER51-99% and 100% respectively. As expected, a higher differentiation grade correlated with lower levels of ER expression. Differential gene expression demonstrated that expression of immune-related signatures, such as *IDO1*, antigen presenting machinery, CD8+ T cells and IFNγ, was comparable in tumors with ER1-50% as compared to ER0%, but statistically significantly higher as compared to tumors with ER100%. **Conclusions:** Our data suggest that breast tumors with low levels of ER expression (1-9%, 10-50%) comprise a separate entity within ER-positive breast cancer regarding their immune landscape. Here we show that not only tumors with very low ER levels (1-9%) mimic TNBC in terms of immune landscape but also that tumors with low ER levels (10-50%) might be more likely to respond to ICB than tumors with high levels of ER expression. Research Sponsor: None.

ER expression subgroup	Median % sTILs (range)	Median % stromal CD8+ cells (range)
ER 0%	20 (1-90)	10 (1-70)
ER 1-9%	10 (1-80)	10 (1-60)
ER 10-50%	20 (5-80)	10 (1-60)
ER 51-99%	10 (1-30)	5 (1-30)
ER 100%	10 (1-80)	5 (1-60)

567 **Poster Session**

Disparity between Ki67 measurements and tumor gene expression tests in patients with hormone-sensitive early breast cancer from the OPTIMA preliminary trial. *First Author: Robert C. Stein, National Institute for Health Research University College London Hospitals Biomedical Research Centre, London, United Kingdom*

Background: Tumor gene expression tests are increasingly used in breast cancer management. The Ki67 biomarker has been proposed as an inexpensive alternative for making chemotherapy decisions, has demonstrated utility for determination of endocrine therapy responsiveness and is included in the FDA license for adjuvant abemaciclib. We have compared Ki67 measurements with tumor gene expression test results for patients included in the OPTIMA prelim trial. **Methods:** We compared Ki67 %staining with the results of Oncotype DX, Prosigna and MammaPrint performed by the test vendor. Ki67 was determined in a single laboratory on triplicate tissue micro-arrays using quantitative image analysis including a 10% manual quality control check. We used kappa statistics to measure agreement between tests, divided into groups using the pre-defined test score boundaries for high vs. not high risk. **Results:** Data were available for 259 patients. Using ≥20% staining to define a high Ki67 score, kappa values (95% CI) for agreement with Prosigna were: 0.39 (0.28-0.49); Oncotype DX: 0.27 (0.18-0.36); and MammaPrint: 0.38 (0.27-0.49). Kappa values <0.2 are conventionally interpreted as showing slight agreement and 0.21-0.4 as fair agreement. A detailed breakdown of the comparisons of Ki67 with Prosigna and Oncotype DX is tabulated. **Conclusions:** Agreement between Ki67 and tumor gene expression tests is limited. Therefore, Ki67 values cannot accurately be used to reflect any of the molecular scores assessed here, all of which are well validated prognostic biomarkers. The use of Ki67 to determine suitability for adjuvant chemotherapy requires validation before it can replace the existing tests. Tumor gene expression tests may prove superior to Ki67 for the identification of patients likely to benefit from adjuvant abemaciclib. OPTIMA prelim is registered as ISRCTN42400492 and funded by the UK NIHR Health Technology Assessment Programme, award number 10/34/01. Clinical trial information: ISRCTN42400492. Research Sponsor: National Institute for Health Research.

		Ki67 <20%	Ki67 ≥20%
Prosigna	Median score (IQR)	40 (28-55)	64 (45-75)
	Prosigna score >60	23%	77%
	Prosigna score ≤60	64%	36%
Oncotype DX	Median score (IQR)	13 (10-18)	20 (16-28)
	Recurrence Score >25	12%	88%
	Recurrence Score ≤25	57%	43%

568 **Poster Session**

Impact of neighborhood disadvantage on biological and clinical indicators of anxiety among newly diagnosed patients with breast cancer. *First Author: Neha Goel, University of Miami Miller School of Medicine/Sylvester Comprehensive Cancer Center, Miami, FL*

Background: Women living in disadvantaged neighborhoods consistently having worse breast cancer (BC) survival. Recent studies have identified that disparities by neighborhood disadvantage persist after controlling for patient, tumor, and National Comprehensive Cancer Network-guideline concordant treatment. This persistent disparity suggests unaccounted mechanisms by which neighborhood disadvantage "gets under the skin" to impact to shorter BC survival. **Methods:** Women with stage 0-3 BC between 1998-2005 were enrolled in a clinical trial for stress management 2-10 weeks post-surgery and before initiating adjuvant treatment. At baseline, women provided an evening-time serum cortisol sample and were administered a structured clinical interview of anxiety symptoms (Hamilton Anxiety Rating Scale; HAM-A). Of the 240 women who enrolled in the study and completed baseline procedures, home addresses were provided by 225 women (93.8%). The addresses were used to determine the Area Deprivation Index (ADI), a validated measure of neighborhood disadvantage, using the University of Wisconsin Neighborhood Atlas. Women were categorized as low (1-3) versus high (4-10) ADI. Linear regression analyses was used to assess the relationship between ADI and serum cortisol and logistic regression to assess whether ADI group predicted the presence of clinically significant anxiety per the HAM-A. **Results:** The average age of our population was 50.4 years old (range 23-70 years) and the majority were non-Hispanic White (63.6%). Most patients had stage 1 (37.8%) or 2 (38.2%) disease. The majority lived in advantaged neighborhoods (low ADI, 77.8%). On the HAM-A, 46.8% of women reported clinically significant anxiety symptoms. When controlling for age, stage, and type of surgery, women with a high ADI had higher cortisol levels than women in with a low ADI (Beta = .19, $t(117) = 2.18$, $p = .031$). Moreover, accounting for age, stage, and type of surgery, women with a high ADI were nearly two times as likely to have clinically significant anxiety symptoms in the HAM-A clinical interview (OR 1.99, 95%CI 1.01, 3.90, p = .046). **Conclusions:** This study identified that neighborhood disadvantage is significantly associated with higher levels of cortisol and clinical anxiety. Future studies need to evaluate stress pathways as a potential mechanism by which neighborhood disadvantage "gets under the skin" to impact BC-specific survival. Research Sponsor: U.S. National Institutes of Health.

569 **Poster Session**

Assessment of FOXC1 expression as a predictor of response to neoadjuvant taxane plus platinum regimens in primary triple-negative breast cancer: Retrospective analysis of three clinical trial cohorts. *First Author: Partha Ray, Onconostic Technologies, Evanston, IL*

Background: Taxane and platinum (TP) NAC regimens, e.g. Carboplatin and Docetaxel (CbD), in TNBC are currently of great interest, having good pathologic complete response (pCR) rates but with a significantly more manageable toxicity profile compared to anthracycline-based NAC regimens. Forkhead Box C1 (FOXC1), a transcriptional driver of cell plasticity/partial EMT/metastasis is an established mesenchymal marker diagnostic of basal-like breast cancer having proven prognostic value, but of uncertain predictive value. We sought to evaluate the potential of FOXC1 in predicting pCR to neoadjuvant TP regimens in patients diagnosed with TNBC. **Methods:** Pre-NAC tumor biopsy FOXC1 mRNA expression status was correlated with rate of pCR in a pooled, ambispective cohort (prospective cohort GEICAM/2006-03, NCT00432172 pooled with multi-institutional retrospective cohort, n = 119). A specific FOXC1 mRNA expression cutoff value was derived to maximize Negative Predictive Value (NPV) and Sensitivity for pCR prediction. The pCR-predictive ability of FOXC1 mRNA expression was then assessed in two validation cohorts of evaluable patients who had been enrolled in prospective clinical trials (UCONN/FIOCRUZ, n = 222, HGUGM, NCT01560663, n = 221). All evaluated patients had been diagnosed with TNBC and had received a Taxane plus Platinum-based NAC regimen. **Results:** FOXC1 mRNA expression was associated with pCR in CbD/TP treated TNBC patients with pCR rates of 43.48%, 47.89% and 52.73% observed in the discovery and two validation cohorts (two tailed T-test p-values of 0.0005, 0.002, 0.009, respectively). FOXC1 expression above the pre-determined cutoff value was associated with pCR to CbD/TP NAC in patients diagnosed with TNBC in both validation cohorts (OR 4.894, 1.504-15.924; p = 0.004 and OR 2.293, 1.208-4.352; p = 0.006). **Conclusions:** We report the retrospective validation of pre-NAC breast cancer biopsy FOXC1 mRNA expression for predicting efficacy of CbD/TP NAC in two independent, prospectively accrued TNBC patient cohorts. The described strategy may be acceptable for patient stratification to guide CbD/TP NAC recommendations in TNBC. FOXC1 mRNA or protein expression, assessed using qRT-PCR or routine immunohistochemistry (IHC), respectively, could potentially be utilized in future fixed-arm/adaptive clinical trials to further optimize NAC efficacy, in terms of achieved pCR rates, and to extend disease-free survival in patients diagnosed with TNBC. Research Sponsor: None.

570 **Poster Session**

miR-150 expression in breast cancer attracts and activates immune cells, and is associated with better patient outcome. *First Author: Masanori Oshi, Roswell Park Comprehensive Cancer Center, Buffalo, NY*

Background: MicroRNA (miRNA) epigenetically regulate a large number of cancer-related genes and is known as a key player in cancer biology. MiR-150 promote cancer cell proliferation, migration, and invasion. However, there has been no study that investigated the role of miR-150 in the tumor microenvironment (TME) of breast cancer patients. **Methods:** Total of 1,961 breast cancer patients from multiple independent large cohorts were analyzed. These observational results were validated by in vitro experiments. Lymphocyte attraction was assessed using Transwell system. **Results:** miR-150 expression was the highest in triple negative breast cancer (TNBC) among subtypes and correlated with Nottingham histological grade (all $p<0.001$). A high miR-150 was significantly associated with better overall survival (OS) in both METABRIC and TCGA cohorts regardless of subtypes (all $p<0.05$ except for TNBC in TCGA). MiR-150 expression was strongly correlated with Hallmark immune-related gene sets (Allograft rejection, IL6 signaling, IFN-γ response, Inflammatory response, IL2 signaling, and apoptosis), with cytolytic activity, with infiltration of CD8+ T cells, CD4+ memory T cells, and dendritic cells, as well as with gene expressions of major immune checkpoint molecules (PD-1, CTLA4, IDO1, TIGIT, BTLA, and LAG3), consistently in both METABRIC and TCGA cohorts (all $r>0.65$, $p<0.01$). Unexpectedly, overexpression of miR-150 by mimic did not increase growth, migration, nor invasion of neither MDA-MB231 or BT-549 breast cancer cell lines. On the other hand, overexpression of miR-150 in either MDA-MB231 or BT-549 significantly increased attraction of lymphocyte cell line (Jurkart cells), which was abolished by addition of miR-150 inhibitor. By comparing the gene expression profile between miR-150 overexpressed and control cells, we found that many inflammation related gene sets including NF-kB signaling that enhance cell migration was enriched to miR-150 overexpressed cells, implicating that is how miR-150 high cells attract lymphocytes to TME. **Conclusions:** miR-150 expression is associated with immune cell infiltration and immune response, as well as with better survival in breast cancer patients. Overexpression of miR-150 in breast cancer cells did not promote cancer cell proliferation, migration, nor invasion; however, increased attraction of lymphocytes. Multiple inflammation-related genes were expressed higher in miR150 overexpressed MDA-MB231. Research Sponsor: U.S. National Institutes of Health.

571 **Poster Session**

Mode of detection of second breast cancers in patients undergoing surveillance after treatment of ductal carcinoma in situ. *First Author: Bethany Waites, Department of Obstetrics and Gynecology, Kaiser Permanente San Francisco, San Francisco, CA*

Background: The incidence of ductal carcinoma in situ (DCIS) has increased, resulting in more women undergoing post-treatment surveillance for second breast cancers. National Comprehensive Cancer Network (NCCN) guidelines recommend annual breast imaging and physical exam every 6-12 months for five years, and then annually. We assessed mode of detection (imaging, patient-reported, or physical exam) of secondary DCIS and/or invasive breast cancer in a large cohort of DCIS patients undergoing surveillance after treatment of primary DCIS. **Methods**: We performed a retrospective cohort study of DCIS patients treated between 1/1/2008 and 1/1/2011 within a large integrated health care system. Patients had a minimum of 5 years of follow up. Patient demographics, treatment for primary DCIS, and tumor characteristics (of both primary DCIS and secondary cancer) were obtained from the electronic health record or from manual chart review. Chart review also included mode of detection of secondary breast cancers. **Results**: Our study cohort consisted of 1561 women with DCIS, with a median age of 59 years (range 32-92) at time of diagnosis. Among initial DCIS tumors, tumor grade was low/intermediate in 942 (60.3%) and high in 619 (39.7%); 1274 (81.6%) were estrogen receptor positive, and 988 (63.3%) progesterone receptor positive. Surgical treatment for the initial DCIS included lumpectomy (n=1134, 72.6%), unilateral mastectomy (n=320, 20.5%), or bilateral mastectomy (n=61, 3.9%), and included sentinel lymph node biopsy in 211 (14%) of patients. Additionally, 691 (44.3%) received radiation therapy and 440 (28.2%) received endocrine therapy. The cohort was followed for a median of 120 months, during which we identified 179 women (11.5%) with a secondary cancer detected at a median time of 57 months. Of the second breast cancers, 77 (43.0%) were ipsilateral, 98 (54.8%) contralateral, and 4 (2.2%) presented with distant metastases; 110 (61.5%) were invasive, 65 (36.3%) were DCIS, and 4 (2.2%) Paget's disease. See table for mode of detection of second breast cancers. **Conclusions**: In our cohort of patients undergoing surveillance following initial diagnosis and treatment of DCIS, 2% of secondary breast cancers were detected by clinical breast exam, a rate similar to incidental detection at time of plastic surgery. These results can help inform future recommendations for surveillance of second breast cancers in DCIS patients. Research Sponsor: None.

Mode of detection of second breast cancers.

	N (%), total cases 179
Imaging	137 (77%)
Patient	34 (19%)
Provider exam	4 (2%)
Incidental*	4 (2%)

**Incidentally detected cases were identified on pathology report following plastic surgery procedure*

572 **Poster Session**

Primary results of ANZ 1002: Post-operative radiotherapy omission in selected patients with early breast cancer trial (PROSPECT) following pre-operative breast MRI. *First Author: Bruce Mann, The Royal Melbourne and Royal Women's Hospital, Parkville, Australia*

Background: Selective use of radiotherapy (RT) after surgery for early breast cancer (EBC) has been an elusive goal. The role of breast MRI in localised EBC is controversial. We aimed to determine if preoperative MRI could identify patients with EBC in whom the ipsilateral invasive recurrence (IIR) rate was sufficiently low without RT, such that RT might be safely omitted. Here we report primary and secondary outcomes, and imaging/biopsy findings for occult lesions. **Methods:** PROSPECT is a prospective single-arm study. Criteria for omission of RT included age at least 50, nil/minimal or mild Background Parenchymal Enhancement (BPE) on MRI, unifocal pT1N0 cancer, not Triple Negative (TNBC), no LVI. All patients who underwent PROSPECT MRI were included in the analysis. Imaging findings on MMG, US and MRI were documented and all biopsies were recorded. Pathology of lesions identified by MRI was described. The primary outcome was the IIR at 5 years of those treated without RT. An IIR rate of 5% or less was considered acceptable. The protocol specified primary analysis occurred after the 100th patient reached 5 years follow up in May 2021. **Results:** Between 9/2011 and 5/2019, 443 patients had MRI after diagnosis. BPE was nil/minimal or mild in 344 patients. MRI detected 194 occult lesions in 144 (33%) patients; 139 (72%) were ipsilateral. 61 MMG/US occult malignant lesions - 36 invasive and 25 DCIS - were identified in 48 patients (11% of total cohort). Of 38 ipsilateral lesions in 32 patients (7% of total cohort), 23 were DCIS, 4 were T1a, 7 T1b and 4 T1c. 201 patients were treated on trial without RT. The median age was 63 years (range: 50 to 84), median tumour size 11 mm (range: 2 to 20), grade 1 (104), grade 2 (86) or grade 3 (11). The rate of IIR at 5 years was 1% (1/101). There were 2 IIRs at 4.6 and 7.7 years follow up, 1 regional recurrence, and 1 patient with both a regional and distant recurrence with 1 breast cancer death. There was 1 contralateral (CL) breast cancer, 1 CL DCIS, 2 other cancer diagnoses and 1 death from other causes. Of 242 patients undergoing MRI but not in the main study, median age was 63 range: 50-80, median tumour size, 13mm (range: 4-145). 9 underwent mastectomy (2% of total cohort). Followup is complete for 235. There was 3 IIR, 3 CL primary and no distant metastases or breast cancer deaths. **Conclusions:** Breast MRI in selected, low risk patients identified occult malignancy in 11% of patients. At a median of 5 years follow up the IIR and other breast cancer events was very low. This suggests that local recurrences may be due to occult breast cancers, and MRI may allow the identification of truly localised cancers for which radiation may be safely omitted. The event rate for the entire cohort was very low, suggesting that identification of occult malignancy in apparently unifocal EBC is beneficial. Confirmatory trials are needed. Clinical trial information: 12610000810011. Research Sponsor: ANZ Breast Cancer Trials Group, NBCF Australia, Cancer Council of Victoria.

573 **Poster Session**

The percentage of unnecessary mastectomy due to false size prediction by preoperative imaging studies in patients with breast cancer who underwent neoadjuvant chemotherapy. *First Author: Yireh Han, Seoul National University Hospital, Seoul, South Korea*

Background: It was shown that, with neoadjuvant chemotherapy (NCT), about 40-50% of breast conserving surgery (BCS) ineligible breast cancer converted to BCS-eligible. Because the estimated tumor extent with imaging after NCT tend to be discordant with pathologic extent, we assumed that proportion of unnecessary total mastectomy (TM) might be greater in NCT patients compared with non-NCT patients. We aimed to determine the proportion of TM for potential BCS candidate due to false size prediction after NCT and factors affecting that. **Methods:** We prospectively enrolled patients with invasive breast cancer (Stage II or III) who were scheduled for TM from 2018 to 2021 at Seoul National University Hospital (SNUH). Patients who were determined to undergo TM by only patient's preference, who had BRCA1/2 mutation, multicentric cancer, diffuse malignant calcification over more than a quadrant, and inflammatory cancer were excluded. The decision of TM was done by operating surgeon considering the tumor extent, location, and breast size. Breast imaging including mammography, ultrasonography (USG), and MRI were done in patients. Before surgery, each surgeon recorded a hypothetic maximum tumor size (HMS) that the surgeon would have been able to try BCS if the patient had actually less than that size of tumor at that location in the patient. After operation, the HMS was compared with final pathologic total extent of the tumor including invasive and in situ cancer. In SNUH, decisions and tries of BCS led to eventual BCS with negative margin in 97.4% of patients during same period with this study. **Results:** Among 360 patients enrolled, 130 were patients who underwent NCT, and 230 were chemotherapy naïve as a control group. 62 of 130 (52.3%) in the NCT group and 49 of 230 (21.3%) in the non-NCT group were found to have smaller tumor extent than the pre-recorded HMS, respectively (NCT vs non-NCT p-value <0.001). Further analyses were done only for NCT group. In an analysis according to subtype, the proportion of TM with false size prediction were more in HER2-positve (63.3%) and triple-negative breast cancer (TNBC) (57.6%) than in ER-positive/HER2-negative breast cancer (25.0%) (p-value <0.001). In an imaging analysis, MRI size were larger than HMS in 73.8% of all patients. Both MRI-pathology size and USG-pathology size discrepancies were significantly associated with false decision of TM (both p<0.001), but not with mammography. Without MRI, the false decision would have been reduced by 26.1%. **Conclusions:** We found that 52.3% of patients who received TM after NCT were actually BCS eligible, which was significantly higher than non-NCT patients. The proportion of false prediction were more in HER2-positive and TNBC. MRI imaging contributed to false size prediction and subsequent TM for BCS eligible patients. Clinical trial information: NCT04689529. Research Sponsor: None.

575 **Poster Session**

A prospective ultrasonographic surveillance study on the incidence and recovery period of COVID-19 vaccination-related axillary lymphadenopathy following a booster shot. *First Author: Kumiko Kida, Department of Breast Surgical Oncology, St. Luke's International Hospital, Tokyo, Japan*

Background: COVID-19 vaccination-related lymphadenopathy is a frequent imaging finding that may be indistinguishable from malignant nodes and can lead to diagnostic difficulties in patients with cancer or healthy individuals on cancer screening. However, no prospective trials regarding COVID-19 vaccination-related lymphadenopathy following a booster shot have been conducted. The purpose of this study was to determine the incidence and imaging characteristics of COVID-19 vaccination-related axillary lymphadenopathy and assess the recovery period following a booster shot. **Methods**: We prospectively enrolled healthy women working at St. Luke's International Hospital, who would receive the third shot of the Pfizer-BioNTech COVID-19 vaccine between December 6 and 28, 2021. Women with a history of cancer, atopic dermatitis, auto-immune disease, or axillary surgery were excluded. All participants underwent ultrasound (US) examinations for the bilateral axilla at baseline (prior to the third shot), early phase (1–3 days after the shot), and late phase (6 weeks after the shot) if lymphadenopathy was detected at the early phase. We evaluated the incidence and US characteristics of lymphadenopathy. As for US characteristics mimicking a malignant node, focal cortical thickening, absence of the echogenic hilus, and vascularity were examined. In this study, abnormal lymphadenopathy was defined as [1] an increase in the short-axis size by more than 2 mm compared with the baseline, [2] an increase in the number of nodes with short-axis diameter more than 5 mm, and [3] demonstrating US characteristics mimicking malignant nodes. **Results**: A total of 100 women were enrolled in this study. The median age was 41 years (range 23–63). Abnormal axillary lymphadenopathy on the vaccinated side was observed in 59% of participants in the early phase and 8% in the late phase. In the contralateral axilla, abnormal lymphadenopathy was observed in 1% of participants in the early phase and 2% in the late phase. The median short-axis size of ipsilateral abnormal lymphadenopathy was 7.6 mm in the early phase and 5.7 mm in the late phase. In the early phase, US characteristics mimicking malignant nodes were observed, including focal cortical thickening in 54% of participants, absence of the echogenic hilus in 16%, and hypervascularity in 33%. **Conclusions**: COVID-19 vaccination-related axillary lymphadenopathy indistinguishable from malignant nodes was observed in more than half of the participants compared with the baseline, which improved in most cases within 6 weeks after the latest booster shot. To avoid a diagnostic conundrum, patients with breast cancer should be vaccinated on the arm contralateral to the cancer side. It is recommended that non-urgent imaging screening for the axilla should be scheduled after 6 weeks following the latest vaccination. Research Sponsor: None.

576 **Poster Session**

A randomized, prospective, multicenter trial of 3D printing, a patient-specific surgical guide for breast-conserving surgery after neoadjuvant chemotherapy: Comparative evaluation according to the presence or absence of surgical guide. *First Author: Hong-Kyu Kim, Seoul National University Hospital, Seoul, South Korea*

Background: To obtain a clear resection margin during breast-conserving surgery (BCS) after neoadjuvant chemotherapy (NCT), accurate targeting of the location and assessment extent of the tumor are essential. However, conventional targeting methods such as USG/MMG guided hook wire insertion have disadvantages in that they could only localize the tumor, not reflecting its extent. To assess this problem, we developed an MRI-based 3D printed breast surgical guide (3DP-BSG) and conducted a multicenter randomized clinical study to prove its clinical effectiveness. **Methods:** In this multicenter, randomized (1:1), controlled trial (KCT0004469), we assigned 566 patients who underwent NCT and planned to undergo BCS, to use customized 3DP-BSG for lumpectomy, or not to use 3DP-BSG for lumpectomy. We assumed that 3DP-BSG group achieve non-inferior outcomes compared with control group with conventional targeting method. The primary endpoint was the margin positivity of the first resected margin. Under the assumption that the proportion of margin positivity would be 23% in both groups, a total of 438 patients were calculated to have 80% power to establish non-inferiority with a margin of 10% at a one-sided significance level of 0.05. Efficacy was assessed in the intention-to-treat (ITT) population. **Results:** Between 2019 and 2021, 282 (49.8%) patients were assigned to 3DP-BSG group, and 284 (50.2%) patients were assigned to control group with conventional targeting method. The median age was 51 years. In the ITT analysis, first resected margin was positivity in 5 (2.1%) of 235 patients in 3DP-BSG group and 7 (2.9%) of 244 patients in control group (difference -1.15 [95% CI -3.58 to -1.28], pnon-inferiority < .0001). In the analysis of population excluding patients assessed as complete response (CR), first resected margin was positivity in 5 (3.40%) of 147 patients in 3DP-BSG group and 7 (4.8%) of 145 patients in control group (difference -1.43 [95% CI -5.25 to -2.40], pnon-inferiority < .0001). Most of the cases, marked areas with 3DP-BSG were partially different from those with conventional targeting method, and there were some cases where completely different areas were marked. In most of these cases, pathological CR made it difficult to compare the accuracy of the targeting methods, but in one case, a malignant tumor was diagnosed only in the 3DP-BSG targeting region. Even lesions that have been incorrectly targeted by conventional methods can be properly removed using 3DP-BSG, which is believed to be helpful in surgery. **Conclusions:** Lumpectomy using 3DP-BSG showed non-inferiority compared to the conventional targeting group, and the surgeon's satisfaction was higher by quantitatively presenting the extent of initial tumor. Clinical trial information: KCT0004469. Research Sponsor: This research was supported by the Ministry of Trade, Industry & Energy(MOTIE), Korea Institute for Advancement of Technology(KIAT) through the Industrial Technology Innovation Program, P0008801.

577 **Poster Session**

Associations between axillary staging, adjuvant treatment, and survival in older women with early-stage breast cancer: A population-based study. *First Author: Matthew Castelo, Institute of Health Policy, Management and Evaluation, Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada*

Background: The Choosing Wisely guidelines recommend against surgical axillary staging (AS) in women ≥70 years with ER+/HER2- early stage breast cancer (BC). However, there has been little change in practice patterns, which may be influenced by observational studies reporting worse survival among women not receiving AS. Previous analyses did not take into account comorbidities, specific adjuvant treatments and HER2 status which may confound the association between AS omission and survival. This study examined the impact of AS omission on survival in older patients with Stage I/II BC, and secondarily emulated the Choosing Wisely population in a subgroup of those ≥70 years undergoing sentinel node biopsy (SLNB) vs. no AS for ER+/HER2- tumors. **Methods:** This was a population-based cohort study using linked health administrative data in Ontario, Canada. From the Ontario Cancer Registry, we identified women aged 65-95 years who underwent surgery for Stage I/II BC between 2010 and 2016. We excluded women who received neoadjuvant chemotherapy. To address confounding between those who did and did not receive AS, we built a propensity score model including patient and disease characteristics. Patients were weighted by propensity scores using overlap weights. Association with overall survival (OS) was calculated using weighted Cox proportional hazards models, and breast cancer-specific survival (BCSS) was calculated using weighted Fine and Gray models, adjusting for biomarkers and adjuvant treatments. Adjuvant treatment receipt was modelled with weighted log-binomial models. **Results:** Among 17,546 older women, 1,807 (10.3%) did not undergo AS, who were older, more comorbid, less likely to undergo mastectomy, and more likely to have tumors ≥ 2 cm. After propensity score weighting, baseline characteristics including comorbidity were balanced between the two groups. Women who did not undergo AS were less likely to receive adjuvant chemotherapy (adjusted RR 0.70. 95% CI 0.58-0.84), endocrine therapy (adjusted RR 0.85, 95% CI 0.82-0.89) and radiotherapy (adjusted RR 0.69, 95% CI 0.65-0.73). Unadjusted 5-year survival was lower for women who did not undergo AS (68.1%, 95% CI 65.8-70.2 vs. 87.6%, 95% CI 87.0-88.1; $p< 0.001$), and there was a higher 5-year incidence of BC deaths (7.6%, 95% CI 6.2-9.2 vs. 4.3%, 95% CI 3.9-4.7; $p< 0.001$). After weighting and adjustment, women who did not undergo AS continued to have worse OS (adjusted HR 1.13, 95% CI 1.03-1.24), however, there was no significant difference in BCSS (adjusted HR 1.00, 95% CI 0.78-1.26). The results among 6,286 ER+/HER2- women ≥70 years undergoing SLNB vs. no AS were similar for OS (adjusted HR 1.22, 95% CI 1.05-1.42) and BCSS (adjusted HR 1.08, 95% CI 0.67-1.76). **Conclusions:** The omission of AS in older women with early stage BC was associated with worse OS, reflecting selection bias, but no significant difference in BCSS. Research Sponsor: Canadian Institutes of Health Research.

578 **Poster Session**

Patient interest in exploring nonsurgical treatment approaches for early-stage breast cancer: A qualitative study. *First Author: Maya Guhan, UT MD Anderson Cancer Center, Houston, TX*

Background: Advances in radiotherapy allow the ability to deliver ablative treatments without compromising outcomes, but there has been limited application of these treatments to early-stage breast cancers. The purpose of this study was to explore patients' interest in pursuing nonsurgical treatment approaches for their early-stage breast cancer. **Methods:** Investigators conducted a qualitative descriptive study involving semi-structured interviews with 21 early-stage breast cancer patients eligible for participation in a phase 2 trial offering omission of surgery. Interviews were transcribed, and three independent reviewers performed an inductive, thematic analysis to generate themes and subthemes. **Results:** Data analysis revealed the following factors that impacted patients' willingness and desire to explore nonsurgical treatment options: Perceptions and feelings about their cancer; Current quality of life and the level of support available in their daily life; External conversations focusing on family members' and friends' experiences with cancer and/or cancer treatments; Personal healthcare experiences, including with their current breast cancer diagnosis; Perceptions and feelings about their physicians; Conversations with their physicians about their treatment options; and Self-identified desire to direct care decisions. Specifically, patients described fearing surgery and surgical recovery and wanting to avoid negative surgery-related events previously experienced by friends, family, and themselves. Participants also expressed a desire to preserve their breast(s), receive treatment per the latest research, match the level of treatment with the severity of their cancer, and avoid other comorbidities as reasons for omitting surgery. Patient reasons for pursuing surgery included the desire to remove their cancer immediately, prior positive experiences of friends, family, and themselves with surgery, lack of concern about preserving their breast(s), and prior negative experiences of friends, family, and themselves with radiation. **Conclusions:** The results of this study highlight that there is patient interest in nonsurgical options for biologically favorable early stage breast cancers. A key factor hindering patient education and awareness of nonsurgical options is how the physician frames the discussion and presents treatment options. In addition, patients' self-identity and the prior experiences of friends, family, and self with cancer treatment and surgery in general appear to be key factors in their decision-making. The findings from this study demonstrate an unmet need to explore nonsurgical options for early-stage breast cancer. Study results can help shape conversations around shared decision making and clinical trial design and result in more personalized treatment options for women with early-stage breast cancer. Research Sponsor: University of Texas MD Anderson Cancer Center Start Up Funds.

579 **Poster Session**

Three-year disease-free survival in randomized trials of chemotherapy and HER2-targeted therapy: A meta-analysis. *First Author: Abhenil Mittal, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: The Katherine trial reported a 3-year invasive disease-free survival (DFS) of 77% in patients not achieving pathological complete response (pCR) and continuing on adjuvant trastuzumab. Case series suggest better outcomes and data support that some patients with residual disease have similar outcomes to those with pCR (Steenbruggen et al). The absolute benefit of adjuvant trastuzumab emtansine (T-DM1) would be smaller in patients with favourable outcomes despite residual disease. As such, a more precise estimate of 3-year DFS is needed for treatment planning. **Methods:** We reviewed reports of randomized trials of neoadjuvant chemotherapy and HER2-directed therapy and extracted the 3-year DFS, a validated surrogate endpoint in HER2-positive early-stage breast cancer. Data were extracted for patients with residual disease and with pCR. The mean 3-year DFS weighted by study sample size was calculated. Meta-regression comprising linear regression weighted by sample size (mixed effects) was performed to explore associations between 3-year DFS and trial-level patient, disease and treatment factors and changes in 3-year DFS over time. Quantitative significance was explored using methods described by Burnand et al. **Results:** Eleven studies comprising 3908 patients were included in the analysis. The mean 3-year DFS for patients with pCR and for residual disease was 90.1% and 80.0%, respectively. DFS improved over time. For trials whose final year of accrual was after 2010, mean 3-year DFS for residual disease was 84.7% compared to 78.0% for trials completing accrual before that time (p<0.001). In a subgroup analysis of patients with residual disease, those receiving dual HER2-targeted therapy in the neoadjuvant setting had a 3-year DFS of 85.3% compared to 73.3% for those receiving only trastuzumab (p<0.001). Meta-regression results for residual disease are shown in the Table. Positive quantitative significance was observed for final year of accrual, ER-expression, dual anti-HER2 therapy and concurrent vs sequential anti-HER2 therapy. Negative quantitative significance was observed for larger clinical tumor size and nodal involvement. **Conclusions:** 3-year DFS for patients with residual disease and HER2-targeted therapy is better than reported in the Katherine trial and has improved over time, possibly due to increased use of dual HER2-targeted therapy in the neoadjuvant setting. In this context, the absolute benefit of adjuvant T-DM1 may be smaller than anticipated. Research Sponsor: None.

Variable	Beta coefficient	p
Final year of accrual	0.57	0.11
ER positivity	0.675	0.046
Median age	0.155	0.71
≥T3	-0.696	0.19
Lymph node positive	-0.54	0.35
Dual HER2-targeted therapy	0.431	0.25
Anthracycline-containing regimen received	-0.288	0.45
Concurrent/sequential Trastuzumab	0.343	0.37

580 **Poster Session**

NOHA: A sensitive, low-cost, and accessible blood-based biomarker to determine breast cancer estrogen receptor status in low-resource settings. *First Author: Srinidi Mohan, University of New England, Portland, ME*

Background: Significant challenges to breast cancer control in low- and middle-income countries (LMICs) include late-stage disease presentation because of few/no early detection programs, inadequately staffed and equipped pathology laboratories, and constrained treatment options. Estrogen receptor (ER) expression is critical to determining candidacy for cost efficient and accessible hormonal agents in LMICs; however, access to standard immunohistochemistry (IHC)-based ER analysis is grossly limited/nonexistent due to cost and technical requirements. We have identified N^{ω}-hydroxy-L-Arginine (NOHA) as a low cost and accessible blood-based biomarker to distinguish estrogen-receptor negative (ER^-) from estrogen-receptor positive (ER^+) breast cancer, differentiate ER^- high grade versus low grade tumors, and correlate ER^- molecular phenotype with ethnic variation. Our studies with US patients suggest the NOHA threshold of <4nM as a reliable indicator of ER^- versus ER^+ disease (Table 1). Here we examine the clinical utility of NOHA as an alternative to IHC in distinguishing ER^- from ER^+ breast tumors in Tanzanian patients. **Methods:** Following informed consent, 70 newly diagnosed breast cancer patients were recruited at Kilimanjaro Christian Medical Center (KCMC; Moshi, Tanzania). Prior to any treatment, a needle prick amount of blood was collected from each patient on a Noviplex plasma card (Shimadsu, U.S.) and stored at -80˚C. Plasma cards and unstained tumor pathology slides were shipped at 2-3 months intervals to US labs for NOHA and immunohistochemistry (IHC) ER testing. Statistical difference was set at p<0.01, with NOHA and IHC assay operators blinded to patient clinical status. **Results:** Our early data show correlation between NOHA levels and ER IHC results, providing a means to distinguish ER^- from ER^+ breast cancer in the low-resource setting. Plasma cards stored at -80˚C for up to 3 months retained NOHA stability in assays involving a proprietary antibody-based ELISA, and by LC-MS. **Conclusions:** This study suggests the clinical utility of NOHA as a cost-effective, accessible replacement for standard IHC testing in determining ER status among breast cancer patients in LMICs, promising to extend access to cost efficient and available hormonal agents and improving outcomes and quality of life. The present study provides foundational knowledge for broader studies of NOHA utility in global breast cancer control, as well as in ongoing development of NOHA rapid-testing technologies. Research Sponsor: UNiversity of New England Seed, and Research Infrastructure Funds.

Distinction in plasma NOHA between ER^- and ER^+ breast cancer patients diagnosed with stage I, low-grade tumors, at n = 65/group.

Tested conditions	NOHA (nM) Mean ± Standard Deviation
ER^- patients, low-grade, stage I	2.51 ± 1.03*
ER^+ patients, low-grade, stage I	6.28 ± 0.72
Healthy controls	7.04 ± 0.49

*Represents significance from ER+/healthy controls, p < 0.01.

581 **Poster Session**

Low TMB as predictor for additional benefit from neoadjuvant immune checkpoint inhibition in triple-negative breast cancer. *First Author: Thomas Karn, Goethe-Universität Frankfurt, UCT-Frankfurt-Marburg, Frankfurt, Germany*

Background: It is commonly anticipated that a high tumor mutational burden (TMB) is a predictor of response to immune checkpoint blockade (ICB). We previously showed that triple-negative breast cancer (TNBC) from the GeparNuevo study with high TMB displayed increased response both to neoadjuvant chemo-ICB with durvalumab but also to chemotherapy alone, with no significant interaction with treatment arm (Karn et al. Ann Oncol 2020). In contrast, we also observed that cases with very low TMB more often displayed a pCR after treatment with chemo-ICB than with chemotherapy alone. This may in fact suggest a benefit of ICB to those TNBC with rather low TMB. **Methods:** We have analyzed the distant disease-free survival (DDFS) of GeparNuevo patients according to TMB and treatment arm (neoadjuvant chemotherapy plus durvalumab or chemotherapy plus placebo). For TMB (mut/Mb) we applied the identical cutoff of the upper tertile as in our previous analysis. **Results:** The median follow-up of the time-to-event data was 43.7 months. Data of TMB was available in 149 of 174 patients. We found that within the high-TMB tumors (durvalumab: n=27; placebo: n=23), DDFS was similar between both arms of the trial (durvalumab vs. placebo: HR (hazard ratio) 0.95 [95%CI 0.19-4.69], p=0.95). Strikingly however, within the low-TMB group (durvalumab: n=47; placebo: n=52) we observed a significantly better DDFS in the durvalumab-chemotherapy combination arm, in contrast to the arm treated only with chemotherapy (durvalumab vs. placebo: HR 0.23 [95%CI 0.06-0.79], p=0.02; interaction test for TMB and treatment arm p=0.17). The observation was also robust to alternative TMB cutoffs. Similar results were obtained for invasive disease-free survival. **Conclusions:** Our results show, in contrast to other published data, that patients with early TNBC and low TMB/neoantigen counts may benefit from short-term neoadjuvant durvalumab treatment, while for those with high TMB, durvalumab plus chemotherapy does not improve efficacy over chemotherapy alone. Research Sponsor: None.

582 **Poster Session**

Peripheral lipidomics analyses with ensemble machine learning predict response to neoadjuvant therapy in breast cancer. *First Author: Jiani Wang, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: Neoadjuvant therapy (NAT) is critical in the therapeutic strategy for locally advanced breast cancer (BC) patients. Biomarkers to predict the pathologic complete response (pCR) and to screen beneficial responders need to be urgently explored. Lipidomics is a high-throughput analysis technique, which has potential applications for peripheral biomarkers' detection to overcome the difficulty in serial pathological biopsies and tumor heterogeneity. Machine learning is a method for mining high-dimensional information with high group and low intermolecular correlation. Here we construct multidimensional models with machine learning approach combining clinical clinicopathological and lipidomics data to predict NAT response. **Methods:** Plasma samples were collected from 119 BC patients before after two cycles of NAT. Peripheral lipidomic profiles at multiple levels of lipid composition, concentration, chain length, and saturation were dynamically monitored by using absolute quantitative lipidomics. Responders (pCR) and non-responders (non-pCR) groups were randomly sampled in a 1:1.5 ratio for subsequent analysis. Screening of candidate lipidomic biomarkers were performed according to the criteria "VIP>1, FC>2 or FC<0.5 and p<0.05". Above feature screening were validated by using ensemble machine learning algorithms (Logistic regression, Random forest and Support vector machine). Pearson correlation coefficients were calculated for the expressions of candidate biomarkers. Multidimensional prediction models with the logistic regression algorithm were constructed by correlating candidate lipidomics features with clinicopathologic phenotypes prospectively collected with baseline and dynamic changes. The performance of the models constructed above were assessed by ROC analysis. **Results:** A total of 8 major classes, 39 subclasses, and 2292 molecules of lipid metabolites were identified in the 235 plasma samples. Most of the candidate biomarkers had lower correlations, indicating lower overlapping and more optimal combination of panels. The prediction models constructed by baseline correlating candidate lipidomics features with ensemble machine learning achieved an Area under the Curve (AUC) of 0.84 for the training set and 0.72 for the validation set with the accuracy 0.84, the specificity 0.92, and the sensitivity 0.71 when the cutoff value is 0.57.The prediction models constructed with lipidomics dynamic changes also achieved good performance. **Conclusions:** The study suggested a possibility that peripheral lipidomics provided a potential tool to develop multidimensional models with ensemble machine learning for predicting response to NAT for BC patients with good discrimination power, which might guide individual optimal NAT strategies and avoid unnecessary treatment. Research Sponsor: Chinese Society of Clinical Oncology (CSCO) Roche Oncology Research Fund Program(Y-Roche2019/2-0046) and Chinese Society of Gerontology and Geriatrics Clinical Oncology Research Program (YXJL-2018-0067-0058).

583 **Poster Session**

Biomarkers for response to immunotherapy in triple-negative breast cancer: Differences between survival and pCR biomarkers. *First Author: Carsten Denkert, Institute of Pathology, Philipps-University Marburg and University Hospital Marburg, Marburg, Germany*

Background: Immunotherapy is entering clinical practice as a promising new neoadjuvant therapeutic approach in triple-negative breast cancer, and it is important to identify biomarkers to focus this therapy on those patients that have the highest benefit. Interestingly, an improved survival outcome is observed in pCR and non-pCR patients, which raises the hypothesis that biomarkers might also be different for pCR prediction as well as prognosis. In this study, we investigated this hypothesis in the neoadjuvant GeparNuevo trial. **Methods:** A total of 174 patients were randomized to receive neoadjuvant chemotherapy with durvalumab vs. placebo. HTG EdgeSeq mRNA analysis was performed for a total of 2549 genes in 162 pretherapeutic core biopsies. In addition, tumor-infiltrating lymphocytes (stromal and intratumoural) as well as PD-L1 protein expression was evaluated by IHC. We systematically compared the distant disease-free survival (DDFS) of 5 predefined gene signatures (including the GeparSixto immune signature) as well as 12 single mRNA markers identified in previous projects between treatment arms using univariate Cox proportional-hazard regression analyses. In addition, exploratory biomarker analyses were performed. **Results:** The PSIP1 gene expression (per 1 unit hazard ratio [HR]: 0.58 95%CI 0.41-0.83; p=0.002), TAP1 (per 1 unit HR: 0.68 95%CI 0.48-0.95; p=0.025) as well as stromal TILs (sTILs) (per 10% HR: 0.73 95%CI 0.56-0.95; p=0.019) were significant for improved DDFS in the complete cohort. In the placebo arm PSIP1 (HR 0.50 95%CI 0.29-0.87; p=0.014) as well as sTILs (HR 0.73 95%CI 0.53-0.99; p=0.044) were significant for improved DDFS. In the durvalumab arm, the gene expression of PSIP1 (HR 0.54 95%CI 0.31-0.94; p=0.029), PD-L1/CD274 (per 1 unit HR: 0.41 95%CI 0.21-0.77; p=0.006), CD38 (per 1 unit: HR 0.52 95%CI 0.29-0.92; p=0.026) as well as the GeparSixto immune signature (per 1 unit HR: 0.51 95%CI 0.27-0.97; p=0.041) were significant for improved DDFS, with a positive test for interaction with treatment arm for PD-L1/CD274 (interaction p=0.020). Additional analyses, including multivariate Cox regressions for DDFS as well as systematic comparisons for biomarkers for DDFS and for pCR, will be presented. **Conclusions:** Our analysis suggests that biomarkers for immune response are linked to improved survival with neoadjuvant durvalumab therapy and that in this setting, survival biomarkers are not identical to pCR biomarkers. The results are a basis for a further dissection of the contribution of pCR to survival effects of immunotherapy. Research Sponsor: Integrate-TN project (Deutsche Krebshilfe), Oncobiome Project (EU-H2020), Pharmaceutical/Biotech Company.

584 **Poster Session**

Real-world outcomes of patients with human epidermal growth factor 2 (HER2)–positive breast cancer receiving neoadjuvant therapy without adjuvant ado-trastuzumab emtansine (T-DM1). *First Author: Massimo Di Iorio, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: HER2-positive early-stage breast cancer (EBC) treated with neoadjuvant chemotherapy and HER2-targeted therapy has favourable outcomes, especially for those attaining pathologic complete response (pCR). Among those with residual invasive disease (RD), outcomes are variable. Replacing adjuvant trastuzumab with ado-trastuzumab emtansine (T-DM1) reduces the risk of recurrence, but increases toxicity and cost. The magnitude of benefit of T-DM1 may be small among patients with RD and favourable prognostic features. Here we report on real-world outcomes of patients with HER2-positive EBC treated with neoadjuvant therapy without adjuvant T-DM1. **Methods:** We performed a single institution, retrospective review of HER2-positive EBC treated with neoadjuvant chemotherapy and trastuzumab between January 1st, 2012 and February 1, 2021. We excluded patients who received adjuvant T-DM1. We collected clinical and pathologic characteristics, treatment data, and outcomes events. We estimated 3-year disease-free survival (DFS), a validated endpoint in HER2-positive EBC, using Kaplan-Meier with recurrence and/or death as events. Outcomes were reported in subgroups based on known prognostic factors. The study was approved by the University Health Network Research Ethics Board. **Results:** The study comprised 193 patients with a median follow-up of 30 months. The majority (n=160, 83%) received neoadjuvant anthracycline and taxane-based chemotherapy; 42 (22%) received neoadjuvant pertuzumab. All received adjuvant trastuzumab. Median age was 53 years (range 25-87), 113 (59%) patients had estrogen receptor (ER) positive disease, and 82 (42%) had pCR. In total, 16 events were observed, of which 13 (81%) were distant recurrences (including 5 (31%) in the brain) and 3 (19%) were locoregional. Of these, 14 (88%) occurred in the first 3 years of follow-up. Estimated 3-year DFS was 98.6% in patients with pCR, and 85.4% in patients with RD. Patients with ER positive disease had excellent outcomes, regardless of pathologic nodal (ypN) status. The highest risk of recurrence was in ER negative and ypN positive disease (Table). **Conclusions:** Real-world outcomes of patients with HER2-positive EBC treated with neoadjuvant therapy without adjuvant T-DM1 are favorable, including those with RD if ER positive. The expected benefit of adjuvant T-DM1 in this group is therefore likely to be small. Patients with ER- disease had poorer outcomes irrespective of nodal status. Further research to identify patients with RD for whom the benefit of T-DM1 is unlikely to merit its added toxicity and cost is warranted. Research Sponsor: None.

	Overall (n)	Residual Disease (n)	Recurrence (n)	3y DFS (%)
All Groups	193	111	15	85.4
ER-	80	38	12	68.2
ER+	113	73	3	96.2
ypN-	140	58	5	88.7
ypN+	53	53	10	81.8
ER-, ypN-	61	19	4	68.9
ER-, ypN+	19	19	8	57.4
ER+, ypN-	79	39	1	97.2
ER+, ypN+	34	34	2	95.8

585 **Poster Session**

Identification of transcriptional changes with MammaPrint and BluePrint in early-stage breast cancer after neoadjuvant chemotherapy. *First Author: Alice P. Chung, Cedar-Sinai Medical Center, Los Angeles, CA*

Background: The use of neoadjuvant chemotherapy (NAC) in patients with early-stage breast cancer (EBC) increases the opportunity for genomic testing which can help predict treatment response and optimize outcomes. MammaPrint (MP) classifies tumors as having a Low Risk (LR) or High Risk (HR) of distant recurrence. MP with BluePrint (BP), a molecular subtyping assay, categorize tumors as Luminal A (MP LR), Luminal B (MP HR), HER2, or Basal-Type. Our recent analysis comparing matched pre- and post-NAC tumors found 25% of pre-NAC Luminal B tumors changed to Luminal A post-NAC, which corresponded with improved 5-year outcomes compared with patients who remained Luminal B. Here, we report differential gene expression (DGE) and pathway analyses in these matched tumors that may distinguish the different responses. **Methods:** Among the patients with EBC who received NAC at Cedars Sinai Medical Center between 2007-2016, 38 with residual disease (RD) had paired pre- and post-NAC tissues. In patients with Luminal tumors, 8 were Luminal B pre- and post-NAC (HR/HR), and 7 were Luminal B pre-NAC but changed to Luminal A post-NAC (HR/LR). Limma R package was used for quantile normalization and DGE analyses. Differentially expressed genes (DEG) with < 0.05 false discovery rate and > 2-fold change were considered significant. Functional pathway enrichment was performed using Metascape. **Results:** Within HR/LR tumors, a DGE analysis identified 104 DEGs in post-NAC tissues relative to pre-NAC, with changes in cell cycle/proliferation pathways. Interestingly, there was a more robust transcriptional change in HR/HR tumors, with 956 DEGs between post- and pre-NAC samples, with enrichment of extracellular matrix organization, angiogenesis, and wound healing pathways. Notably, immune pathway enrichment was in both HR/LR and HR/HR groups, although the nature of enrichment differed. Immune deconvolution identified significant increases in activated myeloid dendritic cells (DC) and CD8+ T cells in HR/LR but not in HR/HR post-NAC tumors, suggestive of a host immune response. **Conclusions:** Although post-NAC RD correlates with poor prognosis, even in Luminal tumors, these data suggest gene expression profiling may distinguish a subset with good prognosis. Using matched samples, we assessed the transcriptional differences in tumors that changed MP risk (HR/LR) with tumors that stayed MP HR post-NAC (HR/HR). Overall, HR/HR tumors had a larger transcriptional response with metastatic-related pathway enrichment. Given these patients with HR/HR tumors displayed worse outcomes, pathway changes may indicate resistance and patients may need additional therapy. Differential changes in immune cells between HR/HR and HR/LR tumors were also observed. The activated immune response in HR/LR tumors may be a biomarker for therapy response and improved outcome and will be the focus of further evaluation. Research Sponsor: Agendia Inc.

586 **Poster Session**

Association of facility volume with pathologic complete response and overall survival in patients with non-metastatic breast cancer. *First Author: Sung Jun Ma, Roswell Park Comprehensive Cancer Center, Buffalo, NY*

Background: High facility volume has been previously shown to be associated with a higher likelihood of pCR among patients with breast cancer following neoadjuvant chemotherapy. However, factors underlying the association of high facility volume with pCR and the impact of facility volume on survival remain unclear. We performed an observational cohort study to investigate the association of overall survival (OS) with facility volume and identify variables associated with high facility volume. **Methods:** The National Cancer Database (NCDB) was queried for women diagnosed between 2010 and 2017 with non-metastatic breast cancer treated with neoadjuvant chemotherapy followed by surgery. Facility volume was stratified by tertiles of low, intermediate, and high. Logistic and Cox multivariable analyses (MVA) were performed to evaluate factors associated with facility volume and OS, respectively. Propensity score matching was used to reduce selection bias. **Results:** A total of 105,804 women met our inclusion criteria (low facility volume: n=6,172; intermediate facility volume: n=20,199; high facility volume: n=79,433). The median follow up was 49.2 months (IQR 32.7-71.3). On logistic MVA, both intermediate (adjusted odds ratio [aOR] 1.24, 95% confidence interval [CI] 1.14-1.35, p<0.001) and high (aOR 1.53, 95% CI 1.42-1.65, p<0.001) facility volumes were associated with pCR. On Cox MVA, high (adjusted hazards ratio [aHR] 0.89, 95% CI 0.83-0.96, p=0.001), but not intermediate (aHR 0.97, 95% CI 0.90-1.04, p=0.40), facility volume was associated with improved OS. Similar findings were noted in 18,671 matched pairs between high versus low or intermediate facility volumes (HR 0.90, 95% CI 0.85-0.94, p<0.001). On logistic MVA, patients were more likely to receive treatments at high volume facilities if they were academic (adjusted odds ratio [aOR] 5.47, 95% CI 5.24-5.71, p<0.001), African American (aOR 1.25, 95% CI 1.20-1.30, p<0.001) with private insurance (aOR 1.13, 95% CI 1.04-1.22, p=0.005), and higher tumor grades (grade 2: aOR 1.10, 95% CI 1.03-1.18, p=0.008; grade 3: aOR 1.12, 95% CI 1.05-1.20, p=0.001). Patients were less likely to undergo treatments at high volume facilities if they reside in urban (aOR 0.63, 95% CI 0.60-0.66, p<0.001) or rural (aOR 0.75, 95% CI 0.67-0.85, p<0.001) areas with limited education (aOR 0.90, 95% CI 0.87-0.93, p<0.001), had government-led insurance (aOR 0.87, 95% CI 0.80-0.94, p=0.001), and had time interval of <180 or >240 days between diagnosis and surgery (aOR 0.92, 95% CI 0.90-0.95, p<0.001). **Conclusions:** To our knowledge, this is the largest study using a nationwide oncology database to report the association of high facility volume with pCR and improved OS, with various patient demographics associated with high facility volume. Our findings suggest an integral role of facility volume on pCR and survival for breast cancer. Research Sponsor: None.

587 **Poster Session**

Dapagliflozin associated to sacubitril/valsartan and relationship with cardioprotection in human cardiac cells exposed to doxorubicin and HER2-blocking agents through MyD88, NLRP3 mediated pathways. *First Author: Nicola Maurea, Istituto Nazionale per lo Studio e la Cura dei Tumori "Fondazione G. Pascale"-IRCCS, Naples, Division of Cardiology, Naples, Italy*

Background: The cumulative incidence of cardiac events in breast cancer patients treated with anthracycline and trastuzumab at 1 year after the diagnosis of cancer was 16.4%, at 2 years 23.8 %, and at 3 years 28.2%. Sodium glucose co-transporter 2 inhibitors, a new class of antidiabetic drugs, has shown measurable benefits in reduction of HF hospitalization and cardiovascular mortality. LCZ696 (neprilysin inhibitor + valsartan) as able to lower the risk of cardiovascular events in chronic heart failure. We hypothesize that dapagliflozin associated to LCZ696 could exerts cardioprotective effects in cellular models of doxorubicin and trastuzumab-induced cardiotoxicity. **Methods:** Human cardiomyocytes (HL-1 cells) were exposed to subclinical concentration of doxorubicin and trastuzumab (100 nM) alone or in combination with dapagliflozin (50 nM) or LCZ696 (at 100 mM) or both in combination for 48h. Cell viability, apoptosis and necrosis were performed. Quantification of malondialdehyde, 4-hydroxynonenal and intracellular Ca2+ were performed through spectrophotometric methods. Anti-inflammatory studies were also performed (expression of NLRP3 inflammasome, TLR4/MyD88 pathways, nuclear expression of NF-kB). Intracellular concentration of IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL17-α, IL-18, IFN-γ, TNF-α, G-CSF, and GM-CSF were also performed. **Results:** Dapagliflozin and LCZ696 increased synergistically the cell viability during exposure to doxorubicin and trastuzumab. Combination of dapagliflozin and LCZ696 reduces intracellular Ca2+ overload (-68,4% vs cells treated only to anticancer drugs; p<0,001), lipid peroxidation (mean reduction of 57-63,4 % compared to cells exposed only to anticancer drugs; p<0,05). The expression of MyD88, NLRP3 and NF-kB were strongly reduced after treatment with dapagliflozin and LCZ-696 (-52,5, -43,7 and -57,3 % vs cells exposed only to anticancer drugs, respectively; p<0.05). Notably, combination of dapagliflozin and LCZ-696 enhanced the expression Of IL-10; contrary, pro-inflammatory cytokines were reduced, such as IL-1α, IL-1β, IL-6, IL-8, IL17-α and IL-18 (p<0.05). **Conclusions:** During exposure to doxorubicin and trastuzumab, dapagliflozin associated to LCZ-696 exerts additive cardioprotective and anti-inflammatory effects compared to each drug alone. Their properties are mediated by the reduction of iCa2+ content that consequently reduces peroxidation and NLRP3- MyD88 expression. These results indicating the potential use of SGLT-2 inhibitors associated to LCZ696 in preclinical models of cardiotoxicity. Research Sponsor: Ricerca Corrente.

588 **Poster Session**

Primary analysis of MUKDEN 01: A multicenter, single-arm, prospective, phase 2 study of neoadjuvant treatment with pyrotinib and letrozole plus dalpiciclib in triple-positive breast cancer. *First Author: Nan Niu, Shengjing Hospital of China Medical University, Shenyang, China*

Background: Despite the use of multiple lines of targeted therapy has revolutionized treatment for HER2-positive breast cancer, these methods still have limited efficacy for triple-positive breast cancer (TPBC), which calls for persistent exploration for optimized treatment strategy. This MUKDEN-01 prospective trial aimed to evaluate the efficacy of oral, chemo-sparing neoadjuvant therapy with pyrotinib, letrozole and dalpiciclib, which also meet the need for treatment convenience under COVID-19 pandemic, for patients with TPBC. **Methods:** The MUKDEN 01 was an investigator-initiated, multicentre, single arm, prospective phase II trial, which was performed at twelve hospitals in China(NCT04486911). Treatment-naïve patients with stage II-III tumors that according to the AJCC 8th edition criteria were eligible. Patients were treated with each cycle of 4 weeks with oral administration of pyrotinib 320 mg, and letrozole 2.5mg once daily for 4 weeks, and dalpiciclib 125 mg once daily for three weeks, followed by one week off, for five cycles. The primary endpoint was pathological complete response (pCR) in the breast and axilla (ypT0/is ypN0). Secondary endpoints included pCR in the breast (ypT0/is). residual cancer burden (RCB) score, Ki67 index change at surgery compared with baseline, and safety. Safety was analyzed in all patients, who received treatment. The study is still ongoing, and the enrollment has been completed. **Results:** Between June 20, 2020 and Sep. 6, 2021, 68 patients were screened for eligibility and 61 patients were recruited into this first stage of study. After surgery, 18 (29.5%, 95% CI 18.5-42.6) out of 61 patients achieving tpCR(ypT0/is ypN0), 21 (34.4%, 95% CI 22.7-47.7) patients achieved bpCR(ypT0/is). The patients with excellent pathologic response (RCB 0-1) to the combined therapy accounted for 54.1% (33/61, 95% CI 40.9-66.9). Mean Ki67 expression was reduced from 38.7% (95%CI: 31.3-46.0) at baseline to 19.3% (95% CI:13.6-25.0; p=0.0001) in the surgical samples. The most frequent grade 3 AE were neutropenia (35 [57%]), leukopenia (13 [21%]), diarrhea (9 [15%]) and oral mucositis (4 [7%]). There were five grade 4 neutropenia (8%) and one grade 4 increased AST (2%), but without other SAE and death throughout the study. **Conclusions:** Neoadjuvant therapy with pyrotinib, letrozole and dalpiciclib yielded a pCR rate comparable to standard chemotherapy plus dual HER2 blockade in TPBC patients. The combined therapy was also well-tolerated and provided a chemo-sparing neoadjuvant approach for TPBC patients. To our knowledge, this is the first study to evaluate the therapeutic efficacy of a chemo-free neoadjuvant treatment with HER2 TKI pyrotinib and letrozole plus CDK4/6 inhibitor dalpiciclib for TPBC patients. Further validation in a large-scale randomized controlled trial is warranted. Clinical trial information: NCT04486911. Research Sponsor: None.

589 **Poster Session**

Neoadjuvant giredestrant (GDC-9545) plus palbociclib (P) versus anastrozole (A) plus P in postmenopausal women with estrogen receptor–positive, HER2-negative, untreated early breast cancer (ER+/HER2– eBC): Final analysis of the randomized, open-label, international phase 2 coopERA BC study. *First Author: Peter A. Fasching, University Hospital Erlangen, Comprehensive Cancer Center (CCC) Erlangen-EMN, Friedrich-Alexander University Erlangen-Nürnberg, Erlangen, Germany*

Background: Endocrine therapy (ET) is the therapeutic mainstay for ER+ BC. Giredestrant is a highly potent, nonsteroidal, oral, selective ER antagonist and degrader (SERD) which has demonstrated robust ER occupancy, is well tolerated, and has previously shown encouraging antitumor activity as monotherapy and in combination with P in metastatic BC. coopERA BC (NCT04436744) evaluated giredestrant in eBC and met its primary endpoint, highlighting superior Ki67 suppression with single-agent giredestrant vs A at Week 2. Giredestrant was well tolerated. Here, we report the final analysis. **Methods:** Eligible patients (pts) with measurable ER+/HER2– untreated eBC and baseline Ki67 score ≥5% (202 planned) were randomized 1:1 to receive, on Days 1–14 of a neoadjuvant window-of-opportunity phase, 30 mg oral daily (PO QD) giredestrant or 1 mg PO QD A followed by a 16-week neoadjuvant phase of QD giredestrant or A for four 28-day cycles with 125 mg PO P on Days 1–21. Randomization was stratified by tumor size, baseline Ki67 score, and progesterone receptor status. Endpoints assessed here included Ki67 suppression from baseline to surgery, complete cell cycle arrest (CCCA; Ki67 ≤2.7%) at surgery, objective response rate (ORR), and safety. **Results:** At final analysis (cutoff: Nov 24, 2021), 112 and 109 pts were randomized to the giredestrant and A arms, respectively (median age: 62 years each; stage I/IIa disease: 60% vs 54%). Consistent with the primary analysis, greater suppression of Ki67 was observed at surgery with giredestrant + P (–81% [95% confidence interval (CI): –86%, –75%]) vs A + P (–74% [95% CI: –80%, –67%]). Similarly, greater CCCA was achieved at surgery with giredestrant + P (20%) vs A + P (14%). ORR was similar between the two arms (giredestrant + P: 50% [95% CI: 40%, 60%]; A + P: 49% [95% CI: 39%, 59%]). ET-related adverse events (AEs) were non-serious and occurred at similar rates between the two arms. Related Grade ≥3 AE rates were also similar at 6% each. Interruption/withdrawal of ET due to AEs was low and similar for both arms. **Conclusions:** In this final analysis of coopERA BC, the greater suppression of Ki67 with giredestrant vs A observed at Week 2 in the primary analysis was maintained at surgery, and safety data remained consistent with the known safety profile of giredestrant. coopERA BC is the first randomized study to show superior antiproliferative activity of an oral SERD (giredestrant) over an aromatase inhibitor (A) in ER+/HER2– eBC; studies are ongoing to further assess giredestrant's clinical benefit. Clinical trial information: NCT04436744. Research Sponsor: F. Hoffmann-La Roche Ltd.

590 **Poster Session**

Collaborative federated learning behind hospitals' firewalls for predicting histological complete response to neoadjuvant chemotherapy in triple-negative breast cancer. *First Author: Jean Ogier du Terrail, Owkin, Paris, France*

Background: Triple-Negative Breast Cancer (TNBC) is characterized by high metastatic potential and poor prognosis with limited treatment options. Neoadjuvant chemotherapy (NACT) is the standard of care in non-metastastic setting due to the ability to assess pathologic responses providing important prognostic information and guidance in adjuvant therapy decisions. However, the histological response heterogeneity is still poorly understood. We investigate the use of Machine Learning (ML) to predict from diagnosis Whole-Slide Images (WSI) of early TNBC the positive histological Complete Response (pCR) to NACT on surgical specimens. To overcome the known biases of small scale studies while respecting data privacy, we conduct a study in a multi-centric fashion behind hospitals' firewalls using collaborative Federated Learning (FL). Thereby allowing access to enough TNBC data to sustain a complete response heterogeneity investigation. **Methods:** We collected in both comprehensive cancer centers: Centre Léon Bérard (A)(n=99) and Institut Curie (B) (n=420), WSI of biopsies performed at diagnosis and relevant clinical variables. We use traditional Multiple Instance Learning pipelines by tiling the matter on each WSI with a pre-trained Neural Network (NN). We train a second NN to predict the NACT pCR using the mean feature of each WSI. ML trainings are performed using either one cohort in isolation (NN Local) or both cohorts using FL. We compare the performance of this federated WSI based model to the best clinical model (Clin.) simulating clinical practice (using grade and Tumor-Infiltrating Lymphocytes (TILs) percentage) on both centers. **Results:** Performance of models to predict NACT pCR (AUC). All results are evaluated in 5 repeated 4-folds cross validations. **Conclusions:** The final ML model, that was trained in a privacy preserving fashion on both hospitals, provides better prediction of NACT pCR than current clinical standards. This study shows that 1. Not all relevant information is routinely extracted from WSI and 2. Non simulated FL is possible in Healthcare and gives better results than siloed studies on open medical questions. Additional interpretability results of the model show that it has rediscovered known biomarkers such as TILs and apocrine tumor cells without any tile-level annotation, and hints at potential new biomarkers. Research Sponsor: Owkin, French Public Investment Bank (BPI France).

Methods	A (n=79)	B (n=360)
NN FL	75.3, 95% CI [71.6, 78.9]	60.2, 95% CI [57.7, 62.7]
NN Local A	70.4, 95% CI [66.9, 73.9]	58.1, 95% CI [55.4, 60.8]
NN Local B	68.9, 95% CI [64.5, 73.2]	56.9, 95% CI [54.6, 59.3]
Grade + TILs	68.5, 95% CI [65.0, 72.0]	56.9, 95% CI [54.8, 59.0]

The remaining WSI are used to test the final models. On A (n=20), NN FL performs on par with Clin. 61.5 vs 66.7 AUC (comparison p-value > 0.05 with z-test), on B (n=60) NN FL performs significantly better than Clin. 78.0 vs 63.2 AUC (p-value 3.38e-2).

591 **Poster Session**

Improved pathologic complete response rates for triple-negative breast cancer in the I-SPY2 Trial. *First Author: Douglas Yee, Masonic Cancer Center, University of Minnesota, Minneapolis, MN*

Background: The I-SPY2 Trial evaluates multiple investigative agents in neoadjuvant breast cancer therapy with the primary endpoint of estimated pathologic complete response (pCR) rate. As a platform phase 2 trial it utilizes an adaptive design to compare new regimens with control chemotherapy (weekly paclitaxel followed by AC). **Methods:** Specific regimens are assigned based on clinically relevant signatures, including triple negative breast cancer (TNBC). Drug regimens graduate from the trial when the predicted pCR rate in any signature meets the prespecified threshold of 85% probability of success in a hypothetical 300-patient, 1:1 randomized, phase 3 trial. The strong correlation between pCR rate and event free survival has been reported. To establish the benefit of administering investigational agents in combination with control weekly paclitaxel x 12 in TNBC, we report estimated pCR rates for the first 7 investigational agents. **Results:** TNBC accounted for 37% (363/987) of enrolled patients. Only veliparib and carboplatin (VC) and pembrolizumab (Pembro) met the graduation criteria for TNBC. However, compared to control chemotherapy, each drug tested in TNBC resulted in a numerically superior pCR rate compared to control. These findings imply that stratification of TNBC by response-predictive biomarkers may lead to improved pCR rates. For example, we have used gene expression profiling to further refine TNBC classification into Immune enhanced (Immune+), Immune-/DNA Repair Deficient (DRD)+, and Immune-/DRD- classes. TNBC identified as immune enhanced (63%) have an 89% pCR rate to pembrolizumab, while VC is less effective with pCR rate of 71%. Similarly, Immune-/DRD+ (11%) identifies TNBCs with a 80% pCR rate to VC, while pembrolizumab's pCR rate in this group is only 33%. For tumors that are neither immune enhanced or DRD-positive (Immune-/DRD-; 25%) show numerically improved pCR rates for neratinib (20%), MK2206 (25%), ganitumab (24%), and ganetespib (22%) compared to control (12%). pCR rates for VC (10%) and pembrolizumab (20%) in this group were similar to drugs that did not graduate. For TNBC, many agents in I-SPY2 showed numerically improved pCR rates compared to conventional chemotherapy even when they did not meet our specified definition of graduation. **Conclusions:** Further refinement of TNBC signatures should yield improved therapeutic strategies while also sparing women unnecessary systemic therapy. Clinical trial information: NCT01042379. Research Sponsor: U.S. National Institutes of Health, Other Foundation, Pharmaceutical/Biotech Company.

	Cont	Neratinib	VC	Treb	MK2206	Ganit	Ganet	Pembro
est. pCR [95% CI]	28% [21-35%]	38% [22-50%]	51% [36-66%]	37% [21-53%]	40% [25-55%]	32% [17-46%]	38% [23-53%]	60% [44-75%]

592 **Poster Session**

Distribution of breast cancer molecular subtypes within receptor classifications: Lessons from the I-SPY2 Trial and FLEX Registry. *First Author: Jaeyoon Cha, University of California San Francisco, San Francisco, CA*

Background: Expression-based molecular subtypes of breast cancer (BC) predict tumor behavior and therapeutic response. Subtype distributions by age and sociodemographics can inform strategies for BC screening, treatment, and prognosis. The conventional approach, adopted by NCI's Surveillance, Epidemiology, and End Results (SEER) Program, uses HR and HER2 to label: "triple negative" (HR-HER2-), "HER2-enriched" (HR-HER2+), "luminal A" (HR+HER2-), and "luminal B" (HR+HER2+). However, immunohistochemical (IHC)-based receptor labels may not reflect clinically and epidemiologically relevant molecular subtypes that share the same nomenclature, e.g., luminal B. **Methods:** We compared IHC labels by HR/HER2 to molecular subtypes by MammaPrint (MP) and BluePrint (BP) for patients in the phase II neoadjuvant I-SPY2 TRIAL for high-risk, stage II-III BC (NCT01042379, n = 981) and in the multicenter, prospective FLEX Registry for stage I-III BC (NCT03053193, n = 5,679). **Results:** IHC labels were discordant with MP/BP in 52% of I-SPY2 and 43% of FLEX cases (Table 1). HR-HER2- had the highest concordance with basal-type (99% in I-SPY2, 88% in FLEX). HR+ labels had the least agreement with MP/BP: HR+HER2- tumors were molecularly luminal B and basal in 71% and 29% of I-SPY2 and 40% and 4% of FLEX cases, respectively. HR+HER2+ tumors were molecularly luminal A and HER2-type in 10% and 60% of I-SPY2 and 15% and 36% of FLEX cases, respectively. Of molecularly luminal B cases, only 14% in I-SPY2 and 7% in FLEX were HR+HER2+. **Conclusions:** IHC markers collected by population-based registries (SEER) enable BC surveillance. However, IHC labels cannot be used as surrogates for molecular subtypes by MP/BP, especially for luminal B tumors. Given the unmet need to improve management of luminal B BC, we anticipate the growing importance of molecular subtyping to inform treatment and epidemiological research. We propose that the BC research community work with SEER to update its IHC labels to avoid overlap with molecular subtype nomenclature and incorporate such modern classifications when available. Research Sponsor: U.S. National Institutes of Health, Other Foundation, Pharmaceutical/Biotech Company.

	I-SPY2				FLEX			
	HR-HER2-	HR-HER2+	HR+HER2-	HR+HER2+	HR-HER2-	HR-HER2+	HR+HER2-	HR+HER2+
Basal-type	359 (99%)	17 (19%)	108 (29%)	4 (3%)	295 (88%)	28 (25%)	216 (4%)	10 (3%)
HER2-type	0	70 (79%)	1 (0%)	94 (60%)	1 (0%)	80 (72%)	2 (0%)	119 (36%)
Luminal A	1 (0%)	0	0	15 (10%)	13 (4%)	1 (1%)	2708 (55%)	49 (15%)
Luminal B	1 (0%)	2 (2%)	266 (71%)	43 (28%)	25 (8%)	2 (2%)	1974 (40%)	156 (47%)
Total	361	89	375	156	334	111	4900	334

593 **Poster Session**

Combined assessment of metabolic response and tumor infiltrating lymphocytes as a predictor of outcomes following neoadjuvant therapy for HER2-positive breast cancer: Results from the randomized PREDIX HER2 trial.

First Author: Alexios Matikas, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden

Background: Abundance of tumor infiltrating lymphocytes (TIL) is prognostic in early HER2-positive breast cancer (BC). Response to neoadjuvant therapy (NAT) according to positron emission tomography combined with computed tomography (PET-CT) has been shown to predict pathologic complete response (pCR). There is paucity of data regarding long-term prognostication using PET-CT and the potential value of the combined assessment of both these biomarkers. **Methods:** PREDIX HER2 (NCT02568839) is a prospective randomized phase 2 trial that compared standard NAT (docetaxel, trastuzumab, pertuzumab) with trastuzumab emtansine, in patients with HER2-positive BC. Overall, 202 patients were included (197 evaluable) and the primary efficacy analysis showed no difference in pCR or event-free survival (EFS) between the two groups (Hatschek, JAMA Oncology 2021). Assessment with fluorine 18–labeled fluorodeoxyglucose PET-CT was performed at baseline and after 2 and 6 treatment cycles, and SUVmax was evaluated as a continuous variable. TILs were assessed at baseline biopsies according to guidelines from the International TIL Working Group (J.H.). The aim of this secondary analysis was to investigate the combined assessment of TIL and PET-CT as an early predictor of response to NAT. **Results:** Overall, 112 patients underwent baseline PET-CT and 109 after C2, whereas 173 had baseline TIL. In multivariable analysis, baseline SUVmax did not predict pCR (OR_{adj}= 1.04, 95% CI 0.97-1.12, p = 0.259) or EFS (HR_{adj}= 1.07, 95% CI 0.98-1.17, p = 0.117). In contrast, higher SUVmax at C2 predicted lower pCR (OR_{adj}= 0.65, 95% CI 0.48-0.87, p = 0.005) and worse EFS (HR_{adj}= 1.18, 95% CI 1.04-1.34, p = 0.01). Baseline TIL > 10% (median cut-off) provided additional prognostic information to clinical parameters (stage and hormone receptor expression) and C2 SUVmax (LR-$\Delta\chi^2$ = 7.19, p = 0.007; OR_{adj}= 3.52, 95% CI 1.37 – 9.06, p = 0.009). 75% of patients with high TIL and C2 SUVmax < 2.49 achieved pCR, compared with 13.8% of those with low TIL and high C2 SUVmax and 39.1%-41.3% for the intermediate groups (p = 0.001). **Conclusions:** SUVmax after two cycles of NAT for HER2-positive BC is an independent predictor of both short- and long-term outcomes. A combined assessment with TIL may facilitate early selection of good responders for de-escalation and poor responders for alternative treatment strategies. Clinical trial information: NCT02568839. Research Sponsor: Region Stockholm, Cancer Research KI, Swedish Cancer Society, Swedish Research Council, Roche Sweden.

594 **Poster Session**

Prediction of pathologic complete response to neoadjuvant chemotherapy in breast cancer (SWOG S0800) using image analysis-based tumor infiltrating lymphocyte measurements.

First Author: Kim Blenman, Yale University, New Haven, CT

Background: Image analysis-based tumor infiltrating lymphocyte (TIL) quantitation methods are being developed to eliminate reader-to-reader variation in TIL assessment that hinders its clinical adoption as prognostic and chemotherapy response predictive marker. We evaluated the ability of an image analysis-based TIL score to predict pathologic complete response (pCR) and event free survival (EFS) in breast cancer. **Methods:** 113 pretreatment samples were analyzed from the SWOG S0800 trial that randomized stage IIB-IIIC HER-2-negative breast cancers to neoadjuvant chemotherapy with or without bevacizumab. TIL quantitation was performed on H&E sections using QuPath open-source software and a convolutional neural network cell classifier (CNN11). The digital easTILs% score was calculated as [sum of TIL Area (mm^2) / Stromal Area (mm^2)] x 100. Pathologist-read stromal TIL score (sTILs%) was defined using international guidelines. A previously validated threshold of easTILs% > 19.9% defined high easTILs% status. **Results:** Pretreatment easTILs% was significantly higher in cases with pCR compared to residual disease (RD) (means, 31% vs. 17%, p < 0.001). easTILs% high and low cases had pCR rates of 41% and 21% (p = 0.019), respectively. In logistic regression adjusting for other factors, easTILs% was prognostic for pCR as continuous score (p < 0.001) and as high *vs* low categories (p = 0.035). There was strong positive correlation between easTILs% and sTILs% (r = 0.606, p < 0.0001), and sTILs% was also predictive of pCR. The areas under the prediction curve (AUC) were 0.709 and 0.627 for easTILs% and sTILs%, respectively. There was no statistically significant interaction between easTILs% and bevacizumab benefit (p = 0.26), and higher easTILs% or sTILs were not associated with better EFS. **Conclusions:** Image analysis-based TIL quantification is predictive of pCR in breast cancer and had better pCR outcome discrimination than pathologist-read sTIL count. Research Sponsor: Susan Komen Foundation Leadership Award (SAC160076) and Breast Cancer Research Foundation Investigator Award (BCRF-21-133), Pharmaceutical/Biotech Company, U.S. National Institutes of Health.

	Digital easTILs% RD	pCR	p-value	Pathologist-read sTILs% RD	pCR	p-value
All (median)	14.84	36.13	< 0.001	8.75	17.50	0.037
Chemotherapy Alone (median)	16.76	27.25	0.130	10.00	11.25	0.541
Chemotherapy + Bevacizumab (median)	13.37	36.28	0.001	7.50	20.00	0.027
pCR Rate (N/total N)	High TIL (> 19.9%)	Low TIL (≤19.9%)	p-value	High TIL (> 20%)	Low TIL (≤19.9%)	p-value
All	19/46	14/67	0.019	15/39	18/74	0.116
Chemotherapy Alone	6/24	6/35	0.461	4/19	8/40	0.925
Chemotherapy + Bevacizumab	13/22	8/32	0.012	11/20	10/34	0.063

595 **Poster Session**

Artificial intelligence (AI)–powered spatial analysis of tumor-infiltrating lymphocytes (TIL) for prediction of response to neoadjuvant chemotherapy (NAC) in triple-negative breast cancer (TNBC).

First Author: Hee Jin Lee, Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

Background: Stromal TIL are a well-recognized prognostic and predictive biomarker in breast cancer. There is a need for tools assisting visual assessment of TIL, to improve reproducibility as well as for convenience. This study aims to assess the clinical significance of AI-powered spatial TIL analysis in the prediction of pathologic complete response (pCR) after NAC in TNBC patients. **Methods:** H&E stained slides and clinical outcomes data were obtained from stage I – III TNBC patients treated with NAC in two centers in Korea. For spatial TIL analysis, we used Lunit SCOPE IO, an AI-powered H&E Whole-Slide Image (WSI) analyzer, which identifies and quantifies TIL within the cancer or stroma area. Lunit SCOPE IO was developed with a 13.5 x 109 micrometer2 area and 6.2 x 106 TIL from 17,849 H&E WSI of multiple cancer types, annotated by 104 board-certified pathologists. iTIL score and sTIL score were defined as area occupied by TIL in the intratumoral area (%) and the surrounding stroma (%), respectively. Immune phenotype (IP) of each slide was defined from spatial TIL calculation, as inflamed (high TIL density in tumor area), immune-excluded (high TIL density in stroma), or desert (low TIL density overall). **Results:** A total of 954 TNBC patients treated from 2006 to 2019 were included in this analysis. pCR (ypT0N0) was confirmed in 261 (27.4%) patients. The neoadjuvant regimens used were mostly anthracycline (97.8%) and taxane (75.1%) -based, with 116 (12.1%) patients receiving additional platinum and 41 (4.3%) patients treated as part of immune checkpoint inhibitor or PARP inhibitor clinical trials. The median iTIL score and sTIL score were 4.3% (IQR 3.2 – 5.8) and 8.1% (IQR 6.3 – 13.4), respectively. The mean iTIL score was significantly higher in patients who achieved pCR after NAC (5.8% vs. 4.5%, p < 0.001), and a similar difference was observed with sTIL score (12.1%.1 vs. 9.4%, p < 0.001). iTIL score was found to remain as an independent predictor of pCR along with cT stage and Ki-67 in the multivariable analysis (adjusted odds ratio 1.211 (95% CI 1.125 – 1.304) per 1 point (%) change in the score, p <0.001). By IP groups, 291 (30.5%) patients were classified as inflamed, 502 (52.6%) as excluded, and 161 (16.9%) as desert phenotype. The patients with inflamed phenotype were more likely to achieve pCR (44.7%) than other phenotypes (19.8%, p < 0.001). **Conclusions:** AI-powered spatial TIL analysis could assess TIL densities in the cancer area and surrounding stroma of TNBC, and TIL density scores and IP classification could predict pCR after NAC. Research Sponsor: Lunit Inc.

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Final result for SAFIA trial for neoadjuvant palbociclib in patients with operable luminal breast cancer responding to fulvestrant.

First Author: Khalid A. Al-Saleh, Mcmaster University LTCC, Ancaster, ON, Saudi Arabia

Background: Luminal, human epidermal growth factor receptor 2 (HER2)-negative breast cancer (BC) encompasses the most common subtype of breast malignancies. Neoadjuvant strategies of operable BC are primarily based upon chemotherapy (CT), while neoadjuvant hormone therapy (NAHT) has not been well studied in the Middle East and North Africa (MENA) region. However, these tumors might respond poorly to neoadjuvant CT with significant side effects, emphasizing the need to identify patients who could be candidates for NAHT. **Methods:** The SAFIA trial is a prospective multicentre, international, double-blind, neoadjuvant phase-III trial using upfront 21-gene Oncotype DX Breast Recurrence Score assay (RS) <31) to select operable Luminal HER2-negative patients for induction hormonal therapy with Fulvestrant 500 mg +/– Goserelin (F/G) before randomizing responding patients to F/G + Palbociclib (Cyclin-Dependent Kinase 4/6 inhibitor / CDK 4/6) versus F/G + Placebo. The primary endpoint of this study was the complete pathologic response (pCR) rate. **Results:** A total of 354 patients were enrolled, leading to 277 patients treated with induction F/G. Of these, 253 responding patients were randomized to F/G fulvestrant with palbociclib or Placebo. Two hundred and thirty patients were evaluable for pathologic response. No statistically significant differences were identified in terms of pCR rates between F/G with palbociclib or placebo: 2% versus 7%, respectively. According to the radiologic responses post- induction F/G, the hormone sensitivity rate was 89.8%, while the clinical benefit of 8–9 months of neoadjuvant F/G was 96%. Safety in the MENA population was acceptable with a grade 3-4 neutropenia rate of 25% in the F/G plus palbociclib arm. The feasibility of performing the 21-gene breast recurrence score assay on core biopsy specimens was optimal in 96.4% of cases. **Conclusions:** The addition of palbociclib to neoadjuvant F/G did not show any additional benefit in terms of pathologic response, including pCR in neoadjuvant therapy of Luminal HER2-negative BC responding to induction F/G. The use of an upfront 21-gene assay appeared feasible on biopsy specimens, and the identification of tumors with RS<31 allowed to select endocrine sensitive patients, leading ultimately to a 96% clinical benefit with 8–9 months of F/G neoadjuvant therapy. Clinical trial information: NCT03447132. Research Sponsor: AstraZeneca, Pfizer, King Saud University.

Radiological response to induction F/G, according to hormone sensitivity (response > 0%) and RS levels (n = 266).

Radiological Response	RS [0 -10] N=34	RS [11 – 25] N=147	RS [26 – 30] N=25	Without RS N=60	Total
Complete response	2 (6%)	4 (3%)	0 (0%)	1 (2%)	7 (2.6%)
Partial Response (>50%)	22 (65%)	82 (55%)	18 (72%)	46 (76%)	168 (63.2%)
Minor Response (0 to 50%)	9 (26%)	47 (32%)	2 (8%)	6 (10%)	64 (24.0)%
Minor Progression (Up to 25%)	0 (0%)	10 (7%)	3 (12%)	1 (2%)	14 (5.3%)
Progressive Disease (>25%)	1 (3%)	4 (3%)	2 (8%)	6 (10%)	13 (4.9%)

597 **Poster Session**

Harnessing artificial intelligence to automate delineation of volumetric breast cancers from magnetic resonance imaging to improve tumor characterization. *First Author: Ryle Zhou, Stanford University, Stanford, CA*

Background: Automated breast tumor identification and segmentation in magnetic resonance imaging (MRI) is a difficult and crucial area of study in breast cancer research. Artificial intelligence (AI) models are increasingly being developed for automated localization of lesions in imaging studies to facilitate quantitative assessment of features for improved diagnostic, prognostic and predictive performance. Such models have had success in detecting breast cancers in mammography, ultrasound and CT, but few have achieved three-dimensional (3D) volumetric tumor segmentation from breast MRI. The purpose of this study was to apply two state-of-the-art AI – specifically, deep learning (DL) - algorithms to 3D MRI breast cancer data and identify the higher performing algorithm for precise segmentation of breast tumors. **Methods:** We evaluated pre-treatment, T1 post-gadolinium contrast enhanced breast MRI from 222 patients with known breast cancers (n = 262). Images were split into training (n = 142), validation (n = 36), and hold-out test (n = 44) datasets. Two DL algorithms, U-Net and VAE-UNet, were trained to classify tumors on the training dataset across 1000 epochs. The output for each is a precise localization and segmentation of each tumor at the pixel level from every MRI image. We evaluated the performance of each algorithm using 5-fold cross-validation and testing on the validation and test sets. We calculated a dice accuracy score for each model as the performance comparison metric. **Results:** The highest dice accuracy score achieved on the validation dataset by generic U-Net was 83.38%, with an average across 1000 epochs of 62.41%. The highest dice accuracy achieved on the validation dataset by VAE-UNet was 82.62%, with an average across epochs of 61.28%. On our test dataset, the highest dice accuracy score achieved by U-Net was 93.09%, with an average across epochs of 66.31%, and the highest accuracy score for VAE-UNet was 90.98%, with average across epochs of 50.47%. Although U-Net appeared to perform slightly better than VAE-Unet for most cases, there were distinct cases where VAE-UNet outperformed U-Net (dice score up to 59% better than U-Net). Subsequent analysis indicated that VAE-UNet preferentially outperforms U-Net for tumors with low sphericity (p = 0.001). **Conclusions:** Our results suggest that U-Net is well suited for segmenting breast tumors from breast MRI in most cases, but that VAE-UNet outperforms U-Net when the tumor shapes are less spherical. Our findings could inform the choice of DL algorithms in research and clinical endeavors that rely on accurate breast cancer tumor segmentation. In particular, these two tools could be configured to facilitate tumor assessment from breast MRI in the clinical setting for: breast cancer screening in high-risk patient populations, pre-surgical planning, and monitoring of treatment response. Research Sponsor: Stanford Women's Cancer Center, Cancer League.

598 **Poster Session**

Prediction of response to neoadjuvant therapy (NAT) in early breast cancer (EBC) at community hospitals: SimBioSys TumorScope Validation Study. *First Author: John R. Pfeiffer, SimBioSys, Inc., Chicago, IL*

Background: While most cancer patients are treated at community hospitals, specialized equipment, diagnostic tests, and therapeutic regimens are generally validated at academic settings. Here we present a novel approach to precision medicine to improve outcomes in breast cancer care in the community setting. TumorScope (TS) is a biophysical modelling platform that uses only pretreatment standard of care (SoC) diagnostic data (demographics, drug regimen, imaging (DCE MRI) & pathology) to construct a 3D model of the tumor. TS integrates models for tumor morphology, metabolism, vascularity, and drug behavior and simulates predicted tumor response longitudinally to NAT. With this information TS predicts the reduction in tumor volume and the pathological complete response (pCR), a surrogate marker of long-term outcome, to anticipated NAT in EBC. **Methods:** We performed a single center validation study to show the clinical applicability of TS. Patients at Northwest Community Healthcare that received NAT with corresponding pretreatment MRI were identified in a chart review. A validation set, independent from the training set, was generated from this list and data processed through TS (n=50). Pretreatment patient SoC diagnostic data was loaded into TS. TS predicted the weekly volumetric response throughout the treatment, and it simulated residual volume to predict pCR. The validation was performed using ground truth from post treatment assessment of pCR, radiographic volumes extracted from MRIs. **Results:** TS predicted pCR, prospectively defined as a simulated residual tumor volume <0.01 cm^3 or a 99.9% or greater reduction in tumor volume. Performance metrics of TS were calculated. TS tumor volume prediction accuracy had an area under the curve (AUC)=0.947 with sensitivity and specificity of 93.3% and 94.3% respectively. Performance was robust across all subtypes (See Table 1). TS predicted the reduction in tumor volume with a median absolute volumetric error of 3.4% as compared to radiographic volume from pre-surgery MRIs (n=50). **Conclusions:** In summary, TS accurately predicts patient-specific tumor volume reduction and pCR prior to NAT in EBC using only SoC pretreatment data, which could lead to a more personalized cancer care for the patient. Moreover, we demonstrate the feasibility of implementing TS at community hospitals. Research Sponsor: None.

Prediction accuracy.

	Overall n=50 (95% CI)	TNBC n=10 (95% CI)	HER2+ n=12 (95% CI)	HR+/HER2- n=18 (95% CI)	HR+/HER2+ n=10 (95% CI)
Volume AUC	0.947	0.905	1.000	0.941	1.000
pCR Accuracy	0.940 (0.835, 0.988)	0.900 (0.555, 0.998)	0.917 (0.615, 0.998)	0.944 (0.727, 0.999)	1.000 (0.692, 1.000)
pCR Sensitivity	0.933 (0.680, 0.998)	0.667 (0.094, 0.991)	1.000 (0.630, 1.000)	1.000 (0.025, 1.000)	1.000 (0.292, 1.000)
pCR Specificity	0.943 (0.808, 0.993)	1.000 (0.590, 1.000)	0.75 (0.194, 0.994)	0.941 (0.713, 0.999)	1.000 (0.590, 1.000)

599 **Poster Session**

Real-world effectiveness of prophylactic granulocyte colony-stimulating factor (G-CSF) early (week 1) and late (weeks 2-3) in the cycle for the prevention of febrile neutropenia (FN) among patients (pts) with breast cancer (BC) after high FN–risk chemotherapy (chemo). *First Author: Douglas W. Blayney, Stanford University, Stanford, CA*

Background: G-CSF mitigates chemotherapy-induced neutropenia (CIN) and reduces FN risk. G-CSF moves the nadir of absolute neutrophil count (ANC) earlier (to week 1) in the chemo cycle and shortens nadir duration (Crawford, NEJM 1991), suggesting the potential for suboptimal CIN protection early (week 1) in the chemo cycle. The relative FN risk in week 1 vs. weeks 2-3 of the cycle with G-CSF is unknown and was analyzed compared with no G-CSF in the real-world setting with high FN risk chemo. **Methods**: Using a database of administrative claims representing 100% of fee-for-service Medicare, we analyzed BC pts who initiated docetaxel (T), doxorubicin (A), or cyclophosphamide (C) monotherapy or combination therapy between 01/01/2015 – 12/31/2019. Sample pts included adults aged ≥ 65 years with continuous coverage in Medicare Parts A, B, and D for 6 months before and 20 days after chemo initiation. Pts were categorized as receiving vs. not receiving G-CSF therapy within 3 days after chemo. Rate of FN events starting in week 1 vs. weeks 2-3 in cycle 1 was calculated. We defined FN as an inpatient admission with a primary or secondary diagnosis of neutropenia and measured the interval between chemo initiation and FN admission. **Results**: Among 18,788 Medicare beneficiaries with BC treated with T, A, and/or C, 72% received G-CSF therapy. More pts receiving G-CSF were treated with ≥ 2 of T, A, and/or C compared to pts who did not receive G-CSF (71% vs. 51%). Overall FN incidence in cycle 1 was significantly lower among pts receiving G-CSF (4.0%; n=546) compared to pts not receiving G-CSF (8.8%; n=462) (p<0.0001). In pts with G-CSF, 81% (440/546) of all 1st-cycle FN events started in week 1 vs. 19% (106/546) in weeks 2-3. In pts not receiving G-CSF, the start of 1st-cycle FN events was more equally distributed: 41% (190/462) started in week 1 vs. 59% (272/462) in weeks 2-3. Results were robust to sensitivity analyses restricted to pts receiving ≥ 2 of T, A, and/or C. The rates of 1st-cycle FN events starting in weeks 1 and 2-3 with and without G-CSF following chemo initiation is shown below. **Conclusions**: Prophylactic G-CSF was highly effective for the prevention of FN in weeks 2-3, but relatively ineffective in week 1 of cycle 1 in the real-world setting, leaving pts largely unprotected during the first week. This represents an unmet medical need in week 1 of the cycle, despite use of G-CSF. Clinical trial information: NCT03294577. Research Sponsor: BeyondSpring Pharmaceuticals Inc.

	Pts receiving G-CSF (N=13,544)	Pts not receiving G-CSF (N=5,244)	p-value
Rate of FN events starting in week 1 of cycle 1	3.2% (n=440)	3.6% (n=190)	0.20
Rate of FN events starting in weeks 2-3 of cycle 1	0.8% (n=106)	5.2% (n=272)	<0.0001

600 **Poster Session**

Deep learning algorithm to predict pathologic complete response to neoadjuvant chemotherapy for breast cancer prior to treatment. *First Author: Rachel Choi, Dept. of Therapeutic Radiology, Yale School of Medicine, New Haven, CT*

Background: Pathologic complete response (PCR) to neoadjuvant chemotherapy (NAC) is associated with improved disease-free survival and overall survival in patients with breast cancer. Predicting PCR at the patient level prior to treatment initiation would allow physicians and patients to focus on therapies with the highest likelihood of success and minimize unnecessary toxicities from chemotherapy. We hypothesize that pre-treatment prediction of PCR is possible through a deep neural network algorithm trained on breast MRI imaging obtained prior to treatment. **Methods:** 126 tumors from patients treated with neoadjuvant chemotherapy for T3 stage breast cancer at a single institution from 2002 to 2006 were analyzed. In total, 3780 MRI slices were included. 3 MRI contrast phases (pre, immediate post, delayed post) from each slice were used as individual inputs to create separate model predictions of PCR. The 2-D CNN was trained over 50 epochs on the training set. The model was tested on the isolated test set (30% of samples). **Results:** Average model prediction accuracy over the total test set using a single phase of contrast (pre-, immediate post-, or delayed post-) was 90.4%. Concordance adjustment was conducted, with exclusion of slices that had produced discordant predictions across different contrast phase inputs. This resulted in an increase of overall model accuracy to 97.6%. Model accuracy was similar across subsets of age and tumor size despite differences in PCR rates. However, model accuracy was significantly lower in the triple-negative disease group. **Conclusions:** We demonstrate a deep neural network that accurately predicts PCR based on breast MRI imaging taken prior to NAC initiation. Our findings represent the promise of deep learning algorithms in providing personalized prognostic data for physicians and patients. Research Sponsor: Radiological Society of North America, U.S. National Institutes of Health, Yale School of Medicine.

Model Performance.

Cases in Validation Set (Total cases/Unique patients)	Cases of Pathologic Complete Response (%)	Gross Model Prediction Accuracy	Sensitivity	Specificity	Model Prediction Accuracy Excluding Discordant Cases
All Cases (406/120)	**105 (25.9%)**	**Pre: 89.9% Immediate: 91.6% Delay: 89.7%**	**Pre: 0.790 Immediate: 0.829 Delay: 0.829 Net: 0.676**	**Pre: 0.937 Immediate: 0.947 Delay: 0.920 Net: 0.837**	**97.6%**
Stratified by Tumor Size					
0-65 mm (191/63)	61 (31.9%)	Pre: 88.0% Immediate: 89.5% Delay: 90.1%			98.0%
65+ mm (215/57)	44 (20.5%)	Pre: 91.6% Immediate: 93.5% Delay: 89.3%			97.3%
Stratified by Hormone Receptor Profile					
ER positive (222/65)	33 (14.9%)	Pre: 93.6% Immediate: 94.6% Delay: 91.9%			99.5%
PR positive (185/53)	22 (11.9%)	Pre: 94.6% Immediate: 95.7% Delay: 90.3%			99.4%
HR positive (233/69)	33 (14.2%)	Pre: 94.0% Immediate: 94.8% Delay: 92.3%			99.5%
Triple Negative (171/50)	72 (42.1%)	Pre: 84.2% Immediate: 87.1% Delay: 86.0%			94.8%

For net sensitivities and specificities, cases were considered accurate if all 3 phase predictions were accurate.

601 **Poster Session**

Multimodal machine learning model prediction of complete pathological response to neoadjuvant chemotherapy in triple-negative breast cancer. *First Author: David Groheux, Hôpital Saint Louis, AP-HP, Paris, France*

Background: Triple negative breast cancer (TNBC) is a biologically and clinically heterogenous disease, associated with poorer outcomes when compared with other subtypes of breast cancer. In early-stage TNBC, surgery with curative intent remains the mainstay of therapy. Neoadjuvant chemotherapy is often given prior to surgery and achieving pathological complete response (pCR) has been associated with improved long-term outcomes in terms of progression-free survival (PFS) and overall survival (OS). There is thus high clinical interest in the ability to accurately predict pCR status using baseline data. **Methods:** A retrospective cohort of 57 patients with early-stage TNBC treated with neoadjuvant chemotherapy was analyzed to develop a machine learning-based algorithm predictive of pCR likelihood at the individual patient level. Multimodal baseline data were collected including clinical, biological (e.g., histology, genomic profile including CDC2, CDC20, KPNA2, MYBL2, complete blood count, Ki67), imaging data (baseline PET/CT scan), the radiology report and clinical outcomes data (pCR, PFS, OS). For each patient, tumors were segmented in 3D by an experimented nuclear physician using the SOPHiA Radiomics platform. Radiomics features were then extracted following the IBSI standards and then combined with the other data modalities. A filter-based variable selection method was applied before training several machine learning algorithms. The optimization criterion was the Area Under the ROC Curve (AUC). Due to the small size of the cohort, a nested leave-pair-out cross-validation approach was used to properly estimate the model performance. **Results:** The best result was obtained with the SVM algorithm with a linear kernel, reaching an AUC of 0.82, a precision of 71%, a sensitivity of 71% and a specificity of 70%. The features with highest weight in the algorithm were a mix of radiological, radiomics, biological and clinical features, highlighting the importance of a truly multimodal analysis. Indeed, withdrawing a specific data modality (e.g., radiomics features or biological features), led to a decrease of ~10% of the AUC. Patients were then stratified into two groups based upon their predicted pCR status. These two groups displayed a statistically significant difference in PFS ($p<0.001$), suggesting that baseline multimodal data analysis could help predict long-term outcomes. **Conclusions:** This proof of concept study suggests that machine learning applied to baseline multimodal data can help predict pCR status after neoadjuvant chemotherapy for TNBC at the individual patient level, as well as stratify patients to inform long-term outcomes. Patients that would be predicted as non-pCR could benefit from concomitant treatment with immunotherapy, or dose intensification. This algorithm will be further validated in a larger, multicentric cohort. Research Sponsor: None.

602 **Poster Session**

Neoadjuvant ipilimumab and nivolumab in combination with paclitaxel following anthracycline-based chemotherapy in patients with treatment resistant early-stage triple-negative breast cancer (TNBC): A single-arm phase 2 trial. *First Author: Sherene Loi, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia*

Background: We examined the efficacy and safety of neoadjuvant ipilimumab and nivolumab combined with paclitaxel following suboptimal response to anthracycline-based chemotherapy in patients with early-stage TNBC. **Methods:** This single arm multicentre phase 2 study enrolled 34 patients in 8 sites. Patients were aged ≥18 years with previously untreated stage 3 TNBC and were required to have ≥15mm of tumor remaining or 10mm of tumor with one positive lymph node after 4 cycles of anthracycline-based therapy. A suboptimal response subset at baseline was defined as < 50% reduction in tumor volume after initial anthracycline-based chemotherapy. Patients received neoadjuvant ipilimumab 1mg/kg IV 6 weekly for 2 doses and nivolumab 240mg every 2 weeks for 6 doses, with weekly paclitaxel at 80mg/m^2 for 12 weeks, followed by surgery. Nivolumab (480mg 4-weekly) continued post operatively for further 9 months. Primary endpoint was pathological complete response (pCR) in breast and axilla, with secondary endpoints pCR in the suboptimal responders, pCR in PD-L1 positive patients (≥1% by SP142 assay), clinical response in the breast (ORR by RECIST), event-free (EFS) and overall survival (OS). **Results:** Between December 2018 and April 2020, 34 patients were enrolled, 33 were evaluable for the primary endpoint. Median age was 46.6yrs. At diagnosis, all patients were clinical stage III (AJCC v8), 16/34 (47%) were node positive, 8/31 (26%) were PD-L1 positive. At study entry (following anthracycline-based chemo), the median tumor size by ultrasound was 28mm (12-62). 16/33 (48%) were considered suboptimal responders. The pCR rate (ypT0ypN0) was 24.2% (95% CI, 11.09-42.26) in all evaluable, 37.5% [3/11] in PD-L1+ and 23% [5/22] in PD-L1- patients. In patients with suboptimal anthracycline response (< 50% tumor reduction), the pCR rate was 18.8% (95% CI, 8.52-75.51) (3/16). ORR in the breast was 57.6% (19/33) in all evaluable patients and 43.7% (8/20) in the suboptimal responders. The number of patients with residual cancer burden (RCB) class 0,1,2,3 was 8 (24%), 1 (3%), 19 (57.5%) and 5 (15%) respectively. With 14 months median follow up, 12-months EFS was estimated at 85% and OS 94%. For patients with pCR vs non-pCR, the hazard ratio (HR) for EFS was 0.62, 12 mo EFS was 100% vs 75%. In the neoadjuvant phase, 15/33 (45%) patients experienced at least one grade 3-4 adverse event. Most common immune-related event was grade 1 or 2 pneumonitis 9/33 (27%), which generally occurred with fever after the first dose of ipilimumab, and resolved. There was one case of grade 3 colitis. **Conclusions:** In these high risk patients, the addition of ipilimumab and nivolumab to neoadjuvant paclitaxel resulted in promising ORR and pCR rates, regardless of PD-L1 status. Rates of low grade pneumonitis were high. Follow up continues. Clinical trial information: ACTRN12617000651381. Research Sponsor: Bristol-Myers Squibb, Other Foundation.

603 **Poster Session**

Copy number aberration burden on circulating tumor DNA predicts recurrence risk after neoadjuvant chemotherapy in patients with triple-negative breast cancer: Post-hoc analysis of phase III PEARLY trial. *First Author: Min Hwan Kim, Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea*

Background: Our previous study reported prognostic significance of copy number aberration (CNA) burden on low-pass whole genome sequencing (LP-WGS) based circulating tumor DNA (ctDNA) analysis in metastatic breast cancer patients. Here, we report the prognostic value of ctDNA CNA burden measured before neoadjuvant chemotherapy in stage II-III triple-negative breast cancer (TNBC) patients enrolled in phase III PEARLY trial (NCT02441933, BIG Supporter Study BIG 19-01, KCSG BR15-01). **Methods:** The PEARLY trial was performed as a randomized, open-label, multicenter, phase III study to test the efficacy and safety of adding carboplatin to (neo)adjuvant chemotherapy in patients with stage II-III TNBC. Patients were randomized in a 1:1 ratio to receive 4 cycles of AC followed by the taxane or taxane plus carboplatin (AUC 5, tri-weekly 4 cycles) as neoadjuvant or adjuvant therapy. This post-hoc baseline ctDNA analysis (before neoadjuvant chemotherapy) included only the neoadjuvant patient cohort with available baseline ctDNA results (n = 465, median follow-up 16.8 months), while it was blinded for randomization information (carboplatin or not). We used "l-score" method to estimate CNA burden of ctDNA by LP-WGS to be matched with disease-free survival (DFS) after primary surgery. **Results:** The baseline ctDNA l-score level was positively associated with clinical T and N stage, while baseline l-score was not different between patients with pathologic complete response (pCR) and non-pCR. We listed 465 patients in the order in which they underwent primary surgery, and then alternated patients to be assigned to exploratory cohort (n =232) and validation cohort (n = 233). The DFS was significantly shorter in high l-score (l-score ≥ 7.81) patients compared with low l-score (l-score < 7.81) patients in exploratory cohort. The high l-score independently predicted poor DFS adjusted for clinical T stage, clinical N stage, and pCR status (hazard ratio [HR] 3.88, $p = 0.003$). In the validation cohort, high l-score was validated to be associated poorer DFS, and multivariate Cox analysis validated the independent prognostic impact of l-score on DFS (HR 2.04, $p = 0.050$). The high baseline l-score patients showed shorter DFS both in pCR-positive and pCR-negative patients. The 12-month DFS rate for pCR (+)/Low l-score patients was 98%, whereas that of pCR(-)/High l-score patients was 61.3 % in the validation cohort. **Conclusions:** The baseline ctDNA CNA burden on LP-WGS before neoadjuvant chemotherapy robustly predicts recurrence risk in stage II-III TNBC patients. The ctDNA l-score showed prognostic value independently from pCR status, suggesting ctDNA l-score can serve as a useful clinical determinant for escalating or de-escalating (neo)adjuvant strategy in TNBC patients. Clinical trial information: NCT02441933. Research Sponsor: Ministry of Trade, Industry & Energy (MOTIE, Korea), Other Government Agency.

604 **Poster Session**

Effect of neoadjuvant versus adjuvant chemotherapy on ipsilateral breast tumor recurrence after breast-conserving surgery and whole-breast irradiation. *First Author: Jong-Ho Cheun, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul, South Korea*

Background: Early Breast Cancer Trialists' Collaborative Group conducted a large meta-analysis and reported that patients who underwent neoadjuvant chemotherapy (NAC) had higher ipsilateral breast tumor recurrence (IBTR) rate than those with adjuvant chemotherapy. However, since the study was conducted with patients treated two decades ago, the results could not reflect the advance in treatments and IBTR rate was much higher than in recent studies, Thus, we investigated the association between chemotherapy settings and IBTR rates in breast cancer patients. **Methods:** We retrospectively reviewed the data of 5,307 patients who underwent breast conserving surgery followed by whole breast irradiation between January 2004 and December 2018 in a single institution. Patients who underwent mastectomy or omitted chemotherapy were excluded. **Results:** The 1,473 patients who underwent NAC showed significantly higher IBTR rate than the 3,564 patients who underwent adjuvant chemotherapy (10-year risk: 4.5% vs. 4.0%; log-rank p=0.045, hazard ratio 1.42 [95%CI,1.01-1.99]). The difference was more evident for patients with hormone receptor (HR) positive and human epidermal growth factor receptor-2 (HER2) negative tumor (unadjusted p=0.001, hazard ratio 2.27 [95%CI,1.37-3.74; adjusted p=0.002, hazard ratio 2.80 [95%CI,1.45-5.42]], and the statistical significance was still remained after 1:1 propensity score matching (p=0.026). In contrast, patients with other subtypes did not show significant differences between two groups. **Conclusions:** Patients who underwent NAC for HR+/HER2- tumors carry increased risk of IBTR than those who underwent adjuvant chemotherapy. Our observation supports the need for considering tumor subtypes in initial treatment. In addition, more intensive surveillance would be needed for patients with HR+/HER2- tumors after NAC. Research Sponsor: None.

605 **Poster Session**

Intratumoral (IT) INT230-6 can cause tumor necrosis in vivo: Preliminary results of a phase II randomized presurgical window-of-opportunity study in early breast cancers (the INVINCIBLE study). *First Author: Angel Arnaout, Department of Surgery, The Ottawa Hospital, University of Ottawa & The Ottawa Hospital Research Institute, Ottawa, ON, Canada*

Background: The INVINCIBLE study is a randomized, Phase 2 presurgical Window-Of-Opportunity trial for IT INT230-6 (comprising VINblastine (VIN) Cisplatin (VIN)) evaluating clinical and BioLogical Effects in patients with early-stage operable Breast Cancer. INT230-6 also contains a dispersion enhancer molecule designed to facilitate diffusion of the cytotoxic agents into cancer cells and cause tumor necrosis. We have previously demonstrated that INT230-6 halts cancer cell replication and induces apoptosis while maturing dendritic cells and recruiting T-cells to the tumor microenvironment. In this trial, IT injections of INT230-6 are conducted to 1) exploit the potential of regional cytotoxic chemotherapy on breast cancer *in vivo* and 2) assess the potential for an immune response in the tumor microenvironment and host prior to surgical resection. **Methods:** Up to 90 women with newly diagnosed operable early-stage intermediate or high-grade T1-T2 invasive breast cancers are randomly allocated (2:1) prior to resection to IT injections of INT230-6, no treatment or saline sham. This study has two parts. Part I (N=29) was a randomized trial comparing 1-3 doses of INT230-6 injected weekly vs no treatment prior to surgery to evaluate safety, feasibility, and optimal drug dosing. Part II is a double-blinded randomized trial of up to 60 patients where patients will receive one IT dose of INT230-6 vs saline injection (2:1). The primary endpoint is to estimate the proportion of patients who achieve a complete cell cycle arrest post-surgery compared to the diagnosis biopsy. Secondary endpoints include an evaluation of the rate of pathological complete response, the percent of residual cancer, and safety. The study will also profile changes in CD4/CD8 and the T-cell repertoire. **Results:** Part I demonstrated feasibility, safety and tolerability of presurgical IT injections in breast cancer patients. Twenty patients with tumors ranging from 1-4.4cm were injected with at least one dose up to 48 hours prior to surgery. No surgeries were delayed or altered and the most common (>10%) AEs were injection site pain (100%), infusion site extravasation, injection site reaction and vomiting (10% each). Preliminary data show histologic evidence of up to 95% tumor necrosis in varying biologic subtypes and an increase in intratumoral TILs in injected tumors compared to controls. Part II is ongoing. **Conclusions:** Preliminary evidence shows that a single dose of INT230-6 can cause intratumoral necrosis and stimulate an immune response in breast cancers prior to surgery with minimal adverse effects and good tolerability. The results of Part II of the study will further evaluate the potential cytotoxic, immunomodulatory and other biologic effects of INT230-6 and its role as a potential cancer therapy in breast cancer patients awaiting surgery. Clinical trial information: NCT04781725. Research Sponsor: Intensity Therapeutics, Inc.

606 **Poster Session**

Does race influence long-term outcomes after neoadjuvant chemotherapy in breast cancer: A National Cancer Database analysis. *First Author: Arya Mariam Roy, Roswell Park Cancer Institute, Buffalo, NY*

Background: Pathologic complete response (pCR) after neoadjuvant chemotherapy (NACT) is a surrogate predictor for long-term survival in breast cancer (BC). Patients who attain pCR have improved relapse-free and overall survival (OS) when compared to patients with residual disease (RD). We examined the pCR in Black and White BC patients who received NACT and their OS after attaining pCR and RD. **Methods:** The National Cancer Database (NCDB) was queried for Black and White females with non-metastatic BC from the years 2010 – 2016 who received NACT. Logistic regression was used to analyze pCR/RD and Cox proportional hazards regression to analyze OS, with adjustment for age, race, stage, grade, body mass index, treatments received, insurance status and comorbidities. STATA/IC 16.0 was used for analysis and a two-sided p-value < 0.05 was considered significant. **Results:** A total of 101,014 White and Black BC patients were identified, including 24,852 (Whites - 74.43%, Black - 25.57%) triple negative breast cancer (TNBC), 51,043 (Whites - 84%, Blacks - 16%) hormone receptor positive HER2 negative (HR+HER2-) and 17,818 (Whites - 83%, Blacks - 17%) HER2 positive. Whites had a slightly higher odds of attaining pCR compared to Blacks (adjusted Odds Ratio (aOR) = 1.040, 95% Confidence Interval (CI) = 1.02 - 1.19, $p = 0.02$). The difference was largest in TNBC subtype (TNBC: aOR = 1.34, 95% CI = 1.20 - 1.56, $p < 0.001$; HR+HER2-: aOR = 1.1; 95% CI = 1.02 - 1.32, $p = 0.038$; HER2+: aOR = 1.13, 95% CI = 1.08 - 1.27, $p < 0.001$). Among those who attained pCR, Blacks had worse OS when compared to Whites in HER2+ subtype (adjusted Hazard Ratio (aHR) = 1.41, 95% CI = 1.04 - 1.93, $p = 0.028$) but not in TNBC or HR+HER2- subtypes. Among those with RD, Blacks had worse OS in the whole cohort compared to Whites (aHR = 1.43, 95% CI = 1.26 - 1.58, $p < 0.001$), and in all subtypes: TNBC (aHR = 1.17, 95% CI = 1.11 - 1.23, $p < 0.001$), HR+HER2- (aHR = 1.38, 95% CI = 1.31 - 1.45, $p < 0.001$) and HER2+ (aHR = 1.45, 95% CI = 1.32 - 1.59, $p < 0.001$). **Conclusions:** Black BC patients with TNBC were less likely to achieve pCR than Whites after NACT. When Black patients with HER2+ subtype did attain pCR, they still had worse OS than Whites. The same racial difference in OS was observed in all BC subtypes - TNBC, HR+HER2- and HER2+ among patients with RD. This highlights the importance to investigate novel personalized treatment strategies for Black patients. Research Sponsor: None.

TPS607 **Poster Session**

Adjuvant study of amcenestrant (SAR439859) versus tamoxifen for patients with hormone receptor-positive (HR+) early breast cancer (EBC), who have discontinued adjuvant aromatase inhibitor therapy due to treatment-related toxicity (AMEERA-6). *First Author: Thomas Meyskens, European Organisation for Research and Treatment of Cancer (EORTC), Brussels, Belgium*

Background: There are currently limited treatment options for patients with HR+ EBC who have discontinued adjuvant treatment with aromatase inhibitors (AIs) due to treatment-related toxicity. Amcenestrant is an optimized oral selective estrogen receptor degrader (SERD) with potent dual activity which antagonizes and degrades the ER resulting in inhibition of the ER signalling pathway. Preliminary clinical evidence from the phase 1/2 AMEERA-1 trial has demonstrated meaningful antitumour activity and a favourable safety profile of amcenestrant in the treatment of HR+ advanced breast cancer (Linden HM, Campone M, Bardia A, et al: Abstract PD8-08: A phase 1/2 study of SAR439859, an oral selective estrogen receptor (ER) degrader (SERD), as monotherapy and in combination with other anti-cancer therapies in postmenopausal women with ER-positive (ER+)/human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer (mBC): AMEERA-1. SABCS 2020 PD8-08). **Methods:** AMEERA-6 is a prospective, randomized, international, double-blind, double-dummy, phase 3 study. 3738 patients will be randomized 1:1 to receive either amcenestrant 200 mg daily or tamoxifen 20 mg daily. Eligible patients are pre-or postmenopausal women or men with HR+ EBC (stage IIB-III) who have received at least 6 months of adjuvant AIs (at least 3 months in the adjuvant setting if they have received prior neoadjuvant AI therapy) and discontinued them within 30 months of initiation due to treatment-related toxicity. Participants will be centrally assessed to have ER+ and/or PgR+ (≥10% positive stained cells) status by immunohistochemistry assay. Prior use of adjuvant CDK4/6 inhibitors are allowed. Patients are eligible irrespective of HER2 status; for patients with HER2-positive disease adjuvant anti-HER2 treatment and chemotherapy must be completed prior to randomization. Stratification factors include: duration of AI therapy, HER2 status, prior chemotherapy, prior CDK4/6 inhibitors, geographic region, and menopausal status. Planned treatment duration is 5 years. Patients will be followed-up for 10 years from randomization. The primary endpoint is invasive breast cancer-free survival (IBCFS). Invasive disease-free survival is a key secondary endpoint, while other secondary endpoints include distant relapse-free survival (RFS), locoregional RFS, overall survival, breast-cancer specific survival, safety, patient reported outcomes and pharmacokinetics. Adherence to treatment is an exploratory endpoint. AMEERA-6 opened for recruitment in January 2022. Clinical trial information: NCT05128773. Research Sponsor: Sanofi.

TPS608 **Poster Session**

A phase 3, single arm, open-label study evaluating ovarian suppression following 3-month leuprolide acetate for injectable suspension in combination with endocrine therapy in premenopausal subjects with HR+, HER2-negative breast cancer (OVELIA). *First Author: Ryan Tooker, Tolmar, Inc, Fort Collins, CO*

Background: In US clinical practice, GnRH agonists are widely used to suppress ovarian function in pre/perimenopausal patients with breast cancer that is moderate-to high-risk for recurrence. Despite extensive use of leuprolide acetate (LA) for ovarian suppression, regulatory approval for this indication has not been established in the US. Additionally, existing three month formulations may not reliably provide ovarian suppression, as demonstrated by escapes in estradiol (E2). An extended-release LA product with a 3-month dosing period specifically developed for ovarian suppression in patients with breast cancer could fill this unmet need. TOL2506 is a 3-month, extended-release formulation of 30 mg of LA. This combination of active drug and in situ polymeric extended release technology is expected to deliver higher exposure to drug than the currently available 3-month (22.5 mg) formulations of LA marketed for advanced prostate cancer and potentially reduce escapes in E2 over the dosing period. **Methods:** TOL2506A (OVELIA) is a phase 3, single arm, open-label study evaluating the effectiveness of TOL2506 to suppress ovarian function in premenopausal women with HR+, HER2-negative breast cancer. Approximately 250 subjects will be enrolled, with 30% aged 40 years or younger. Subjects must be premenopausal women, age 18-49, with a diagnosis of Stage I, II, or III HR+, HER2-negative breast cancer (ER > 1% and/or, PR > 1%, HER2-negative per ASCO CAP guidelines), who are candidates for ovarian suppression with endocrine therapy. For subjects receiving chemotherapy, premenopausal status will be determined, and confirmed by central lab hormone testing, prior to initiating chemotherapy. Male subjects with HR+, HER2-negative breast cancer may also be eligible, but will be evaluated for safety analyses only. Eligible subjects will enter the 48 week treatment period in 2 groups: those receiving tamoxifen concurrently with TOL2506 or those who initiate therapy with an aromatase inhibitor (AI; letrozole, anastrozole, or exemestane) beginning 6 weeks after the first administration of TOL2506, if E2 < 20 pg/mL has been achieved. After Week 12, subjects will be allowed to switch from receiving an AI to receiving tamoxifen or from tamoxifen to AI at the Investigator's discretion. Subjects will receive 4 doses of TOL2506 every 12 weeks over the 48 week study duration. Achievement of ovarian suppression will be defined as ≥ 90% of subjects with luteinizing hormone (LH) levels < 4 IU/L at Week 6. Secondary endpoints include suppression of LH, E2 (< 20 pg/mL for tamoxifen cohort and < 2.72 pg/mL for AI cohort) and absence of menses at weeks 6, 12, 24, 36, and 48. Clinical trial information: NCT04906395. Research Sponsor: Tolmar, Inc.

TPS609 **Poster Session**

Adjuvant dynamic marker-adjusted personalized therapy comparing endocrine therapy plus ribociclib versus chemotherapy in intermediate-risk HR+/HER2- early breast cancer: ADAPTcycle. *First Author: Nadia Harbeck, Breast Center, Dept. Obstetrics & Gynecology, University of Munich (LMU) and CCCLMU and West German Study Group, Munich, Germany*

Background: The WSG ADAPT trial program focusses on individualization of (neo)-adjuvant decision-making in EBC in a subtype-specific manner. Clinical feasibility of the WSG ADAPT trial goals - early response assessment and subtype-specific therapy tailoring to those patients (pts) who are most likely to benefit - has recently been confirmed by the 5-years survival data of the ADAPT HR+/HER2- clinical trial. **Methods:** WSG-ADAPTcycle is a prospective, multi-center, interventional, two-arm, (neo)adjuvant, non-blinded, randomized, controlled phase III trial (NCT04055493) investigating whether treatment with the CDK4/6 inhibitor ribociclib (600mg/day) together with ET is superior to standard-chemotherapy (CT) in intermediate-risk HR+/HER2- EBC. Definition of intermediate-risk is either based on Oncotype DX and endocrine responder status (measured by Ki67-response after 2-4 weeks of induction endocrine therapy (ET)) or on low-intermediate baseline Ki67 and high estrogen receptor (ER)/progesterone receptor (PR)-expression (Dowsett et al. NPJ Breast Cancer 2020). Co-primary endpoints are DFS and dDFS. It is planned to screen 5600 pts and to randomize 1670 pts (1002 to ribociclib + ET; 668 to standard CT followed by ET). Study start was in July 2019 (88 sites, enrollment period 42 months) and until date of submission, 3079 pts have been screened and 811 randomized (490 ribociclib / 321 CT). Pre-/postmenopausal pts with histologically confirmed invasive HR+/HER2- EBC with high clinical risk (cT2-4 or Ki-67 20% or G3 or cN+) are eligible if they fulfil the ADAPT intermediate-risk criteria: Recurrence Score (RS) ≤25 plus several risk factors and poor ET responder, RS >25 and ET-responder in p/cN0-1 pts, or RS ≤25 with c/pN2-3 in ET-responder. Direct randomization of premenopausal patients (irrespective of ET-response) with c/pN0 and RS 16-25 or c/pN1 with RS 0-25 is allowed according to investigator's decision; however, based on the ADAPT results, ET+ovarian function suppression alone is strongly recommended in ET-responders. Treatment duration is 2 years for the ribociclib + aromatase inhibitor (AI) (premenopausal: AI + GnRH)-arm and 16-24 weeks for the CT-arm; neoadjuvant or adjuvant treatment is allowed. The minimum 5-year follow-up phase includes standard adjuvant ET. ePROs are collected using CANKADO; ECG monitoring is performed using a novel eHealth method. Translational analyses: Tumor tissue will be collected prior to ET, after at least 3 weeks of ET, if residual tumor is diagnosed (neoadjuvant treatment), and at recurrence, to identify potential resistance markers. Exploratory tissue biomarker research will be conducted to assess alterations in molecular markers. In addition, ctDNA/ctRNA from optional blood samples will be assessed for mutations and gene expression relevant for HR+/HER2- EBC. Clinical trial information: NCT04055493. Research Sponsor: Novartis, Exact Sciences.

TPS610 **Poster Session**

Phase II trial to evaluate immune-related biomarkers for pathological response in stage II-III HER2-positive breast cancer receiving neoadjuvant chemotherapy with subsequent randomization to multi-epitope HER2 vaccine versus placebo in patients with residual disease post-neoadjuvant chemotherapy. *First Author: Saranya Chumsri, Mayo Clinic, Jacksonville, FL*

Background: Several studies demonstrated worsening disease-free survival in patients who failed to achieve complete pathological response after neoadjuvant chemotherapy (NAC), particularly in HER2-positive (HER2+) breast cancer. Despite the recent approval of trastuzumab emtansine (T-DM1) in patients with residual disease after NAC approximately 12% of patients still develop recurrent and metastatic disease. TPIV100 is a multi-epitope vaccine that includes a pool of 4 degenerate HER2-derived HLA-DR epitopes, which activate CD4 helper T cells, admixed with GM-CSF. In our previous phase I trial this vaccine was shown to be safe in combination with trastuzumab in stage II-III HER2+ breast cancer after completion of standard of care chemotherapy. Furthermore, this vaccine also generated robust long-lasting T-cell immune responses and antibody immunity against HER2. **Methods**: This trial is a multi-center, randomized, placebo-controlled, phase II trial of TPIV100 in combination with T-DM1 in stage II-III HER2+ breast cancer patients with residual disease after NAC. This trial is currently opened through the ACCRU consortium. Eligible patients include those with stage II-III HER2+ with residual disease, in the breast and/or lymph nodes, after trastuzumab ± pertuzumab-based NAC, with ECOG PS ≤ 2 and adequate organ function. Patients with baseline left ventricular ejection fraction < 50%, history of trastuzumab-related cardiac toxicity, myocardial infarction or stroke < 6 months, history of congestive heart failure, autoimmune disease, immunocompromised patients with known HIV or those on chronic steroid, hypersensitivity to GM-CSF, and other active malignancy < 3 years are excluded. TPIV100 or placebo, in combination with GM-CSF, will be given concurrently with T-DM1. To ensure that TPIV100 in combination with T-DM1 is safe, there is a run-in phase with 20 patients treated with the combination. If there is no significant dose-limiting toxicity observed in the run-in phase, the trial will be expanded to the randomized phase II portion, which will include 240 patients. Eligible patients will be randomized in a 2:1 fashion with ER/PR as a stratification factor. The primary endpoint is invasive disease-free survival, and the secondary endpoint includes immunogenicity of TPIV100 as assessed by IFN-g ELIspot analysis. Correlative studies include assessment of helper T-cell response distribution (including Th1, Th2, Th17, Tfh), HER2-specific antibody immunity, and HLA genotype. Currently, 20 patients in the run-in phase have been enrolled. Enrollment to the randomized phase II portion is expected to begin in March 2022. Clinical trial information: NCT04197687. Research Sponsor: Department of Defense.

TPS611 **Poster Session**

A phase 3, randomized, open-label study of the anti-Globo H vaccine adagloxad simolenin/obi-821 in the adjuvant treatment of high-risk, early-stage, Globo H-positive triple-negative breast cancer. *First Author: Hope S. Rugo, Department of Medicine, University of California San Francisco, Helen Diller Family Comprehensive Cancer Center, San Francisco, CA*

Background: Adagloxad simolenin (A-S) is an anti-Globo H immunogen comprised of the carbohydrate tumor antigen Globo H, covalently linked to keyhole limpet hemocyanin, a carrier protein that deploys T cells to enhance the humoral response. Administration of A-S in combination with the immune adjuvant OBI-821 serves as an anti-tumor associated carbohydrate antigen vaccine intended to generate anti-Globo H humoral responses in patients with Globo H-expressing tumors. **Methods:** Study OBI-822-011, a phase 3 study, was initiated in 2018. Following feedback from investigators and advisors the study design was changed from a double-blind, placebo-controlled study to an open-label, standard of care (SOC) study. The revised protocol includes patients who have recovered from surgery and completed all planned neoadjuvant and/or adjuvant multiagent chemotherapy and/or radiation therapy. SOC in the A-S/OBI-821 arm is concomitant therapy of capecitabine or immune checkpoint inhibitor. In the SOC arm patients will receive SOC therapy consisting of observation alone, or adjuvant capecitabine alone, or immune checkpoint inhibitor alone. The key protocol changes included a change from open-label to standard of care, providing unblinding and reconsent guidelines for patients enrolled into the study prior to the protocol amendment, allowing concurrent adjuvant single agent chemotherapy, revising the stratification algorithm from a non-hierarchical to a hierarchical structure and aligning the stratification factors with prognostic factors more representative of the study population, revising the eligibility criteria, number and frequency of assessments to reduce patient burden, revising the interim analysis timepoints for futility, and removed an interim analysis for superiority. Study Objectives: Primary Objective: To determine the effect of A-S/OBI-821 treatment on improving IDFS in the study population. Secondary Objectives: To determine the impact of A-S/OBI-821 treatment on Overall survival (OS), Quality of life (QoL), Breast cancer-free interval (BCFI), Distant disease-free survival (DDFS) in the study population; To determine the safety and tolerability of A-S/OBI-821 in the study population. Key Exploratory Objectives: Beyond the safety, efficacy, and QoL endpoints of this trial, exploratory endpoints will evaluate the relationship between aberrant Globo H expression and baseline characteristics, including tumor pathology and immune factors. Conclusion: An estimated 668 subjects will be enrolled, treated for up to 2 years, and followed until occurrence of 187 events (invasive disease recurrence or death) or 3 years from last subject randomized. Survival follow-up is for 5 years from randomization of last subject. Clinical trial information: NCT03562637. Research Sponsor: OBI Pharma Inc.

TPS612 **Poster Session**

FLEX, the 30,000 breast cancer transcriptome project: A platform for early breast cancer research using full-genome arrays paired with clinical data. *First Author: Cynthia X. Ma, Washington University School of Medicine, St. Louis, MO*

Background: The ongoing, multi-center FLEX trial (NCT03053193) began in the United States in 2017, with the ultimate goal of 30,000 patients enrolled. The primary objective is to create a large-scale collaborative registry of early-stage breast cancer patients that links comprehensive clinical and full genome expression data to reveal new prognostic and/or predictive gene signatures. A key secondary objective of the trial is to enable investigator-initiated studies to explore early-stage breast cancer at a relatively low cost to the investigator. **Methods:** The prospective FLEX trial enrolls patients aged ≥ 18 years with histologically proven stage I-III breast cancer, with negative or 1-3 positive lymph nodes. Eligible patients have received MammaPrint, with or without BluePrint testing as standard of care, and consent to clinically annotated full transcriptome data collection. The FLEX base study protocol permits investigators to submit their own concept proposal, and upon review and approval by the Research and Scientific Review Committees, investigators interrogate clinical and genomic data from the FLEX database. The 10-year enrollment goal is a minimum of 30,000 patients. Since April 2017, 9,170 patients have been enrolled at over 109 sites in the United States. To date, 38 investigator-initiated substudies have been approved and are in progress, and 28 abstracts have been published in the US scientific congresses. To ensure inclusion of diverse populations, patients from local communities and 11 National Cancer Institute-designated Comprehensive Cancer Centers were included. Our diverse data set is helping meet the needs of historically under-represented patients with breast cancer. Of the self-reported ethnicities within the FLEX database, 65% are White or Caucasian, 8% Black or African American, 4% Latin American, and 2% Asian. There are 5 ongoing FLEX sub studies investigating racial disparities. The molecular profiling and differential gene expression analysis in early-stage breast cancer patients of African American, Asian, Hispanic ancestries helps to provide critical insights that correlate tumor biology with treatment outcomes. FLEX is expanding globally with sites anticipated in multiple European countries. The FLEX trial continues to expedite the discovery and development of novel genomic profiles, bringing precision oncology into the clinic to improve breast cancer management. Clinical trial information: NCT03053193. Research Sponsor: Agendia.

TPS613 **Poster Session**

NRG-BR007: A phase III trial evaluating de-escalation of breast radiation (DEBRA) following breast-conserving surgery (BCS) of stage 1, hormone receptor+, HER2-, RS ≤18 breast cancer. *First Author: Julia R. White, The Ohio State University Comprehensive Cancer Center, Columbus, OH*

Background: Approximately 50% of newly diagnosed breast cancers are stage 1, with the majority being ER/PR-positive, HER2-negative. Genomic assays such as the Oncotype DX® have identified patients (pts) with reduced risk of distant metastasis and without benefit from chemotherapy added to endocrine therapy, freeing them from excess toxicity. Genomic assays are also recognized as prognostic for in-breast recurrence (IBR) after BCS and could similarly allow de-escalation of adjuvant radiotherapy (RT). Reducing overtreatment is of interest to pts, providers, and payers. **Methods:** We hypothesize that BCS alone is non-inferior to BCS plus RT for in-breast recurrence and breast preservation in women intending endocrine therapy (ET) for stage 1 breast cancer (ER &/or PR positive, HER2-negative with an Oncotype DX Recurrence Score [RS] of ≤18). Stratification is by age (<60; ≥60), tumor size (≤1 cm; >1-2cm), & (RS <11, RS 11-18). Pts are randomized post-BCS to Arm 1 with breast RT using standard methods (hypo- or conventional-fractionated whole breast RT with/without boost, APBI) with ≥5 yrs of ET (tamoxifen or AI) or Arm 2 with ≥5 yrs of ET (tamoxifen or AI) alone. The specific regimen of ET in both arms is at the treating physician's discretion. Eligible pts are stage 1: pT1 (2 cm), pN0, age ≥50 to <70 yrs, s/p BCS with negative margins (no ink on tumor), s/p axillary nodal staging (SNB or ALND), ER &/or PR positive (ASCO/CAP), HER2-negative (ASCO/CAP), and Oncotype DX RS of ≤18 (diagnostic core biopsy or resected specimen). Primary endpoint is in-breast recurrence. Secondary endpoints are breast conservation rate, invasive in-breast recurrence, relapse-free interval, distant disease-free survival, overall survival, patient-reported breast pain, patient-reported worry about recurrence, and adherence to ET. We assume a clinically acceptable difference in of 4% at 10 yrs to judge omission of RT as non-inferior (10-yr event-free survival for RT group is 95.6% *vs* 91.6% for the omission of RT group). The study is powered to detect a non-inferiority with 80% power and a one-sided α=0.025, assuming that there would be a ramp-up in accrual in the first two years (leveling off in Yrs 3-5); 1,670 (835 per arm) pts are required to be randomized. Conservative loss to follow-up is 1% per yr. Some of the T1a pts screened may have Oncotype DX scores >18, making them ineligible for the study. In the accrual process, pts will be required to register (1,714 pts) to ensure that our final randomized cohort is 1,670 pts. Current accrual (2-2-2022) is 52 screened and 45 randomized. Support: U10CA180868, -180822, NCT04852887. Clinical trial information: NCT04852887. Research Sponsor: U.S. National Institutes of Health.

TPS614 **Poster Session**

SMALL: Open surgery versus minimally invasive vacuum-assisted excision for small screen-detected breast cancers. *First Author: Stuart McIntosh, Queens University Belfast, Belfast, United Kingdom*

Background: Mammographic screening programmes reduce breast cancer mortality but detect many small tumours with favourable biology which may not progress. These are treated with surgery and adjuvant therapies, but associated morbidities mean there is a need to reduce overtreatment. Minimally invasive treatments such as vacuum-assisted excision (VAE) have been described but there is no prospective randomised evidence to support their routine use. SMALL (ISRCTN 12240119) is designed to establish the feasibility of using VAE to treat small tumours detected within the UK NHS Breast Screening Programme (BSP). **Methods:** Phase III multicenter randomized trial comparing surgery with VAE for screen-detected good prognosis cancers. Eligibility criteria are age ≥47 years, unifocal grade 1 tumors (maximum diameter 15mm), strongly ER/PR+ve and HER2-ve, with negative axillary staging. Patients are randomized 2:1 to VAE or surgery, with no axillary surgery in the VAE arm. Excision is assessed radiologically, and if incomplete, patients undergo surgery. Adjuvant radiotherapy and endocrine therapy are mandated in the VAE arm. Coprimary end-points are: (1) Non-inferiority comparison of the requirement for a second procedure. (2) Single-arm analysis of local recurrence (LR) at 5 years after VAE. Recruitment of 800 patients will permit demonstration of 10% non-inferiority of VAE for requirement of a second procedure, ensuring sufficient patients for single arm analysis of LR rates, where expected LR free survival is 99% at 5 years, with an undesirable survival probability after VAE of 97%. The DMC will monitor LR events to ensure these do not exceed 3% per year. Secondary outcome measures include time to ipsilateral recurrence, overall survival, complications, quality of life and health economic analysis. A QuinteT Recruitment Intervention (QRI) is integrated throughout SMALL to optimize recruitment and informed consent. Recruitment challenges are identified by analyzing recruiter/patient interviews, audio-recordings of trial discussions, and by review of screening, eligibility and recruitment data and study documentation. Solutions are developed collaboratively, including recruiter feedback and recruitment tips documents. Results: SMALL opened in December 2019, but recruitment halted for 5 months due to COVID-19. At 11th February 2022, 91 patients had been recruited from 22 centers, with an approached/consented ration of 50%. Drawing from preliminary QRI findings, a recruitment tips document has been circulated (on discussing SMALL, providing balanced information on treatment options and explaining randomization). Individual recruiter feedback has commenced, with wider feedback planned shortly. Conclusion: Despite pandemic-related challenges, SMALL has excellent recruitment to date and is expected to have a global impact on treatment of screen-detected breast cancer. Clinical trial information: 12240119. Research Sponsor: UK National INstitute for Health Research Health Technology Assessment Programme.

TPS615 **Poster Session**

ATNEC: A multicenter, randomized trial investigating whether axillary treatment can be avoided in patients with T1-3N1M0 breast cancer with no residual cancer in the lymph glands after neoadjuvant chemotherapy. *First Author: Amit Goyal, Royal Derby Hospital, Derby, United Kingdom*

Background: Neoadjuvant chemotherapy (NACT) results in eradication of cancer in the axillary nodes in 40-70% of patients. This raises questions about the benefit of further axillary treatment in patients with no evidence of residual nodal disease (ypN0) post NACT. **Methods:** Design: ATNEC is a phase 3, randomized (1:1), multi-center UK trial, with embedded economic evaluation. Patients with proven axillary node metastases on needle biopsy receive NACT followed by sentinel node biopsy (SNB). If the sentinel nodes have converted to benign (ypN0), ATNEC randomly assigns patients to axillary treatment (nodal radiotherapy [ART] or axillary nodal clearance [ALND]) vs no further axillary treatment. Stratification: Institution, type of surgery (breast conserving surgery vs mastectomy), receptor status (triple negative vs HER2 positive vs ER positive and/or PR positive and HER2 negative).Inclusion criteria: Age ≥ 18; Male or female; T1-3N1M0 breast cancer at diagnosis (pre-NACT); FNA or core biopsy confirmed axillary nodal metastases at presentation; ER and HER2 status evaluated on primary tumor; Received standard NACT as per local guidelines; Imaging of the axilla to assess response to NACT;Dual tracer SNB post-NACT and at least 3 nodes removed (sentinel nodes and marked node): If a single tracer is used, the patient is eligible if the involved node is marked pre-NACT and at least 3 nodes removed (including the marked node), If axillary node sampling is performed following failed localization of sentinel nodes, patient is eligible if at least 3 nodes removed (including the marked node), If node is not marked, or marked node is not removed, patient is eligible if the histology report shows evidence of down-staging with complete pathological response in at least one node and at least 3 nodes removed; No evidence of nodal metastases post NACT (ypN0). Exclusion criteria: Bilateral invasive breast cancer; SNB prior to NACT; Previous ipsilateral axillary nodal surgery; Previous cancer within last 5 years or concomitant malignancy. Aims: To assess whether omitting further axillary treatment (ALND & ART) for patients with early-stage breast cancer and axillary nodal metastases on needle biopsy - who after NACT have no residual nodal disease on SNB (ypN0) - is non-inferior to axillary treatment in terms of disease-free survival, and reduces lymphoedema at 5 years. Statistical methods: All analyses will be carried out on an intention-to-treat basis to preserve randomization, avoid bias from exclusions and preserve statistical power. Radiotherapy Quality Assurance: Study has in-built radiotherapy QA program that will be coordinated by National Radiotherapy Trials QA (RTTQA) group. Target accrual: 1,900 Status: Recruiting. As of 11-Feb-2022, 39 sites open, 87 patients enrolled, 31 randomized. Clinical trial information: NCT04109079. Research Sponsor: UK National Institute for Health Research - Health Technology Assessment Programme (NIHR128311).

TPS616 **Poster Session**

Comparing an operation to monitoring, with or without endocrine therapy (COMET), for low-risk ductal carcinoma in situ (DCIS). *First Author: Thomas Lynch, Duke University, Durham, NC*

Background: Approximately 50,000 women in the U.S. are diagnosed with ductal carcinoma *in situ* (DCIS) each year. Without treatment, it is estimated that only 20-30% of DCIS will lead to invasive breast cancer (IBC). However, over 97% of women are currently treated with surgery +/- radiation. An alternative to surgery is active monitoring (AM), a management approach in which mammograms/physical exams are used to monitor breast changes and determine when, or *if*, surgery is needed. The COMET Study will compare risks and benefits of AM versus surgery for low-risk DCIS in the setting of a Phase III multicenter prospective randomized trial. The study is funded by the Patient-Centered Outcomes Research Institute. The COMET trial opened in the U.S. in June 2017 (Clinicaltrials.gov reference: NCT02926911). In November 2021, the Data Safety Monitoring Board reviewed the trial and suggested that it continue as planned. Patient accrual will continue until 12/31/2022. **Methods:** The primary objective is to assess whether the 2-year ipsilateral IBC rate for AM is non-inferior to that for surgery. Secondary objectives include determining whether AM is non-inferior to surgery for 2-year mastectomy rate; breast conservation rate; contralateral breast cancer rate; overall and breast cancer-specific survival. Patient reported outcomes will enable comparison of health-related quality of life and psychosocial outcomes between surgery and AM groups at baseline, 6-months, and years 1-5. Eligibility criteria include: age > 40 at diagnosis; pathologic confirmation of grade I/II DCIS or atypia verging on DCIS without invasion by two pathologists; ER and/or PR ≥ 10%; no mass on physical exam or imaging. The accrual goal is 1200 randomized patients across 100 Alliance for Clinical Trials in Oncology sites. Sample size is estimated using a 2-group test of non-inferiority of proportions, with the 2-year IBC rate in the surgery group assumed to be 0.10 based on published studies and non-inferiority margin of 0.05. Based on a 1-sided un-pooled z-test, with alpha = 0.05, a sample size of n = 446 per group will have 80% power to detect the specified non-inferiority margin. Final analysis plan will include a per protocol component as well as a pragmatic component for patients who are randomized and decline participation in their assigned arm. Primary analyses will adjust for dropout, non-compliance and contamination by utilizing instrumental variable methods. Clinical trial information: NCT02926911. Research Sponsor: Patient-Centered Outcomes Research Institute (PCORI).

TPS617 **Poster Session**

A single-arm, phase 2 study of perioperative ipilimumab, nivolumab, and cryoablation in women with hormone receptor-negative, HER2-negative, early-stage/resectable breast cancer. *First Author: Heather L. McArthur, University of Texas Southwestern Medical Center, Dallas, TX*

Background: Local tumor destruction with cryoablation (cryo) induces inflammation and releases antigens that can activate tumor-specific immune responses. Pre-clinically, cryo with checkpoint inhibition augmented tumor-specific immune responses and prevented recurrence. Clinically, we established that peri-operative (peri-op) cryo with ipilimumab (ipi) +/- nivolumab (nivo) was not only safe in patients (pts) with operable, early stage breast cancer (ESBC) but also generated robust intra-tumoral and systemic immune responses. In this phase 2 study, we evaluate the disease specific impact of peri-op ipi/nivo/cryo in women with residual triple negative breast cancer (TNBC) after neoadjuvant chemotherapy (NAC), a subset at high risk of early relapse. **Methods:** Eligible pts are ≥18y, with ER < 10%, PR < 10%, HER2 negative (per ASCO/CAP definition), ≥ 1.0 cm, residual operable disease after taxane-based NAC. Approximately 80 pts will be enrolled and treated with ipi/nivo/cryo followed by breast surgery and adjuvant nivo. Pts undergo percutaneous, image-guided cryo with concurrent research core biopsy 7-10 days prior to surgery and will receive ipi (1mg/kg IV) with nivo (240mg IV) 1 to 5 days prior to cryo. After surgery, pts will receive 3 additional doses of nivo at 240mg IV Q2 weeks. Adjuvant capecitabine is recommended for all patients per local standard-of-care. Patients will be stratified by NAC platinum administration, NAC anthracycline administration, and clinical nodal status (positive versus negative). The primary endpoint is 3-year Event Free Survival (EFS). Secondary endpoints include Invasive Disease-Free Survival (IDFS), Distant Disease-Free Survival (DDFS), overall survival (OS) and safety. Exploratory correlative studies will be performed on tumor and serum to characterize the immunologic impact of the intervention and to explore predictors of efficacy and toxicity. Clinical trial information: NCT03546686. Research Sponsor: BMS, Conquer Cancer Foundation of the American Society of Clinical Oncology, Other Foundation, BTG.

TPS618 **Poster Session**

Anlotinib plus tislelizumab combined with chemotherapy as neoadjuvant treatment in triple-negative breast cancer: A prospective, single-arm, open-label phase II study. *First Author: Jing Luo, Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, Chengdu, China*

Background: Neoadjuvant anti-PD-(L)1 therapy confers an improvement in pathological complete response (pCR) rate in unselected triple-negative breast cancer (TNBC). Combination of antiangiogenic agent plus immune checkpoint inhibitor and chemotherapy therapy for advanced TNBC is reported as a promising anti-tumor strategy presented in the FUTURE-C-PLUS study. Tislelizumab is a humanized immunoglobulin G4 anti-PD-1 monoclonal antibody engineered to minimize binding to $Fc\gamma R$ on macrophages. Anlotinib is a novel multi-target tyrosine kinase inhibitor that effectively inhibit VEGFR, FGFR, c-KIT, c-MET and RET. Previous studies have proven the efficacy of both anlotinib monotherapy and combination with immune checkpoint inhibitor in advanced breast cancer. This phase II study aims to evaluate the efficacy and safety of anlotinib plus tislelizumab combined with chemotherapy as neoadjuvant treatment in TNBC. **Methods:** This is a prospective, single-arm, open-label, phase II trial. Eligible patients (pts) were women, aged 18-75 years, ECOG status 0-1, previously untreated invasive TNBC with histologically confirmed (cT1N1-2M0 or cT2-4N0-2M0). 32 pts will be enrolled and received 5 cycles of anlotinib (8 mg qd, d1-14; 21 days per cycle) with 6 cycles of tislelizumab (200 mg, once every 3 weeks) plus nab-paclitaxel (260 mg/m^2, once every 3 weeks) and anthracycline (epirubicin 75 mg/m^2 or doxorubicin 60 mg/m^2), followed by surgery. The primary endpoint is pathological complete response rate (pCR, ypT0/Tis ypN0) and the secondary endpoints include invasive disease-free survival (iDFS), event-free survival (EFS), overall survival (OS), and safety. A sample size of 32 patients was estimated to provide a 80% power to detect a difference of 25% in pCR at a significance level of $\alpha = 0.05$. The study was initiated in August 2021. Clinical trial information: NCT04914390. Research Sponsor: BeiGene, Ltd. and Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

TPS619 **Poster Session**

PARTNER: A randomized, phase II/III trial to evaluate the safety and efficacy of the addition of olaparib to platinum-based neoadjuvant chemotherapy in patients with triple-negative and/or germline BRCA-mutated breast cancer. *First Author: Lynsey Drewett, Department of Oncology, University of Cambridge and Cambridge Breast Cancer Research Unit, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom*

Background: Triple negative breast cancers (TNBCs) are a biologically diverse and aggressive subgroup lacking targeted therapy. TNBC and germline BRCA (gBRCA) breast cancer share certain phenotypic and molecular similarities, with gBRCA mutations seen in 10% to 20% of TNBC patients. Homologous recombination-deficient tumors, especially those caused by germline or somatic BRCA mutations, are thought to be particularly sensitive to PARP inhibitors. **Methods:** This is a 3-stage open-label randomized phase II/III trial of neoadjuvant paclitaxel and carboplatin +/- olaparib, followed by clinicians' choice of anthracycline regimen. The aim is to establish whether the addition of olaparib to neoadjuvant platinum-based chemotherapy in the treatment of basal TNBC and/or gBRCA breast cancer is safe and increases efficacy. In stages 1 and 2, all patients receive 4 cycles of 3-weekly carboplatin AUC5/weekly paclitaxel 80mg/m^2. They are randomly assigned 1:1:1 to a control arm, or to one of two research arms. These research arms include different treatment schedules of olaparib 150 mg BD for 12 days. In stage 3, patients are randomly assigned 1:1 to either the control or research arm chosen following stage 2. The primary endpoints are: Stage 1: Safety; Stage 2: Schedule selection based on pCR rate and olaparib completion rate using a "pick-the-winner" design. Stage 3: pCR rate. Key eligibility criteria are age 16-70; histologically confirmed invasive breast cancer; ER-negative, HER2-negative with TNBC basal phenotype or gBRCA positive, HER2-negative irrespective of hormone status; stage T1-4 N0-2; performance status 0-1; treatment within 6 weeks of diagnostic biopsy; biomarker scores: TILs, CK 5/6, EGFR +/- AR. The recruitment of TNBC non-gBRCA and gBRCA patients is independent. Enrichment design is applied with an overall significance level 0.05(α) and 80% power. A minimum of 780 patients will be included to detect an absolute improvement of 15% (all patients) and 20% (gBRCA patients) by combining olaparib with platinum-based chemotherapy. This trial includes an optional pathway called PARTNERING for patients with residual disease after six chemotherapy cycles. This aims to establish if adding new agents (ATR inhibitor and PD-L1 inhibitor) improves treatment response. Each cohort will consist of 15 patients. Since May 2016, 756 patients from 30 sites have been enrolled. An IDSMC review following stages 1 and 2 identified no safety concerns and Research Arm 2 was selected (olaparib administration on days 3-14). Stage 3 phase I (recruitment of non-gBRCA and gBRCA patients) completed December 2021. Stage 3 phase II (recruitment of gBRCA patients) remains open to patients in the U.K. and internationally. 5 patients have enrolled in PARTNERING. Follow-up duration is 10 years. Clinical trial information: NCT03150576. Research Sponsor: Sponsored by Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge, Other Foundation, Pharmaceutical/Biotech Company.

TPS620 **Poster Session**

Phase II neoadjuvant pyrotinib combined with epirubicin and cyclophosphamide followed by docetaxel in HER2-low–expressing and HR-positive early or locally advanced breast cancer (PILHLE-001): A single-arm trial. *First Author: Yuan Xia, Breast Tumor Center, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China*

Background: As a latent new subtype, HER2-low-expressing breast cancer has attracted increasing attention. However, HER2-low-expressing/HR-positive early or locally advanced breast cancer (E/LABC) has the lowest pathological complete response (pCR) rate among all types of breast cancer. Pyrotinib, a small-molecule HER1/HER2/HER4 tyrosine kinase inhibitor, combined with chemotherapy regimen showed excellent efficacy and safety in the treatment of patients with HER2-positive early, locally advanced and metastatic breast cancer. In-vitro experiment showed pyrotinib can significantly inhibit colony formation in breast cancer cell lines with different HER2 expression levels including HER2-positive and HER2-low-expressimg [immunohistochemistry (IHC) 2+/in situ hybridization (ISH) negative]. Therefore, the investigator-driven, ongoing PILHLE-001 trial has been conducted to evaluate the potential role of neoadjuvant pyrotinib plus chemotherapy in the treatment of HER2-low-expressing/HR-positive E/LABC, which may provide a novel neoadjuvant therapeutic strategy for these patients. **Methods:** PILHLE-001, as a single-arm, phase II study, is the first trial to evaluate the efficacy and safety of neoadjuvant pyrotinib combine with chemotherapy in HER2-low-expressing (defined as IHC 2+ with ISH negative) and HR-positive (ER or PR > 1% stained cells) E/LABC (cT1c with histologically involved lymph nodes or ≥cT2). Patients who have HER2 IHC 1+, or severe heart diseases or basic gastrointestinal diseases are excluded. The trial has 80% power to detect true difference from previous reported pCR rate of 17.5%, to an expected pCR rate of 35% at two-sided alpha level of 0.05. Considering a drop rate of 10%, a total of 46 patients will be needed. Since May 19, 2021 until now, 19 patients have been enrolled. All eligible patients will receive pyrotinib 320mg orally daily with all chemotherapy cycles (epirubicin 90 mg/m^2 intravenously plus cyclophosphamide 600 mg/m^2 intravenously on day 1 for four 3-week cycles followed by docetaxel 100 mg/m^2 intravenously on day 1 for four 3-week cycle). The primary outcome is the rate of total pCR, defined as no residual invasive tumor cells in the breast and axillary nodes, regardless of ductal carcinoma in situ (ypT0/is ypN0) after neoadjuvant treatment. The secondary outcomes include Miller-Payne grade, residual cancer burden score, overall response rate, breast conservation rate, disease-free survival, overall survival, exploratory biomarkers and drug related safety. Primary efficacy outcomes will be analyzed in the intention-to-treat population and safety outcomes in the safety set population. Long-term efficacy outcomes will be assessed later with enough follow-up. Clinical trial information: NCT05165225. Research Sponsor: None.

TPS621 **Poster Session**

DECRESCENDO: De-escalation of adjuvant chemotherapy in patients with HER2+/HR-/node-negative early breast cancer who achieve pCR after neoadjuvant taxane and subcutaneous dual anti-HER2 blockade. *First Author: Veronique Debien, Institut Jules Bordet, Université Libre de Bruxelles (U.L.B.), Brussels, Belgium*

Background: Human Epidermal growth factor Receptor-2 positive (HER2+) breast cancer (BC) heterogeneity can be captured at the mRNA level by the PAM50 classification. The HER2 "Enriched" (HER2-E) intrinsic subtype is encountered more often in HER2+ Hormone Receptor negative (HR-) tumors compared to HER2+ HR+ tumors and is particularly sensitive to HER2 blockade. HER2+ HR- and HER2-E achieve high pathological complete response (pCR) rates with neoadjuvant chemotherapy (CT) and dual anti-HER2 blockade with trastuzumab and pertuzumab. Additionally, the patients with pCR have improved outcomes. However, standard CT with common drugs such as anthracyclines has significant short and long-term toxicities, including cardiac events and secondary leukemias. Thus, tailoring the neoadjuvant treatment among carefully selected patients in order to reduce toxicity while preserving efficacy is a priority in early HER2-positive BC. **Methods:** DECRESCENDO is a large, multicentric, single-arm, phase 2 de-escalation study evaluating the efficacy of neoadjuvant CT with paclitaxel 80mg/m2 weekly or docetaxel 75mg/m2 every 3 weeks (Q3W) with pertuzumab and trastuzumab (P+T) 600/600mg fixed-dose combination (FDC) for subcutaneous (SC) injection Q3W for patients with early HER2+, HR- (ER<1% and PR<1%) BC. After surgery, the patients with pCR (defined as Residual Cancer Burden (RCB)=0, per local assessment) will receive 14 additional cycles of P+T FDC SC. Patients with RCB≥1 will receive adjuvant T-DM1 (preceded by anthracycline-based CT if RCB≥2). Eligible patients must be candidates for neoadjuvant treatment, with a tumor between 15 and 50mm, N0, ECOG PS 0-1, with LVEF ≥55%. 1,065 patients will be enrolled in 12 countries. A baseline tumor sample is required to retrospectively assess the intrinsic tumor subtype. The primary objective is to evaluate 3-year recurrence-free survival (RFS) in patients with HER2-E tumors who achieve pCR after neoadjuvant treatment. The key secondary objective is to evaluate 3-year RFS in all patients with pCR. If a 3-year RFS ≥94% with the lower boundary of a 1-sided 95% CI ≥92% is observed in the target group, the study treatment will be considered an acceptable alternative to strategies that include the addition of other chemotherapies such as anthracyclines, alkylating agents and platinum salts. A flexible care sub-study will enroll 121 patients with pCR in Belgium, France, Ireland, Israel and Italy to receive adjuvant P+T FDC SC in a location outside the hospital, such as at home or workplace. The aim is to compare patient preference for administration of P+T FDC SC outside the hospital vs in the hospital. The first patient was enrolled in January 2022. The trial is co-led by the Breast International Group (BIG) and Institut Jules Bordet. Clinical trial information: NCT04675827. Research Sponsor: Research grant from Pharmaceutical Compagny (Roche).

TPS622 **Poster Session**

Assessing response to neoadjuvant docetaxel and trastuzumab in Nigerian women with HER2-positive breast cancer (ARETTA). *First Author: Atara Isaiah Ntekim, Department of Radiation Oncology, Oyo, Nigeria*

Background: Breast cancer rates are increasing in Nigeria and across sub-Sahara Africa without the necessary infrastructure to manage the disease. Adequate clinical trial resources are needed to address the growing need for high quality, patient centered cancer care on the Continent. The ARETTA clinical trial was initiated by the Nigerian Breast Cancer Study Team in partnership with the University of Chicago Comprehensive Cancer Center. To build local capacity for biomarker informed clinical trials and translational research. Clinical investigators receive extensive training and local facilities at four University-based Cancer Centers in Southwest Nigeria were upgraded. The study is a pragmatic single-arm, phase II clinical trial to determine the safety and efficacy of neoadjuvant taxotere and trastuzumab in women with HER2-positive breast cancer. The study sought to 1) determine the pathological complete response (pCR) rate of patients with early stage breast cancer to neoadjuvant docetaxel and subcutaneous trastusumab 2) assess the feasibility of conducting oncology clinical trials using upgraded facilities and trained personnel and 3) determine accrual rate of participants. **Methods:** The study is currently open to accrual. Inclusion criteria include treatment naïve women aged 18 years to 70 years with Her-2 positive breast cancer stages II-IIIC (AJCC). Eligible participants receive four cycles of docetaxel 75mg/m^2 and trastuzumab every 3 weeks. Those with incomplete clinical response by breast ultrasound volume measurements receive 3 additional cycles of chemotherapy; cyclophosphamide 600mg/m^2, epirubicin 90mg/m^2 and 5-fluorouracil 600mg/m^2 every 3 weeks before re-evaluation for surgery. All participants receive a fixed dose of sub-cutaneous Herceptin (600mg) every 3 weeks (total of 18 doses). The primary endpoint is pCR rate. Secondary objectives are to evaluate invasive disease-free survival (iDFS), the pattern of response and mechanisms of resistance to treatment based on genomic markers, the pharmacokinetics of Herceptin SC, quality of life, and adverse event rates, including cardiac toxicity. Planned enrollment is 47 evaluable patients, which will provide 90% power to test the null hypothesis that the pCR rate is 20% versus a 40% alternative (one-sided alpha=0.05). More protocol details can be found at ClinicalTRial.gov NCT03879577 and JCO Glob Oncol2020 doi: 10.1200/GO.20.00043. *Progress:* Accrual commenced on 3rd April 2020 and is 75% completed. To date, monitoring, regulatory, as well as Data Safety and Monitoring Board progress evaluation did not identify any logistical or safety issues such as underdeveloped infrastructure, unacceptable rate of non-compliance with study protocol, poor informed consent procedure or serious adverse events to warrant stopping the trial. Clinical trial information: NCT03879577. Research Sponsor: U.S. National Institutes of Health, Other Foundation, Pharmaceutical/Biotech Company.

TPS623 **Poster Session**

TRIO-US B-12 TALENT: Phase II neoadjuvant trial evaluating trastuzumab deruxtecan with or without anastrozole for HER2-low, HR+ early-stage breast cancer. *First Author: Sara A. Hurvitz, Department of Medicine, Division of Hematology/Oncology, David Geffen School of Medicine, University of California-Los Angeles, Jonsson Comprehensive Cancer Center, Los Angeles, CA*

Background: Although patients with hormone receptor-positive (HR+)/HER2-negative breast cancer (BC) frequently experience disease response to neoadjuvant therapy, fewer than 10% achieve a pathologic complete response (pCR) with standard chemotherapy or endocrine therapy, even in combination with CDK4/6 inhibitors. Thus, finding more effective therapies for this disease remains an area of unmet need. HER2 amplification is a known driver of endocrine resistance and HER2 may be expressed at a low level (IHC 1+ or 2+) in approximately 60% of HR+ BC. Trastuzumab deruxtecan (DS-8201a, T-DXd) is a novel HER2-targeting antibody drug conjugate (ADC) that is FDA approved in the US for HER2-positive (with boxed warnings for interstitial lung disease) and has demonstrated promising clinical efficacy in HER2-low BC with an objective response rate of ~37%. The aim of TALENT (TRIO-US B-12, NCT04553770) is to evaluate the clinical activity and safety of neoadjuvant T-DXd alone or in combination with endocrine therapy in patients with HR+/HER2-low early BC. **Methods:** This is an ongoing randomized, multicenter, open-label, two-stage, phase II neoadjuvant trial for participants with early stage, HR+, HER2-low (1+ or 2+/ISH- by IHC) BC. Eligible participants include men and women with previously untreated, operable invasive BC greater than 2.0 cm (cT2). Pts with recurrent, metastatic, or inflammatory BC are excluded. Pts are randomized 1:1 to receive six to eight cycles of T-DXd (5.4 mg/kg IV q21 days) alone or in combination with anastrozole AI (1 mg PO QD). Men and pre/peri menopausal women randomized to the AI arm also receive routine care GnRH agonist. Stratification factors include HER2 expression and menopausal status (men stratified as postmenopausal). Tumor tissue is taken at baseline, cycle 1 day 17-21, and at surgery. Blood samples are taken at 4 time points for biomarker analysis. The primary endpoint is pCR rate (breast and lymph node) at definitive surgery. In stage I, 58 participants will be randomized (29/arm). If >2 participants in an arm achieve pCR, that arm will expand (stage II) to enroll an additional 15 participants (total of 44/arm). A pCR rate of > 10% (5/44) would be considered favorable, warranting further evaluation in a larger trial. Other endpoints include safety, changes in Ki67 expression, Residual Cancer Burden index, biomarker analysis (including serial cfDNA analysis), and health-related quality of life. As of January 2022, 37 participants have enrolled, 24 have completed treatment, and 14 have had surgery. To our knowledge this is the first and only ongoing study evaluating T-DXd with or without endocrine therapy for HR+, HER2-low BC in the neoadjuvant setting. The study will shed light on clinical activity and biomarkers, which may guide larger confirmatory studies for this population. Clinical trial information: NCT04553770. Research Sponsor: Daiichi Sankyo.

TPS624 **Poster Session**

Neoadjuvant HER2-targeted therapy +/- immunotherapy with pembrolizumab (neoHIP): An open-label randomized phase II trial. *First Author: Heather L. McArthur, University of Texas Southwestern Medical Center, Dallas, TX*

Background: Immune checkpoint inhibition (ICI) is synergistic with HER2-directed therapy in pre-clinical models. Clinically, pembrolizumab (K)-mediated ICI plus HER2-directed therapy with trastuzumab (H) was safe and demonstrated modest activity in H-resistant HER2-positive (HER2+) metastatic breast cancer. Because ICI may confer more robust activity when administered earlier in the course of disease, H and K administered in the curative-intent, treatment-naive setting may allow for de-escalation of cytotoxics; confer life-long, tumor-specific immunity; and ultimately, improve cure rates. Moreover, the synergy of H and K with paclitaxel (T) may overcome the need for dual HER2-blockade with H plus pertuzumab (P). In this randomized, multicenter, phase II, open-label trial the efficacy and safety of neoadjuvant THP vs THP-K vs TH-K are explored. **Methods:** 174 patients (pts) ≥18y with previously untreated, stage II-III, HER2+ breast cancer will be randomized and stratified by clinical nodal status (positive vs. negative) and hormone receptor status (positive vs. negative). In arm A, pts receive T at 80mg/m2 weekly for 12 weeks, H at 8mg/Kg (loading dose) and then 6mg/Kg every 3 weeks x 3 doses, P at 840 mg (loading dose) and then 420mg/Kg every 3 weeks x 3 doses (THP). In arm B, pts receive THP plus K at 200mg every 3 weeks x 4 doses (THP-K). In arm C, pts receive TH-K. Definitive surgery is 3-6 weeks after the last dose. After surgery, pts are treated per the treating physician's discretion including radiotherapy per local clinical standard. Pts whose tumors are hormone-receptor positive will receive hormone therapy per local standard-of-care. The primary end point is pathologic complete response (pCR) rate in the breast and axilla (ypT0/Tis ypN0). Secondary end points include pCR rate by ypT0ypN0 and ypT0/Tis, residual cancer burden index, event free survival, breast conserving surgery rate, safety and overall survival. Exploratory correlative studies will characterize potential immune biomarkers predictive of efficacy and/or toxicity. Clinical trial information: NCT03747120. Research Sponsor: Merck, Other Foundation.

1000 **Oral Abstract Session**

Trastuzumab deruxtecan (T-DXd) versus trastuzumab emtansine (T-DM1) in patients (pts) with HER2-positive (HER2+) unresectable and/or metastatic breast cancer (mBC): Safety follow-up of the randomized, phase 3 study DESTINY-Breast03. *First Author: Erika P. Hamilton, Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN*

Background: In the DESTINY-Breast03 (NCT03529110) primary analysis (data cutoff [DCO], May 21, 2021), T-DXd showed superiority over T-DM1 in pts with HER2+ mBC, with a significant improvement of progression-free survival by blinded independent central review (HR, 0.284; 95% CI, 0.217-0.373; $P < 0.001$), and a safety profile consistent with prior studies. This analysis provides updated safety data with longer follow-up. **Methods:** Pts were randomized 1:1 to T-DXd or T-DM1. Prespecified safety analysis of treatment-emergent adverse events (TEAEs) was conducted; endpoints included time to event, duration of event, and resolution. **Results:** At DCO (September 7, 2021), 116 (45.1%) pts vs 39 (14.9%) pts remained on treatment in the T-DXd vs T-DM1 arms; median treatment duration was 16.1 mo (range, 0.7-33.0) for T-DXd vs 6.9 mo (range, 0.7-28.5) for T-DM1. Any-grade (G), G≥3, and serious AE (SAE) rates were similar for T-DXd vs T-DM1 (99.6% vs 95.4%; 53.3% vs 49.8%; and 21.0% vs 19.2%), while exposure-adjusted incidence rates (EAIRs; per pt-year) for G≥3 and SAEs were lower for T-DXd vs T-DM1 (0.42 vs 0.70 and 0.17 vs 0.27). Median time to TEAE associated with drug discontinuation or dose reduction was longer with T-DXd vs T-DM1 (224.0 vs 147.0 d and 96.0 v 19.0 d, respectively). Most TEAEs in ≥20% of pts were hematologic or gastrointestinal. Median time to first onset of select any-G TEAEs was 70.0 vs 42.0 d for anemia, 196.0 vs 168.0 d for lymphopenia, 132.0 vs 8.0 d for thrombocytopenia, 22.0 vs 24.0 d for fatigue, 74.5 vs 92.0 d for leukopenia, and 64.0 vs 105.0 d for neutropenia, with T-DXd vs T-DM1, respectively. In both arms, most nausea and vomiting events were G1/2; while G≥3 events with T-DXd vs T-DM1 were 6.6% vs 0.4% for nausea and 1.6% vs 0.8% for vomiting, respectively. Rates of nausea, vomiting, and alopecia were highest in cycle 1 and lower in subsequent cycles for T-DXd. Rates of hematologic events were generally lower in earlier cycles vs cycle ≥8 in both arms. Rates of adjudicated, drug-related ILD/pneumonitis were 10.9% (1 G2 event since previous DCO) with T-DXd vs 1.9% with T-DM1, with no G4/5 events. Median time to first adjudicated, drug-related ILD/pneumonitis event was 5.9 vs 9.5 mo for T-DXd vs T-DM1, respectively; at DCO, most events resolved (57.1% vs 80.0%), and follow-up is ongoing. **Conclusions:** In this updated safety analysis, T-DXd demonstrated a tolerable safety profile consistent with prior studies. Despite longer treatment duration with T-DXd, EAIRs of G≥3 and SAEs were lower for T-DXd vs T-DM1. Rates of ILD/pneumonitis for T-DXd were similar to those in the previous DCO. Nausea, vomiting, and alopecia rates decreased over time. This longer safety update reinforces the consistent safety profile of T-DXd, supporting the clinical benefit of T-DXd over T-DM1 in patients with HER2+ mBC. Clinical trial information: NCT03529110. Research Sponsor: Daiichi Sankyo Inc. and AstraZeneca.

LBA1001 **Oral Abstract Session**

Primary results from TROPiCS-02: A randomized phase 3 study of sacituzumab govitecan (SG) versus treatment of physician's choice (TPC) in patients (Pts) with hormone receptor–positive/HER2-negative (HR+/HER2-) advanced breast cancer. *First Author: Hope S. Rugo, Department of Medicine, University of California San Francisco, Helen Diller Family Comprehensive Cancer Center, San Francisco, CA*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

1002 **Oral Abstract Session**

Results from the phase 1/2 study of patritumab deruxtecan, a HER3-directed antibody-drug conjugate (ADC), in patients with HER3-expressing metastatic breast cancer (MBC). *First Author: Ian E. Krop, Dana-Farber Cancer Institute, Boston, MA*

Background: Patritumab deruxtecan (HER3-DXd) is a novel, investigational ADC composed of a human anti-HER3 monoclonal antibody covalently bound to a topoisomerase I inhibitor payload via a stable tetrapeptide-based cleavable linker. Here we report updated safety and efficacy data from this ongoing study (U31402-A-J101; NCT02980341; JapicCTI-163401) of HER3-DXd in pts with previously treated MBC. **Methods:** U31402-A-J101 is a phase 1/2, multicenter, open-label, first-in-human study of HER3-DXd in pts with HER3-expressing MBC (N = 182). The study enrolled pts in dose-escalation (3.2-8.0 mg/kg IV Q3W) and dose-finding portions across molecular subtypes (n = 66; including HER2+ MBC, n = 14) followed by dose expansion in the following subtypes: HER3 high (4.8 mg/kg [n = 33] or 6.4 mg/kg [n = 31]), HER3 low (6.4 mg/kg [n = 21]) HR+/HER2– MBC or HER3-high TNBC (6.4 mg/kg [n = 31]). HER3-high and -low were defined as ≥75% and 25% – < 75% membrane positivity. The primary objective was to assess safety and efficacy; secondary objectives included determining the relationship between efficacy and HER3 expression. **Results:** At data cutoff (16 Aug 2021), median study duration was 31.9 mo (range, 15-56). Median age was 57 y (range, 30-83); 132 (72.5%) and 50 (27.5%) pts had an ECOG PS of 0 or 1. Pts had a median of 5 (range, 1-13) prior lines of therapy for locally advanced/metastatic disease. Median treatment duration with HER3-DXd was 5.9 mo (range, 0.7-30.6). In a pooled evaluation of dose escalation/finding and expansion, efficacy is shown in pts with HR+/HER2– MBC, TNBC, and HER2+ MBC in the Table. Overall, 130 pts (71.4%) had grade ≥3 TEAEs; the most common (≥15%) were decreased neutrophil count (39.6%), decreased platelet count (30.8%), anemia (18.7%), and decreased white blood cell count (18.1%). 12 pts (6.6%) experienced treatment-related interstitial lung disease according to central adjudication, including 1 grade 5 event. **Conclusions:** A pooled analysis in this heavily pretreated population showed promising efficacy in pts with HR+/HER2– and HER2+ MBC as well as TNBC. The safety profile with longer follow-up is consistent with previous reports and showed adequate safety and tolerability. Studies are ongoing in MBC tumor types, with a focus on biomarkers associated with efficacy. Clinical trial information: NCT02980341. Research Sponsor: Daiichi Sankyo, Co., Ltd.

	HR+/HER2–, HER3 high and low All doses (n = 113)	TNBC/HER3 high All doses (n = 53)	HER2+/HER3 high All doses (n = 14)
Best overall response, n (%)			
CR	0	0	0
PR	34 (30.1)	12 (22.6)	6 (42.9)
SD	57 (50.4)	30 (56.6)	7 (50.0)
PD	13 (11.5)	9 (17.0)	1 (7.1)
NE	9 (8.0)	2 (3.8)	0
ORR, % (95% CI[b])	30.1 (21.8-39.4)	22.6 (12.3-36.2)	42.9 (17.7-71.1)
Median DOR (95% CI[b]), mo	7.2 (5.3-NR)	5.9 (3.0-8.4)	8.3 (2.8-26.4)

Blinded independent central review, with confirmation.
2 pts in dose escalation/finding had unknown subtype.
[a] Exact binomial confidence interval.
[b] Brookmeyer-Crowley method.

LBA1003 **Oral Abstract Session**

Overall survival (OS) with first-line palbociclib plus letrozole (PAL+LET) versus placebo plus letrozole (PBO+LET) in women with estrogen receptor–positive/human epidermal growth factor receptor 2–negative advanced breast cancer (ER+/HER2− ABC): Analyses from PALOMA-2. *First Author: Richard S. Finn, David Geffen School of Medicine at UCLA, Los Angeles, CA*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

LBA1004 **Oral Abstract Session**

A randomized, phase II trial of fulvestrant or exemestane with or without ribociclib after progression on anti-estrogen therapy plus cyclin-dependent kinase 4/6 inhibition (CDK 4/6i) in patients (pts) with unresectable or hormone receptor–positive (HR+), HER2-negative metastatic breast cancer (MBC): MAINTAIN trial. *First Author: Kevin Kalinsky, Winship Cancer Institute, Emory University, Atlanta, GA*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

1005 **Oral Abstract Session**

Fulvestrant plus capivasertib versus fulvestrant plus placebo after relapse or progression on an aromatase inhibitor in metastatic, estrogen receptor–positive breast cancer (FAKTION): Overall survival and updated progression-free survival data with enhanced biomarker analysis. *First Author: Robert Hugh Jones, Velindre Cancer Centre and School of Medicine Cardiff University, Cardiff, United Kingdom*

Background: Previous results from the Phase 2 FAKTION trial (NCT01992952) showed progression free survival (PFS) in patients with aromatase inhibitor (AI) resistant ER+/HER2– advanced breast cancer was significantly longer with fulvestrant plus capivasertib vs fulvestrant plus placebo. At the time of analysis, PFS benefit associated with capivasertib was not restricted to patients with activating mutations in PIK3CA (E542K, E545K, H1047R or H1047L) or PTEN protein null. We report now mature overall survival (OS) data with enhanced biomarker analysis. **Methods:** For the enhanced analysis, available tissue and plasma samples were sent for targeted next generation sequencing (NGS) with Foundation One CDx and GuardantOMNI assays. 'Pathway altered' (PA) was defined as any activating mutation in PIK3CA (exons 1,4,7,9,20) or AKT1 (E17K only) or inactivating alterations in PTEN. For samples not tested by targeted NGS, previously reported digital droplet PCR (ddPCR) results for PIK3CA were used, in addition to tissue AKT1 ddPCR analysis performed after the initial publication. Concordance between mutations identified by ddPCR and subsequent NGS was 97%. **Results:** In January 2022, 108 OS events were reported (77% maturity) in the intention to treat (ITT) population. The median OS was 29.3 vs 23.4 months (mo) in the capivasertib (n = 69) vs placebo (n = 71) arms respectively (HR 0.66, 95% CI 0.45–0.97; p = 0.035). In the enhanced biomarker analysis, 76 participants were classified as PA compared to 59 in the original analysis. In the PA group, OS was 39.0 vs 20.0 mo in the capivasertib vs placebo arms respectively (HR 0.46, 95% CI: 0.27–0.79; p = 0.005). Within the pathway non-altered (PNA) group, median OS was 26.0 vs 25.2 mo in the capivasertib vs placebo arms respectively (HR 0.86, 95% CI: 0.49–1.52; p = 0.60). In the updated PFS analysis, the advantage in the ITT population persisted with capivasertib vs placebo (median 10.3 vs 4.8 mo, HR 0.56, 95% CI: 0.38–0.81; p = 0.002). PFS analysis against the updated biomarker subgroups shows a significant improvement in PFS in the PA group: 12.8 vs 4.6 mo in the capivasertib vs placebo arms respectively (HR 0.44, 95% CI: 0.26–0.72; p = 0.001). In the PNA group, median PFS was 7.7 vs 4.9 mo in the capivasertib vs placebo arms respectively (HR 0.70, 95% CI: 0.40–1.25; p = 0.23). **Conclusions:** Updated analysis of the FAKTION trial data show a significant improvement in OS in the ITT population. Enhanced subgroup analysis suggests that the benefit of capivasertib in both PFS and OS may be predominantly in patients with PIK3CA/AKT1/PTEN pathway altered tumours, but further elucidation will be forthcoming from the ongoing Phase 3 CAPItello-291 study in which participants with PA and PNA tumours have been recruited. Clinical trial information: NCT01992952. Research Sponsor: AstraZeneca, Cancer Research UK.

1006 **Oral Abstract Session**

Alpelisib (ALP) + fulvestrant (FUL) in patients (pts) with hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2−) advanced breast cancer (ABC): Biomarker (BM) analyses by next-generation sequencing (NGS) from the SOLAR-1 study. *First Author: Dejan Juric, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA*

Background: *PIK3CA* mutations (mut; ~ 40% of HR+, HER2– ABC) are linked to poor prognosis. In SOLAR-1, ALP (PI3Kα-selective inhibitor and degrader) + FUL improved progression-free survival (PFS) vs placebo (PBO) + FUL in pts with *PIK3CA*-mutated HR+, HER2– ABC. Here, we focus on efficacy data by gene alterations in SOLAR-1 *PIK3CA*-altered (alt) cohort. **Methods:** SOLAR-1 was a phase 3, randomized, double-blind study of ALP (or PBO) + FUL in HR+, HER2– ABC progressing on/after an aromatase inhibitor. Baseline tissue samples with enough quantity/quality (N = 398) were retrospectively tested by NGS (FoundationOne CDx 324-gene panel) and pts grouped by *PIK3CA*-alteration status. Clinical benefit was assessed using PFS and hazard ratio (HR) based on tumor mutational burden (TMB) and gene alteration status in the *PIK3CA*-alt cohort. No multiplicity adjustment was made. **Results:** *PIK3CA*-alt (ALP, n = 120; PBO, n = 117) and *PI3KCA*-non-alt (ALP, n = 81; PBO, n = 80) cohorts had differential gene alteration landscapes. In the *PIK3CA*-alt cohort, ALP + FUL clinical benefit was seen across TMB quartiles (Q1: 0 -<2.52, Q2: 2.52 -<3.78, Q3: 3.78 -<5.04, Q4: ≥ 5.04 mut/megabase). ALP + FUL had greater benefit in pts with alt vs non-alt *FGFR1/2* (Table). ALP + FUL benefit was independent of alterations in *TP53, ESR1, CCND1, MAP3K1*, and *ARID1A* and limited in *MYC*- and *RAD21*-alt cohorts. ALP + FUL benefit was seen in pts with alt genes in the MAPK (HR [95% CI] vs PBO: alt 0.43 [0.23 - 0.80]; non-alt 0.56 [0.40 - 0.79]) and PI3K (in addition to *PIK3CA*; alt 0.68 [0.38 - 1.23]; non-alt 0.48 [0.34 - 0.68]) pathways, and implicated in CDK4/6i resistance (alt 0.52 [0.30 - 0.89]; non-alt 0.53 [0.37 - 0.76]). **Conclusions:** The unique mut profile of *PIK3CA*-alt tumors did not affect ALP + FUL benefit in pts with HR+, HER2– ABC. Clinical benefit was maintained regardless of alterations in most BMs, including *ESR1* and genes implicated in CDK4/6i resistance, consistent with ALP targeting the *PIK3CA* driver oncogene. Clinical trial information: NCT#02437318; EUDRA CT#2015-000340-42. Research Sponsor: Novartis Pharmaceuticals Corporation.

mPFS and HR in pts receiving ALP + FUL (*PIK3CA*-alt cohort).

Genes	Alt mPFS, mo (N)	Alt HR (95% CI) vs PBO	Non-alt mPFS, mo (N)	Non-alt HR (95% CI) vs PBO
FGFR1	12.7 (22)	0.36 (0.16-0.77)	11.0 (98)	0.54 (0.39-0.75)
FGFR2	9.6 (9)	0.28 (0.09-0.88)	11.0 (111)	0.55 (0.41-0.75)
TP53	8.5 (26)	0.49 (0.28-0.87)	12.0 (94)	0.56 (0.39-0.80)
ESR1	12.0 (13)	0.70 (0.29-1.67)	11.0 (107)	0.51 (0.37-0.70)
CCND1	9.2 (31)	0.77 (0.43-1.37)	11.2 (89)	0.47 (0.33-0.66)
MAP3K1	17.3 (13)	0.44 (0.17-1.10)	10.9 (107)	0.54 (0.40-0.75)
ARID1A	22.1 (11)	0.50 (0.17-1.49)	10.9 (109)	0.51 (0.37-0.70)
MYC	5.8 (13)	1.01 (0.45-2.28)	11.6 (107)	0.49 (0.35-0.67)
RAD21	6.1 (20)	1.02 (0.54-1.95)	11.6 (100)	0.46 (0.33-0.64)

ALP, alpelisib; Alt, altered; FUL, fulvestrant; HR, hazard ratio; mPFS, median progression-free survival; PBO, placebo.

1007 **Oral Abstract Session**

NRG-BR002: A phase IIR/III trial of standard of care systemic therapy with or without stereotactic body radiotherapy (SBRT) and/or surgical resection (SR) for newly oligometastatic breast cancer (NCT02364557). *First Author: Steven J. Chmura, The University of Chicago Medicine, Chicago, IL*

Background: Prospective and retrospective studies of patients (pts) with oligometastatic (OM) disease have supported that metastases (mets) directed treatment (MDT) with SBRT or SR in addition to standard of care systemic therapy (SOC ST) can improve progression-free (PFS) and overall survival (OS) compared with SOC ST alone. However, randomized evidence in oligometastatic breast cancer (OMBC) are lacking. NRG-BR002, a randomized Phase IIR/III trial, sought to determine the efficacy of SOC ST + MDT (SBRT or SR) as first line treatment of OMBC. **Methods:** OMBC pts with ≤ 4 extracranial mets on standard imaging with controlled primary disease were eligible if on first line SOC ST for ≤ 12 months without progression. Pts were randomized (1:1) to ARM 1 – SOC ST (mainly chemotherapy, endocrine therapy, anti-HER2) or ARM 2 – SOC ST with MDT of all mets. Stratification included mets number (1 vs > 1), ER/PR and Her2 status, and chemotherapy use. Phase IIR targeted sample size was 128 total/116 eligible pts, for 92% power and 1-sided significance level = 0.15 to determine if adding MDT shows a signal for improved PFS (hazard ratio [HR] = 0.55, corresponding to median PFS (mPFS) from 10.5 to 19 months), in order to continue to the full phase III trial for OS. PFS and OS were estimated by Kaplan-Meier and arms compared with log-rank. **Results:** 125 of the 129 pts randomized were eligible (ARM 1 = 65, ARM 2 = 60). Key characteristics included median age 54, 79% ER+ or PR+/HER2-, 13% HER2+, 8% triple negative. 60% had 1 metastasis and 20% presented synchronously with primary disease. Following randomization, systemic therapy was delivered to 95% in ARM 1 and 93% in ARM 2; ablation: SBRT 93%, SR 2%, and 5% none. The median follow-up was 30 mo. The mPFS (70% CI) in ARM 1 was 23 mo (18, 29) and 19.5 mo (17, 36) in ARM 2; 24 and 36-mo PFS (70% CI) for ARM 1 were 45.7% (38.9, 52.5) and 32.8% (26.0, 39.5) compared with 46.8 (39.2, 54.3) and 38.1 (29.7, 46.6) in ARM 2; HR (70% CI): 0.92 (0.71, 1.17); and 1-sided log-rank p = 0.36. As PFS did not show signal, OS reporting is included: median OS was not reached in either arm; 36-mo OS (95% CI) in ARM 1 71.8% (58.9, 84.7) and ARM 2 68.9% (55.1, 82.6; 2-sided log-rank p = 0.54). Analysis of first failure showed new mets outside index area (Arm 1) /RT field (Arm 2) developed similarly in both arms at 40%. There were fewer new mets inside treated/index area for Arm 2 6.7% vs ARM 1 29.2%, respectively. There were no grade 5 treatment-related adverse events (AEs), 1 grade 4 AE in ARM 1, and 9.7% and 5.3% grade 3 AEs in ARMS 1 and 2, respectively. Circulating tumor cell counts (0 vs ≥1) at baseline were similar in both arms and were not prognostic HR (95% CI): 1.04 (0.54, 2.02). **Conclusions:** The addition of MDT to SOC ST did not show signal for improved PFS, nor OS difference in patients with OMBC. The trial will not proceed to the Phase III component. Clinical trial information: NCT02364557. Research Sponsor: National Cancer Institute (NCI).

1008 **Oral Abstract Session**

Contributions of screening, early-stage treatment, and metastatic treatment to breast cancer mortality reduction by molecular subtype in U.S. women, 2000-2017. *First Author: Jennifer Lee Caswell-Jin, Stanford University, Stanford, CA*

Background: Treatment for metastatic breast cancer has advanced since 2000, but we do not know if those advances have reduced mortality in the general population. **Methods**: Four Cancer Intervention and Surveillance Network (CISNET) models simulated US breast cancer mortality from 2000 to 2017 using national data on mammography use and performance, efficacy and dissemination of estrogen receptor (ER) and HER2-specific treatments of early-stage (stages I-III) and metastatic (stage IV or distant recurrence) disease, and competing mortality. Models compared overall and ER/HER2-specific breast cancer mortality rates from 2000 to 2017 relative to estimated rates with no screening or treatment, and attributed mortality reductions to screening, early-stage or metastatic treatment. Results of an exemplar model are shown. **Results**: The mortality reduction attributable to early-stage treatment increased from 35.8% in 2000 to 48.2% in 2017, while the proportion attributable to metastatic treatment decreased slightly from 23.9% to 20.6%. The increasing contribution of early-stage treatment reflects the transition of effective metastatic treatments to early-stage disease: accordingly, ten-year distant recurrence-free survival improved (82.5% in 2000, 87.3% in 2017; for ER+HER2+, 78.2% to 90.9%). Survival time after metastatic diagnosis also increased, doubling from 1.48 years in 2000 to 2.80 years in 2017, with the best survival for women with ER+HER2+ cancers (4.08 years) and worst for ER-HER2- (1.22 years). **Conclusions**: Advances in metastatic breast cancer treatment are reflected in lower population mortality, both through transition to early-stage treatment and gains for women with metastatic disease. These results may inform patient/physician discussions about breast cancer prognosis and expected benefits of treatment. Research Sponsor: U.S. National Institutes of Health.

	Year	All Subtypes	ER+HER2+	ER+HER2-	ER-HER2+	ER-HER2-
Mortality reduction (%) from screening, early-stage and metastatic treatment (vs. estimated mortality with no screening or treatment)	2000	39.5	40.6	41.5	34.2	34.9
	2010	52.0	62.8	55.4	44.9	36.7
	2017	56.5	69.5	58.1	59.6	39.1
Fraction of mortality reduction (%) from screening	2000	40.3	41.3	36.7	45.3	50.7
	2010	31.5	27.1	29.9	32.9	45.6
	2017	31.2	25.1	30.0	31.8	44.8
Fraction of mortality reduction (%) from early-stage treatment	2000	35.8	41.5	39.9	19.1	24.1
	2010	46.3	53.7	47.5	41.6	32.3
	2017	48.2	57.6	50.4	42.1	31.0
Fraction of mortality reduction (%) from metastatic treatment	2000	23.9	17.1	23.4	35.7	25.2
	2010	22.2	19.2	22.6	25.6	22.0
	2017	20.6	17.3	19.6	26.1	24.2
Ten-year distant recurrence-free survival with early-stage disease (%)	2000	82.5	78.2	85.9	68.5	75.0
	2010	86.6	88.3	89.0	78.7	77.4
	2017	87.3	90.9	89.1	81.4	78.5
Median time (years) from distant recurrence to breast cancer death	2000	1.48	1.68	1.66	1.55	0.92
	2010	2.48	3.62	3.18	2.45	1.16
	2017	2.80	4.08	3.47	3.30	1.22

1009 **Clinical Science Symposium**

***ESR1* F404 mutations and acquired resistance to fulvestrant in the plasmaMATCH study.** *First Author: Belinda Kingston, Breast Cancer Now Toby Robins Research Centre, Institute of Cancer Research, London, United Kingdom*

Background: The selective estrogen receptor modulator (SERD) fulvestrant is commonly used to treat patients with hormone receptor positive advanced breast cancer, although potential mechanisms of acquired resistance are poorly understood. plasmaMATCH cohort A (NCT03182634) investigated the activity of fulvestrant in patients with activating *ESR1* mutations in circulating tumor DNA (ctDNA). Here we present analysis of baseline and end-of-treatment (EOT) ctDNA to identify potential resistance mutations to fulvestrant. **Methods:** Paired baseline and EOT plasma samples from patients enrolled into plasmaMATCH underwent ctDNA sequencing (Guardant360, Guardant Health) to identify acquired mutations. For F404 analysis, MCF-7 cells were transiently transfected with estrogen receptor expression constructs containing either wildtype *ESR1* (WT), single *ESR1* mutations (D538G, E380Q, F404L), or compound mutations (D538G_F404L, E380Q_F404L), alongside an estrogen response element (ERE)-luciferase reporter construct. Transfected cells were treated with or without fulvestrant and ERE-luciferase activity compared. **Results:** Of 84 patients enrolled in cohort A, 69 had paired baseline and EOT sequencing. Patients with baseline *ESR1* Y537S had shorter progression free survival (PFS), and Y537C longer PFS, than those wild-type for each respective mutation ($p = 0.03$ and $p = 0.04$). Patients frequently acquired mutations at EOT (n = 35, 51%), including potentially targetable mutations in 25% (including 3 *PTEN*, 3 *BRCA1/2*, 2 *PIK3CA*, 2 *HER2*, 1 *BRAF*). Three (4%) patients acquired *ESR1* p.F404 mutations (F404L, F404I, F404V), with 7 mutations in total. Of 26 patients with PFS of ≥16 weeks, 3 patients (12%) acquired *ESR1* F404. In 800 patients screened for entry to plasmaMATCH, one harbored a F404 mutation (0.13%), with a prior history of fulvestrant. F404 mutations resided in *cis* with E380Q in 6/7 assessable mutations. *In vitro* structural modelling revealed that *ESR1* p.F404 resides within the *ESR1* ligand binding domain, and contributes to estrogen and fulvestrant binding through a pi-stacking bond between the aromatic ring of phenylalanine and estrogen/fulvestrant, with all F404 mutations disrupting this bond. Transient transfection demonstrated that single mutations D538G, E380Q, F404L and wild-type *ESR1* were sensitive to fulvestrant ($p < 0.0001$, $p = 0.0006$, $p = 0.04$ and $p = 0.0001$), whereas compound mutations D538G_F404L and E380Q_F404L were resistant. Further investigation of relative sensitivity of the F404 mutant *ESR1* to other anti-estrogens will be presented. **Conclusions:** We have identified a novel resistance mechanism to fulvestrant, with F404 mutations acquired in patients with pre-existing activating *ESR1* mutations. F404 confers fulvestrant resistance through the loss of a pi-stacking bond and likely reduced fulvestrant binding affinity, identifying a new potential target to overcome endocrine therapy resistance. Research Sponsor: Cancer Research UK and Breast Cancer Now.

1010 **Clinical Science Symposium**

Allelic dosage of *RB1* drives CDK4/6 inhibitor treatment resistance in metastatic breast cancer. *First Author: Anton Mikhailovich Safonov, Hospital of University of Pennsylvania, Philadelphia, PA*

Background: We recently reported inferior outcomes to CDK4/6 inhibitors and endocrine therapy (CDK4/6i-ET) associated with germline *BRCA2* (g*BRCA2)* in a cohort of estrogen receptor (ER) positive breast cancers. Co-occurrence of *gBRCA2* with loss of heterozygosity (LOH) of neighboring *RB1* was found to portend particularly poor outcomes. Here, we sought to define the effects of pre-treatment *RB1* allelic copy number status on outcomes of CDK4/6i-ET and the likelihood of developing *RB1* loss-of-function (LOF) mutations on CDK4/6i through the analysis of an expanded cohort of metastatic ER+ breast cancer patients. **Methods:** Patients who underwent sequencing on MSK-IMPACT from April 2014 to May 2021 were included. For every sample preceding CDK4/6i-ET, we performed FACETS to infer *RB1* allele specific copy number, ploidy, tumor purity and fraction genome altered (FGA). Patients were categorized based on *RB1* allelic status: HetLoss (total of one allelic copy), copy neutral LOH (CNLOH), other allelic imbalance including all other aneuploidy states, and diploid. Progression free survival (PFS) was assessed using univariate and multivariate Cox proportional hazard models adjusted for ET partner and FGA. Firth penalized logistic regression was used to study association of pre-treatment *RB1* status with acquired *RB1* LOF variants in paired post-CDK4/6i samples. **Results:** Of 2,630 potentially eligible patients, 279 patients had genomic sequencing performed prior to 1st line CDK4/6i-ET. Of these, 75 (26.8%) exhibited *RB1* HetLoss, 39 (14.0%) had CNLOH of *RB1*, 111 (39.7%) exhibited diploid *RB1* state, while 54 (19.4%) had other patterns of *RB1* allelic imbalance. All non-diploid *RB1* states were associated with significantly shortened PFS relative to diploid (univariate HetLoss HR: 2.05, 95% CI: 1.42, 2.97; CNLOH HR: 2.08, 95% CI: 1.32, 3.25; other imbalance HR: 1.70, 95% CI: 1.11, 2.58). Only HetLoss remained significant when adjusted for FGA (HR 1.61, 95% CI: 1.09, 2.38, $p = 0.017$). *RB1* LOF was rare in pre-CDK4/6i tumors (< 1%); excluding these cases did not change our results. Of the 176 patients with paired pre- and post-CDK4/6i samples, only *RB1* HetLoss in pre-CDK4/6i sample was significantly associated with development of *RB1* LOF mutations in post-CDK4/6i sample (18.4%) as compared to diploid (4.2%, OR 4.25, 95% CI 1.02, 17.7, $p = 0.047$). These results indicate that tumors with one functional copy of *RB1* are more likely to acquire *RB1* LOF on CDK4/6i to achieve biallelic RB1 loss as a mechanism of CDK4/6i resistance. **Conclusions:** We demonstrate that LOH and allelic imbalance of *RB1* are associated with shorter PFS on CDK4/6-ET. We postulate this may occur partly as a result of more frequent acquired *RB1* LOF mutations under selective pressure of CDK4/6i. These data supports the implementation of more refined allele-specific copy number methods and identifies a high-risk population for escalated monitoring and treatment approaches. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

1011 **Clinical Science Symposium**

Use of real-world data (RWD) to assess the utility of cell-free circulating tumor DNA (cfDNA) in identifying resistance to early treatment in advanced breast cancer (aBC). *First Author: Seth Andrew Wander, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: The approvals of CDK4/6 inhibitors (CDK4/6i) and alpelisib (a PI3Ka inhibitor, PI3Ki) have overhauled early treatment of hormone positive aBC. While some clinical trials have investigated mechanisms of resistance to these drugs, their impact on tumor evolution requires further exploration. Here we use cfDNA to examine molecular changes pre- and post-CDK4/6i or PI3Ki treatment and use RWD to assess the impact of putative resistance alterations on response to treatment. **Methods:** Patients (pts) with aBC were identified via the Guardant INFORM database and included if they had a cfDNA test within 90 days prior to therapy initiation and/or 90 days after therapy discontinuation with CDK4/6i or PI3Ki. Pts with *RB1* loss of function (LOF) alterations (alts) who received CDK4/6i and pts with *PTEN* LOF alts who received PI3Ki were separately identified, and these cohorts were matched 1:3 with a *RB1/PTEN* negative population respectively, by age (+/- 5 years), sex, year of cfDNA test, and line of therapy. Log-rank tests were used to assess differences in time to discontinuation (TTD) and time to next treatment (TTNT). **Results:** Differences in the frequencies of certain alts detected in pts pre- and post-CDK4/6i or PI3Ki treatment are shown (Table). Pts with *RB1* LOF alts prior to the start of CDK4/6i had significantly worse TTD and numerically worse TTNT versus controls (TTD = 3 mos vs 4.7 mos, p=0.018; TTNT = 7.3 mos vs 8 mos, p=0.082). Pts with *PTEN* LOF alts prior to start of PI3Ki had no significant difference in TTD or TTNT versus controls (TTD = 4.1 mos vs 4.1 mos, p=0.92; TTNT = 7.4 mos vs 7 mos, p=0.32). Notably, 54% of pts receiving CDK4/6i and 84% of pts receiving PI3Ki were on their third or later line of therapy. **Conclusions:** Using cfDNA, we were able to further characterize the resistance landscape of both CDK4/6i and PI3Ki, and identified specific *ESR1, RB1* and *PTEN* alterations that appear likely to occur under the pressure of therapy. Our real-world analysis examining *RB1* LOF alts added further evidence to suggest it may be both a primary and acquired resistance mechanism to CDK4/6i. As a non-invasive alternative to tissue biopsies, this data further illustrates that cfDNA can provide unique insight into tumor evolution and disease progression in the aBC setting. Research Sponsor: None.

Biomarker	N of Pts+ Pre-CDK4/6i (%) (n = 800)	N of Pts+ Post-CDK4/6i (%) (n= 2,408)	Chi-square p value	N of Pts+ Pre-PI3Ki (%) (n = 399)	N of Pts+ Post-PI3Ki (%) (n = 93)	Chi-square p value
***ESR1* Alts**	156 (20)	709 (29)	< 0.0001	195 (49)	42 (45)	0.52
D538G	75 (9)	399 (17)	< 0.001	111 (28)	21 (23)	0.31
Y537S	50 (6)	234 (10)	0.003	68 (17)	15 (16)	0.83
Y537N	24 (3)	154 (6)	< 0.001	39 (10)	7 (8)	0.50
***PIK3CA* Alts**	273 (34)	814 (34)	0.87	374 (94)	75 (81)	< 0.001
***RB1* LOF**	13 (2)	116 (5)	< 0.0001	46 (12)	7 (8)	0.26
Splice Site Mutations	5 (1)	25 (1)	0.29	13 (3)	1 (1)	0.25
****PTEN* LOF**	-	-	-	19 (5)	8 (9)	0.14
T319fs	-	-	-	3 (1)	6 (6)	< 0.001

*Detected at ≤ 2%.

1012 **Clinical Science Symposium**

Circulating tumor DNA (ctDNA) and serum thymidine kinase 1 activity (TKa) matched dynamics in patients (pts) with hormone receptor–positive (HR+), human epidermal growth factor 2–negative (HER2-) advanced breast cancer (ABC) treated in first-line (1L) with ribociclib (RIB) and letrozole (LET) in the BioItaLEE trial. *First Author: Grazia Arpino, Department of Medical Clinics and Surgery, Universitàa Federico II, Napoli, Italy*

Background: Independent early dynamic assessment (baseline [D0] and day 15 of first cycle [D15]) of both TKa and ctDNA was prognostic and predictive in pts with HR+, HER2– ABC treated with RIB+LET enrolled in the BioItaLEE trial (NCT03439046). Here we performed a combined analysis of these two biomarkers. **Methods:** 287 pts were enrolled in the study. Overall, early dynamics were assessable for both biomarkers in 241/287 pts (84.0%). Methods applied for ctDNA and TKa evaluation were previously reported. For ctDNA, samples were defined as wild type (WT) if no mutations were observed at D0 and D15, ctDNA positive (+) if with or negative (-) if without a primary target mutation at D15. Samples were TKa+ or TKa- if TKa levels were above or below the limit of detection at D15. According to ctDNA and TKa pts were classified as: WT/TKa-, WT/TKa+, ctDNA-/TKa-, ctDNA-/TKa+, ctDNA+/TKa- and ctDNA+/TKa+ and then divided into 3 main study groups (GRs) WT/TKa- (GR1, n = 126), WT/TKa+, ctDNA-/TKa-, ctDNA-/TKa+, ctDNA+/TKa- (GR2, n = 96) and ctDNA+/TKa+ (GR3, n = 19). The association between biomarkers and PFS (progression-free survival) was estimated using Kaplan-Meier analysis and multivariate Cox models with 95% confidence intervals (CIs) adjusted for clinical variables. **Results**: Median follow-up was 26.9 months. In multivariate Cox models both TKa dynamics and mutational tumor burden at D15 were independently predictive of PFS. Hazard ratios (HRs) were 0.37 (95% CI: 0.23-0.60; p < 0.0001) for WT vs ctDNA+ and 0.56 (95% CI: 0.32-1.00; p = 0.0506) for ctDNA- vs ctDNA+. For TKa, HR was 0.49 (95% CI: 0.30-0.80; p = 0.0040) in TKa- vs TKa+. Interestingly combining the two variables further improve prediction of outcome. HRs for TKa- vs TKa+ were 0.17 (95% CI: 0.09-0.32; p < 0.0001), 0.28 (95% CI: 0.13-0.59; p = 0.0009) and 0.44 (95% CI: 0.23-0.86; p = 0.0169) in WT, ctDNA- and ctDNA+ pts, respectively. Considering the 3 study GRs, median PFSs (95% CI) were not reached (27.89, NE), 19.58 (13.83, 23.39) and 6.65 (2.83, 12.16) months in GR1, GR2 and GR3, respectively, p < 0.001. At multivariate Cox models, HRs of GR1 and GR2 compared with GR3 were 0.17 (95% CI: 0.09-0.32; p < 0.0001) and 0.37 (95% CI: 0.20-0.67; p = 0.001) respectively. **Conclusions**: These findings suggest that combining the early dynamic assessment of both ctDNA and TKa may improve outcome prediction in pts treated with RIB+LET. Pts with ctDNA+/TKa+ are strongly enriched for non-responders. TKa and ctDNA capture different features of tumor biological activity and their combination warrants further evaluation in relation to other treatments, settings, and diseases. Clinical trial information: NCT03439046. Research Sponsor: Novartis Farma SpA.

1013 **Poster Discussion Session**

Effect of socioeconomic status as measured by Neighborhood Deprivation Index on survival in metastatic breast cancer. *First Author: Susrutha Puthanmadhom Narayanan, University of Pittsburgh Medical Center Cancer Center, Pittsburgh, PA*

Background: Socioeconomic status (SES) and race are major determinants of health outcomes in the United States. We aim to assess the effect of SES as measured by the Neighborhood Deprivation Index (NDI) and race on outcomes in metastatic breast cancer patients at our center. **Methods:** The NDI scores for patients with metastatic breast cancer who were treated at our center between 2000 and 2017 were obtained from the Neighborhood Atlas using their Zip-Code (N = 1246). The SES groups were defined as low deprivation with an NDI score in the bottom tertile and high deprivation with NDI in the top or middle tertiles. Baseline characteristics were compared between the SES groups with Bonferroni correction. Univariate and multivariate survival analysis were performed using the R packages "survival" and "survminer". **Results:** Race was the only baseline characteristic that was significantly different between the SES groups, the high deprivation group had a higher proportion of African Americans (10.5%) than the low deprivation group (3.7%, P = 9.3e-05). In univariate Kaplan-Meier survival analysis, both SES and race had significant effect on overall survival such that the high deprivation group had worse survival than low deprivation (Log Rank P = 0.01) and African Americans had worse survival than Caucasians (P = 0.008). In multivariate Cox proportional hazard model, SES, but not race, had a significant effect on overall survival (hazard ratio for high deprivation was 1.19 [95% Confidence interval 1.04 - 1.37], P = 0.01; Table). Progression-free survival on first-line chemotherapy was not different between the SES groups or racial groups in both univariate and multivariate analysis. **Conclusions:** The current study shows that patients from the high deprivation group (i.e., low SES), have worse survival in metastatic breast cancer. Race was no longer a significant predictor of survival when SES was accounted for in the analysis. This possibly suggests that poor outcomes in the African American population is explained by the association between low SES and African American race. Based on these results, there is an urgent need for healthcare investments in the low SES neighborhoods. Research Sponsor: None.

Cox proportional hazard model for survival in metastatic breast cancer.

	Hazard ratio [95% confidence interval]	P value
Race = Caucasian	0.8145 [0.6430 - 1.0318]	0.09
SES group = High deprivation (i.e., low SES)	1.1911 [1.0367 - 1.368]	0.01
Age at metastatic diagnosis	1.0095 [1.0045 - 1.0145]	0.0002
Subtype = ER+/HER2-	0.9685 [0.7702 - 1.2178]	0.78
Subtype = ER+/HER2+	0.8140 [0.6196 - 1.0692]	0.14
Subtype = Triple negative	2.0315 [1.5827 - 2.6077]	2.64e-08

1014 **Poster Discussion Session**

Increasing Black patient participation in metastatic breast cancer clinical trials: The BECOME (Black Experience of Clinical Trials and Opportunities for Meaningful Engagement) project. *First Author: Stephanie Walker, Metastatic Breast Cancer Alliance, New York, NY*

Background: Among U.S. racial/ethnic groups, Black people with breast cancer have the highest death rate and shortest survival. Although ~15% of cancer patients in the U.S. are Black, only 4-6% of clinical trial participants are Black. Only when trial participants reflect the diversity of the general population can oncologists understand how a drug works across subpopulations. The objectives of the BECOME initiative are to understand barriers to trial participation by Black patients with metastatic breast cancer (MBC) and to identify actions to increase participation. **Methods**: BECOME is sponsored by the Metastatic Breast Cancer Alliance, a consortium of representatives from nonprofit organizations, pharmaceutical/biotech companies, and patient advocates, many of whom are living with MBC. Findings from a literature review and Key Informant interviews informed a survey of U.S. adults living with MBC. **Results**: Of 424 survey respondents, 102 (24%) self-identified as Black. Black respondents' trust and satisfaction with their oncology care team were high (> 90%), and 83% of Black respondents were somewhat or very likely to consider trial participation. However, 40% of Black respondents reported no one on their care team had discussed trials. Black respondents' reasons to not participate in a trial included concerns about side effects (73%) and effectiveness (63%). Black respondents were more likely than non-Black respondents to believe unstudied treatments may be harmful (57% vs 31%). Black respondents were less likely than non-Black respondents to indicate they trust trials (73% vs 91%) and trust that people of all races/ethnicities get fair treatment in trials (32% vs 56%). Black respondents were more likely than non-Black respondents to value receiving trial information from someone with the same racial/ethnic identity (67% vs 10%), who has had breast cancer (73% vs 44%) or MBC (73% vs 51%), or who has been in a trial (72% vs 48%). Black respondents were also more likely to be motivated to participate to ensure people with their racial or ethnic identity will benefit (83% vs 51%). **Conclusions**: Black patients with MBC are willing to consider participating in clinical trials. Actionable steps to increase Black patient participation include: 1) enhancing awareness about trials by informing patients, increasing education, training healthcare providers to deliver patient-friendly information in an unbiased manner, and providing messaging from people of shared racial/ethnic identity and health experience; 2) building trust through clear communication; 3) addressing concerns about side effects, effectiveness, harm, and fair treatment; and 4) helping patients find and access trials. All stakeholder groups have a role to play in increasing Black patient participation in MBC clinical trials. Research Sponsor: Metastatic Breast Cancer Alliance.

1015 **Poster Discussion Session**

Quality of life (QOL) with ribociclib (RIB) plus aromatase inhibitor (AI) versus abemaciclib (ABE) plus AI as first-line (1L) treatment (tx) of hormone receptor-positive/human epidermal growth factor receptor–negative (HR+/HER2−) advanced breast cancer (ABC), assessed via matching-adjusted indirect comparison (MAIC). *First Author: Hope S. Rugo, Department of Medicine, University of California San Francisco, Helen Diller Family Comprehensive Cancer Center, San Francisco, CA*

Background: The combination of a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) + endocrine therapy is the recommended 1L tx for HR+/HER2– ABC. A statistically significant overall survival (OS) benefit with RIB + AI was recently reported for MONALEESA-2 (ML-2); final OS results for the MONARCH 3 (MON-3) trial of ABE + AI are pending. QoL is an important end point that affects tx decisions. Understanding the impact of CDK4/6i on QoL is of increasing importance given use in earlier tx lines for ABC and an emerging role in treating early breast cancer, where QoL considerations may be more relevant. MAIC analysis allows for comparative effectiveness in the absence of head-to-head trial data. In this analysis, patient (pt)-reported QoL for the Phase III ML-2 (RIB + AI) and MON-3 (ABE + AI) trials were compared using MAIC with a focus on individual domains; the PALOMA-2 trial could not be considered for this analysis because of the different pt-reported outcome measures evaluated in the trial compared to ML-2 and MON-3. **Methods:** An anchored MAIC of QoL with RIB + AI vs ABE + AI was performed using data from EORTC QLQ-C30 and BR-23 questionnaires, individual participant data from ML-2 (data cutoff: 6/10/2021), and published data from MON-3 (data cutoff: 11/3/2017). All available QoL data were used in this analysis; the median follow-up for ML-2 was 79.7 months, and the median duration of follow-up at which QoL data were reported for MON-3 was 26.73 months. Inclusion and exclusion criteria were generally similar. Pts in both arms of ML-2 were weighted to match baseline characteristics in the corresponding arms of MON-3. Cox proportional hazards model was used to generate hazard ratios (HRs); anchored HRs were calculated using the Bucher method. Time to sustained deterioration (TTSD) was calculated as the time from randomization to a ≥ 10-point deterioration with no later improvement above this threshold. **Results:** 205 and 149 pts from the ML-2 arms of RIB/PBO were matched to 328 and 165 pts from the ABE/PBO arms of MON-3. After weighting, pt characteristics were well balanced. TTSD significantly favored RIB vs ABE in appetite loss (HR, 0.46; 95% CI, 0.27-0.81), diarrhea (HR, 0.42; 95% CI, 0.23-0.79), and fatigue (HR, 0.63; 95% CI, 0.41-0.96) as measured by QLQ-C30 and arm symptoms (HR, 0.49; 95% CI, 0.30-0.79) as assessed by BR-23. TTSD did not significantly favor ABE vs RIB in any functional or symptom scale of the QLQ-C30 or BR-23. **Conclusions:** This MAIC suggests that RIB + AI is associated with better symptom-related QoL vs ABE + AI for postmenopausal pts with HR+/HER2– ABC in the 1L setting. QoL differences between CDK4/6i and their associated adverse event profiles may impact clinical decisions in HR+/HER2– ABC. Research Sponsor: Novartis Pharmaceuticals.

1016 **Poster Discussion Session**

Characterization of alpelisib-associated hyperglycemia in metastatic breast cancer. *First Author: Sherry Shen, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: For women with metastatic hormone receptor (HR)-positive, human epidermal growth factor 2 (HER2)-negative breast cancer, the combination of alpelisib and fulvestrant improves progression-free survival in those with *PIK3CA* mutations. Hyperglycemia is a major toxicity of PI3K inhibitors including alpelisib, which limits the clinical efficacy of these drugs due to interrupted/reduced dosing and discontinuation. In the SOLAR-1 trial that led to the Food and Drug Administration (FDA) approval of alpelisib, over 60% of patients developed hyperglycemia of any grade, and over 36% developed grade 3-4 hyperglycemia. Here we describe the incidence and treatment of alpelisib-associated hyperglycemia in a single center cohort. **Methods:** Patients with metastatic breast cancer who received alpelisib on a clinical trial or as part of standard care from 2013-2021 at Memorial Sloan Kettering Cancer Center were included in this retrospective study. Patient and tumor characteristics and pre-treatment body mass index (BMI), hemoglobin A1c, and serum glucose levels were abstracted from medical records. Alpelisib dose interruptions, reductions, or discontinuation was recorded as well as endocrinology consultation and use of anti-hyperglycemic agents. Date of progression and/or death were recorded where applicable. **Results:** 247 patients were included in this study, among whom 245 (99.1%) were female and 198 (80.1%) were white. 100 (40.5%) were treated on a clinical trial. Median baseline BMI was 25.4 kg/m^2. Among 164 patients with baseline hemoglobin A1c levels available, 93 (56.7%) patients had normal hemoglobin A1c, 54 (32.9%) had prediabetes, and 17 (10.4%) had diabetes. 152 patients (61.5%) developed hyperglycemia of any grade; 56 (22.7%) developed grade 3 and 16 (6.5%) developed grade 4 hyperglycemia. The median time to onset of hyperglycemia was 16 days. BMI ≥25 kg/m^2 or hemoglobin A1c ≥5.7% were strongly predictive of development of any-grade hyperglycemia (p= 0.036 and p< 0.001, respectively) and grade 3-4 hyperglycemia (p< 0.001 for both). Among those who developed hyperglycemia, 101 (40.9%) received treatment; 69 patients (27.9%) required only 1 anti-hyperglycemic agent whereas 9 (3.6%) required ≥3 anti-hyperglycemic agents. 49 (19.8%) were referred for endocrinology consult. In 66 patients (26.7%), alpelisib was held until resolution of hyperglycemia; 42 patients (17%) required dose reductions, and 11 (4.5%) discontinued alpelisib due to hyperglycemia. There was no significant difference in progression-free survival by hyperglycemia status or severity of hyperglycemia. **Conclusions:** Overweight BMI and hemoglobin A1c in the prediabetes or diabetes range were strongly predictive of developing alpelisib-associated hyperglycemia. Management of these co-morbidities prior to alpelisib treatment should be strongly considered. Research Sponsor: None.

1017 **Poster Discussion Session**

Impact of ribociclib (RIB) dose modifications (mod) on overall survival (OS) in patients (pts) with HR+/HER2- advanced breast cancer (ABC) in MONALEESA(ML)-2. *First Author: Lowell L. Hart, Florida Cancer Specialists and Research Institute, Fort Myers, FL*

Background: The phase 3 ML-2, -3, and -7 trials all demonstrated consistent and statistically significant OS benefit with RIB (starting dose: 600 mg/d 3 wk on/1 wk off) vs PBO in pts with HR+/HER2– ABC. RIB dose mod (reductions and/or interruptions) when needed did not impact OS benefit with RIB + endocrine therapy (ET) in previous analyses of ML-3/-7. Here we present data on the effect of RIB dose mod on OS in postmenopausal pts with HR+/HER2– ABC in ML-2. **Methods:** ML-2 (NCT01958021) enrolled postmenopausal pts randomized 1:1 to first-line RIB + letrozole (LET) or PBO + LET. Landmark (LM) analyses of OS were performed to evaluate the association between dose reductions (yes vs no) and OS. Multiple LM times were considered to determine the sensitivity of the findings. As an alternative to LM analysis, a Cox proportional hazards model with a time-varying covariate was performed. Two time-dependent variables, dose reduction (with/without mod from 600 mg starting dose) and relative dose intensity 2 (RDI2), were included in the respective model as covariates to explore the association with OS. To account for differences in time to first dose mod, RDI2 reflects the post–dose mod period. Median (m) OS was obtained using a modified Kaplan-Meier method. **Results:** At data cutoff (June 10, 2021; m follow-up, 49.35 [range, 0-86.7] mo), 209 of 334 pts (62.6%) had ≥ 1 RIB dose reduction and 125 of 334 (37.4%) had 0 RIB dose reduction. LM analyses by dose reduction are presented (Table). mOS was 66.0 (95% CI, 57.6-75.7) mo in pts with ≥ 1 RIB dose reduction vs 60.6 (95% CI, 42.5-79.2) mo in pts with no RIB dose reductions (HR, 0.87 [95% CI, 0.65-1.18]). RDI2 was classified according to tertile: low (< 64.27%), medium (64.27%-95.86%), and high (> 95.86%). In pts with low, medium, and high RDI2, mOS was 62.6 (95% CI, 50.0-80.7) mo, 63.9 (95% CI, 48.8-not reached [NR]) mo, and 65.3 (95% CI, 50.5-NR) mo, respectively (HR low vs high, 0.99 [95% CI, 0.69-1.42]; HR medium vs high, 0.97 [95% CI, 0.62-1.38]). **Conclusions:** In this exploratory analysis of ML-2, OS benefit was maintained in pts with HR+/HER2– ABC who required mod from the recommended starting dose of RIB (600 mg/d 3 wk on/1 wk off). No relationship was observed between OS and RIB dose reduction or RDI2; OS benefit with RIB was observed in all groups. Clinical trial information: NCT01958021. Research Sponsor: Novartis Pharmaceuticals.

OS analysis for 3 LMT points.

LMT, mo[a]	Pts on treatment > LMT, n (%)	Dose reductionprior to LMT	Subgroup, n (%)	No. of events	2-year post-LMT OS rate (95% CI)[b]	Post-LMT HR (95% CI): Dose reduction Yes vs No
6	261 (78.1)	Yes	120 (46.0)	63	0.86 (0.80-0.93)	1.19 (0.85-1.68)
		No	141 (54.0)	68	0.88 (0.83-0.94)	
12	211 (63.2)	Yes	117 (55.5)	53	0.89 (0.83-0.95)	1.20 (0.79-1.82)
		No	94 (44.5)	38	0.89 (0.83-0.96)	
18	176 (52.7)	Yes	101 (57.4)	37	0.90 (0.84-0.96)	0.94 (0.57-1.53)
		No	75 (42.6)	29	0.88 (0.80-0.96)	

LMT, landmark time. [a]Each LMT represents a distinct pt population treated on and after the LM. [b]OS rate 2 years after given LMT.

1018 **Poster Discussion Session**

Alpelisib (ALP) + endocrine therapy (ET) in patients (pts) with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–), *PIK3CA*-mutated (mut) advanced breast cancer (ABC): Baseline biomarker analysis and progression-free survival (PFS) by duration of prior cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) therapy in the BYLieve study. *First Author: Dejan Juric, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA*

Background: ALP (PI3K-α selective inhibitor and degrader) + fulvestrant (FUL) is approved for pts with HR+, HER2– ABC and a tumor mutation in *PIK3CA* (~ 40% of these pts). Primary analyses from the Phase 2 BYLieve study demonstrated efficacy and safety of ALP + ET in pts with *PIK3CA*-mut, HR+, HER2– ABC in the post-CDK4/6i setting. Post hoc analyses, including pts with disease progression within 6 mo of CDK4/6i + ET treatment (Tx), confirmed ALP benefit regardless of duration of prior CDK4/6i. Here we assess baseline biomarkers in circulating tumor DNA (ctDNA) by duration of prior CDK4/6i Tx and PFS in pts from BYLieve Cohorts A and B. **Methods:** In the BYLieve study, pts with *PIK3CA*-mut, HR+, HER2– ABC had CDK4/6i + aromatase inhibitor (Cohort A) or + FUL (Cohort B) as immediate prior Tx to receiving ALP + FUL and ALP + letrozole (LET), respectively. At data cutoff dates, pts had ≥ 18-mo follow-up in Cohort A and ≥ 6-mo in Cohort B. In each cohort, pts were grouped based on duration of prior CDK4/6i Tx (≤ 6 mo or >6 mo). Alterations were detected on ctDNA using next-generation sequencing (PanCancer V2 Panel). PFS was assessed in each cohort and by duration of prior CDK4/6i Tx. **Results:** Of 127 and 126 pts enrolled in Cohorts A and B, respectively, 98 (≤ 6-mo: 24; >6-mo: 74) and 94 (≤ 6-mo: 28; >6-mo: 66) were included in this analysis based on availability of ctDNA samples, data on duration of prior CDK4/6i, and centrally confirmed *PIK3CA*-mut disease. In this population, median (m) PFS (95% CI) was 8.2 mo (5.6 - 9.5) and 5.6 mo (3.7 - 7.1) in Cohorts A and B, respectively. In Cohort A, mPFS (95% CI) was 12.0 mo (5.5-non estimable) and 6.2 mo (5.4 - 8.5) in the ≤ 6-mo and >6-mo groups, respectively. The OncoPrint genomic profiles showed that pts in the ≤ 6-mo vs >6-mo group had a lower median ctDNA fraction and fewer detected gene alterations, including in genes associated with ET and/or CDK4/6i resistance, and fewer chromosomes 8/11 amplifications (linked to early relapse). In Cohort B, mPFS was 5.9 mo (3.5 - 11.0) and 5.6 mo (3.7 - 7.1) in the ≤ 6-mo and >6-mo groups, respectively. Both groups had high median ctDNA fractions and complex tumor mutation profiles reflecting more extensive treatment history. **Conclusions:** Lower median ctDNA fraction and lower mutational complexity observed in Cohort A ≤ 6-mo vs >6-mo group was associated with numerically longer mPFS, potentially indicating increased dependence on the mutant PI3K-α. In Cohort B, both ≤ 6-mo and >6-mo groups had high median ctDNA fractions and similar tumor mutation profiles. Additional ctDNA and tissue analyses are needed to elucidate the correlation between ALP + ET efficacy and treatment timing and baseline genomic complexity. Research Sponsor: Novartis Pharmaceuticals Corporation.

1019 **Poster Discussion Session**

Baseline and longitudinal ctDNA biomarkers in GEICAM/2013-02 (PEARL) trial cohort 2 comparing palbociclib and fulvestrant (PAL + FUL) versus capecitabine (CAPE). *First Author: Javier Pascual, Royal Marsden Hospital and The Institute of Cancer Research, London, United Kingdom*

Background: The randomized PEARL trial found no superiority of PAL plus endocrine therapy over CAPE in patients (pts) with metastatic HR-positive, HER2-negative breast cancer resistant to aromatase inhibitors (Martin M, Ann Oncol 2020). We investigated associations between baseline genomic landscape and on-treatment plasma ctDNA dynamics with progression free survival, in pts from cohort 2 of the trial. **Methods:** Plasma was collected for ctDNA analysis from -7 days to cycle 1-day 1 (C1D1) for baseline prognostic analysis and cycle 1-day 15 (C1D15) when available, and sequenced with an in-house error-corrected targeted capture panel encompassing 21 genes commonly altered in breast cancer. For predictive ctDNA dynamics analysis, a pre-specified criteria of 14 minimum days of treatment in first cycle was required and variants with VAF <0.5% in C1D1, set as limit of detection, were excluded. The circulating DNA ratio (CDR) was calculated as a weighted mean for potentially clonal mutations at C1D1. The optimal cut-off for predicting PFS was assessed by fitting a range of cut-offs, identifying the one with lower p-value on the log-rank test. Adjusted p-values, potential overestimation corrected by a shrinkage factor and bootstrapping techniques to calculate the CI95% were used in the cutpoint Cox regression model. **Results:** A total of 201 pts had a C1D1 sample sequenced for baseline prognostic analysis, 146 (73%) had baseline mutations identified and 55 (27%) had no mutations. 187 (93%) pts had a paired C1D15 sample for CDR calculations. Of these, 134 (72%) had baseline mutations detected, 120 of them (90%) above 0.5%, 14 (10%) had no calls, 1 pair failed sequencing. Both baseline and CDR subsets were representative of the overall study population. Pts with *TP53* mutations had worse PFS in the overall population (4.4 vs 9.3 months, logrank p= 0.04), with no differences between treatments. For on-treatment ctDNA dynamic analysis, median CDR (suppression) was lower in the CAPE arm (0.07 vs 0.21, p<0.01). There was an association between optimal cut-offs predicting PFS both in CAPE (suppressed 16.6 months vs high ctDNA 4.2 months, HR 2.37, CI95% 0.96-5.83, p=0.05) and PAL + FUL arms (suppressed 15.7 months vs high ctDNA 5.5 months, HR 2.14, CI95% 0.92-5, p=0.06). More ctDNA suppression associated with likelihood of objective responses (median CDR 0.1 in objective responders vs median CDR 0.2 in progressive disease p=0.03), with no statistical significance when stratified per treatment. **Conclusions:** In PEARL cohort 2, *TP53* mutations associated with poor outcome regardless of treatment allocation, suggesting aggressive behaviour not specifically linked to endocrine resistance. Lack of ctDNA suppression associated with worse outcome in both patient groups. Capecitabine resulted in greater ctDNA suppression at C1D15, likely reflecting faster ctDNA suppression. Research Sponsor: Pfizer and AstraZeneca.

1020 **Poster Discussion Session**

Survival in patients with breast cancer and history of autoimmune disease. *First Author: Demitrios Dedousis, University Hospitals, Case Medical Center - Cleveland VA Hospital, Cleveland, OH*

Background: Patients with autoimmune disease, specifically systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and Sjogren syndrome, are at reduced risk of developing breast cancer compared to those without a prior history of autoimmune disease. Despite this, little is known about the survival of patients with concurrent autoimmune disease and breast cancer. This study compared outcomes in patients with breast cancer with and without autoimmune disease. **Methods:** This study was a retrospective analysis of patients from SEER-Medicare databases from 2007-2014 with breast cancer. Patients with a history of autoimmune disease were identified using ICD-9 codes. The effects of autoimmune disease on overall survival (OS) and cancer-specific survival (CSS) were estimated using multivariable Cox regression and Gray's method respectively controlling the effects of age, race and chronic kidney disease (CKD). The cumulative CSS was estimated taking death as a competing risk. **Results:** The overall prevalence of investigated autoimmune diseases among the 137,324 patients with breast cancer was 26.69%. The most common autoimmune diseases identified were RA (23.35%), psoriasis (2.41%) and SLE (1.12%). In stage IV breast cancer patients the OS and CSS were significantly higher in patients with autoimmune disease (p values < 0.0001), with a median OS of 36 months compared to 30 months in patients without autoimmune disease. After adjusting for the effects of age, race, and CKD, autoimmune disease was still predictive of higher OS (HR: 1.46, 95% CI: 1.37 – 1.57, p < 0.0001) and CSS (HR: 1.39, 95% CI: 1.29 – 1.5, p < 0.0001). Patients with autoimmune disease and stage I-III breast cancer, had lower OS (p < 0.0001, p < 0.0001, and p = 0.026 respectively) compared to patients without autoimmune disease. **Conclusions:** We found a higher prevalence of RA, Crohn disease, ulcerative colitis, and SLE in patients with breast cancer compared to cohorts of similar age ranges in the general population. History of autoimmune disease resulted in significantly improved OS and CSS in patients with stage IV breast cancer even when controlling for age, race and CKD, in this pre-immunotherapy cohort. These results suggest that that anti-tumor immunity plays an important role in late-stage breast cancer, and could be potentially exploited to improve the effectiveness of immunotherapy. Further research into the relationship between autoimmunity and breast cancer is warranted. Research Sponsor: Department of Hematology and Oncology at University Hospitals Cleveland Medical Center.

1021 **Poster Discussion Session**

A phase 1a/b trial of imlunestrant (LY3484356), an oral selective estrogen receptor degrader (SERD) in ER-positive (ER+) advanced breast cancer (aBC) and endometrial endometrioid cancer (EEC): Monotherapy results from EMBER. *First Author: Komal L. Jhaveri, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Imlunestrant is a novel, orally bioavailable SERD with pure antagonistic properties that result in sustained inhibition of ER-dependent gene transcription and cell growth. In dose escalation, imlunestrant showed favorable safety, pharmacokinetics (PK) and preliminary efficacy in patients with ER+, HER2- aBC and ER+ EEC (Phase 1a EMBER, Jhaveri 2021). Here we present updated data from the dose escalation (Phase 1a) and dose expansion (Phase 1b) of imlunestrant monotherapy in EMBER (NCT04188548). **Methods:** Phase 1a/1b enrolled patients with ER+ aBC (prior ET sensitivity; ≤3 prior therapies for aBC in Phase 1a following protocol amendment and ≤2 in Phase 1b) and ER+ EEC (prior platinum therapy; no prior fulvestrant or aromatase inhibitor). Premenopausal women received a concomitant GnRH agonist. Serial plasma samples were obtained for PK and ctDNA analysis. Key endpoints included recommended phase 2 dose (RP2D) determination, safety and tolerability, PK, objective response rate per RECIST v1.1 (ORR: complete response [CR] or partial response [PR]) in patients with measurable disease and ≥1 post-baseline tumor assessment or discontinued prior to tumor assessment, and clinical benefit rate (CBR: CR or PR, or stable disease ≥24 weeks) in patients enrolled ≥24 weeks prior to data cut. **Results:** As of January 14, 2022, 138 patients (n = 114 aBC, n = 24 EEC) received imlunestrant monotherapy at doses ranging from 200-1200 mg QD. Median age was 62.0 years (range 32-95). Median number of prior therapies for aBC and EEC was 2 (range 0-8) and 1 (0-5), respectively. aBC patients had received a prior ET (94.7%), CDK4/6 inhibitor (92.1%), fulvestrant (50.9%) and chemotherapy (26.3%). No dose-limiting toxicities were observed. Most treatment-emergent adverse events (TEAEs) were grade 1. At the RP2D (400 mg QD, n= 69), the most common all grade TEAE's were nausea (33.3%), fatigue (27.5%), and diarrhea (23.2%). Across all doses, the incidence of treatment-related grade 3 AEs was low (3.6%). No patient discontinued due to a TEAE. In evaluable aBC patients, ORR was 8.0% (6/75) and CBR was 40.4% (42/104). In evaluable EEC patients, ORR was 5.0% (1/20 had a PR- ongoing pending confirmation) and CBR was 47.1% (8/17). Clinical benefit was observed regardless of baseline *ESR1* mutation status as determined by ctDNA sequencing. Additional biomarker analyses will be presented at the meeting. **Conclusions:** Imlunestrant continues to demonstrate a favorable side effect profile, with no cardiac or opthalmic safety signals, and has continued evidence of clinical activity in heavily pre-treated ER+ aBC and EEC patients. Clinical trial information: NCT04188548. Research Sponsor: Eli Lilly and Company.

1022 **Poster Discussion Session**

Open-label, phase 2, multicenter study of lasofoxifene (LAS) combined with abemaciclib (Abema) for treating pre- and postmenopausal women with locally advanced or metastatic ER+/HER2− breast cancer and an *ESR1* mutation after progression on prior therapies. *First Author: Senthil Damodaran, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Resistance to endocrine therapy can develop when treating estrogen receptor positive (ER+), metastatic breast cancer (mBC). Treatment with aromatase inhibitors can lead to acquired mutations in the estrogen receptor 1 (*ESR1*), which can constitutively activate the ER, leading to endocrine resistance and worse disease prognosis. Treatment options for mBC patients with an *ESR1* mutation are limited. Further, data suggest that patients could derive clinical benefit from Abema after progression on prior cyclin-dependent kinase 4/6 inhibitor (CDK4/6i). LAS, a third-generation selective estrogen receptor modulator, as monotherapy or combined with a CDK4/6i, was shown to have superior efficacy over fulvestrant (FVT) in preclinical breast cancer models expressing *ESR1* mutations. Based on these results, a phase 2 clinical trial of LAS combined with Abema was initiated in mBC patients with *ESR1* mutations. **Methods:** ELAINE 2 is an open-label, phase 2, multicenter trial evaluating the safety and efficacy of LAS combined with the CDK4/6i, Abema. Study participants were pre- and postmenopausal women with ER+/HER2- mBC with acquired *ESR1* mutation (identified by ctDNA testing), whose disease had progressed on one or two lines of hormonal therapy for metastatic disease with or without a CDK4/6i (including Abema). Patients took oral LAS 5 mg/day and Abema 150 mg BID. Treatment continued until evidence of disease progression, death, unacceptable toxicity, or withdrawal from the study. The primary endpoint was safety, and secondary endpoints were progression free survival (PFS), objective response rate (ORR), and clinical benefit rate (CBR). **Results:** 29 patients were enrolled at 16 US sites (Oct 2020 to June 2021). Mean age was 58.3 y (35-79 y); 86% were Caucasian. Most had progressed with at least 2 previous hormonal treatments (80%). All except 1 patient received a prior CDK4/6i and 72% had received prior FVT; 48% had chemotherapy in the metastatic setting. Four patients discontinued the trial due to adverse events (AEs, n = 2), consent withdrawal (n = 1), or investigator withdrawal (n = 1). No deaths occurred during the study and few Grade 3/4 AEs were observed. Most common AEs were diarrhea, nausea, and leukopenia. Five patients had an Abema dose reduction from 150 mg to 100 mg BID. To date, 11 patients have progressed and 14 continue treatment. The censored median PFS was 13.9 mos (95% CI, 8.0–NE), the ORR 33.3% (95% CI, 16.3–56.3) with 6 confirmed partial responses, and the CBR 62.1% (95% CI, 44.0–77.3). **Conclusions:** LAS combined with Abema in the ELAINE 2 trial was well tolerated and demonstrated robust and meaningful efficacy in women with ER+/HER2- mBC and an *ESR1* mutation who had progressed on previous CDK4/6i therapies. Clinical trial information: NCT04432454. Research Sponsor: Sermonix Pharmaceuticals.

1023 **Poster Discussion Session**

A phase 1b/2 study of the BET inhibitor ZEN-3694 in combination with talazoparib for treatment of patients with TNBC without gBRCA1/2 mutations. *First Author: Philippe Georges Aftimos, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium*

Background: Metastatic triple negative breast cancer (mTNBC) is an aggressive and heterogeneous cancer with limited therapeutic options. PARP inhibitors (PARPi), approved to treat patients with HER2- breast cancer with a germline BRCA1/2 (gBRCA1/2) mutation, have not shown efficacy in homologous recombination repair (HRR) proficient tumors. In pre-clinical models, the BET inhibitor (BETi) ZEN-3694 sensitizes wild-type (WT) BRCA1/2 tumors to PARPi through downregulation of HRR gene expression, providing a rationale for combination therapy. We previously reported results from the Ph 1b portion of the trial evaluating the combination of ZEN-3694 plus talazoparib, in TNBC patients without gBRCA1/2 mutations; here we present results from the completed Ph 1b/2 study. **Methods:** A Ph 1b dose finding portion (n = 15) was followed by a single arm Ph 2 Simon 2-stage portion (n = 17+20 (37)). The primary endpoint of the Ph 1b portion of the study was safety and recommended Ph 2 dose (RP2D). The secondary endpoints were pharmacokinetics (PK), pharmacodynamics (PD), and clinical benefit rate (CBR = confirmed objective response rate (ORR) + stable disease > 16 weeks). Ph 2 measured CBR as the primary endpoint, ORR and duration of response (DOR) as key secondary endpoints. Eligibility criteria for Ph 1b included TNBC (ER/PR < 10%, HER2-), WT gBRCA1/2, and > 1 prior cytotoxic regimen for mTNBC, and in the Ph2 portion ER/PR < 1% and < 2 prior cytotoxic regimens for mTNBC. Patients were dosed daily in continuous 28 day cycles until disease progression or unacceptable toxicity. Adverse events, PK, and PD in whole blood and tissue biopsies were assessed. Response endpoints were assessed per RECIST 1.1 every 2 cycles. **Results:** RP2D was determined to be 48mg qd ZEN-3694 plus 0.75mg qd talazoparib. The most common AE for the Ph 1b/2 study was thrombocytopenia (TCP) (55% any grade, 34% G3/4), which was managed with dose holds and reductions. Dose intensity analysis showed average daily doses of ZEN-3694 and talazoparib could be maintained above 40mg and 0.5mg, respectively, over 8 cycles. Robust target engagement was demonstrated using BET-dependent and HRR transcripts assessed in paired tumor biopsies. Ph 2 portion of the trial met its primary endpoint with a CBR of 30% (11/37). For the Ph 1b/2 trial, investgator assessed ORR was 22% (11/50), including 2 CR, CBR was 35% (18/51) and the median DOR was 24 weeks. For the subset of TNBC at diagnosis patients (no history of HR+ disease) , ORR was 32% (11/34), and CBR was 44% (15/34). **Conclusions:** Combination of ZEN-3694 and talazoparib demonstrated anti-cancer activity in pretreated mTNBC WT gBRCA1/2 patients. All confirmed responses were observed in TNBC at diagnosis patients, whose tumors are expected to be more sensitive to the combination due to their basal-like properties. The trial is being expanded to Ph. 2b to accrue an additional 80 TNBC at diagnosis patients. Clinical trial information: NCT03901469. Research Sponsor: Zenith Epigenetics.

1024 **Poster Discussion Session**

Results from plasmaMATCH trial cohort E: A phase II trial of olaparib and ceralasertib in patients with triple-negative advanced breast cancer (CRUK/15/010). *First Author: Alistair E. Ring, The Royal Marsden NHS Foundation Trust, Surrey, United Kingdom*

Background: The plasmaMATCH trial was an open label platform trial, consisting of circulating tumour DNA (ctDNA) testing in ~1000 patients with advanced breast cancer (ABC) linked to parallel treatment cohorts with therapies matched to mutations identified in ctDNA. Cohorts A-D have already reported (Turner N et al, Lancet Oncol 2020). Cohort E recruited patients with triple negative breast cancer (TNBC) without a targetable mutation identified at ctDNA screening, treating with olaparib (PARP inhibitor) plus ceralasertib (ATR inhibitor). **Methods:** Patients with TNBC who had received 1 or 2 lines of chemotherapy for advanced disease or relapsed within 12 months of (neo)adjuvant chemotherapy were eligible. Treatment was olaparib 300mg b.i.d continuously and ceralasertib 160mg qd on days 1–7 on a 28 day cycle, until disease progression. The primary endpoint was confirmed objective response rate by RECIST v1.1. Secondary endpoints included clinical benefit rate, progression-free survival (PFS) and safety. Biomarker analysis included response according to *BRCA* and somatic DNA repair gene status and ATM loss. Using a two-stage design with a target response rate of 25%, unacceptable response rate of 10%, alpha=2% and power=90%, ≥13 responses out of 69 evaluable stage 2 patients were required to infer efficacy (5/37 stage 1). **Results:** Between 17/09/18 and 5/10/20 75 patients enrolled in Cohort E of whom 70 were evaluable for response. The median age was 55.6 years. 42 (56%) patients had 1 and 13 (17.3%) had 2 prior line(s) of chemotherapy for metastatic disease. Efficacy is shown in Table. The most common grade ≥3 adverse events were: hypertension 12 (17%) and anaemia 9 (13%). Dose reductions and interruptions occurred in 19 (26.4%) and 34 (47.2%) patients respectively. **Conclusions:** The response rate to olaparib and ceralasertib did not meet pre-specified criteria for efficacy in the overall evaluable population. Responses were observed in patients without germline or somatic BRCA1/2 mutations. Translational analyses are underway to identify potential biomarkers of response in this population and will be presented at the meeting. Clinical trial information: ISRCTN16945804. Research Sponsor: Cancer Research UK and Stand Up To Cancer, Pharmaceutical/Biotech Company.

Response rates and median PFS.

Population	N	Number of confirmed responses	Confirmed response rate, % (95%CI)	Median PFS (IQR), months
All evaluable patients	70	12	17.1 (9.2, 28.0)	4.3 (1.9, 10.0)
***BRCA1/2* germline mutation**	10	3	30 (6.7, 65.2)	8.4 (6.1, 25.4)
***BRCA1/2* germline or somatic mutation**	13	3	23.1 (5.0, 53.8)	7.3 (4.5, 25.4)
No germline or somatic *BRCA1/2* mutation ^	55	9	16.4 (7.8, 28.8)	3.7 (1.9, 10.0)
ATM loss*	14	3	21.4 (4.7, 50.8)	3.4 (1.4, 10.2)
No ATM loss*	29	4	13.8 (3.9, 31.7)	2.5 (1.9, 10.0)

*ATM loss defined as H score ≤10. ATM loss subgroup analysis was restricted to those with no *BRCA1/2* germline or somatic mutation. 12 patients had either a missing or inadequate sample.
^2 patients did not have somatic BRCA testing.

1025 **Poster Session**

The mutational profile of ER-, PR+, HER2- metastatic breast cancer. *First Author: Neal A. Fischbach, Yale Cancer Center, New Haven, CT*

Background: ER-PR+Her2- breast cancer is a rare subtype occurring at approximately 1% of all breast carcinomas. Most of these cancers behave in an aggressive fashion with limited benefit from anti estrogen therapy, similar to triple negative breast cancer (TNBC). Better characterization of these tumors is needed for predicting clinical behavior, response to endocrine therapy, and eligibility for clinical trials. Here we sought to evaluate the mutational profile of a well curated set of ER-PR+HER2- metastatic breast cancers and compare to other receptor phenotypes. **Methods:** 2049 consecutive breast cancers submitted to Foundation Medicine for comprehensive genomic profiling (CGP) were included. ER, PR and HER2 expression were abstracted from submitted pathology reports. Cases without complete ER, PR and HER2 information in pathology reports were excluded. CGP was performed as previously described (Frampton, 2013). **Results:** Patient ages were similar across subgroups. Generally, ER-PR+HER2- tumors were rare (n = 23, 1.1%) and most similar to TNBC in their genomic profiles. These tumors harbored high rates of *TP53* and *BRCA1* alterations and low rates of *PIK3CA, ESR1,* and *CDH1* alterations. Genomic loss of heterozygosity (gLOH) was similar in the ER-PR+HER2- and ER+PR+HER2-subtypes (8.18% and 8.66% respectively), and lower than TNBC (17.19%). Notably, a high rate of *RB1* alterations were identified in the ER-PR+HER2- patients (13%, 3/23), numerically higher than the other subtypes. *EGFR*, *MET*, *PTEN*, *CDKN2A* and *KRAS* alterations were also observed at a higher frequency in ER-PR+Her2- cancers (8.7, 4.2, 39.1, 13.0 and 13.0% respectively) relative to the other subtypes. IO drug biomarkers including MSI, TMB and PD-L1 IHC were similar among the groups. **Conclusions:** The mutational profile for ER-PR+Her2- metastatic breast cancer more closely resembles TNBC than ER+ breast cancer. These data suggest molecular profiling may be a useful adjunct to optimize treatment strategies for this rare subset of cancers. Based on molecular characteristics, we recommend including ER-PR+Her2- patients in clinical trials for TNBC. Finally, genes including RB1, *CKDN2A*, *PTEN*, *EGFR* and *MET* are mutated at higher frequency in ER-PR+Her2- cancers than other subsets, suggesting unique biology with potential therapeutic implications. Research Sponsor: None.

	Overall cohort	ER+ PR+ HER2-	ER+ PR- HER2-	ER- PR+ HER2-	HER2+	TNBC
Number of Cases (% cohort)	2049	906 (44.2%)	388 (18.9%)	23 (1.1%)	178 (8.7%)	554 (27.0%)
Median Age (range)	59 (24-89+)	60 (26-89+)	61 (24-89+)	54 (29-85)	54 (30-89)	56 (22-89+)
CDH1	14.32%	17.70%	23.50%	4.30%	4.80%	5.90%
TP53	51.53%	27.80%	43.10%	91.30%	72.50%	88.10%
RB1	4.06%	3.00%	5.90%	13.00%	3.00%	4.50%
PIK3CA	37.86%	48.60%	43.30%	21.70%	36.50%	17.70%
BRCA1	3.37%	1.30%	2.30%	8.70%	1.20%	8.00%
RAD21	21.91%	18.80%	16.80%	13.00%	35.30%	26.70%
ESR1	8.97%	14.40%	9.50%	4.30%	5.40%	1.10%

1026 **Poster Session**

A phase II, single-arm, open label, Simon two-stage study of pembrolizumab in patients with metastatic HER2-negative breast cancer: Evaluation of impact of germline variants in APOBEC3B (AUROR). *First Author: Gwo Fuang Ho, Department of Clinical Oncology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia*

Background: A germline deletion in the *APOBEC3B* cytosine deaminase gene [A3Bdel] occurs more frequently in Asian women (45% heterozygous deletion (hetD) and 15% homozygous deletion (homD)) compared to in Caucasian women (15% hetD and 4% homD). Carriers are more likely to develop breast cancer, and cancers in carriers are more likely to have a hypermutator phenotype (with C > T transitions) and to be immune-enriched. In this clinical trial, we aim to evaluate whether the immune activation increases response to checkpoint immunotherapy. **Methods:** In this open label, single arm Phase II study of single agent pembrolizumab in metastatic HER2-receptor negative breast cancer patients with germline deletion in A3B, 40 evaluable subjects who have received > = 1 but < = 3 lines of therapy in a metastatic setting will be enrolled and given pembrolizumab 200 mg intravenously (IV) every 3 weeks (Q3W) for up to 35 administrations (2 years), with Objective Response Rate (ORR) using RECIST 1.1 as the primary study endpoint. The study applies a Simon two-stage design, where if at least 3 out of 22 evaluable patients achieve CR/PR in stage I, the study will proceed to stage II. **Results:** To date, 84 breast cancer patients were screened for germline A3Bdel, of whom 46 (54.8%) were heterozygous carriers and 12 (14.3%) were homozygous carriers. The study enrolled 22 female A3Bdel carriers with a median age of 59.4 years (range: 32.1, 82.9 years) between September 2020 and September 2021 for stage I analysis. On average, patients received 2 prior lines of chemotherapy in a metastatic setting [6 with 1, 8 with 2 and 8 with 3 lines of prior chemotherapy]. Complete response (CR) was observed in one patient, while partial response (PR) was observed in 4 patients, with an ORR of 22.7% (5 over 22 subjects) in stage I, meeting the predefined criteria to proceed to stage II. Notably, the patient with complete response had received 2 prior lines of chemotherapy, whereas of the patients with partial response, 1 had received 1 prior line and 3 had received 3 prior lines of chemotherapy in a metastatic setting. As the observed ORR was greater than the value of r_1 (13.6%), the study has met the statistical criteria to proceed to the stage II enrolment with an additional 18 patients required to complete the entire study. **Conclusions:** Single agent pembrolizumab demonstrates promising efficacy in germline A3Bdel carriers, who constitute almost two-thirds of Asian patients. Clinical trial information: NCT03989089. Research Sponsor: Cancer Research Malaysia, Other Foundation.

1027 **Poster Session**

Targetable genomic mutations in young women with advanced breast cancer. *First Author: Norin Ansari, Yale New Haven Hospital, New Haven, CT*

Background: Advanced breast cancer in women < 40 years is more aggressive, with worse prognosis and disease-free survival, compared to older women with the disease. With increasing availability of targeted and immune therapies, we aimed to compare genomic alterations (GA) using comprehensive genomic profiling (CGP) of tumor tissue. **Methods:** We analyzed 2,049 breast cancers submitted to Foundation Medicine for CGP. Hybrid-capture based CGP was performed to evaluate all classes of GA. Tumor mutational burden (TMB) was determined on at least 0.8 Mbp of sequenced DNA and microsatellite instability was determined on at least 95 loci. Tumor cell PD-L1 expression (defined as tumor proportion score >/= 1) was determined by IHC (Dako 22C3). We identified 28 (1.37%) patients <30 years, 159 (7.76%) between 30-39 years, and 1862 (90.87%) >/= 40 years. Breast tissue was used for CGP in 69.5% of cases and remainder of specimens were lymph node, metastatic, or unspecified. **Results:** Breast tumors were less likely to be estrogen receptor positive in younger women (54% of those <30 years, 60% of those 30-39 years, 69.4% of those >/= 40 years) and more likely to be triple negative (43%, 33%, 26.1% in the same respective groups). There was no clear pattern in HER2+ status by age (0%, 15.1%, 7.2%). Younger women had higher rates of *BRCA1* (17.9%, 10.1%, 2.6%), *BRCA2* mutations (7.10%, 5.70%, 4.1%), and *RB1* mutations (14.3%, 9.4%, 6.1%), and lower rates of *CDH1* (7.1%, 5%, 15.4%) and *PIK3CA* mutations (17.9%, 17.6%, 40.0%). Younger women were more likely to have PD-L1 expression (55.6%, 54.4%, 51.5%) but had lower frequencies of TMB >10 (0.0%, 5.0%, 8.7%). Differences are statistically significant in *BRCA1*, *CDH1*, and *PIK3CA*. **Conclusions:** These findings confirm that young women with breast cancer have actionable GA. Different mutational profiles may support differential use of targeted and immune therapies. Statistically and clinically significant differences include higher *BRCA1* mutations which may lend to PARP inhibitor use and lower *PIK3CA* mutations which may reduce alpelisib use. Higher *RB1* mutations and immunotherapy biomarker differences were not statistically significant. However, these may clinically translate into CDK4/6 resistance and reduced immunotherapy options, respectively. Research Sponsor: None.

	All Cases All Ages (n = 2049)	<30 Years of Age (n = 28)	30-39 Years of Age (n = 159)	>/= 40 Years of Age (n = 1862)	<30 Comparison to >/= 40	30-39 Comparison to >/= 40
ER+ / PR+ Status by IHC	70.0% / 49.0%	54% / 57%	60% / 45%	69.4% / 49.3%	NS / NS	P<0.0001 / NS
HER2+ (ERBB2 Amplification by CGP)	8.7%	0%	15.10%	7.2%	NS	P=.0005
TNBC Status	27.0%	43%	33%	26.1%	NS (P=.052)	NS (P=.051)
BRCA1* / *BRCA2	3.37% / 4.25%	17.90% / 7.10%	10.10% / 5.70%	2.6% / 4.1%	P=0.0009 / NS	P<.0001 / NS
RB1	6.9%	14.30%	9.40%	6.1%	NS	NS
CDH1	14.32%	7.10%	5.00%	15.4%	NS	P.0001
PIK3CA	37.86%	17.90%	17.60%	40.0%	P=.02	P<.0001
TMB > 10	8.60%	0.00%	5.00%	8.7%	NS	NS
PD-L1 Positive	51.10%	55.60%	54.40%	51.5%	NS	NS

1028 **Poster Session**

Neratinib plus fulvestrant plus trastuzumab (N+F+T) for hormone receptor-positive (HR+), HER2-negative, *HER2*-mutant metastatic breast cancer (MBC): Outcomes and biomarker analysis from the SUMMIT trial. *First Author: Komal L. Jhaveri, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: N is an oral, irreversible pan-HER TKI with activity against *HER2* mutations. Genomic analyses from the SUMMIT MBC cohort following N±F suggest that resistance to N may occur via mutant allele amplification or secondary *HER2* mutations. Adding T to N+F in SUMMIT showed encouraging durable responses in patients (pts) with HR+, *HER2*-mutant MBC and prior CDK4/6 inhibitors (CDK4/6i). **Methods:** SUMMIT (NCT01953926) enrolled pts with HR+, HER2-negative MBC with activating *HER2* mutation(s) and prior CDK4/6i. Pts received N+F+T (oral N 240 mg/d with loperamide prophylaxis, im F 500 mg d1&15 of cycle 1 then q4w, iv T 8 mg/kg initially then 6 mg/kg q3w). During the small, randomized portion of the trial, pts received N+F+T, F+T or F (1:1:1 ratio). Pts randomized to F+T or F could crossover to N+F+T at progression. Efficacy endpoints: investigator-assessed ORR and CBR (RECIST v1.1); DOR; best overall response. Pre-treatment tumor tissue was centrally assessed retrospectively by next-generation sequencing. ctDNA from patient samples was assessed by NGS. **Results:** SUMMIT has completed enrolment; we report efficacy from 45 pts in the N+F+T cohort, plus 10 pts who progressed on F (n=6) or F+T (n=4) and crossed over to N+F+T (Table). *HER2* allelic variants in the 45 N+F+T pts and ORR (%) (pts may have >1 mutation) were: V777L (n=6, 50%), L755S/P (n=15, 40%), S310F (n=4, 50%), exon 20 insertion (n=11, 36%), other KD missense (n=6, 33%), TMD missense (n=2, 0%), exon 19 deletion (n=1, 0%). **Conclusions:** N+F+T is a promising combination for HR+, *HER2*-mutated MBC with prior exposure to CDK4/6i, across a range of activating *HER2* mutations. Results from the upcoming Apr 2022 data cut, including biomarkers, safety, mechanisms of acquired resistance, and preclinical mechanism of N+T, will be presented. Clinical trial information: NCT01953926. Research Sponsor: Puma Biotechnology, Inc.

Efficacy findings: HR+, *HER2*-mutant MBC with prior CDK4/6i.

	All HR+ prior CDK4/6i (N+F+T) (n=45)	Randomized HR+ (F+T) (n=7)	F+Tcrossover to N+F+T (n=4)	Randomized HR+ (F) (n=7)	Fcrossover to N+F+T (n=6)
Objective response,[a] n (%) (95% CI)	17 (38) (24–54)	0 (0–41)	1 (25) (0.6–81)	0 (0–41)	2 (33) (4–78)
CR PR	1 (2)16 (36)	00	01 (25)	00	02 (33)
Median[b] DOR, months (95% CI)	14.4 (6.4–NE)	NE	NE	NE	6.3 (6.2–6.4)
Clinical benefit,[c] n (%) (95% CI)	21 (47) (32–62)	0 (0–41)	1 (25) (0.6–81)	0 (0–41)	5 (83) (36–100)
CR PR SD ≥ 24 weeks	1 (2)16 (36)4 (9)	000	01 (25)0	000	02 (33)3 (50)
Median PFS, months (95% CI)	8.2 (4.2–15.1)	3.9 (1.9–4.1)	NE	4.1 (1.6–4.1)	8.3 (3.9–10.3)

[a]CR or PR confirmed ≥ 4 weeks after response criteria met.
[b]Kaplan-Meier analysis.
[c]Confirmed CR or PR or SD for ≥ 24 weeks. Tumor response based on investigator assessment (RECIST v1.1).
CI, confidence interval; CR, complete response; DOR, duration of response; F, fulvestrant; HR+, hormone receptor-positive; N, neratinib; NE, not evaluable; PR, partial response; SD, stable disease; T, trastuzumab.

1029 **Poster Session**

Detection of presumed germline pathogenic variants of hereditary breast cancer predisposition genes in circulating tumor DNA: SCRUM-Japan MONSTAR-SCREEN. *First Author: Masaya Hattori, Department of Breast Oncology, Aichi Cancer Center, Nagoya, Japan*

Background: Approximately 5-10% of breast cancer are hereditary. Variant allele frequency (VAF) of hereditary breast cancer predisposition genes in circulating tumor DNA (ctDNA) may be useful for detecting presumed germline pathogenic variants. **Methods:** One hundred and sixty-eight patients with advanced breast cancer (ABC) who underwent ctDNA and tumor tissue sequencing analyses in the SCRUM-Japan MONSTAR-SCREEN, a cancer genome screening project in Japan, from December 2019 to November 2021 were included. The patients were tested and monitored for their genomic alterations by FoundationOne Liquid assay or FoundationOne Liquid CDx assay. The pathogenic variants (PV) of hereditary breast cancer predisposition genes with VAF of 30% or higher in ctDNA were defined as PGPV. The VAF of *BRCA1/2* on ctDNA analyses in *BRCA1/2* germline pathogenic variant (GPV) carriers and the prevalence of PGPV in five hereditary breast cancer predisposition genes, including *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, and *PALB2*, were investigated. **Results:** From 168 patients with ABC, including 115 Luminal, 32 HER2-positive, and 21 triple negative breast cancer, with a median age of 58 years, 39 PVs in 5 genes were identified with a median VAF of 0.62% (range: 0.1-84.77). ctDNA identified GPV of known *BRCA1/2* GPV carriers (1 with *BRCA1* and 6 with *BRCA2*), with a median VAF of 51.4% (range: 48.2-77.5). The VAF of GPV on ctDNA were higher than 30% in subsequent consecutive samples. Among 161 patients with ABC, excluding 7 known *BRCA1/2* GPV carriers, 6 PGPV (1 with *BRCA1,* 3 with *BRCA2,* and 2 with *PALB2*) were detected, with a median VAF of 65.5% (range: 51.2-84.8). Subsequent confirmatory tests were performed for two PGPV, and the variants were confirmed to be of germline origin. **Conclusions:** VAF on ctDNA analysis can help to easily detect PGPV of hereditary breast cancer predisposition genes. The PGPV detected in ctDNA analysis should be validated by established germline tests, and the results could provide opportunities for targeted therapies, as well as cancer risk assessment of patients and their relatives. Research Sponsor: None.

1030 **Poster Session**

Association of interleukin-enhanced factor 2 (ILF2) expression with prognosis and clinico-genomic features in breast cancer (BC). *First Author: Matias A. Bustos, Saint John's Cancer Institute at Providence Saint John's Health Center, Santa Monica, CA*

Background: Novel prognostic and predictive biomarkers beyond traditional histological subtypes are needed to better inform outcomes and enhance therapy guidance in breast cancer (BC). We have previously reported that ILF2 was overexpressed in TNBC cell lines and has a functional role in DNA and RNA metabolism, making it a promising biomarker for risk assessment and treatment decisions. Herein, we aim to leverage a large clinico-genomic dataset to further characterize ILF2 in BC patients (pts). **Methods:** A total of 9456 BC tissue samples underwent molecular profiling at Caris Life Sciences (Phoenix, AZ). Analyses included next generation sequencing of DNA (592 Gene Panel, or Whole Exome Sequencing), and RNA (Whole Transcriptome Sequencing), and immunohistochemistry (IHC). Wilcoxon and Fisher's exact were used to determine statistical significance. Overall survival (OS) was obtained from insurance claims and Kaplan-Meier estimates were calculated. Spearman correlation was used to identify highly correlated genes (ρ>0.6) with ILF2 and significant genes that were subsequently analyzed via pathway analysis using STRING. **Results:** BC pts were grouped into ILF2-High (H, top quartile) and ILF2-Low (L, bottom quartile) based on mRNA expression (TPM). ILF2-H pts were significantly younger (73 vs 80% for pts >50), enriched in ductal histology (90.9 vs 77.7%), TNBC subtype (48.9 vs 18.9%), and had a higher CNS metastases rate (4.3 vs 1.4%) compared to ILF2-L pts (all q<0.0001). ILF2 overexpression was associated with significantly inferior OS in all BC pts (HR 3.38, 95%CI: 2.97 – 3.84); when stratified into known BC hormonal receptor (HR) subtypes, ILF2 was prognostic in both HR+ BC (HR 1.7, 95 CI: 1.34-2.19) and TNBC (HR 3.8, 95 CI: 3.1-4.7), all p<0.0001. In TNBC (n=2468), ILF2-H was associated with a higher frequency of TP53 mutations(mt), lower rate of PIK3CA mt and higher amplification of CCNE1 and FGF23; in HR+/HER2- BC (n = 5071), an association with a higher rate of TP53 mt, PD-L1 expression, NOTCH2 and CCND2 amplification was seen (Table). No significant molecular correlation with ILF2 was seen in HR-/HER2+ BC (n=682). In TNBC, ILF2 expression was significantly correlated with genes involved in spliceosome, cell cycle and RNA transport pathways. In HR+/HER2- BC, ILF2-correlated genes were significantly enriched in mismatch repair and DNA replication pathways (p<0.05 for all factors individually). **Conclusions:** High expression of ILF2 is associated with a poorer prognosis independent of subtype in BC and our study warrants further investigation on ILF2 as a diagnostic and therapeutic target. Research Sponsor: None.

Fold change of ILF2 median in altered/WT tumors (>1, positive; <1, negative association, q <0.05).

Mt	TNBC	Mt	HR+/HER2-
TP53	1.4	TP53	1.2
PIK3CA	0.7	MAP2K4	0.8
ARID1A	0.7	IHC	
HRAS	0.5	IHC-PD-L1	1.2
KRAS	0.6	IHC-AR	0.7
TERT	0.6	Amp	
		NOTCH2	2.1
Amp		FGF23	2.3
FGF23	1.5	CCND2	2.3
CCNE1	1.4	CCNE1	1.6

1031 **Poster Session**

Zanidatamab (zani), a HER2-targeted bispecific antibody, in combination with docetaxel as first-line (1L) therapy for patients (pts) with advanced HER2-positive breast cancer: Preliminary results from a phase 1b/2 study. *First Author: Keun Seok Lee, National Cancer Center, Center for Breast Cancer, Goyang, South Korea*

Background: HER2-targeted agents have improved outcomes in HER2-positive breast cancer, but some pts develop resistance, relapse, or do not respond to current 1L therapies. Zani, also known as ZW25, is a novel HER2-targeted bispecific antibody that binds to two distinct extracellular domains of HER2. In a Phase 1 trial (NCT02892123) zani was well tolerated and demonstrated preliminary antitumor activity as monotherapy/with chemotherapy in pts with pre-treated advanced HER2+ breast cancer. **Methods:** Cohort 1 of this ongoing open-label, Phase 1b/2 study (NCT04276493) is evaluating zani in combination with docetaxel as a 1L therapy in adult females with advanced HER2+ breast cancer who may have received prior neoadjuvant/adjuvant treatment. Cohort A pts received zani 30 mg/kg IV, Cohort B pts received zani 1800 mg IV, both with docetaxel 75 mg/m^2 IV Q3W. Primary endpoints were safety and investigator (INV)-assessed objective response rate (ORR) per RECIST v1.1. Secondary endpoints included INV-assessed duration of response (DoR), disease control rate (DCR) and progression-free survival (PFS). **Results:** As of Nov 26, 2021, 25 pts with a median age of 57.0 years (range: 33.0–80.0) were assigned to Cohort A (n=11) or B (n=14). Median study follow-up was 7.0 months (range: 1.1–17.4) and the median number of treatment cycles was 10 (range: 2–20), 16 (64.0%) pts remained on treatment. Of the 22-efficacy evaluable (EE) pts, confirmed ORR was 86.4% (95% CI: 65.1, 97.1). The 6 months PFS rate was 90.9% (95% CI: 68.3, 97.7). Efficacy data are summarized in Table 1. All pts experienced ≥ 1 treatment emergent adverse event (TEAE) and 17 (68.0%) pts experienced ≥ Grade 3 TEAEs. In total, 23 (92.0%) pts experienced treatment related TEAEs (trTEAEs), and 17 (68.0%) pts experienced ≥ Grade 3 trTEAEs. The most common trTEAEs were diarrhea (56.0%) and decreased neutrophil count (52.0%). Serious trTEAEs occurred in two (8.0%) pts, trTEAEs leading to treatment discontinuation occurred in one (4.0%) pt and no trTEAEs led to death. **Conclusions:** Zani and docetaxel combination demonstrated antitumor activity in 1L therapy for advanced HER2+ breast cancer, with a manageable safety profile. Clinical trial information: NCT04276493. Research Sponsor: This study was sponsored by BeiGene, Ltd. Medical writing support, under the direction of the authors, was provided by Victoria Dagwell, MSc, of Ashfield MedComms, an Ashfield Health company, and funded by BeiGene, Ltd.

Summary of efficacy results (EE analysis set*).

	Cohort A (n=9)	Cohort B (n=13)	Total (n=22)
Confirmed best overall response, n (%)			
Complete response	1 (11.1)	0 (0)	1 (4.5)
Partial response	7 (77.8)	11 (84.6)	18 (81.8)
Stable disease	0 (0)	1 (7.7)	1 (4.5)
Progressive disease	1 (11.1)	1 (7.7)	2 (9.1)
Confirmed ORR, n (%) 95% CI	8 (88.9) 51.8, 99.7	11 (84.6) 54.6, 98.1	19 (86.4) 65.1, 97.1
Confirmed DCR, n (%) 95% CI	8 (88.9) 51.8, 99.7	12 (92.3) 64.0, 99.8	20 (90.9) 70.8, 98.9
Confirmed DoR, range	1.4–12.4	1.5–5.6	1.4–12.4

*Three pts without any post-baseline tumor assessments were excluded from EE analysis set.
Data cut-off: Nov 26, 2021.

1032 **Poster Session**

Serena-1: Updated analyses from a phase 1 study (parts C/D) of the next-generation oral SERD camizestrant (AZD9833) in combination with palbociclib, in women with ER-positive, HER2-negative advanced breast cancer. *First Author: Mafalda Oliveira, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain*

Background: SERENA-1 (NCT03616587) is a Phase 1, multi-part, open-label study of camizestrant in women with ER+, HER2– advanced breast cancer (ABC). Parts A/B (escalation/expansion) assessed camizestrant monotherapy and have been presented previously. Parts C/D examine camizestrant in combination with palbociclib; here we present mature data from camizestrant 75 mg in combination with palbociclib; 75 mg being the camizestrant dose currently under investigation in the Phase 3 studies SERENA-4 (NCT04711252) and SERENA-6 (NCT04964934). **Methods:** The primary objective was to determine the safety and tolerability of camizestrant once daily (QD) with palbociclib. Secondary objectives included anti-tumor response and pharmacokinetics (PK). Prior treatment with < 2 lines of chemotherapy in the advanced setting was permitted. There was no limit on the number of lines of prior endocrine treatment in the advanced setting; prior treatment with CDK4/6 inhibitors and fulvestrant (F) was permitted. **Results:** As of 9 September 2021, 25 patients had received camizestrant 75 mg QD in combination with palbociclib. Tolerability of the combination of camizestrant 75 mg and palbociclib was consistent with that of each drug individually. No patient required camizestrant dose interruption/reduction/discontinuation due to a camizestrant-related adverse event (AE); moreover, none experienced a Grade ≥3 camizestrant-related AE. All camizestrant-related heart rate reductions were Grade 1 (asymptomatic). All camizestrant-related visual effects were Grade 1 (mild), apart from one patient who experienced transient Grade 2 (moderate) visual effects that resolved to Grade 1 without dose modification. Camizestrant-related gastrointestinal disorders were all Grade 1, except one instance of Grade 2 nausea lasting one day. PK data for camizestrant 75 mg QD and palbociclib combined were broadly consistent with camizestrant as monotherapy and published palbociclib steady-state PK data, further supporting the use of camizestrant 75 mg QD (Phase 3 dose) in combination with the approved palbociclib doses. In these heavily pre-treated patients (48% prior chemotherapy, 80% prior CDK4/6i, 68% prior F; all in advanced disease setting) and of whom 60% had visceral metastases, the clinical benefit rate at 24 weeks was 7/25 (28%). **Conclusions:** The PK and safety profile of camizestrant 75 mg QD in combination with palbociclib is favorable in this mature Phase 1 dataset. Despite extensive pre-treatment - including chemotherapies, CDK4/6i, and F - camizestrant 75 mg QD in combination with palbociclib exhibits encouraging clinical activity. The results from the ongoing Phase 3 studies, SERENA-4 and SERENA-6, will further elucidate the role of this combination in the treatment of patients with HR+/HER2– ABC. Clinical trial information: NCT03616587. Research Sponsor: AstraZeneca.

1033 **Poster Session**

Pyrotinib in combination with metronomic oral vinorelbine in patients with HER2-positive advanced breast cancer who had failed prior trastuzumab-based therapy: A single-center, single-arm, prospective phase 2 study. *First Author: Chunfang Hao, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China*

Background: In 15% to 30% of breast cancers, human epidermal growth factor receptor 2 (HER2) is overexpressed, this is related to aggressive disease and poor prognosis. Although important clinical benefits for patients have been achieved by the use of the HER2 antibody trastuzumab, 50% to 74% of patients with metastatic disease have no response to treatment, and approximately 75% progress within one year. The purpose of this study was to evaluate the efficacy and safety of oral pyrotinib in combination with oral metronomic vinorelbine in patients with HER2-positive advanced breast cancer who had failed prior trastuzumab-based therapy. **Methods:** This prospective phase 2 study enrolled patients aged 18-75 years with HER2-positive advanced breast cancer who had failed prior trastuzumab-based therapy, and had an Eastern Cooperative Oncology Group performance score of 0-2. Patients received pyrotinib 400 mg once daily and vinorelbine 40 mg once on Monday, Wednesday, Friday of each week until disease progression or unacceptable toxicity. Both pyrotinib and vinorelbine were orally administered 30 min after meals. The primary endpoint was progression-free survival (PFS). The secondary endpoints were objective response rate (ORR), disease remission rate (DCR), overall survival (OS), quality of life (QoL) and safety (CTCAE 5.0). The follow-up of this study is ongoing, but enrolment is closed. This study is registered on Clinical Trials.gov, number NCT04903652. **Results:** Between Oct 21, 2019, and Jan 21, 2022, 36 patients were enrolled and all of them were included in the intent-to-treat (ITT) population. 20 of 36 patients had disease progress or death. Median follow-up was 16.23 months. The median PFS (mPFS) was 14.23 months (95% CI 8.13-20.33). The ORR and DCR were 38.9% and 83.3%, respectively. The median OS was not reached. Grade 3 adverse events (AEs) occurred in 17 of 36 patients, the most common were diarrhea 27.8% and stomachache 5.6%. No grade 4 AEs were observed. **Conclusions:** Pyrotinib combined with metronomic oral vinorelbine showed promising efficacy and manageable safety in patients with HER2-positive advanced breast cancer who had failed prior trastuzumab-based therapy. This study might represent a potential treatment option for these patients. Clinical trial information: NCT04903652.. Research Sponsor: CSCO-Hengrui Cancer Research Fund (Y-HR2018-075).

1034 **Poster Session**

Pyrotinib monotherapy or pyrotinib in combination with capecitabine could significantly prolong progression-free survival and overall survival in patients with HER2-positive metastatic breast cancer. *First Author: Xiuwen Guan, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: In the NALA phase III trial, irreversible pan-ErbB tyrosine kinase inhibitor (TKI) neratinib plus capecitabine demonstrated significant improvement in the progression-free survival (PFS), but no significant benefit in overall survival (OS) compared to lapatinib plus capecitabine. However, another TKI pyrotinib plus capecitabine showed significant benefits in PFS and a trend of OS benefits in the PHOEBE phase III study. But in general, current data on survival of irreversible TKIs in patients with HER2-positive metastatic breast cancer (MBC) was limited. Thus, we performed a pooled analysis of individual patient data from the phase I to III trials in HER2-positive MBC patients receiving pyrotinib or pyrotinib combined with capecitabine, to provide a cumulative assessment on long-term outcomes of irreversible TKI. **Methods:** Individual patient data was collected and analyzed from the phase I trial for pyrotinib and pyrotinib plus capecitabine, the Pivotal phase II trial and the PHOEBE phase III trials that enrolled patients in China National Cancer Center. Next-generation sequencing was performed on circulating tumor DNA for predictive biomarkers in the phase I trial. **Results:** Between August 2013 and October 2018, a total of 120 patients were assigned to received pyrotinib (n = 38), pyrotinib plus capecitabine (n = 53) and lapatinib plus capecitabine (n = 29) across the above four trials. The median follow-up duration for OS was 73.6 months (95% CI:69.9-77.3 months). The estimated median PFS was 8.2 months (95% CI:5.6-10.9 months) in the pyrotinib monotherapy group and 22.0 months (95% CI:13.2-30.8 months) in the pyrotinib plus capecitabine group (P= 0.002), while the median OS was 27.1 months (95% CI: 21.6-32.5 months) in the pyrotinib monotherapy group and 44.5 months (95% CI: 30.8-58.1 months) in the pyrotinib plus capecitabine group (P= 0.065). In this pooled analysis, pyrotinib 400mg in combination with capecitabine, recommended for phase II and III trials, had significantly longer PFS (22.0 vs 6.9 months, P< 0.001) and OS (59.9 vs 31.2 months, P= 0.035) than lapatinib plus capecitabine. Analysis of all genetic alterations in baseline blood samples suggested that the patients harbored concomitant mutations in HER2-related signaling network (including HER2 bypass signaling pathway, PI3K/Akt/mTOR pathway and TP53) were observed with significantly poorer PFS and OS compared to none or one genetic alteration (median PFS, 7.3 vs. 26.1 months, P= 0.003; median OS, 25.1 vs. 48.0 months, P= 0.013). **Conclusions:** This pooled analysis based on phase I to III trials revealed promising PFS and OS was achieved in pyrotinib and pyrotinib plus capecitabine. Concomitant mutations in HER2-related signaling network may be a potential efficacy and prognosis biomarker for pyrotinib in HER2-positive MBC. Clinical trial information: NCT01937689,NCT02361112,NCT02422199,NCT03080805. Research Sponsor: National Nature Science Foundation of China(82103634).

1035 **Poster Session**

Pyrotinib plus nab-paclitaxel in patients with HER2-positive advanced or metastatic breast cancer: A multicenter, single-arm, open-label phase 2 trial. *First Author: Huan Li, Department of Breast internal medicine, Liaoning Cancer Hospital and Institute, Shenyang, China*

Background: For human epidermal growth factor receptor 2 (HER2) positive advanced or metastatic breast cancer, the standard therapeutic strategy is HER2-targeted agents combined with a taxane. This multicenter, single-arm phase 2 trial was designed to assess the efficacy and safety of pyrotinib (a brand-new generation, irreversible anti-HER2 tyrosine kinase inhibitor) plus nab-paclitaxel in patients with HER2-positive advanced or metastatic breast cancer. **Methods:** This was a multicenter, single-arm, open-label phase 2 trial conducted at seven centers in China (ChiCTR1900023653). Women aged 18-75 years, with histologically or cytologically confirmed HER-2 positive (immunohistochemistry [IHC] 3+ or positive confirmed by fluorescence in situ hybridization) advanced or metastatic breast cancer and with Eastern Cooperative Oncology Group performance score (ECOG PS) of 0-1 were enrolled. Patients with primary resistance to trastuzumab and bone-only metastases were excluded. Eligible patients received pyrotinib (400 mg, po, qd) plus nab-paclitaxel (125 mg/m^2, iv, day 1/8/15) for each 28-day cycle until disease progression, unacceptable toxicity, consent withdrawal or death. The primary endpoint was objective response rate (ORR), defined as the proportion of patients with complete response (CR) or partial response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Secondary endpoints included progression-free survival (PFS), overall survival, safety and quality of life. **Results:** Between December 2019 and December 2021, 51 patients were enrolled. The median age was 55 years (range 35–72). Twenty-three patients (45.1%) had ECOG PS of 0. Ten patients (19.6%) with metastatic disease had previously received first-line treatment and 28 (54.9%) had received prior treatment with trastuzumab. More than half (29 of 51, 56.9%) had hormone receptor-positive disease. Visceral metastases occurred in 56.9% of the patients (29 of 51) and 26 patients (51.0%) were menopausal. The data cutoff for the present analysis was January 21, 2022. Among 38 evaluable patients, four patients (10.5%) had CR, 27 (71.1%) had PR, six (15.8%) had stable disease, and one (2.6%) had progressive disease. The confirmed ORR was 81.6% (95% CI 65.1-91.7%). The PFS data were still immature. The most common grade ≥3 treatment-emergent adverse events included neutropenia (14 of 51, 27.5%), diarrhea (10 of 51, 19.6%), fatigue (5 of 51, 9.8%) and peripheral neuropathy (4 of 51, 7.8%). **Conclusions:** Pyrotinib combined with nab-paclitaxel showed a promising antitumor activity with good tolerance in patients with HER2-positive advanced or metastatic breast cancer. Clinical trial information: ChiCTR1900023653. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

1036 **Poster Session**

Monitoring and management of interstitial lung disease/pneumonitis among patients with metastatic breast cancer treated with trastuzumab deruxtecan. *First Author: Jonathan K. Kish, Cardinal Health, Dublin, OH*

Background: Trastuzumab Deruxtecan (T-DXd) was associated with an increased risk of interstitial lung disease (ILD)/pneumonitis (P) in metastatic breast cancer (mBC) patients (pts) in clinical trials, leading to ILD/P monitoring and management guidelines in the product label. This study aims to describe the monitoring and management of ILD/P during T-DXd therapy among US community oncology practices. **Methods:** Oncologists in the Cardinal Health Oncology Provider Extended Network (OPEN) participated in a cross-sectional survey on monitoring approaches for ILD/P among mBC pts. Participating physicians provided data from medical charts of up to 10 pts who were treated with T-DXd regarding presence of ILD/P symptoms, management, and outcomes of ILD/P symptoms. **Results:** Twenty-eight physicians from across the U.S participated and provided data on 149 T-DXd pts. Nearly all physicians reported they were monitoring ILD/P after T-DXd initiation by physical examination (n = 27), symptoms checklist (n = 25) and pulse oximetry (n = 23) at every visit, whereas fewer reported performing lung CT scan (n = 18), echocardiogram (n = 13), chest X-ray (n = 12), lung PET scan (n = 10), pulmonary function tests (n = 8) and diffusion testing (n = 7) on a less frequent basis. Among 149 T-DXd pts, 4 pts were diagnosed with ILD/P over an average T-DXd treatment duration of 5.5 months. All 4 cases initiated T-DXd treatment at 5.4mg/kg every 3 weeks, experienced ILD/P within the first 5 cycles of T-DXd, were diagnosed with lung CT scan and initially presented with Grade 2 symptomology (2 cases progressed to Grade 3). For both cases that remained as Grade 2, ILD/P completely resolved within 23 days. One case received IV methylprednisolone (1000mg daily; duration of therapy (DOT): 3 days) during hospitalization, oxygen therapy and T-DXd was permanently discontinued; whereas the other one received oral prednisone (started at 40mg daily and tapered to 5mg daily; DOT: 7 days) and T-DXd dose was held. For the two grade 3 cases, one received IV methylprednisolone (125mg daily; DOT: 7 days) during hospitalization, T-DXd dose was held, and ILD/P completely resolved within 11 days; whereas the other case received oral prednisone (started at 80mg daily and tapered to 5mg daily; DOT: 63 days), oxygen therapy, T-DXd was permanently discontinued, and ILD/P resolved with sequela within 46 days. **Conclusions:** ILD/P incidence in this small study sample of patients receiving T-DXd treatment was 2.7%. Although general awareness of ILD and routine screening by pulse oximetry and physical exam were common, management approaches for ILD/P were not always consistent with T-DXd prescribing information. Further physician education may be needed to improve appropriate management of ILD/P and outcomes for T-DXd pts. Research Sponsor: Daiichi Sankyo.

1037 **Poster Session**

Updated results and biomarker analyses from the phase I trial of A166 in patients with HER2-expressing locally advanced or metastatic solid tumors. *First Author: Xichun Hu, Department of Medical Oncology, Fudan University Cancer Hospital, Shanghai, China*

Background: A166, an antibody-drug conjugate, with an anti-HER2 antibody site-specifically conjugated to Duo-5 (anti-microtubule agent), via a stable protease-cleavable valine citrulline linker, has proved its safety and efficacy in patients with HER2 positive breast cancer (Xichun Hu et al. ASCO 2021). Here, we report updated data and biomarker analyses from this single-arm, multi-center, open-label, phase I trial (CTR20181301). **Methods:** This study has two parts: dose escalation and dose expansion. In the expansion part, dose cohorts were expanded at 4.8 and 6.0 mg/kg Q3W, and the primary endpoint was ORR, as assessed according to the RECIST 1.1. Next-generation sequencing was performed on tissue-derived DNA and blood-derived circulating tumor DNA (ctDNA). **Results:** As of Dec 10, 2021, in total 58 female pts were enrolled in the expansion dose cohorts. Median age was 53.5 years (range 26-71), 58 pts (100%) had prior HER2-targeted therapy with the median lines of 4, including 100% received trastuzumab ± pertuzumab, 94.8% received anti-HER2 TKIs, and 20.7% received anti-HER2 ADCs in the metastatic setting. Any grade treatment-related AEs (TRAEs) were documented in 100.0% (58/58) of pts. Common TRAEs were corneal epitheliopathy (98.3%), blurred vision (89.7%), peripheral sensory neuropathy (67.2%), muscular weakness (36.2%) and dry eyes (32.8%). Most common grade ≥3 TRAEs were corneal epitheliopathy (34.5%), blurred vision (22.4%) and ulcerative keratitis (10.3%). 7 pts had serious AEs, 3 of whom were possibly related to the study drug, including thrombosis, peripheral motor neuropathy and muscular weakness. TRAEs led to 39.7% (23/58) dose reduction and 1.7% (1/58) treatment discontinuation. All patients were evaluable for efficacy with the best ORR being 73.91% (17/23; 95% CI, 51.59 to 89.77) and 68.57% (24/35; 95% CI, 50.71 to 83.15), mPFS being 12.30 months (95% CI, 6.00 to not reached) and 9.40 months (95% CI, 4.00 to 10.40) in 4.8 and 6.0 mg/kg cohort, respectively. Of 23 pts treated at 4.8 mg/kg dose level, one had a confirmed and sustained complete response lasting 7+ months. At the time of the data cutoff, 24 pts (41.4%) continued to receive A166 treatment.NGS of 520 genes was performed on tissue-derived DNA and ctDNA of baseline tumor tissue samples (n = 42) and blood samples (n = 53), respectively, and post-treatment blood samples (n = 8). Univariate and multivariate analysis showed that baseline PIK3CA/PTEN status had no influence on the PFS, and gave an idea of FGFR1 amplification as a potential negative predictor of A166 efficacy in HER2-positive breast cancer. **Conclusions:** The previously demonstrated preliminary clinical benefit of A166-ADC was maintained with no new safety signals, which demonstrated manageable toxicity and encouraging anti-tumor activity in heavily pretreated HER2-positive metastatic breast cancer patients. Clinical trial information: CTR20181301. Research Sponsor: Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

1038 **Poster Session**

Early clinical safety and pharmacokinetics data of DZD1516, an BBB-penetrant selective HER2 inhibitor for the treatment of HER2-positive metastatic breast cancer. *First Author: Xichun Hu, Department of Medical Oncology, Fudan University Cancer Hospital, Shanghai, China*

Background: Patients with HER2+ metastatic breast cancer (MBC) are at high risk of developing central nervous system metastases. DZD1516 is a reversible HER2-specific tyrosine kinase inhibitor (TKI) with full blood-brain barrier (BBB) penetration. Here we report the preliminary safety and PK data from the ongoing phase 1 study (NCT04509596) in patients with HER2+ MBC who relapsed from multiple prior treatments. **Methods:** Eligible patients received single oral dosing of DZD1516 on C0D1 and then twice daily (BID) oral dosing from C1D1 in a continuous 21-day cycle until disease progression, unacceptable toxicity or withdrawal of consent. The primary objective is to investigate the safety and PK of DZD1516 as a single agent. **Results:** As of 17 January 2022, DZD1516 was explored in 21 HER2+ MBC patients from the USA and China. DZD1516 was well tolerated at doses < 300 mg, BID. Two DLT events were reported in the 300 mg cohort. In all cohorts, 20 (95.2%) patients reported treatment-emergent adverse events (TEAEs), and 3 (14.3%) patients reported grade 3 drug-related TEAE. Two patients had dose interruption and one patient had dose reduction due to TEAE, all in the 300 mg cohort. Majority of TEAEs were reversible. The longest treatment duration was > 3 months. In all cohorts, the most common (> 20%) TEAEs included headache (42.9%), vomiting (38.1%), nausea (23.8%) and hemoglobin decreased (23.8%). At doses < 300 mg, there is no diarrhea or rash reported. PK data showed that combined exposure of DZD1516 and its active metabolite DZ2678 increased in a dose-proportional manner across the dose ranges. Elimination half-life was about 15-19 hrs. About 2-fold accumulation of DZD1516 in AUC was observed on multiple doses. *In vitro*, both DZD1516 and DZ2678 showed good permeability, and were not substrates of P-gp and BCRP. In patients, $K_{puu,CSF}$ of DZD1516 and DZ2678 was around 2.13 and 0.66, respectively, suggesting good CNS penetration. At the time of data cutoff, 16 patients had at least one post treatment anti-tumor assessment. With a median of 7 lines of prior treatment, the best anti-tumor response was stable disease. **Conclusions:** Preliminary clinical data showed that DZD1516 is a full BBB-penetrant HER2 TKI, with good safety profile. Consistent with its high selectivity, no wide type EGFR related AEs have been reported. Further evaluation of its safety and efficacy is ongoing. Clinical trial information: NCT04509596. Research Sponsor: Dizal Pharmaceutical.

Demographics	25 mg (N = 1)	50 mg (N = 4)	100 mg (N = 4)	200 mg (N = 5)	250 mg (N = 3)	300 mg (N = 4)	Total (N = 21)
Median age	64	57.5	50	61	47	42	57
Race, n							
Asian	1	3	2	5	3	3	17
White	0	0	2	0	0	0	2
Other	0	1	0	0	0	1	2
Patient type, n	1	4	4	5	3	4	21
Brain mets	0	4	3	2	2	2	13
Leptomeningeal mets	0	0	1	0	0	0	1
Without CNS mets	1	0	0	3	1	2	7
Median line of prior systemic therapy	7	9	4.5	10	9	5.5	7
Therapy Class, n							
HER2 antibody and/or ADC	1	4	4	5	3	4	21
HER2 TKI	0	3	3	5	3	4	18
Chemo	1	4	4	5	3	4	21
Others	0	2	0	3	3	2	10

1039 **Poster Session**

Survival of elderly patients with HER2+/HR- metastatic breast cancer in clinical practice: SEER-Medicare data 2012-2016. *First Author: Zhonghui Ou, MCPHS University, Boston, MA*

Background: Older patients with human epidermal growth factor 2-positive (HER2+) metastatic breast cancer(mBC) are underrepresented in clinical trials. We aim to assess the overall survival (OS) and breast cancer-specific survival of elderly women with de novo HER2+/hormone receptor-negative (HR-) mBC in a real-world setting. **Methods:** Elderly women with HER2+/HR- mBC treated with chemotherapy and/or HER2-targeted agents and with continuous Medicare Part A, B, and D coverage 1-year before diagnosis were identified from the SEER-MEDICARE database 2012-2016. Patients were retrospectively followed from metastatic diagnosis until death, disenrollment from Medicare A, B, or D, or end of the observation period. Patients' year and month of diagnosis and death were retrieved from SEER. Death dates were verified with Medicare records reported by the Social Security Administration (SSA). For all-cause deaths, Kaplan-Meier analysis was used to estimate overall survival. The cumulative incidence competing risk (CICR) method based on cumulative incidence function (CIF) was used to estimate breast cancer-specific death incidence. **Results:** Seventy-three patients (mean age at diagnosis, 75.0±7.7 years) met the inclusion criteria. Among them, 56 were treated with trastuzumab ± pertuzumab /chemotherapy as first-line treatment, and 17 were treated with chemotherapy only. The median time to initiate trastuzumab-based treatment from diagnosis was 2.5 months, and the longest trastuzumab treatment length was over 44 months. The median follow-up for OS was 13 months. One patient developed stomach cancer 6 months after breast cancer diagnosis. In Kaplan-Meier analysis, censoring or not censoring this patient after second cancer development resulted in a median OS of 19 months (95% CI, 9-24 months) and 18 months (95% CI, 9-22 months). The OS at the end of 46 months was approximately 25%. Five patients died from other causes, including lung cancer, cerebrovascular diseases, aortic aneurysm and dissection, pneumonia and influenza, and heart diseases during treatment. Considering these competing risks, 50% (95% CI, 36%-64%) of patients specifically died from breast cancer between 21 and 22 months, estimated by the CICR method. **Conclusions:** Our study observed a shorter OS among HER2+/HR- mBC elderly patients in clinical practice than the OS of 40.8 and 56.5 months among younger patients in the CLEOPATRA trial, suggesting that age is an important prognostic factor for breast cancer survival. The presence of second cancer and other competing risks led to overestimating the probabilities of breast cancer-specific death and resulted in a shorter OS using the Kaplan-Meier method. The CICR method is more relevant to estimate the breast-cancer-specific death incidence. Research Sponsor: None.

1040 **Poster Session**

Pyrotinib-based therapy for patients with HER2-positive breast cancer: A multicenter, real-world study. *First Author: Haoqi Wang, Fourth Hospital of Hebei Medical University, Shijiazhuang, China*

Background: Pyrotinib, an irreversible pan-ErbB inhibitor, has been approved for the treatment of HER2-positive advanced breast cancer in China. Real-world data is instructive for effect evaluation and application of the drug in clinical practice. Herein, this study was conducted to evaluate the effectiveness and safety of pyrotinib-based therapy in patients with HER2-positive breast cancer in the real-world setting. **Methods:** In this retrospective, multicenter, real-world study, data of patients with HER2-positive breast cancer who received pyrotinib-based therapy from 19 sites were reviewed. Disease characteristics, prior therapies, and treatment patterns were summarized. Progression-free survival (PFS) and the incidence of diarrhea were analyzed. **Results:** Between September 2018 and June 2021, a total of 378 patients with HER2-positive advanced breast cancer were included. Of 378 patients, 47.4% had hormone receptor (HR)-positive disease, 41.3% had HR-negative disease, and 11.4% had unknown HR status. Brain, lung, liver, and bone metastases were found in 24.9%, 35.7%, 31.7%, and 33.1% of all cases, respectively. Most of patients (83.1%) were trastuzumab-exposed, 12.7% were pertuzumab-exposed, and 8.2% had been treated with lapatinib or neratinib before receiving pyrotinib. Pyrotinib plus chemotherapy (211 [55.8%]) was the most commonly used regimen, followed by pyrotinib monotherapy (115 [30.4%]), pyrotinib plus trastuzumab and chemotherapy (29 [7.7%]), other regimens (18 [4.8%]), and unknown regimen (5 [1.3%]). Standard dose (400 mg once daily) was used in 256 (67.7%) patients. With a median follow-up duration of 20.5 months, the median PFS was 13.0 months (95%CI, 12.0-14.0). Further analyses showed that the median PFS did not differ in subgroups by age (≥65 or < 65 years), HR status (positive or negative), brain metastasis (yes or no), lung metastasis (yes or no), liver metastasis (yes or no), bone metastasis (yes or no), prior exposure to trastuzumab (yes or no), treatment regimen (pyrotinib monotherapy or combination therapy). Significant variance was discovered between sufficient dosage group and non-sufficient group (13.2 months vs 10.93 months, p= 0.028). The survival advantage of sufficient dosage was also evident in brain metastasis cases (14.4 months vs 8.3 months, p= 0.043).The most common adverse event was diarrhea (85.7%), and grade ≥3 diarrhea occurred in 18.5% of patients. Diarrhea was the leading cause for does reduction of pyrotinib. **Conclusions:** The PFS data in our study was similar to previous clinical trials referring to HER2-positive advanced breast cancer treated with pyrotinib. Cases with brain metastasis also displayed a satisfactory survival result. Sufficient dosage is of great importance for prolonged survival, prevention of diarrhea may efficiently avoid does reduction and guarantee the drug efficacy. Research Sponsor: None.

1041 **Poster Session**

HER2 alterations and prognostic implications in all subtypes of breast cancer. *First Author: Kaitlyn O'Keefe, Atrium Health Levine Cancer Institute, Charlotte, NC*

Background: Amplification or overexpression of human epidermal growth factor receptor 2 (HER2) oncogene is present in about 15-20% of breast cancers & is a prognostic & predictive biomarker. Additional *ERBB2*/HER2 alterations have become apparent on tumor next generation sequencing (NGS), including activating kinase domain mutations & fusions. **Methods:** DNA NGS (592 gene panel or whole exome) data from 12,153 breast samples retrospectively reviewed for *ERBB2* alterations with RNA whole-transcriptome sequencing (WTS) data available for 7289 (60%) samples. Gene fusions detected using the ArcherDx fusion assay or WTS. Clinicopathologic features were described including breast cancer subtype, age, & biopsy site. HER2 status determined according to 2018 ASCO-CAP guideline. Overall survival obtained from insurance claims & Kaplan-Meier estimates were calculated for defined patient (pt) cohorts. Statistical significance was determined using Chi-square & Wilcoxon rank sum tests. **Results:** ERBB2 mutations (*ERBB2mts*) were identified in 3.2% (n = 388) of tumors overall & most common in liver metastases (113/1972, 5.7%). *ERBB2mts* were found more in breast lobular tumors compared to ductal tumors (10 vs 2.1%, p < 0.001). HER2+ tumors had higher frequency of *ERBB2mts* compared to HER2- (4.3 vs 3%, p = 0.028). Tumors with score of 0 by immunohistochemistry demonstrated lower rate of *ERBB2mts* (0+ 2.2%, 1+ 3.5%, 2+ 4.5%, 3+ 3.45%, p < 0.05). Among HER2- tumors, *ERBB2mts* were present in 3.6% of hormone receptor (HR)+/HER2- & 1.9% of TNBC. Metastatic tumors had a higher rate of *ERBB2mts* compared to locoregional breast tumors (3.8 vs 2%, p < 0.001), with increased rates of activating mutations S310F (0.1 vs 0.0%, p < 0.05) & D769H (0.3 vs 0.1%, p < 0.05), & the resistance mutation L755S (1.2 vs 0.6%, p < 0.01). Compared to *ERBB2*-WT, *ERRB2mts* were associated with decreased *ERBB2* transcripts levels in HER2+ samples (222 vs 441 transcripts per million [TPM], p < 0.001) & increased levels in HER2- samples (73 vs 35 TPM, p < 0.001). High tumor mutational burden (≥ 10 mut/Mb) & *ERBB3* mutations were more common in *ERBB2mts* compared to *ERRB2*-WT (16.7 vs 7.7%, p < 0.001; 10.6 vs 0.8%, p < 0.001). *ERBB2* fusions were rare (0.49%) with 97% occurring in HER2+ tumors. Of 8358 pts with outcome data, prognosis (HR 1.2, P = 0.06) & response to chemotherapy (HR 1.1, P = 0.42) was similar between pts with HER2- *ERBB2mt* & *ERBB2*-WT. **Conclusions:** *ERBB2mts* & fusions were observed in all breast cancer subtypes - more commonly in HER2+, metastatic, & lobular histology tumors - & did not influence prognosis. These alterations may reflect response to treatment pressures in HER2+ disease to reactivate HER2-mediated growth pathways following anti-HER2 therapy & may represent a targetable upregulated oncogenic pathway in HER2- disease. Ongoing identification of *ERBB2* alterations may augment treatment options for breast cancer pts & clinical outcomes from this approach are under investigation. Research Sponsor: Caris Life Sciences.

1042 **Poster Session**

Matched FES and FDG PET imaging in patients with hormone receptor-positive, HER2+ advanced breast cancer. *First Author: Natasha Hunter, University of Washington, Seattle, WA*

Background: The recently FDA approved ^{18}F-Fluoroestradiol (FES) is a PET imaging tracer for characterizing disease in patients with ER+ breast cancer. As FES PET enters clinical practice it will be important to establish its utility in the full population of hormone-receptor positive patients, including those with HER2+ tumors. Historically the consensus around ER+/HER+ disease has been that these tumors are primarily driven by HER2, with therapies focused on targeting this pathway. Emerging research suggests that ER+ and HER2+ tumors represent a distinct phenotype, with bidirectional crosstalk between ER and HER2 pathways contributing to resistance to therapies targeting these critical pathways. **Methods:** Our cross-sectional database of patients with one or more FES scans stretches back to 1996. We selected all patients with HER2+ advanced breast cancer to determine whether ER is functional in the ER+/HER2+ subset. We examined paired FDG and FES scans and recorded SUVmax in matched lesions between the FDG and FES scans. We also looked at a subset of patients who underwent scans at more than one time-points and examined the clinical characteristics of these cases over time. **Results:** 36 patients with metastatic ER+, HER2+ breast cancer underwent concurrent FDG and FES PET scans between 1996 and 2013. 34 subjects (94%) were female; 32 (89%) were Caucasian, and 4 (11%) were Asian. Eight patients underwent serial scans. A total of 200 metastatic sites were recorded with the majority (67%) being bony lesions. No difference in quantitative FES avidity was observed between soft tissue and osseous sites. Six patients (16%) had negative FES scans despite displaying FDG avid lesions; three patients had at least one negative FES scan on serial scans, and two demonstrated FES-avid lesions with no FDG activity. Average FES SUVmax for positive scans was 3.5, with a range of 0.8 to 10.7. Among eight patients with multiple scans, half had 2 scans, three had 3 scans, and one had 4 scans. In 7/8 patients (88%) FES avidity increased over time even as FDG decreased or stayed stable with treatment; in one, both FES and FDG decreased on follow up scan. **Conclusions:** In a cohort of ER+, HER2+ patients undergoing FDG and FES PET scans, robust concordance between FDG and FES uptake was observed. FES avidity increased in patients with multiple scans, suggesting that the ER pathway remained active during treatment. The strong FES positivity in many HER2+ patients in this cohort suggests that FES PET could be used to guide patient selection for trials examining deescalated regimens employing a non-chemotherapy partner for HER2-directed therapy or emphasizing more ER-directed therapies such as CDK4/6 inhibitors, which are not currently approved in this population. With the ongoing development of HER2- PET imaging, combination scans could carry the potential for discrimination between sites, possibly serving as a tool to guide biopsy. Research Sponsor: U.S. National Institutes of Health.

1043 **Poster Session**

Treatment patterns and their impact on the outcome of patients with HR+/HER2+ metastatic breast cancer in a large real-world cohort. *First Author: Marcela Carausu, Institut Curie, Saint-Cloud, France*

Background: The place of endocrine therapy (ET) in the treatment of hormone receptor-positive (HR+), HER2+ metastatic breast cancer (MBC) is still not clearly defined. Data suggest that blocking both HR and HER2 signaling pathways could be an efficacious strategy to overcome secondary resistance. **Methods:** We aimed to retrospectively evaluate the impact of first line (L1) therapy for HR+/HER2+ MBC patients (pts) included between 2008- 2017 in the French real-world ESME MBC database (NCT03275311). Our primary endpoints were median overall survival (mOS) and median first progression-free survival (mPFS1). We used descriptive statistics and the Kaplan-Meier method to report patient characteristics and outcomes. Cox proportional hazards models and a propensity score were constructed to report and adjust for prognostic factors. **Results:** From the 23,501 female pts in the ESME MBC cohort, 1,790 pts had HR+/HER2+ MBC treated with Trastuzumab (T, n=1,089) or Trastuzumab-Pertuzumab (TP, n=701) during L1. Among them, 1,584 pts received antiHER2 therapy+CT+/-ET and 206 pts, antiHER2+ET only. Pts with antiHER2+CT+/-ET had more often ECOG performance status 0 (29.5% vs 15.8%, p<0.001), grade III tumors (36.6% vs 25.6%, p=0.007), time to MBC < 6 mo (51.6% vs 29.1%, p<0.001), TP as antiHER2 therapy (43.2% vs 9.4%, p<0.001), ≥3 metastatic sites (23.2% vs 14.8%, p=0.007), visceral metastasis (56.5% vs 42.4%, p<0.001), and less often bone-only disease (18.4% vs 35%, p<0.001) than pts with antiHER2+ET. In multivariable analysis, antiHER2+CT+/-ET was not superior to antiHER2+ET (Table), while TP was superior to Trastuzumab, and this result was confirmed by matching pts using a propensity score (p=0.76 for mOS and p=0.85 for mPFS1). Using the time-dependent ET variable among pts with antiHER2+CT, pts with maintenance ET had significantly better PFS1 and OS than those without (adjusted HR for PFS1=0.70 [95%CI 0.60-0.82], adjusted HR for OS=0.47 [95%CI 0.39-0.57], p<0.001). **Conclusions:** These data suggest that endocrine therapy could be an interesting less toxic alternative to chemotherapy in combination with antiHER2 therapy as first line treatment for HR+/HER2+ MBC pts. Research Sponsor: Roche, Pfizer, AstraZeneca, MSD, Eisai, Daiichi Sankyo.

Univariate and multivariable analysis for OS and PFS1 for pts treated with T or TP.

Univariate	N	OS			PFS1		
		median	95% CI	*p* value	median	95% CI	*p* value
Trastuzumab							
antiHER2+CT+/-ET	902	58.6	54.9-63.3	0.13	13.8	12.6-15.5	0.05
antiHER2+ET	187	48.7	42.9-63.9		10.1	8.5-14.1	
TP							
antiHER2+CT+/-ET	682	88.9	78.0-NR	0.93	23.1	21.0-27.1	0.69
antiHER2+ET	19	NR	37.8-NR		18.6	9.9-NR	
Multivariable analysis*		**HR**			**HR**		
AntiHER2 therapy							
TP	675	1		<0.001	1		<0.001
Trastuzumab	1,048	1.66	1.38-1.99		1.44	1.28-1.63	
Treatment group							
antiHER2+ET	203	1		0.8	1		1
antiHER2+CT+/-ET	1,520	1.03	0.82-1.28		1	0.84-1.19	

*The multivariable analysis also included: tumor grade, age at MBC, time to MBC, no of metastatic sites, type of metastases, ECOG performance status.

1044 **Poster Session**

Prognostic implications of HER2Neu-low in metastatic breast cancer. *First Author: Shaakir Hasan, New York Proton Center, New York, NY*

Background: HER2-Low (or HER2-equivocal, FISH negative) breast cancer has historically been treated as HER2-negative; however, recent evidence suggests that there may be prognostic and/or predictive differences between the two. We explore demographic characteristics and clinical outcomes of HER2-negative and HER2-low metastatic breast cancer (MBC) patients using real world data. **Methods:** We queried the National Cancer Database to identify MBC patients that were HER2 0, HER2 1+, or HER2 2+ per immunohistochemical staining, with the latter two defined as HER2-low and the former HER2-negative. A multivariable binomial regression analysis identified demographic and clinical correlates of each subtype. A Cox multivariable regression analysis (MVA), propensity matched to HER2 status, was performed to identify correlates of survival. **Results:** After excluding missing data, 24,636 MBC patients diagnosed between 2008-2015 were identified, 6,865 (27.9%) of whom were HER2-negative and 17,771(72.1%) of whom were HER2-low. There were no differences between the two groups with respect to age, race, year treated, location, income, insurance status, Charles Deyo comorbidity score, laterality, T stage, N stage, or use of systemic therapy. HER2-low tumors were half as likely to have concomitant hormone receptor-negative status (OR = 0.49, 95% CI 0.46-0.53). The 3-year survival rate among hormone receptor-negative patients was 33.8% for HER2-low and 32.2% for HER2-negative, and 60.9% and 55.6% in HER2-low and HER2-negative cases among hormone receptor-positive patients, respectively. HER2-low cases were associated with better survival on MVA (HR = 0.91, 95% CI 0.87-0.95), and remained superior with propensity-matching (HR = 0.92, 95% CI 0.89-0.96). In a subset analysis isolated to hormone receptor-positive cases, HER2-low remained correlated with improved survival (HR = 0.93, 95% CI 0.89-0.98) with propensity-matched MVA. Correlates of worse survival include older age as a continuous variable (HR = 1.02), Black race (HR = 1.13), uninsured (HR = 1.18), comorbidity score > 0 (HR = 1.28), higher T stage (HR = 1.17 to 2.34), node positivity (HR = 1.17) and, as the most influential, hormone receptor-negative status (HR = 1.94) [all P < 0.01]. **Conclusions:** Consistent with recent data in non-MBC, our study demonstrates a small but statistically significant association with improved survival for HER2-low tumors compared to HER2-negative tumors in MBC. Randomized data are necessary to further validate this discrepancy and determine if different management is warranted for each subtype. Research Sponsor: None.

1045 **Poster Session**

Brain metastasis as first and only metastatic relapse site portends poor outcomes in patients with advanced HER2+ breast cancer. *First Author: Laura Noteware, Duke University School of Medicine, Durham, NC*

Background: In patients (pts) with stable or no extracranial disease (ECD) presenting with breast cancer brain metastases (BCBrMs), current guidelines recommend pts receive local therapy with radiation +/- surgery, without changing systemic therapy. However, preliminary studies suggest that pts with isolated HER2+ BCBrM without ECD have inferior overall survival (OS) compared to pts with concurrent ECD. Our study further explores the implications of ECD status on intracranial progression free survival (iPFS) and OS. **Methods:** Retrospective analysis was performed on data from 153 pts diagnosed with initial HER2+ BCBrM who received CNS radiation at Duke between 2008 and 2020. Demographics, dates of metastatic and BCBrM diagnosis, ECD status at first CNS event, systemic therapy, and outcomes were collected. The primary endpoint was iPFS defined as the time from first CNS radiation to the subsequent documentation of intracranial progression (RANO-BM). OS was defined as time from first CNS radiation and first metastatic disease to date of death or last known contact. ECD status was defined by RECIST1.1 from systemic staging scans within 30 days of first CNS event. **Results:** In this cohort of 153 pts with HER2+ BCBrMs undergoing CNS radiation, > 70% of pts with known ECD status had controlled systemic disease: either no ECD (27%) or stable/responding disease (44%). 64% of pts' tumors were ER+. Median age was 50 years (range 24 – 75). Most pts (59%) developed first CNS event during adjuvant or $1^{st}/2^{nd}$ line metastatic therapy. CNS radiation treatment included 48% of pts receiving SRS only, 9% WBRT only, and 43% SRS and WBRT. All pts with no ECD presented with isolated BCBrMs as first metastatic disease. Among pts with known ECD status, OS from initial metastatic disease to death was markedly worse for pts with isolated brain metastases or no ECD (median = 28.4m, 95% CI: 18.1 to not reached) compared to those with progressive or stable/responding ECD (48.8m, 95% CI: 40.5 to 65.0; and 68.1m, 95% CI: 55.2 to 85.7, respectively; log-rank p = 0.004). OS from first CNS involvement to death was significantly worse for pts with progressive ECD (17.8m, 95% CI: 13.7 to 28.8) versus stable/responding (36.6m, 95% CI: 29.7 to 45.2) or no ECD (28.4m, 95% CI: 18.1 to not reached; log-rank p = 0.008). iPFS did not differ statistically among subgroups of pts with known ECD status: progressive ECD (median = 7.7m), no ECD (8.3m), or stable/responding ECD (11.2m) (log-rank p = 0.15). **Conclusions:** Overall survival in pts with HER2+ isolated BCBrM was markedly inferior to that of pts with progressive or stable/responding ECD. Studies investigating initiation of brain penetrable HER2-targeted therapies earlier in the disease course of isolated HER2+ BCBrMs pts are warranted. Research Sponsor: None.

1046 **Poster Session**

Dynamic circulating tumor DNA (ctDNA) in monitoring trastuzumab deruxtecan (TDXd) activity for patients (pts) with advanced breast cancer: Preliminary results of a feasibility study. *First Author: Elena Giordani, Regina Elena National Cancer Institute, Rome, Italy*

Background: Trastuzumab Deruxtecan (TDXd), a novel antibody-drug conjugate (ADC) that combines trastuzumab with a topoisomerase I inhibitor, has recently demonstrated high efficacy in HER2-overexpressing breast cancer after trastuzumab failure. Resistance to TDM1 have recently suggested to be dynamically associated with distinct circulating ctDNA species (*Allegretti et al, Mol Cancer 2021*). A prospective study aiming to evaluate the feasibility of Liquid Biobsy (LB) in monitoring ctDNA in pts receiving TDXd in the national Expanded Access Program was conducted. **Methods:** In this prospective study, LB for ctDNA analysis (evaluating '*per pt*' ctDNA species and Variant Allelic Frequencies, VAF) was performed using 52-gene targeted NGS panel, in patients who progressed after two or more prior anti-HER2-based regimens and candidates to TDXd (3-weekly 5.4 mg/kg). This preliminary analysis reports data referring to Time-0 (T0) and T6 (cycle 6) assays. **Results:** From April 2021, LBs were collected for 14 pts and to date 8 are evaluable for LB. Median pts' age was 59 yrs (range 38-72) and median number of previous anti-HER2 lines was 6 (2-11); 4 pts had Pertuzumab/Trastuzumab plus taxane as first-line and all pts received TDM-1. Median cycles of TDXd administered was 7.5 (1-10). At T0, 5/8 pts had at least one detectable ctDNA specie, and the remaining 3 developed at least one ctDNA at T6. ctDNA species and VAFs ranged from 1 to 5, and A0.1% to 68.94%, respectively. Decreases and increases were observed simultaneously in the same pt. The former varied from marginal to drastic, whereas the latter were invariably below 0.5% in VAFs. ctDNA monitoring was possible in 8/8 pts and at T6 ctDNA progression was detectable in 5/8 pts. Two pts displayed multiple HER2 copy number variations. **Conclusions:** The early results of this study suggest that considerable ctDNA burden, marked clonal complexity, and variable clonal response to TDXd can be found in pretreated HER2 positive patients, who progressed after antiHER2 therapies. Although the very small sample, this complex tumor evolution is surprising in light of the bystander payload effect of TDXd. Research Sponsor: None.

1047 **Poster Session**

Factors associated with short- and long-term survival in metastatic HER2+ breast cancer. *First Author: Jose Pablo Leone, Dana-Farber Cancer Institute/Harvard Medical School, Boston, MA*

Background: There have been significant therapeutic advances for HER2+ metastatic breast cancer (MBC) over the past decade. The aim of this study was to evaluate prognostic factors in metastatic HER2+ disease and their relationship with short- and long-term overall survival (OS) in the modern era. **Methods:** We evaluated patients (pts) with de novo metastatic HER2+ breast cancer diagnosed between years (y) 2010 and 2018, reported in SEER. Univariate analyses were performed to determine the effect of each variable on OS. Significant variables were included in a multivariate Cox model for OS that evaluated all pts diagnosed 2010 – 2018. Univariate and multivariate logistic regression was used to evaluate the association of each variable with short (< 2 y) and long (≥ 5 y) term OS. To allow sufficient follow up, only pts diagnosed 2010 – 2016 were included in the logistic regression for OS < 2 y, and only those diagnosed 2010 – 2014 were included for OS ≥ 5 y. **Results:** We included 5,576 pts with a median follow up of 48 months (IQR 25 – 73 months). Median OS was 41 months. The proportion alive at 2 y, 5 y, and 8 y, was 63.3% (95% CI 62.0% - 64.7%), 37.8% (95% CI 36.2% - 39.4%) and 26.8% (95% CI 24.8% - 28.9%), respectively. In multivariate analysis for OS, older vs younger age (HR 2.5), black vs white pts (HR 1.4), non-ductal non-lobular vs ductal (HR 2.7), bone metastases vs not (HR 1.2), brain metastases vs not (HR 1.8), liver metastases vs not (HR 1.6), lung metastases vs not (HR 1.3), 6 metastatic organ sites vs 1 (HR 3.6), ER/PR- vs + (HR 1.3), < $35k income vs ≥ $75k (HR 1.8), and being diagnosed in earlier years (HR 1.06 per each prior year) had significantly worse OS (all p≤0.044). Similar results were seen for breast cancer-specific survival. Factors associated with < 2 y OS in adjusted models were older age (OR 3.8), black race (OR 1.5), non-ductal non-lobular (OR 4.6), brain metastases (OR 3.0), liver metastases (OR 2.0), lung metastases (OR 1.6), ER/PR- (OR 1.7) and lower income (OR 1.6), all p < 0.04. Number of metastatic organ sites was not significant in this model. Factors associated with ≥ 5 y OS in adjusted models were younger age (OR 2.9), white vs black race (OR 1.7), fewer metastatic organ sites (OR 2.6), ER/PR+ (OR 1.3), and higher income (OR 3.3), all p < 0.02. Specific organ sites (bone, brain, liver and lung) were not significant in this model. **Conclusions:** In this cohort of pts with de novo HER2+ MBC, OS improved significantly over the study period, and a considerable proportion of pts were still alive at 8 y. Factors associated with shorter survival included older age, black race, lower income, and the presence of visceral or brain metastases. Long-term (≥ 5 y) survival was associated with both demographic (younger age, white race, higher income) and tumor-related (fewer metastatic sites, ER/PR positivity) factors. Research Sponsor: None.

1048 **Poster Session**

HER2-targeted immunoconjugates for breast cancer: Ancestry and dose adjustment for thrombocytopenia. *First Author: Michael Rainone, City of Hope, Duarte, CA*

Background: Thrombocytopenia (TCP) is a common toxicity of HER2-targeted agents, trastuzumab emtansine (TDM1) and trastuzumab deruxtecan (TDXd). A high incidence of this toxicity was observed in pivotal trials that led to approval of these agents. We investigated whether Asian ancestry increases risk of dose adjustment for TCP on TDM1/TDXd and its impact on dosing in the real-world setting. **Methods:** Females with HER2+ breast cancer who initiated TDM1/TDXd between 1/16/17-10/26/21 were identified by retrospective review. Primary endpoint was number of chemotherapy cycles until adjustment of TDM1/TDXd dose for TCP; competing endpoints included discontinuation for other toxicity, disease progression, and completion of treatment. Individuals who were switched from TDM1 to TDXd contributed an additional observation post-switch. Recurrent events analysis evaluated Asian ancestry (p<0.05) using a proportional means model, with robust sandwich estimate recognizing correlation between repeated observations per individual. Covariates (age, metastatic disease, drug, prior adjustment) were retained if they improved the model. **Results:** The study excluded individuals who declined to self-identify (n=23), self-identified as other than Asian or White (n=28), and/or dissented to research (n=24). The study included n=181 individuals (mean age 55.1+12.8 years), of whom n=48 (26.5%) identified as Asian and n=124 (68.5%) had metastatic disease. Overall, 33 individuals received TDXd exclusively, leaving 148 (81.8%) individuals who received TDM1, including 45 individuals who later switched to TDXd after development of TCP while on TDM1 (n=9) or other toxicity (n=36) on TDM1. For n=226 observations (total 2551 cycles), the endpoint was dose adjustment for TCP (n=32), discontinuation for other toxicity or disease progression (n=112), completion of treatment (n=27), or censoring (n=55). Taking into account history of switching drug for TCP, Asian ancestry was associated with increased risk of dose adjustment for TCP (Table). Neither age, metastatic disease, nor specific drug improved the model (data not shown). **Conclusions:** Among individuals taking TDM1 and/or TDXd for HER2+ breast cancer, we observed that those with Asian ancestry are at greater risk of dose reduction for TCP than their non-Asian counterparts. Upon confirmation in additional individuals with HER2+ cancers of the breast and other sites, this heightened susceptibility to TCP among Asian individuals should be further investigated to elucidate the underlying mechanism and optimize clinical guidelines for prevention and management. Research Sponsor: None.

Predictors of dose adjustment for thrombocytopenia among individuals with breast cancer on HER2-targeted agents.

Independent Risk Factors	Hazards Ratio (95% Confidence Interval)	p
Asian Ancestry	2.84 (1.39-5.82)	0.0044
Prior Discontinuation for Thrombocytopenia	6.96 (2.80-17.30)	<0.0001

1049 **Poster Session**

Post-recurrence survival in asymptomatic compared with symptomatic metastatic breast cancer: A multicenter retrospective study. *First Author: Sayaka Kuba, Nagasaki University Graduate school of biomedical Science, Nagasaki, Japan*

Background: Asymptomatic metastatic breast cancer (mBC) is often detected using tumor marker or imaging tests in Japan. At the ASCO 2019, we reported on mBC detection, the distribution of symptomatic and asymptomatic disease by subtype (abstract e12568). We aimed to determine whether there are differences in post-recurrence survival (PRS), and treatment between asymptomatic and symptomatic MBCs, and identify factors associated with PRS. **Methods:** We performed a multicenter, retrospective analysis of patients with mBC treated in our hospitals from 2008 to 2018. Patients were divided into asymptomatic and symptomatic MBCs to compare their prognosis by breast cancer (BC) subtypes: luminal (hormone receptor positive/human epidermal growth factor 2 [HER2] negative), HER2 (any hormone receptor/HER2 positive), and triple-negative (TN) (hormone receptor negative/HER2 negative). **Results:** Of 204 patients with mBC (114 asymptomatic, 90 symptomatic), PRS was longer in asymptomatic mBC than in symptomatic mBC (median survival: 55 months vs. 29 months; $p < 0.001$) and tended to have longer overall survival (OS) (110 months vs 72 months, respectively; $p = 0.09$). In multivariate analysis, TN, recurrence-free survival (RFS), multiple metastasis sites, and symptomatic disease were independently predictive of PRS (Table). In luminal and HER2, PRS trended higher in the asymptomatic group than in the symptomatic group (luminal: 54 months vs. 41 months; $p = 0.08$, HER2: 71 months vs. 27 months; $p = 0.09$), but without significant difference in OS (luminal: 112 months vs. 124 months; $p = 0.91$, HER2: 113 months vs. 72 months; $p = 0.40$). In the luminal group, 13 patients (11%) were treated with cyclin-dependent kinase 4/6 (CDK4/6) inhibitors. The median PRS was 80 months for luminal patients with three factors — longer than 4 years of RFS, a single metastasis site, and asymptomatic disease. The duration of endocrine therapy did not differ between groups; however, the patients with luminal BC in the asymptomatic group had longer chemotherapy than those in the symptomatic group. In TN, PRS was very short (asymptomatic, 28 months; symptomatic, 10.5 months; p = 0.01). **Conclusions:** We demonstrated that asymptomatic MBC and symptomatic MBC differed in terms of subtypes, prognosis, and duration of chemotherapy in the luminal group. Therefore, unique treatment strategy for asymptomatic or symptomatic MBC should be developed. Research Sponsor: None.

Variable	HR	95% CI	*p* Value
TN vs no-TN	2.56	1.69 to 3.90	<0.001
RFS, year	0.91	0.87 to 0.96	<0.001
Multiple sites of metastasis vs single sites of metastasis	1.86	1.32 to 2.61	<0.001
Symptomatic vs asymptomatic	1.76	1.26 to 2.45	<0.001

HR = hazard ratio; CI = confidence interval; TN = triple-negative; RFS = recurrence-free survival.

1050 **Poster Session**

Chemotherapy shows better efficacy than endocrine therapy in patients with metastatic breast cancer with heterogeneous estrogen receptor expression. *First Author: Yizhao Xie, Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: Heterogeneity of estrogen receptor (ER) expression has long been challenges for diagnosis and treatment strategy of metastatic breast cancer (MBC). A novel convenient way of ER detection using ^{18}F-fluoroestradiol positron emission tomography/computed tomography (^{18}F-FES PET/CT) offers a chance to screen and analyze MBC patients with ER uncertainty. **Methods:** MBC patients who received ^{18}F-FES PET/CT were screened and patients with both FES positive (FES+) and negative (FES-) lesions were enrolled in this study. Progression-free survival (PFS) was estimated by Kaplan-Meier method and compared by log-rank test. **Results:** A total of 635 patients were screened and 75 of 635 (11.8%) patients showed ER uncertainty. 51 patients received further treatment and were enrolled in this study. Among them, 20 (39.2%) patients received chemotherapy (CT), 21 (41.2%) patients received endocrine-based therapy (ET) and 10 (19.6%) patients received combined therapy (CT+ET). CT showed better progression-free survival (PFS) compared to ET (mPFS 7.1 vs 4.6 months, HR 0.44, 95% CI 0.20-0.93, P = 0.03). CT+ET did not improve PFS compared to either CT or ET alone (mPFS 4.4 months, P > 0.2). **Conclusions:** ^{18}F-FES PET/CT could identify patients with ER heterogeneity. Patients with ER uncertainty showed better sensitivity to CT rather than ET. Combined therapy of CT+ET did not improve treatment outcome. Research Sponsor: None.

1051 **Poster Session**

Aromatase inhibitors for breast cancer therapy: Analysis of real-world FAERS data. *First Author: Dawood Findakly, Louisiana State University (Shreveport) Program, Shreveport, LA*

Background: Aromatase inhibitors (AIs) are extremely effective adjuvant treatment in postmenopausal women with hormone receptor-positive breast cancer (HRPBC). We utilized the Food and Drug Administration Adverse Event Reporting System (FAERS) database to evaluate the musculoskeletal (MSK), fractures, and ischemic heart disease (IHD) adverse events (AEs) caused by AIs. **Methods:** We conducted a retrospective FAERS public database review to assess the MSK, fracture, and IHD AEs for the three AIs (anastrozole, letrozole, and exemestane) from 2001 through 2021. Chi-square was used to compare categorical variables. **Results:** A total of 31,683 AEs reports were identified, out of which, 15,140 (47.8%) were MSK, 13,311 (42.0%) were fracture, and 3,232 (10.2%) were IHD. The differences in AEs distributions among the three drug classes were statistically significant for MSK and fracture AEs (P < 0.001) but not reached statistical significance for IHD AEs (P = 0.140). MSK AEs were mostly reported with anastrozole, followed by exemestane, and letrozole in 35.23%, 33.97%, and 32.06%, respectively (P < 0.001). Compared to older individuals, younger adults (≤65 years) had higher rates of MSK AEs—mostly with anastrozole (38.43%, P < 0.001), followed by exemestane (36.37%, P = 0.006) and letrozole (34.28%, P < 0.001). Fracture AEs were mostly reported, in descending order, with letrozole, exemestane, and anastrozole in 12.07%, 11.41%, and 9.34% respectively (P < 0.001). Older adults (> 65 years) had higher rates of fracture AEs with letrozole (16.77%, P < 0.001) and anastrozole (10.37%, P < 0.001), while unable to demonstrate statistical significance with exemestane (13.48%, P = 0.108). Among older adults (> 65 years), IHD AEs were significantly reported with anastrozole (21.56%, P < 0.001) and exemestane (14.18%, P = 0.016) but no statistical significance reached for letrozole (14.12%, P = 0.528). **Conclusions:** The findings in this study highlight trends for selected AEs with various AI regimens, provide further insights, and help guide therapeutic decisions for patients with HRPBC. Research Sponsor: None.

1052 **Poster Session**

Long-term safety of inavolisib (GDC-0077) in an ongoing phase 1/1b study evaluating monotherapy and in combination (combo) with palbociclib and/or endocrine therapy in patients (pts) with *PIK3CA*-mutated, hormone receptor-positive/HER2-negative (HR+/HER2-) metastatic breast cancer (BC). *First Author: Philippe L. Bedard, University of Toronto, Toronto, ON, Canada*

Background: Dysregulating mutations in *PIK3CA*, encoding the PI3K p110α subunit, occur in ~40% of HR+/HER2– BCs. Inavolisib is a PI3Kα-specific inhibitor that also promotes degradation of mutant p110α. It has demonstrated encouraging preliminary antitumor activity in pts with *PIK3CA*-mutated HR+ BC as a monotherapy, and in combo with other anticancer agents. **Methods:** We included pts from NCT03006172 on treatment ≥1 year with inavolisib alone (Arm A), or in combo with palbo + letrozole (letro) (B), letro (C), fulvestrant (fulv) (D), or palbo + fulv (E; + metformin in Arm F for pts with body mass index ≥30 and/or HbA1c ≥5.7%). Inavolisib was administered orally daily (PO QD) at 3, 6, 9, or 12 mg (3+3 dose-escalation design); letro at 2.5 mg PO QD; palbo at 125 mg PO QD for 21/28 days; and fulv at 500 mg intramuscularly every 4 weeks, in 28-day cycles until intolerable toxicity/disease progression. Safety was assessed by NCI-CTCAE v4. **Results:** 57 female pts were included (cutoff 07/26/21; N = 1, 18, 6, 12, 15, 5 in Arms A–F); median age: 57 years (range 33–80); median lines of prior therapy: 2 (1–7). All but 2 pts, both in Arm B (3 mg), were assigned the 9 mg inavolisib recommended phase 3 dose. Overall median treatment duration: 19 months (range 12–45); median inavolisib cumulative dose intensity, 95%. The most frequent treatment-related adverse events (AEs; in ≥20 pts/35%) were hyperglycemia (68%), stomatitis (68%; grouped terms), neutropenia (58%), diarrhea (51%), nausea (39%), alopecia (35%), and rash (35%; grouped terms). The most frequent treatment-related Grade (G) 3–4 AEs (≥2 pts/4%) were neutropenia (47%), hyperglycemia (16%), leukopenia (9%), thrombocytopenia (9%), lymphopenia (7%), weight decreased, and hypokalemia (4% each). G3–4 neutropenia, leukopenia, thrombocytopenia, and lymphopenia were all reported in palbo arms. One G5 AE of pleural effusion was reported (disease progression-related). 39 pts (68%) had ≥1 AE resulting in study treatment modification (drug interruption/dose reduction/treatment withdrawal); 11 (19%) had an inavolisib dose reduction and 2 (4%) discontinued treatment due to an AE (1 related G2 diarrhea, 1 unrelated G3 cerebrovascular disorder). AEs typically occurred during the first 6 months and tended to be less frequent in later cycles. No new safety signals were observed with long-term inavolisib use. **Conclusions:** These data indicate acceptable long-term tolerability. The safety profile of pts on study treatment with inavolisib alone or in combo with endocrine-based anticancer therapies for ≥1 year was similar to that reported for the overall study population. Updated data will be presented. A phase 3 study of inavolisib + palbo + fulv is enrolling (NCT04191499; INAVO120). Clinical trial information: NCT03006172. Research Sponsor: Genentech, Inc.

1053 **Poster Session**

Phase I study combining pembrolizumab and aromatase inhibitor in patients with metastatic hormone receptor–positive breast cancer. *First Author: Xuan Ge, City of Hope, Duarte, CA*

Background: Aromatase inhibitor (AI) is standard of care for patients with hormone receptor positive (HR^+) human epidermal growth factor receptor 2-negative ($HER2^-$) metastatic breast cancer (MBC). The current phase I trial was designed to test the safety and efficacy of AI and the immune checkpoint inhibitor pembrolizumab (NCT 02648477). **Methods:** Key eligibility criteria were HR^+ $HER2^-$ MBC per ASCO/CAP; RECIST 1.1 measurable disease; adequate organ function; and ECOG 0-1. Eligible patients received 200 mg pembrolizumab IV every 3 weeks plus AI until progression or unacceptable toxicity. Primary objectives were to evaluate the safety and efficacy of this combination. This study employed a 3-at-risk design with a lead-in at the standard dosing of both AI and pembrolizumab with a targeted accrual of 20 patients. **Results:** A total of 20 patients were accrued between March 2016 and April 2017. Median age was 62 (range 34-79), with 75% white, 15% Asian and 10% unknown. Median lines of therapy were 3 (0, 9). All but one patient received aromatase inhibitor and/or fulvestrant prior to enrollment. The combination was well tolerated, and the most common adverse events were grade 2 fatigue (35%), rash (15%), and hot flashes (10%). Grade 3 adverse events were elevated AST/ALT (5%), rash (5%), and lymphopenia (5%). Responses were 10% partial response and 15% stable disease, resulting in a clinical benefit rate (CBR) of 20% at 6 months. Median follow-up time was 40.1 months (range 31.3 – 46.8 months). Median progression free survival was 1.8 months (95% CI 1.6, 2.6) and median overall survival was 17.2 months (95% CI 9.4, NA). 14 tumor specimens had programmed death ligand 1–positive (PD-L1) by 22C3 testing, including 3 PD-L1-positive and 11 PD-L1 negative. No association between PD-L1 and response was found. **Conclusions:** The combination of pembrolizumab and AI is well tolerated in patients with HR^+ $HER2^-$ MBC who were not pre-selected for PD-L1. There was minimal overall clinical activity observed beyond what was to be expected with AI alone in this group of patients. Clinical trial information: NCT 02648477. Research Sponsor: Merck.

1054 **Poster Session**

Molecular alterations associated with rapid progression following CDK4/6 inhibitors (CDKi) in metastatic hormone receptor–positive breast cancer (mHRBC). *First Author: Malinda T West, OHSU Knight Cancer Institute, Portland, OR*

Background: Combination of CDKi with endocrine therapy is a key treatment for mHRBC due to survival benefit and favorable safety profile. However, progressive disease inevitably develops and outcomes after CDKi discontinuation (dc) are not well-described. Within our institution, we previously reported clinical characteristics and outcomes for a cohort of 140 mHRBC patients who received CDKi therapy. Median progression-free survival (PFS) and overall survival (OS) post-CDKi dc were 7.0 and 15.4 months, respectively. However, 29% experienced rapid progression or death within 4 months following CDKi dc. Molecular predictors of rapid progression after CDKi are unknown and may help define therapies to improve outcomes. In this study, we sought to identify molecular predictors for rapid disease progression after CDKi dc in mHRBC. **Methods:** We identified within our cohort 34 patients with mHRBC who progressed on CDKi with next-generation sequencing (NGS) performed on pre-CDKi tissue samples. PFS and OS, measured from CDKi dc, were analyzed with the Kaplan-Meier estimator and log-rank test. Rapid progression was analyzed with logistic regression and Fisher's exact test to evaluate association between pre-CDKi tumor mutation and rapid progression post-CDKi. **Results:** NGS of pre-CDKi tumor biopsies found 12 genes (*FGF3, FGF4, FGFR, PIK3CA, PTEN, AKT, RB1, CDKN2A, MYC, CCND1, ESR1, TP53*) that were altered in ≥3 of the 34 patients. The six patients (18%) with a *PTEN mutation (mut)* had a median PFS of 3 months and median OS of 4 mo. In comparison, median PFS and OS of *PTEN wild-type (wt)* patients were 7 mo. (log-rank p=0.008) and 21 mo. (log-rank p<0.001), respectively. Moreover, those with *PTENmut* tumors were more likely to experience rapid progression compared to *PTENwt* (odds ratio = 7.0, 95% CI: 1.1 – 60.5, p=0.048). Notably, in the 10 rapid progression patients with pre-CDKi NGS results, alterations to PI3K pathway constituents were prevalent: *PTENmut* (40%), *FGFRmut* (50%), *AKTmut (*20%) and *PIK3CAmut* (40%). **Conclusions:** PI3K pathway alterations are prevalent in mHRBC patients who develop rapid progression post-CDKi dc, with *PTENmut* being the most significant predictor. These hypothesis-generating findings provide the basis for ongoing investigations to find clinical and molecular biomarkers that can help improve outcomes for mHRBC at risk of rapid progression post-CDKi therapy. Research Sponsor: None.

Relationship of *PTENmut* and other PI3K pathway mutations on post-CDKi outcomes.

Impact of pre-CDKi *PTENmut* on post-CDKi dc outcomes			
PTENmut	***PTENwt***	**log-rank p-value**	
mPFS	3 mo	7 mo	0.008
mOS	4 mo	21 mo	<0.001
Association of pre-CDKi PI3K pathway mutations with rapid progression post-CDKi dc			
	Rapid progression	**No rapid progression**	**Fisher's p-value**
***PTENmut* (n=6)**	66.7%	33.3%	0.053
***AKTmut* (n=3)**	66.7%	33.3%	0.212
***FGFRmut* (n=12)**	41.7%	58.3%	0.433
***PIK3CAmut* (n=14)**	28.6%	64.3%	1.000

1055 **Poster Session**

Clinical outcomes with alpelisib (ALP) plus fulvestrant (FUL) after prior treatment (tx) with FUL in patients (pts) with advanced breast cancer (ABC): A real-world (RW) analysis. *First Author: Joyce O'Shaughnessy, Baylor University Medical Center, Texas Oncology, US Oncology Network, Dallas, TX*

Background: ALP (α-selective PI3K inhibitor and degrader) + FUL was FDA approved and reflected in the NCCN guidelines in 2019 for pts with hormone receptor–positive/human epidermal growth factor receptor 2–negative (HR+/HER2–) ABC with *PIK3CA* mutations following progression on or after endocrine-based therapy (ET). The Phase III SOLAR-1 trial excluded prior FUL, and data on ALP + FUL after FUL are limited. As cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) + ET (including FUL) is the standard in the first line (1L) or second line (2L) for pts with HR+/HER2– ABC, more data on ALP + FUL post-FUL are needed. Here we report patterns and clinical outcomes on RW use of ALP + FUL in pts with HR+/HER2– ABC with prior FUL exposure. **Methods:** This retrospective study used de-identified electronic health record data from the ConcertAI Patient360 Breast Cancer data product sourced from US oncology centers. Adults with HR+/HER2– ABC treated with ALP + FUL (index tx) who received prior FUL (monotherapy or in combination) in the metastatic setting were included; pts with a *PIK3CA* negative test on or prior to the index were excluded. Pts were followed until date of death or last activity. RW progression-free survival (rwPFS), defined as first documented progression/death from ALP + FUL start date, was assessed. **Results:** This analysis included 157 pts (median age, 63 y [57-71 y]) who received ALP + FUL from 2019 to 2021, with 11.5% pts in 1L, 17.8% in 2L, 26.8% in third line (3L), and 43.9% in fourth line and beyond (4L+). Prior FUL tx included CDK4/6i + FUL (74.5%), FUL alone (33.8%), and non-CDK4/6i + FUL (21.0%). In pts who received ALP + FUL in 1L (n = 18), prior FUL exposure was in the same line without documented progression. In the metastatic setting, 28.0% of pts received > 1 FUL-containing regimen and/or 72.0% received prior chemotherapy (CT). At the median duration of follow-up (8.7 mo [4.1-12.5 mo]), the median rwPFS was 5.7 mo (4.0-7.3 mo) in the overall population. The median rwPFS was also analyzed by line of therapy (Table). In pts with CDK4/6i + FUL as immediate prior therapy (n = 39), the median rwPFS was 6.2 mo (3.0-9.1 mo); 79.5% of these pts received ALP in ≤ 3L. At the time of analysis, 107 pts (68.2%) had discontinued ALP + FUL; the median time to discontinuation was 4.7 mo (3.7-6.1 mo). Following discontinuation of ALP + FUL, CT was the most common subsequent therapy (33.8%). **Conclusions:** This analysis on RW data from early years of ALP access in the US shows clinical benefit of ALP + FUL in pts with HR+/HER2– ABC with *PIK3CA* mutation even when exposed to prior FUL, confirming the oncogenic dependence of the tumor on the *PIK3CA* mutation. Research Sponsor: Novartis Pharmaceuticals.

Line of therapy	**1L**	**2L**	**3L**	**4L+**
n	**18**	**28**	**42**	**69**
rwPFS, median, mo	11.9 (1.1-NR)	6.2 (2.5-9.1)	4.0 (2.7-7.5)	4.8 (3.8-7.3)

NR, not reached.

1056 **Poster Session**

CDK4/6 inhibitors outcomes in patients with advanced breast cancer based on HER2-low expression. *First Author: Laura Sabina Lapuchesky, Cramer 1180, CABA, Argentina*

Background: HER2-low expression, defined as HER2 immunohistochemistry (IHC) score of 1+ or 2+ with negative in situ hybridization assay (FISH), accounts for 50% of breast cancers. There is limited and conflicting evidence regarding the efficacy of cyclin-dependent kinase (CDK) 4 and 6 inhibitors in patients with ER+ and HER2-low tumors. This study aimed to investigate the prognostic value of HER2-low expression in patients with ER+/HER2-negative advanced breast cancer treated with CDK 4/6 inhibitors. **Methods:** We retrospectively selected consecutive patients with ER+/HER2-negative advanced breast cancer treated with CDK 4/6 inhibitors plus endocrine therapy in our institution from May 2015 to Feb 2020. Two cohorts were compared, including HER2-0 (IHC score) and HER2-low (HER2 IHC score 1+ and 2+ [negative FISH]) tumors. Comparisons in progression-free survival (PFS) and overall survival (OS) were performed using a log-rank test. The prognostic value of HER2-low was investigated by the Cox regression model. **Results:** Among the 186 patients included, median age at treatment was 55 (r 27-84), and majority had ECOG 0 (126, 67.8%). Progesterone receptor was positive in 155 (83.3%) tumors. Of note, most patients received CDK4/6 inhibitors and endocrine therapy as first-line setting (131, 70.4%). Mostly received palbociclib (161, 86.6%), while ribociclib and abemaciclib were used in 23 (12.4%) and 2 (1.08%) patients, respectively. Overall, 27 patients (14.5%) had de novo metastatic disease, 68 (36.6%) had only bone metastases, and 69 (37.1%) had visceral disease. Of the total population, 64 (34.4%) tumors were HER2-low (43 [23.1%] HER2-1+, and 21 [11.3%] HER2-2+), and 122 (65.6%) were HER2-0. Median PFS among patients with HER2-0 and HER-low were 19 mo. (95% CI, 13.9-24.1), and 15.6 mo. (95% CI, 11.1-20.0), p = 0.074, respectively. In patients treated with CDK 4/6 in the first-line setting, no statistically significant differences were observed in terms of PFS and OS between HER2-0 and HER2-low (PFS HR 0.73 [95% CI, 0.47-1.13; p = 0.160], and OS HR 1.04 [95% CI, 0.51-2.14; p = 0.909]). **Conclusions:** In our study, HER2-low expression did not show a statistically significant impact on patients with ER+/HER2-negative advanced breast cancer treated with CDK 4/6 inhibitors. Our study supports the necessity of real-world evidence and the design of pooled analysis to understand the real implication of this biomarker in patients with ER+/HER2-negative tumors. Research Sponsor: None.

1057 **Poster Session**

***ESR1* mutations in circulating tumor DNA (ctDNA) are associated with CTCs and increased hormone receptors in metastatic tumor tissues of patients with metastatic breast cancer (MBC).** *First Author: Qiang Zhang, Northwestern University, Department of Medicine, Division of Hematology/Oncology, CTC Core Facility, Lurie Cancer Center, Chicago, IL*

Background: The monitoring of ctDNA and circulating tumor cells (CTCs) in patients with MBC predicts metastasis and prognosis. We previously reported that HER2 and *ESR1* alterations in ctDNA were associated with predicted metastasis in MBC (2019 ASCO#1036). Furthermore, ctDNA can be used to evaluate tumor heterogeneity (2020 ASCO #1028). Here, we report that baseline ctDNA *ESR1* mutation is a key point associated with tumor tissue characteristics and CTCs, which may help to elucidate disease resistance in MBC. **Methods:** This study included 288 hormone receptors positive MBC patients who received systemic treatment under an IRB-approved clinical trial (NU16B06) at NU Lurie Cancer Center (2016-2021). Baseline plasma ctDNA was analyzed by Guardant360 NGS for ESR1 mutations. CTC enumerations were performed by using 7.5ml blood in CELLTRACKS (Menarini). Estrogen receptor (ER), progesterone receptor (PR), HER2 and Ki67 in each patient's biopsy tumor tissue before surgery, surgical tumor tissue and metastatic tumor tissue were evaluated by NU PathCore. Kruskal-Wallis was used for statistics. **Results:** Of the 288 patients, *ESR1* mutations were found in 18 hotspots from 38 patients ($ESR1^{Mut}$, 13.19%) and there were 250 patients without any mutation ($ESR1^{WT}$, 86.81%). Median of Total CTCs (/7.5ml) and $HER2^+$ CTCs (/7.5ml) were significantly increased in $ESR1^{Mut}$ group compared to $ESR1^{WT}$ group, total CTCs were 8.0 vs 1.0 (P=0.006) and $HER2^+$ CTCs were 1.5 vs 0 (P=0.014), respectively. There were significant differences on hormone receptors expression (positive cells %) in tumor tissues between $ESR1^{Mut}$ group and $ESR1^{WT}$ group: 1) $ESR1^{Mut}$ group has significant higher expression in ER and PR in biopsy tumor tissues. The mean of ER in $ESR1^+$group was 90.48% vs 48.18% in $ESR1^{WT}$ group (p<0.001). The mean of PR in $ESR1^{Mut}$ group was 40.86% vs 25.60% in $ESR1^{WT}$ group (p<0.001). Meanwhile, there is not significant difference on HER2 expression in $ESR1^{Mut}$ group compared $ESR1^{WT}$group; 2) In the surgical tumor tissues, the mean ER was 97.64% in $ESR1^{Mut}$ group which was significantly higher than 47.90% in $ESR1^{WT}$ group (p<0.001), while the PR was 45.33% and 24.32%, respectively; 3) In metastatic tumor tissues, the mean of ER in $ESR1^{Mut}$ group was 84.75% vs 34.89% in $ESR1^{WT}$group (p<0.001) and the mean of PR in $ESR1^{Mut}$ group was 32.25% vs 9.33% in $ESR1^{WT}$ group (p<0.001). Furthermore, median of Ki67 in $ESR1^{Mut}$ group is 28.33% which was significantly higher than 18.75% in $ESR1^{WT}$ group (p<0.01). **Conclusions:** Baseline ctDNA ESR1 mutations not only had higher total CTCs and $HER2^+$ CTCs but also significantly correlated with high hormone receptors and proliferation in tumor metastatic tumor tissues. The synergy of ctDNA *ESR1* mutation and tissue pathological characteristics expands the early predictive role of ctDNA monitoring metastatic prognosis for clinical decision-making. Research Sponsor: U.S. National Institutes of Health.

1058 **Poster Session**

Longitudinal circulating tumor DNA (ctDNA) whole-exome sequencing (WES) in the phase Ib/II trial of palbociclib and bazedoxifene reveals genomic dynamics and clonal evolution with the acquisition of treatment resistance in hormone receptor-positive, HER2-negative (HR+ HER2-), advanced breast cancer (ABC). *First Author: Albert Grinshpun, Dana-Farber Cancer Institute, Boston, MA*

Background: Patients (pts) with HR+ HER2- ABC ultimately develop endocrine resistance. To gain insights into the genetic mechanisms of resistance we performed WES on serial plasma samples from endocrine resistant pts treated on a clinical trial (NCT02448771). **Methods:** Plasma samples were collected at baseline (n=36), day 1 of cycle 2 (n=33), and at the end of treatment (EOT, n=33). Samples were subjected to ultra-low passage (ULP, 0.19-0.57X) WGS to determine ctDNA tumor fraction (TF) for the selection of samples (TF>0.03) for subsequent WES (193X). Somatic single nucleotide variations, somatic copy number alteration (SCNA), phylogeny, tumor mutational burden, mutational signatures, and germline analyses were performed. **Results:** All 102 samples underwent successful ULP and 68 WES. Overall, most frequent pathogenic mutations were in *ESR1* and *PIK3CA*. At baseline, 32% of pts had *ESR1* mutation and 21% *PIK3CA* mutation. There was no association between *ESR1* mutations and PFS. In contrast, baseline *PIK3CA* mutations were detected only in pts who did not have a clinical benefit, and were associated with worse PFS compared to pts with wild-type *PIK3CA* (1.8 vs. 3.9 months, respectively, HR=0.2, 95% CI 0.06-0.6, *P=0.0019*, log-rank test). Additionally, pts with a baseline truncating mutation, mostly in tumor suppressor genes (*TP53, MEN1, RB1, CDKN1B, NF1, TP53BP1, TP63, SMAD2/4, ARID1A, KMT2C*), also had a significantly worse PFS (1.7 vs 3.8 months, HR=0.3, 95% CI 0.1-0.7, *P=0.006*, log-rank test). At EOT, 20% (4/20) of pts with matched baseline samples had newly acquired mutations that are suggestive of mechanisms of acquired resistance and offer potential therapeutic targets (e.g. *ERBB2, PIK3CA).* SCNA analysis showed that in all pts there were at least 2 SCNAs in cancer-related driver genes, most common in *CCND1* and *ELF3*. Moreover, in all samples we identified at least 1 SCNA related to a potential mechanism of resistance. To better understand tumor heterogeneity and sub-clonal architecture we performed an evolutionary analysis (sufficient TF≥0.15, available in n=7). Phylogenetic analysis revealed sub-clonal dynamics that could explain the acquisition of resistance in at least three pts (3/7), and identified novel genes which might have role in endocrine resistance (e.g. *DCAF13, ZFHX3*). **Conclusions:** Our results demonstrate the feasibility and utility of serial WES in a clinical trial. Serial ctDNA WES and evolutionary studies enabled us to discover novel potential genomic mechanisms of tumor progression, and identified *PIK3CA* mutations as a candidate biomarker of resistance to the combination of palbociclib and bazedoxifene, which may apply to other next generation endocrine treatments. Clinical trial information: NCT02448771. Research Sponsor: Pfizer.

1059 **Poster Session**

Efficacy and safety of tenalisib, a PI3K δ/γ and SIK3 inhibitor in patients with locally advanced or metastatic breast cancer: Initial results from a phase II study. *First Author: Tamta Makharadze, LTD High Technology Hospital Medcenter, Batumi, Georgia*

Background: Hyperactivation of the PI3K pathway in breast cancer is implicated in malignant transformation, cancer progression, and resistance to endocrine therapy. Salt Inducible Kinase-3 (SIK3) is highly expressed in breast cancer and elevated SIK3 expressions are shown to contribute to tumorigenesis. Tenalisib (RP6530), a highly selective PI3K δ/γ and SIK3 inhibitor has been evaluated in > 150 patients with haematological malignancies and demonstrated encouraging activity in T-cell lymphoma with a differentiated safety profile. Tenalisib has a major metabolite (IN0385) which shows potent SIK3 inhibition. Preclinical studies in breast cancer cell lines have demonstrated that Tenalisib potentiated the activity of taxol and doxorubicin. The aim of this phase II study was to investigate the efficacy and safety of single-agent tenalisib in patients (pts) with HR+ HER2- locally advanced or metastatic breast cancer (MBC). **Methods:** This randomized, open-label study was designed to evaluate two doses (800 mg BID and 1200 mg BID) of Tenalisib in HR+/HER2- locally advanced or MBC patients including TNBC patients whose disease had progressed following at least one line of therapy. Tenalisib was given orally in a 28-days cycle until disease progression. Forty pts (20 pts at each dose level) were planned to be enrolled with the primary outcome being the percentage of pts without disease progression at the end of 6 months. The investigator-assessed ORR, PFS, and Clinical Benefit Rate (CBR = CR+PR+SD), using RECIST v1.1 were secondary outcomes. **Results:** All forty pts have been enrolled in the study. Pts had a median of 3 (range 1-7) lines of prior therapy; of these, 87% pts had prior endocrine therapy, and 40% and 30% pts had aromatase inhibitor or fulvestrant as their last prior therapy respectively. The median age was 63.8 (31-71) years, 52.5% of pts had PS 1, 77.5% had visceral disease, and 95.0% had ≥ 2 metastatic lesions at the time of enrollment. As of 07-Feb 2022, twenty-eight pts were efficacy evaluable. Of the 28, 2 pts had a PR (7%), 17 pts had SD (61%) and 6 pts had PD (21%) at the first efficacy assessment after completion of 2 cycles. Three pts discontinued from the study due to adverse events (11%) before the first efficacy assessment. The CBR was 68%. On safety, the most common TEAEs (≥5%) of any grade were transaminitis (All: 22%, ≥G3: 10%), GGT elevation (All: 7%, ≥G3: 5%), fatigue (All: 7%, ≥G3: 0%), rash (All: 7%, ≥G3: 2.5%). Discontinuations due to related TEAEs were infrequent (7%). There were no unexpected TEAEs. Two pts were discontinued due to related TEAEs (rash and GGT elevation). **Conclusions:** Based on the data from the ongoing study, Tenalisib showed encouraging preliminary efficacy as a single agent in patients with advanced MBC. Updated efficacy and tolerability data will be provided at the time of presentation. Clinical trial information: NCT05021900. Research Sponsor: None.

1060 **Poster Session**

Predicting hyperglycemia among patients receiving alpelisib plus fulvestrant for metastatic breast cancer. *First Author: Xuan Ge, City of Hope, Duarte, CA*

Background: Although hyperglycemia is recognized as a common adverse event (AE) on alpelisib (ALP), this AE has been little studied outside clinical trials. We report the frequency of ALP-associated hyperglycemia in a real-world setting and evaluate proposed risk factors. **Methods:** We retrospectively identified patients with PIK3CA-mutated, hormone receptor-positive, metastatic breast cancer who initiated treatment with ALP+fulvestrant (FUL) between August 2019 and December 2021. Five primary characteristics (diabetes, prediabetes, body mass index (BMI), age, Asian ancestry) were evaluated as independent risk factors for ALP-associated hyperglycemia using ordinal logistic regression that considered 3 glycemic levels: normoglycemia, grade 2, and grade 3-4 hyperglycemia. Overall risk of error from multiple hypothesis testing was kept below 5% using the False Discovery Rate method. **Results:** The study included n = 92 subjects, all but 1 female, mean age 59.9 (+11.9) years, 13.0% with Asian ancestry. One third (33.7%) of patients had pre-existing diabetes, another 9.8% had pre-diabetes only. One third (32.6%) were obese, another third (31.5%) were overweight. Hypertension and hyperlipidemia were present in 53.3% and 41.3%, respectively. On ALP+FUL, 59 (64.1%) current subjects developed hyperglycemia of grade 1-4, a rate no different than the 181/284 (63.7%) reported in the ALP+FUL arm of the SOLAR-1 trial. Among our subjects, risk of grade 2-4 hyperglycemia was independently increased by 4 of 5 hypothesized risk factors, specifically pre-existing diabetes (Odds Ratio 3.75, 95% Confidence Interval: 1.40-10.01), pre-diabetes (6.22, 1.12-34.47), Asian ancestry (7.10, 1.75-28.84), each unit of BMI above 20 (1.17, 1.07-1.28), but not by additional year of age (1.01, 0.97-1.05). Exploratory analysis detected no association with pre-existing hypertension or hyperlipidemia. **Conclusions:** These findings suggest that Asian ancestry merits further study as a predisposing factor for ALP-associated hyperglycemia. Our study of this AE also demonstrates that pre-existing hyperglycemia and greater BMI are independent risk factors; diabetes and pre-diabetes confer similar degrees of risk; risk from BMI begins after BMI 20 and rises incrementally; and age is not a contributing factor. Research Sponsor: U.S. National Institutes of Health.

1061 **Poster Session**

Utility of liquid biopsy for identifying emerging mutations (mut) and novel treatment options in luminal metastatic breast cancer (LMBC). *First Author: Alberto Gonzalez-Medina, Cancer Genomics Group, Vall dHebron Institute of Oncology (VHIO), Barcelona, Spain*

Background: Molecular characterization of LMBC for the choice of therapy and inclusion in clinical trials is frequently performed in archival biopsies procured several years before. Emerging mut secondary to therapeutic pressure are hence frequently missed but could be detected by real-time analysis of circulating tumor DNA. Aim: 1) To assess the emergence of *ERBB2* and other mut upon therapeutic pressure; 2) To compare the concordance of mut in tumor and plasma samples between patients (pts) with metachronous and synchronous sample acquisition. **Methods:** Pts with LMBC and available tumor biopsy and plasma samples were identified and divided in two groups: 1) Cohort 1 (metachronous) if the time between tissue and plasma acquisition was > 3 months and systemic treatment was given between the sampling; 2) Cohort 2 (synchronous) if sampling occurred with < 3 months interval in the absence of systemic treatment. Tumor and plasma were analyzed using MiSeq Amplicon-based NGS (custom panel of 60 cancer-related genes). The emergent mut in plasma in Cohort 1 and the concordance of ESCAT Tier I and II mut (*PIK3CA, AKT1, ERBB2, ESR1, PTEN*) in both Cohorts were determined and correlated with clinical features. **Results:** 176 pts were included, 112 in Cohort 1 and 64 in Cohort 2. In Cohort 1, emerging mut in *PIK3CA* were identified in 5 cases (14% of total cases with *PIK3CA* mut), *ESR1* in 22 cases (85% of cases with *ESR1* mut) and *PTEN* in 3 cases (43% of cases with *PTEN* mut). No emerging *ERBB2* or *AKT1* mut were seen in plasma. In Cohort 1 *ERBB2* mut were identified in 10 pts (8.9%), 5 both in plasma and tissue and 5 only in tissue. Concordance between tumor and plasma was 53% in Cohort 1 and 66% in Cohort 2 (95% CI of the difference -2% to 38%, P = .09). In Cohort 1, concordance was not associated with (neo)adjuvant treatment, number of lines for MBC, presence of visceral metastasis, location of biopsy (primary tumor or metastasis), interval between sampling (range 3.6 – 288 months) or type of systemic treatment before plasma sampling. In Cohort 2, higher concordance associated with shorter interval between primary diagnosis and sampling (p = 0.02). *PI3KCA* and *ESR1* were the two genes most frequently altered in both cohorts. *PI3KCA* mut had the highest degree of concordance in both groups (70% in Cohort 1 and 76% in Cohort 2). Concordance for *ESR1* mut was low in both cohorts (20% and 48%, respectively). **Conclusions:** A significant number of *ESR1* mut emerged upon therapeutic pressure in LMBC. Plasma analysis could also detect the emergence of *PIK3CA* and *PTEN*, but not *ERBB2* mut. The trend towards lower concordance between metachronous and synchronous tumor and plasma sampling is probably due to increased tumor heterogeneity and clonal diversity secondary to systemic treatment. Our findings confirm that liquid biopsies provide complementary information respect to tumor tissue that may be potentially useful for clinical decisions. Research Sponsor: Puma Biotechnology.

1062 **Poster Session**

Clinical value of next-generation sequencing in endocrine therapy for advanced hormone receptor–positive/HER2-negative breast cancer. *First Author: Dan Lv, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: Acquired gene mutation is a major mechanism of resistance to endocrine therapy in hormone receptor (HR)-positive advanced breast cancer. Circulating tumor DNA (ctDNA) facilitates the current assessment of the genomic profile in patients with advanced cancer. We performed this clinical trial to determine the landscape of gene mutation before endocrine therapy, to search for molecular markers of endocrine therapy efficacy, and to explore the clinical value of ctDNA to guide precise endocrine therapy in patients with advanced breast cancer. **Methods:** We conducted an open-label, single-center, multicohort, prospective study. Patients were women with pathologically and immunohistochemically confirmed HR-positive/HER-2-negative patients with advanced breast cancer. Patients relapsed during or after adjuvant endocrine therapy or progressed after completing at least one previous line of treatment for advanced breast cancer. Patients were assigned to four parallel treatment cohortsmatched to mutations identified in ctDNA: 1) cohort A comprised patients with abnormal activation of PI3K/Akt/mTOR pathway signal, preferred mTOR inhibitor combined with endocrine therapy; 2) cohort B comprised patients with ESR1 mutation and who did not use fulvestrant before, preferred fulvestrant; 3) cohort C comprised patients with HER2 mutations, preferred pyrotinib combined with endocrine therapy; 4) cohort D comprised patients with no significant gene mutation, making treatment plan according to the actual clinical situation. If more than one mutation was identified, the priority of entry is cohorts C, cohorts A and cohort B. In the A-D cohort, patients who obey the treatment plan are the compliance group, and patients who do not obey the treatment plan are the violation group. The primary endpoints were progression-free survival (PFS), and the secondary endpoints included overall survival time (OS). **Results:** A total of 113 patients underwent NGS detection of ctDNA, and 84 patients were enrolled in the study. In all cohorts, combined median PFS was 4.9 months, and the median PFS in the compliance group was 3.0 months longer than in the violation group (6.03 vs 3.03 months, p = 0.0222, HR = 0.5743, 95%CI 0.3273-1.007). In cohort C, the median PFS was 11.1 months in the compliance group and 2.22 months in the violation group (p = 0.0067, HR = 0.1980, 95%CI 0.032-1.22). There was no significant difference in the median PFS between patients with and without compliance with the treatment protocol in cohort A and cohort B (p = 0.5054 and 0.7325, respectively). **Conclusions:** The study suggested that ctDNA detection may guide the optimal endocrine therapy strategy for patients with advanced breast cancer and achieve the benefit of progression free survival. NGS detection might distinguish patients with HER2 mutation and provide new treatment strategies. Clinical trial information: NCT03786575. Research Sponsor: None.

1063 **Poster Session**

Ribociclib-induced acute kidney injury: Uncover the MONALEESA's dark face. *First Author: Maissoune Hajir, King Hussein Cancer Center, Amman, Jordan*

Background: The phase-3 MONALEESA-2,-3 and -7 randomized trials showed improved progression-free survival (PFS) and overall survival (OS) with the addition of cyclin D-cyclin-dependent kinase 4/6 (CDK4/6) inhibitor ribociclib to endocrine therapy in women with advanced-stage breast cancer. However, ribociclib induced acute renal injury is not recognized in these studies. In this report, we explore ribociclib-induced acute kidney injury (AKI) in breast cancer patients receiving ribociclib. **Methods:** We performed a retrospective chart review of all breast cancer patients who received ribociclib at our institution between April 2019 and September 2021. Patients and disease characteristics were collected, details of creatinine kinetics in relation to administration of ribociclib and other nephrotoxic drugs were obtained. Acute kidney injury grades (AKI-KDIGO classification) were captured. **Results:** 145 females, median age 60.0 years, all with advanced-stage breast cancer treated with aromatase inhibitors (AI) or fulvestrant plus ribociclib were reviewed. A total of 26 (17.9%) patients developed AKI; 3 were grade-I, 21 grade-II and 2 were grade-III. Rate of AKI was significantly higher (n = 15, 48.4%) among 31 patients on other concomitant nephrotoxic drugs, compared to 11 (9.6%) of 114 other patients, p = 0.001. Nephrotoxic drugs include non-steroidal anti-inflammatory (38%), metformin (30%), angiotensin-II receptor blockers (26%), and angiotensin-converting enzyme inhibitors (11%). Median time to develop AKI was 54 (range, 21-168) days, while the median time for creatinine recovery was 5 (range, 4-7) days after holding the drugs. Average creatinine increment for affected patients was 2.28 times the baseline level. Time to AKI was shorter, but not statistically significant, among patients on nephrotoxic drugs and recovery was faster after stopping these drugs (Table). **Conclusions:** Ribociclib-induced AKI is not uncommon and not adequately addressed. Though reversable in majority of patients, some patients may develop grade-III AKI or require treatment interruption. Nephrotoxic medications seem to significantly enhance ribociclib-associated renal injury. Withhold these medications with periodical assessment by nephrologist is strongly recommended in these patients. Larger studies are warranted to validate our findings. Research Sponsor: None.

	Without other nephrotoxic drugs	With Other nephrotoxic drugs	P-Value
Total number of patients (n)	114	31	
Patient with AKI, n (%)	11 (9.6%)	15 (48.4%)	0.001
Time to AKI (mean; range), days	66 (28-98)	52 (21-168)	0.14
Grade-11/III AKI, n (%)	10 (2.6%)	13 (3.38%)	0.88
Time to recovery (mean; range), days	6 (4-10)	5.4 (4-7)	0.12

1064 **Poster Session**

Identifying genetic factors of response and resistance to CDK4/6 inhibitors in metastatic HR+/HER2-breast cancer using real-world data. *First Author: Smita Agrawal, ConcertAI, Bengaluru, India*

Background: CDK4/6 inhibitors plus endocrine therapy are approved for treatment of HR+/HER2- metastatic breast cancer (MBC) and have shown to provide a significant progression free survival benefit over endocrine therapy alone. But not all patients benefit from this treatment and some develop resistance over time. The molecular mechanisms governing this resistance are poorly understood. We have developed a real world dataset that includes data elements from structured EMR tables as well as deeply curated unstructured data from BC patients (ConcertAI Genome360 BC Dataset) who have been treated with CDK4/6 inhibitors and have undergone DNA sequencing to identify somatic mutations. We have leveraged this linked clinical-genomics dataset to identify genetic drivers of resistance and response to CDK4/6 inhibitors. **Methods:** This retrospective study uses the Genome360 BC Dataset (N = 1249). The patient's eligibility to be included in this study (N = 456) was HR+/HER2- MBC patients with age > 18 years treated with at least one of the CDK4/6 inhibitors and have response data based on RECIST criteria (responders = 231, non-responders = 225). For each patient in both cohorts, all pathogenic gene mutations and copy number changes were identified and enrichment analysis was performed. Biomarkers with Z value > 1.96 (p value < 0.05) were considered for further analysis. Pathway analysis was performed using these biomarkers and the CDK4/6 pathway to identify pathways and genes that can potentially be targeted to overcome resistance based on the mutational landscape of the patients receiving therapy. **Results:** We identified 7 potential segments (similar groups of genes) which predicted response or resistance to CDK4/6 inhibitors. Here we present data on 3 such segments which are closely related. Loss of function mutations in RB1 were enriched in the non-responder population (Z value = 2.33; p value = 0.026; N = 31). This is consistent with previously reported findings. In addition, amplifications and gain of function mutations in MYC and associated genes were also significantly enriched in the non-responder population (Z value = 2.71; P value = 0.01; N = 44). Interestingly, loss of function mutations in TSC1/2 genes which are downstream of MYC were predictors of good response to CDK4/6 inhibitors (Z value = 2.19; P value = 0.036; N = 30), strengthening the role of the parallel MYC signaling pathway in resistance to CDK4/6 inhibitors. **Conclusions:** Using our Genome360 BC Dataset, we have identified genetic markers affecting response to CDK4/6 inhibitors. In addition to the known role of RB1 in resistance to CDK4/6 inhibitors, the MYC signaling pathway emerged as a strong candidate. Based on these results, patients with mutations in these pathways may benefit from addition of mTOR or PKL1 inhibitors to CDK4/6 inhibitors to overcome resistance and prolong their effect. Research Sponsor: None.

1065 **Poster Session**

Real-world efficacy of ribociclib (RIB) plus aromatase inhibitor (AI)/fulvestrant (FUL), or endocrine monotherapy (ET), or chemotherapy (CT) as first-line (1L) treatment (tx) in patients (pts) with hormone receptor–positive (HR+), human epidermal growth factor receptor-2–negative (HER2–) advanced breast cancer (ABC): Results of fourth interim analysis (IA) from RIBANNA. *First Author: Diana Lüftner, Charité University Hospital, Berlin, Germany*

Background: RIBANNA is a real-world, noninterventional study conducted in Germany evaluating efficacy, safety, and tolerability of RIB in combination with AI/FUL aiming to gain insights into routine clinical practice for pts with HR+, HER2– ABC. Here, we present results of the fourth IA from RIBANNA. **Methods:** Pre-, peri- and postmenopausal pts who received 1L tx with RIB+AI/FUL, or ET or CT for HR+, HER2– ABC were included in accordance with the German tx guideline. The effect of baseline demographic characteristics, including histological grade, age, previous adjuvant tx, Eastern Cooperative Oncology Group-performance score (ECOG-PS), and metastatic sites on progression-free survival was evaluated using Cox regression model. **Results:** At data cutoff October 11, 2021, 2598 pts were enrolled in the study (RIB+AI/FUL, n = 2177; ET, n = 239; CT, n = 182). Data from 1L tx were available for 2492 pts (95.9%), second-line tx for 689 pts (26.5%), third-line tx for 263 pts (10.1%), and fourth-line tx for 94 pts (3.6%). Significant differences were observed in baseline mean age and metastatic sites for pts in RIB+AI/FUL cohort vs ET and CT cohorts (both < 0.001). At baseline, the mean (SD) ages of pts were 65.5 (11.6), 70.7 (11.5) and 61.6 (11.6) years in RIB+AI/FUL, ET, and CT cohorts, respectively. While comparing the performance status, 44.2% of pts in RIB+AI/FUL, 34.7% of pts in ET and 42.1% of pts in CT cohort were fully active with ECOG-PS = 0. CNS, liver, or lung metastases were recorded in 42.6% of pts in RIB+AI/FUL, 26.8% of pts in ET and 67.1% of pts in CT cohort. Bone only metastases were reported in 30.8%, 47.9% and 15.0% of pts in RIB+AI/FUL, ET, and CT cohorts, respectively. Overall, 32.1%, 37.7%, and 52.7% of pts discontinued the study in RIB+AI/FUL, ET, and CT cohorts, respectively, the most common reasons being deaths (16.1%,17.2%, and 31.9%, respectively) and lost to follow-up (5.9%, 8.8%, and 9.3%, respectively). The most common tx-emergent adverse event (grade 3 or 4) observed in RIB+AI/FUL cohort was neutropenia (14.8%), while 6.6% and 6.9% of pts in ET and CT cohorts, respectively, experienced neutropenia. The efficacy results from all 3 cohorts, including Kaplan-Meier curves, will be presented during ASCO 2022. **Conclusions:** RIBANNA study showed diverse population characteristics among pts who received RIB tx in a real-world setting. Overall higher number of pts were treated in 1L with RIB+AI/FUL followed by ET and CT. The differences in baseline characteristics on metastatic pattern, age, and ECOG-PS reflect different selection strategies for 1L tx decision. No new safety signals were identified. Clinical trial information: CLEE011ADE03. Research Sponsor: Novartis Pharma GmbH, Germany.

1066 **Poster Session**

Dalpiciclib in combination with letrozole/anastrozole or fulvestrant in HR+/HER2- advanced breast cancer: A phase Ib study. *First Author: Qingyuan Zhang, Department of Medical Oncology, Harbin Medical University Cancer Hospital, Harbin, China*

Background: Dalpiciclib (Dalp; SHR6390) is a novel cyclin-dependent kinase 4/6 inhibitor which showed tolerability and preliminary clinical activity as monotherapy for pretreated advanced breast cancer (ABC). Here we conducted a multicenter, phase 1b trial to further assess the safety, pharmacokinetics and efficacy of Dalp in combination with endocrine therapy (ET) in HR+/HER2- ABC. **Methods:** 5 cohorts of patients with HR+/HER2- locally recurrent or metastatic BC and any menopausal status were enrolled (~15 patients/combination regimen). Patients without prior treatment for ABC (cohort1/2) were given Dalp (125 or 150 mg po qd, d1-21, q4w) plus letrozole (LTZ; 2.5 mg po qd) or anastrozole (ATZ; 1 mg po qd); patients who progressed after ET (cohort 3-5) were given Dalp (125, 150, or 175 mg po qd, d1-21, q4w) plus fulvestrant (Fulv; 500 mg im, cycle 1 d1, d15, then d1 q4w). The primary endpoint was safety. The data cutoff date was Sep. 20, 2021. **Results:** 58 patients received Dalp plus LTZ/ATZ and 46 received Dalp plus Fulv. No maximum tolerated dose of Dalp was reached with LTZ/ATZ or Fulv. Across all cohorts, 75.0%-93.8% of patients had a grade ≥3 treatment-related adverse event (TRAE), with the most common being neutropenia (grade 3, 40.0%-87.5%; grade 4, 4.2%-46.7%) and leukopenia (grade 3, 33.3%-80.0%; grade 4, 0%; Table). Treatment-related serious AEs occurred in 2 (3.4%) patients with Dalp plus LTZ/ATZ and none with Dalp plus Fulv. At the tested dose levels, steady-state areas under the concentration curve and peak concentration of Dalp increased with dose in combination with LTZ/ATZ or Fulv. Dalp 150 mg was associated with a numerically higher objective response rate in both ET-untreated (67.6%, 95% CI 49.5-82.6) and ET-pretreated (53.3%, 95% CI 26.6-78.7) patients per investigator. The median progression-free survival with Dalp 150 mg was 20.3 mo (95% CI 16.9-not reached [NR]) and 16.7 mo (95% CI 1.9-24.1) in ET-untreated and ET-pretreated patients respectively. **Conclusions:** Dalpiciclib plus letrozole/anastrozole or fulvestrant showed an acceptable safety profile, with hematological toxicities as the most common TRAEs. The recommended phase 3 dose of dalpiciclib was 150 mg. Together with the promising anti-tumor activity observed with the combination therapy in HR+/HER2- ABC, further trials are warranted. Clinical trial information: NCT03481998. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co. LTD.

Grade ≥3 TRAEs occurring in ≥10% of patients in any cohort.

		Dalp 125 mg +LTZ/ATZ (n=24)	Dalp 150 mg +LTZ/ATZ (n=34)	Dalp 125 mg +Fulv (n=16)	Dalp 150 mg +Fulv (n=15)	Dalp 175 mg +Fulv (n=15)
Neutropenia	Grade ≥3	18 (75.0)	28 (82.4)	15 (93.8)	12 (80.0)	13 (86.7)
	Grade 3	17 (70.8)	21 (61.8)	14 (87.5)	10 (66.7)	6 (40.0)
	Grade 4	1 (4.2)	7 (20.6)	1 (6.3)	2 (13.3)	7 (46.7)
Leukopenia	Grade ≥3	11(45.8)	18 (52.9)	8 (50.0)	5 (33.3)	12 (80.0)
	Grade 3	11(45.8)	18 (52.9)	8 (50.0)	5 (33.3)	12 (80.0)
	Grade 4	0	0	0	0	0

Data are n (%).

1067 **Poster Session**

Survival outcomes in metastatic HR-positive, HER2-negative invasive ductal carcinoma compared to invasive lobular carcinoma and mixed ductal/lobular treated with endocrine therapy in combination with CDK4/6 inhibitors, mTOR inhibitor, or PI3K inhibitor. *First Author: Jason A Mouabbi, MD Anderson Cancer Center, Houston, TX*

Background: The majority of invasive lobular breast cancers (ILC) are hormone receptor (HR)-positive, HER2-negative and are clinically treated similarly to HR+ HER2-negative invasive ductal cancers (IDC). However, ILC differs distinctly from IDC in its clinicopathologic characteristics and molecular alterations. ILC also differs in response to systemic therapy, with studies showing ILC as less sensitive to chemotherapy. It is currently unknown if patients with ILC or mixed ductal/lobular (MDL) histologies derive similar benefits as IDC from endocrine therapy (ET) in combination with cyclin-dependent kinase 4/6 inhibitors (CDK4/6is), mTOR inhibitor everolimus or PI3K inhibitor alpelisib. **Methods:** We retrospectively searched for patients treated at MD Anderson Cancer Center with a diagnosis of HR+, HER2-negative metastatic breast cancer (MBC) with ET in combination with CDK4/6is, everolimus or alpelisib. Patients were divided into 3 groups based on their histology: ILC, IDC and mixed. We obtained data on demographics, estrogen (ER) and progesterone (PR) receptor status, menopausal status, treatment duration and survival status. The Kaplan-Meier product-limit method was used to compare progression-free survival (PFS) and overall survival (OS) between the three different groups stratified by the treatment received. **Results:** We identified 2,971 patients (2,432 IDC [82%], 427 ILC [14%], 112 Mixed [4%]) with HR+ HER2-negative MBC treated with ET in combination with CDK4/6is, everolimus and/or alpelisib between 2010 and 2021. Median age was around 50 years in all groups. Around 80% of patients were white, 10% Hispanic and 5% black. Around 55% of patients were post-menopausal, 99% had ER+ and 88% PR+ tumors; 1,895 patients (81% IDC, 15% ILC, 4% mixed) received CDK4/6is, 1,027 (82% IDC, 14% ILC, 4% mixed) received everolimus and 49 (81% IDC, 19% ILC) received alpelisib. PFS and OS were not statistically different between the 3 groups (Table). **Conclusions:** HR+ HER2-negative MBC patients with IDC, ILC and MDL benefited from ET in combination with CDK4/6is, everolimus or alpelisib similarly with no significant differences in PFS and OS. Research Sponsor: None.

	CDK4/6i + ET N = 1,895			Everolimus + ET N = 1,027			Alpelisib + ET N = 49	
	IDC N = 1,549 (81%)	ILC N = 277 (15%)	Mixed N = 69 (4%)	IDC N = 843 (82%)	ILC N = 141 (14%)	Mixed N = 43 (4%)	IDC N = 40 (81%)	ILC N = 9 (19%)
Median PFS (months)	11.7	14.5 P = 0.54	14.8	6.3	6.7 P = 0.48	6.0	5.2 P = 0.63	3.0
Median OS (months)	34.2	34.6 P = 0.26	26.5	23.6	19.0 P = 0.89	24	13.6 P = 0.67	16.4

1068 **Poster Session**

Hormone therapy (HT) or capecitabine (CAP) as maintenance therapy following the first-line chemotherapy in HR+/HER2-ABC/MBC: Secondary endpoint adverse effects (AEs) and toxicity report of OVERSTEP Trial (ZJCH15001/CBCSG 035). *First Author: Jian Huang, Department of Breast Medical Oncology, Cancer Hospital of the University of Chinese Academy of Sciences, Zhejiang Cancer Hospital, Hangzhou, China*

Background: OVERSTEP (NCT02597868) is a multicenter, randomized clinical trial of capecitabine (CAP) versus endocrine therapy (HT) as maintenance therapy after 1st-line CAP-based combination chemotherapy in HR+/HER2- ABC/MBC. At 2020 SABCS conference, we reported the primary endpoint (progression-free survival, PFS) at follow-up of 24.3 months, at 2021 SABCS, repoted the PFS and OS at follow-up of 41.4 months. Here, we reported the secondary endpoint Adverse effects (AEs) . **Methods:** Total of 181 patients with HR+ and HER2- MBC were enrolled in this study from Jun, 2013 to Jan, 2019. All the patients received at least 4 cycles of CAP-based combination regimen as 1st-line salvage chemotherapy. The patients who achieved CR, PR or durable SD by RECIST criteria entered into the maintenance therapy setting (MT), and randomly (1:1 ratio) assigned to either CAP single or HT group. Randomization was done centrally with stratification by endocrine sensitive or resistance and visceral or non-visceral metastasis. After combined chemotherapy, 75.14% (n=136) cases entered into the maintenance therapy setting, and 24.86% case were disease progressed (PD) during combined chemotherapy. After a median follow-up of 41.4 months (IQR 21.57-79.23), we reported the secondary endpoint Adverse effects (AEs) . **Results:** In PPS, hematologic toxicities in ET group and CT group were as follows, anemia (69.6% vs 64.2%), leukopenia (60.8% vs 50.8%), neutropenia (66.7% vs 31.2%), thrombocytopenia (26.1% vs 26.9%). The non-hematologic toxicities were hand-foot syndrome (HFS) (33.3 vs 41.8%) , increased ALT (50.7 % vs 37.3%), increased AST (53.6% vs 37.3%), hyperbilirubinemia (32.2% vs 25.4%), fatigue (14.5% vs 10.4%), hypokalemia (5.8% vs 4.5%), pneumonia (0.0% vs 6.0%), peripheral neuropathy (4.8% vs 0.0%) ,etc. Duration of maintenance, the AEs in the ET group were significantly lighter, just like anemia (0.0% vs 28.4%), leukopenia (5.8% vs 17.8%), neutropenia (5.8% vs 16.4%), thrombocytopenia (2.9% vs 22.4%) et al., the non-hematologic toxicities were HFS (0.0% vs 23.9%), increased ALT (4.3% vs 16.4%), increased AST (5 .8% vs 16.4%), increased bilirubin (0.0% vs 10.4%), peripheral neuropathy (5.8% vs 0.0%). Moreover, the toxicities of grade 3/4 were in the CT maintenance group, anemia was 1 case (1.5%), neutropenia 2 cases (2.99%), HFS 5 Case (7.5%) and increased AST in 1 case (1.5%). The ET maintenance group had not any grade 3/4 AEs. **Conclusions:** For HR+ and HER2- MBC, after 1st-line salvage combined chemotherapy, HT maintenance therapy is superior to chemotherapy (capecitabine) maintenance in terms of efficacy and safety. But, if toxicity is well managed, the safety is still tolerated during chemotherapy maintenance. Therefore, in the post-CDK4/6 period, chemotherapy is still an option. Clinical trial information: NCT02597868. Research Sponsor: China breast cancer clinical research collaboration group.

1069 **Poster Session**

A novel analysis of data from the PALOMA-3 trial confirms the efficacy of palbociclib and provides an option for efficacy assessments that could accelerate drug approvals. *First Author: Celine Yeh, Columbia University College of Physicians and Surgeons, New York, NY*

Background: Advances in breast cancer (BC) therapy the past few decades have led to higher survival rates. Beginning with palbociclib, cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors have emerged as a treatment option for BC. We analyzed data from PALOMA 3 that could release a biomarker of OS in patients that receive palbociclib. **Methods:** We estimated concurrent rates of growth (g) and regression (d) from the 393 women with advanced BC enrolled in PALOMA-3 who had radiographic tumor measurement data including 261 treated with fulvestrant + palbociclib, and 132 with fulvestrant + placebo. We analyzed data using a model defined as SLD (t) = exp ($-d$ x t) + exp (g x t) – 1, where SLD = sum of longest diameters and t = time. We examined the relationship between g and overall survival (OS) and compared the median growth rates (g) of various cohorts. **Results:** g values associate highly with OS (p<0.0001). Emulating results in the clinical trial, palbociclib slowed the median g values of the entire population and those with sensitivity to previous endocrine therapy but not those deemed resistant. Further cohort analyses found greater benefit with palbociclib in those with visceral metastases, and longer disease-free interval, and benefit independent of ECOG PS, menopausal status, prior lines of therapy, and age. With only the baseline and two additional scans obtained, the median g values of the palbociclib and placebo arms were statistically different: p=0.038 after 28 (19/9) patients and p=0.0043 after 40 (26/14) patients. **Conclusions:** Estimates of palbociclib's impact on tumor growth rates (g) confirm its efficacy in PALOMA 3. Our ability to discern differences in g, a value associated with OS, after only two follow up scans in as few as 28 patients merits considering g an early biomarker of OS benefit that could bring effective drugs to patients as rapidly as possible. Research Sponsor: Pfizer Inc.

		g values x10^{-4}/day					
		Placebo		Placebo		Placebo	
	Cohorts	All	PAL	Resistant	PAL	Sensitive	PAL
All	g	28	12	24	15	34	11
	p	<0.0001		NS		<0.0001	
Non-visceral	g	12	10	14	15	12	9
	p	NS		NS		NS	
Visceral	g	34	14	26	16	41	13
	p	<0.0001		NS		<0.0001	
<65y	g	25	13	24	15	29	12
	p	0.0025		NS		0.0082	
>=65y	g	37	10	1	17	37	9
	p	0.0005		—		0.0002	
Disease-free interval*	cohorts	All		DFI ≤24 mos		DFI >24	
	g	28	12	26	13	30	12
	p	<0.0001		NS		0.0016	
ECOG	cohorts	All		ECOG 1		ECOG 0	
	g	28	12	27	13	30	12
	p	<0.0001		0.0026		0.0023	
Menopausal status	cohorts	All		Pre/Peri		Post	
	g	28	12	27	13	30	12
	p	<0.0001		0.0026		0.0023	
# Prior therapies	cohorts	0		1		3	
	g	22	10	28	14	62	14
	p	0.0374		0.0042		0.0388	
g estimated using only first 3 scans	cohorts	All		Res		Sens	
	g	34	27	31	30	36	26
	p	0.0009		0.4387		0.0005	

*Disease-free interval was defined as the time from diagnosis of primary breast cancer to first relapse in patients who received adjuvant therapy

1070 **Poster Session**

The safety, tolerability, and preliminary antitumor activity of sitravatinib plus tislelizumab in patients with locally recurrent or metastatic triple-negative breast cancer. *First Author: Lei Fan, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: Anti-PD-1 antibody plus chemotherapy has been demonstrated promising anti-tumor activity in patients with locally recurrent or metastatic triple negative breast cancer (TNBC). However, this regime only limited to TNBC patients with PD-L1 positive. As antiangiogenic agents could enhance the response to immune checkpoint inhibitors, we conducted this phase 2 study to assess the efficacy and safety of novel chemotherapy-free regimen of sitravatinib (targets receptor TKI against TYRO3, AXL, MERTK and VEGF family of receptors) in combination with tislelizumab (anti-PD-1 antibody) in patients with locally recurrent or metastatic TNBC regardless of PD-L1 status. **Methods:** Patients with locally recurrent or metastatic TNBC were included and divided into two cohorts. Patients received 70 mg (cohort A) or 100 mg (cohort B) sitravatinib QD PO and 200 mg tislelizumab IV Q3W until disease progression or intolerable toxicity. The primary endpoints included overall response rate (ORR) (cohort A and B) and rate of grade ≥3 treatment-related adverse events (AEs) (cohort B). Secondary endpoints included disease control rate (DCR), progression-free survival (PFS), duration of response (DOR), 1-year overall survival rate and safety/tolerability. In cohort A, the first statistical analysis would be performed when 12 patients were enrolled; if ≥1 of 12 patients were with confirmed response during the first stage, additional 9 patients would be enrolled to the second stage based on Simon's two-stage design. We would deem cohort A to be statistically superior to a historical control of 8% under the settings if > 3 of 21 patients responded (one-sided a = 0.1 and power of 80%). Patients' recruitment in cohort B would begin after completing the recruitment in cohort A. **Results:** Herein we reported the preliminary results in cohort A. Four patients were with confirmed response during the first stage, and additional nine patients were enrolled to the second stage. A total of 21 patients with 0-3 lines of prior chemotherapy were included from April 2021 to September 2021. The median age was 51 (32-66) years and 20 (95%) patients had ECOG PS 0. At data cut off 13 Jan 2022, 19 patients were alive, 11 are still on treatment. The confirmed ORR was 38.1% (95% CI, 18.1%-61.6%) based on current 21 efficacy evaluable patients. DCR was 95.2% (95% CI, 76.2%-99.9%), and median PFS was 7.0 (95% CI, 3.7 - not reached) months. 4/21 (19%) of patients experienced grade 3 treatment-related AEs. Grade 3 AEs reported in ≥5% of patients were aspartate aminotransferase increased (9.5%) and palmar-plantar erythrodysaesthesia syndrome (9.5%). No patients experienced grade 4 AEs. **Conclusions:** Sitravatinib combined with tislelizumab demonstrated clinically meaningful anti-tumor activity and had a manageable safety profile. Clinical trial information: NCT04734262. Research Sponsor: BeiGene (Beijing) Co., Ltd.

1071 **Poster Session**

Sacituzumab govitecan (SG) versus treatment of physician's choice (TPC) in patients (pts) with previously treated, metastatic triple-negative breast cancer (mTNBC): Final results from the phase 3 ASCENT study. *First Author: Aditya Bardia, Department of Hematology/Oncology, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA*

Background: Treatment goals for pts with metastatic breast cancer include extended survival and improved quality of life (QoL). SG is an antibody-drug conjugate composed of an anti–Trop-2 antibody coupled to the cytotoxic SN-38 payload via a proprietary, hydrolyzable linker. SG received FDA approval for pts with mTNBC who received ≥2 prior chemotherapies (at least 1 in the metastatic setting). In the pivotal phase 3 ASCENT study (NCT02574455), SG demonstrated a significant survival benefit over single-agent chemotherapy TPC in the primary analysis population of pts with second line or greater (2L+) mTNBC without known brain metastases at baseline (Bardia A et al. *NEJM* 2021) and QoL (Loibl S. et al. ESMO 2021). With additional follow up, we present the final data on efficacy, including overall survival (OS), safety, and QoL. **Methods:** Pts with mTNBC refractory or relapsing after ≥2 prior chemotherapies with at least 1 in the metastatic setting were randomized 1:1 to receive SG (10 mg/kg IV on days 1 and 8, every 21 days) or TPC (capecitabine, eribulin, vinorelbine, or gemcitabine) until disease progression or unacceptable toxicity. Primary endpoint was progression-free survival (PFS) per RECIST 1.1 by independent review in pts without known brain metastases at baseline. Key secondary endpoints included OS, safety, and health-related QoL. Safety was analyzed in pts who received ≥1 dose of study drug. **Results:** Of 529 pts enrolled, 468 did not have known brain metastases at baseline (median age: 54 y [range, 27-82]; median prior lines: 4 [range, 2-17]). As of Feb 25, 2021 (final database lock), SG (n = 235) vs TPC (n = 233) significantly improved median PFS (5.6 vs 1.7 mo; HR: 0.39; P< 0.0001) and median OS (12.1 vs 6.7 mo; HR: 0.48; P< 0.0001). The OS rate at 24 months was 22.4% (95% CI, 16.8-28.5) in the SG arm and 5.2% (95% CI, 2.5-9.4) in the TPC arm. In the safety population (n = 482), key treatment-related grade ≥3 adverse events with SG (n = 258) vs TPC (n = 224) were diarrhea (11% vs 0.4%), neutropenia (52% vs 33%), anemia (8% vs 5%), and febrile neutropenia (6% vs 2%). There was no grade ≥3 neuropathy and 1 case of grade 3 interstitial lung disease reported with SG. No patient experienced a treatment-related death with SG, and there was 1 treatment-related death with TPC due to neutropenic sepsis. Treatment discontinuations due to AEs were ≤3% in both arms. SG arm showed clinically meaningful and statistically significant improvements than the TPC arm in scores for all five primary focus health-related QoL domains. **Conclusions:** The analysis based on the final database lock of ASCENT confirms the superior survival outcomes of SG over single-agent chemotherapy, with a manageable safety profile and improvement in QoL for pts with mTNBC in the 2L+ setting. These findings reinforce SG as an effective treatment option for this pt population. Clinical trial information: NCT02574455. Research Sponsor: Gilead Sciences, Inc.

1072 **Poster Session**

Apatinib combined with chemotherapy versus single chemotherapy in HER-2 negative advanced breast cancer: A randomized, controlled, open-label phase II study. *First Author: Zhanhong Chen, Department of Breast Medical Oncology, Cancer Hospital of the University of Chinese Academy of Sciences, Zhejiang Cancer Hospital, Hangzhou, China*

Background: Apatinib is an oral, highly potent tyrosine-kinase inhibitor targeting VEGFR2. A series of clinical studies have shown that anti-angiogenic drugs combined with chemotherapy enable to improve the efficacy of HER2-negative advanced/metastatic breast cancer(MBC). **Methods:** Patients with HER2-negative MBC with less than two lines of systemic therapy were enrolled in this open-label, controlled, phase II trial. Patients with measurable disease were randomly assigned, in a 1:1 ratio, to receive oral apatinib (250 mg once daily) combined with chemotherapy(A+CT) or chemotherapy(CT) alone (the physician's choice) until disease progression or intolerable toxicity. The primary end point was progression-free survival(PFS), which was assessed by investigator and was analyzed on an intention-to-treat basis. **Results:** Between August 2017 and January 2021, of the 80 patients who underwent randomization, 40 were assigned to receive apatinib plus chemotherapy(A+CT) and 40 were assigned to receive standard therapy(CT). As of January 2022, 10 patient had not undergone response evaluation or dropout, 70 patients(36 patients in A+CT, 34 patients in CT were finally included with PFS events and 72 patients were included in safety set. Median PFS was significantly longer in A+CT than in CT (182 days vs 63 days; P = 0.043);The median PFS of TNBC subgroup (11 in A+CT group, 14 in CT) was longer in the aptinib group than in CT group (167 days vs 63 days; P = 0.637);The median PFS of HR+ subgroup(25 in apatinib group, 20 in chemotherapy group) was longer in the aptinib group than in CT group (259 days vs 56 days; P = 0.054);The median PFS of patients with liver metastases(19 in apatinib group, 17 in chemotherapy group) was longer in the aptinib group than in the CT group (151 days vs 54 days; P = 0.191); The severe adverse reactions (grade 3/4) were neutropenia(22.2% vs 13.9%), hypertension(11.1% vs 0.0%), leukopenia(8.3% vs 8,3%), hypokalemia(8.3% vs 2.8%), anemia(5.6% vs 11.1%), ALT(2.8% vs 8.3%), AST(0.0% vs 5.6%) in the apatinib group and the CT, respectively. Proteinuria did not occur in both groups. Treatment delay or dose reduction owing to adverse event was 16.7% and 11.1%, respectively. Treatment discontinuation owing to adverse event was 23.5% and 8.8%, respectively. **Conclusions:** Apatinib combined with chemotherapy showed a significant improvements in PFS and a manageable safety profile in HER2 negative MBC. Research Sponsor: None.

1073 **Poster Session**

Leveraging patient engagement to optimize a phase 3 clinical trial design, study participation and recruitment for women diagnosed with triple-negative breast cancer (TNBC). *First Author: Mary E. Elmer, Merck & Co., Inc, North Wales, PA*

Background: The importance of Patient Engagement (PE) on clinical trial design is well established. PE in oncology medicines development can serve many purposes including obtaining input on trial design/procedures, identifying recruitment challenges and barriers to participation, and understanding retention strategies. Designing a clinical trial with procedures that have been confirmed as acceptable to participants is also likely to improve patient adherence to treatments. Triple-Negative Breast Cancer (TNBC) is a virulent subtype associated with early onset and increased risk of early recurrence and accounts for 15% to 20% of breast cancers. In addition, a higher risk exists in premenopausal and Black women. Chemotherapy is the mainstay of curative therapy recommended by guidelines. The aim was to obtain insights from patients to inform key aspects of a clinical study design including choice of chemotherapy regimen, study feasibility and recruitment strategies. **Methods:** Two groups of US women (N = 20) ages 28-54; (race 55% Caucasian, 30% African American, 10% Hispanic, 5% Native American) diagnosed with Stage IIb-IV TNBC and in active or completed treatment were recruited to participate in two in person IRB approved sessions. Trained 3rd party facilitators used qualitative methods to elicit patient feedback. Preliminary research included interviews with key stakeholders, including TNBC advocacy group leaders and a review of online patient communities. Patients reviewed a study design with an investigational agent every 3 weeks plus chemotherapy (nab-paclitaxel; paclitaxel) or placebo plus chemotherapy. **Results:** Patient reaction to the choice of taxane chemotherapy in the standard of care arm was neutral to negative. Approximately 50% of the patients identified taxane treatment as a barrier to participation. All patients requested flexibility in treatment choices, clear information about required tests and visits, and more diversity in recruitment materials. Black and Hispanic women impacted by TNBC did not feel they had equal access to clinical trials due to race, rural location, and other factors. Patient insights reinforced the decision to add another standard-of-care option (carboplatin plus gemcitabine) as a treatment arm to the trial design and was confirmed with investigators. Patient feedback was incorporated into the trial along with additional strategies to support recruitment of diverse patients in the clinical study. **Conclusions:** On November 13, 2020 the FDA approved this regimen in the label for pembrolizumab in combination with chemotherapy, as the 1st line treatment in women with locally recurrent or metastatic TNBC. Both patients and physicians perceived that a flexible chemotherapy backbone was a benefit. Research Sponsor: Merck & Co., Inc.

1074 **Poster Session**

Real-world outcomes of Black women versus non-Hispanic White women with advanced triple-negative breast cancer treated with immune checkpoint inhibitors at an urban cancer center. *First Author: Jeffrey Aldrich, Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA*

Background: Black women (BW) are disproportionately diagnosed with metastatic triple negative breast cancer (mTNBC) compared to Non-Hispanic White women (NHW). Median overall survival (OS) in mTNBC remains poor at 12-18 months. While immune checkpoint inhibitors (ICIs) are a promising treatment strategy, BW were significantly underrepresented in pivotal clinical trials that led to the approval of ICIs in mTNBC. Therefore, the efficacy, safety, and optimal biomarkers of ICI response in BW remain unknown. We sought to compare baseline characteristics and outcomes between BW and NHW with mTNBC treated with an ICI and chemotherapy at an urban tertiary care institution. **Methods:** BW and NHW with advanced unresectable or mTNBC treated with an ICI plus chemotherapy at Emory University between 2019 and 2021 were retrospectively evaluated. Baseline characteristics, including next generation sequencing (NGS), as well as clinical outcomes between BW and NHW were compared using Kruskal-Wallis tests and Fisher's exact tests. Progression free survival (PFS) and OS were analyzed with the Kaplan-Meir method. **Results:** Forty-one women with PDL-1 positive mTNBC treated with an ICI and chemotherapy were identified [BW, n = 26 (63%) and NHW, n = 15 (37%)]. A majority of patients had relapsed disease (73%); however BW were more likely to have de novo metastatic disease compared to NHW (38% vs 7%, p = 0.03). Twenty-seven (66%) patients received atezolizumab and 14 (34%) were treated with pembrolizumab. Of the 23 (56%) patients with NGS testing, alterations in TP53, PIK3CA, and BRCA were seen in 23 (100%), 5 (31%), and 1 (6%) patient, respectively. Median tumor mutational burden was similar between BW and NHW (5 vs 7, p = 0.8). BW had numerically lower median PDL-1 (SP142) compared to NHW (1% vs 2%, p = 0.5). Rates of immune and dose-limiting chemotherapy-related adverse events were similar between BW and NHW (Table). There were no differences in ICI response between groups, though BW had fewer complete responses and a shorter median PFS compared to NHW. Median OS was 12 months in BW compared to 28 months in NHW (p = 0.1). **Conclusions:** Our experience with real-world use of this regimen showed that BW had fewer complete responses and a trend towards worse OS compared to NHW. BW had numerically lower median PDL-1 expression compared to NHW, suggesting further investigation of biomarkers, potentially by Race, are needed to better identify responders to ICI in mTNBC. Research Sponsor: None.

Characteristics N(%)/months [95% CI]	BW (N = 26)	NHW (N = 15)	*P* value
Immune-related adverse events	3 (12)	4 (27)	0.4
Chemotherapy-related adverse events	9 (35)	3 (20)	0.5
Response	16 (64)	11 (73)	0.7
Partial	14 (88)	5 (45)	
Complete	2 (13)	6 (55)	
Progressive or stable disease	9 (36)	4 (27)	0.7
Median PFS	4 [2, 7]	8 [2, not reached]	0.2
Median OS	12 [8, 27]	28 [4, not reached]	0.1

1075 **Poster Session**

Real-world treatment patterns and outcomes among patients (pts) with second-line (2L) and third-line (3L) metastatic triple-negative breast cancer (mTNBC) in England using the Cancer Analysis System (CAS). *First Author: Lawrence Chang, Gilead Sciences, Inc., Foster City, CA*

Background: TNBC is the most aggressive type of breast cancer due to rapid growth, metastasis, and recurrence post-treatment. This study aimed to assess real-world treatment patterns and survival of pts with mTNBC who received 2L and 3L therapy in England and report OS and PFS of pts receiving 2L therapies stratified by treatment-free interval from the curative setting. **Methods:** This retrospective study using the CAS database, included pts with mTNBC who received at least three systemic treatments (at least two in metastatic setting) for TNBC during the years 2012 to 2020. $Cohort_{2L}$ included pts with initial early-stage BC diagnosis and treatment (at least two systemic treatments prior to 2L). $Cohort_{3L}$ included pts initially diagnosed with either early-stage TNBC, or de novo advanced TNBC (at least two systemic treatments prior to 3L). The two cohorts are not mutually exclusive. The study outcomes were stratified by cohort ($Cohort_{2L}$ and $Cohort_{3L}$) and treatment-free interval (<12 m versus ≥12 m from end of curative treatment to start of 1L treatment, $Cohort_{2L}$ only). Kaplan-Meier methods estimated progression-free survival (PFS) and overall survival (OS). PFS was proxied by 'Time to treatment discontinuation or death' (TTDD). Log-rank tests compared the distribution of OS and PFS for 2L stratified by treatment-free interval (<12 m versus ≥12 m). **Results:** $Cohort_{2L}$ included 606 pts and $Cohort_{3L}$ included 374 pts. Tumor morphology was similar across Cohorts. Pts at 3L had worse ECOG performance score compared to 2L, and more pts with de novo advanced TNBC had brain metastasis at any point after diagnosis than pts diagnosed with early-stage TNBC. Regimens at 2L for $Cohort_{2L}$ included capecitabine (32%), eribulin (16%), carboplatin and gemcitabine in combination (12%), and paclitaxel (10%). A similar distribution was seen for $Cohort_{3L}$. Regimens at 3L ($Cohort_{3L}$ only), included eribulin (38%), capecitabine (16%), and paclitaxel (13%). Stratifying $Cohort_{2L}$ by treatment-free interval did not exhibit significant differences in PFS nor OS by log rank tests (Table). **Conclusions:** This nationwide study, in England, accentuates the significant unmet need in 2L and 3L therapy for mTNBC highlighted by the poor prognosis. The stratification by prior treatment-free interval from curative setting did not show a difference in OS or PFS for patients receiving 2L treatment. Research Sponsor: Gilead Sciences.

mTNBC PFS and OS from commencement of treatment line.

Survival outcome	Median PFS_{TTDD} (*in months*)	Median OS (*in months*)
By cohort:		
$Cohort_{2L}$ (n=606)	2.53 (2.30–2.76)	6.70 (6.14-7.62)
$Cohort_{3L}$ (n=374)	2.43 (2.20–2.76)	5.54 (4.90-6.14)
By treatment-free interval ($Cohort_{2L}$):		
<12m (n=255)	2.30 (2.07-2.76)	5.72 (5.06-6.64)
≥12m (n=351)	2.76 (2.46-2.96)	7.49 (6.74-8.31)
	PFS distribution	OS distribution
Log rank test, P-value	0.31	0.10

1076 **Poster Session**

Exposure-response analyses of sacituzumab govitecan (SG) efficacy and safety in patients (pts) with metastatic triple-negative breast cancer (mTNBC). *First Author: Indrajeet Singh, Gilead Sciences Inc., Foster City, CA*

Background: SG is an antibody-drug conjugate composed of an anti–Trop-2 antibody coupled to the cytotoxic SN-38 payload via a proprietary, hydrolyzable linker. SG is approved for pts with mTNBC who received ≥2 prior chemotherapies (> 1 in the metastatic setting). The relationships between exposure of SG, free SN-38, and total antibody (tAB) following SG administration and its efficacy and safety outcomes were evaluated in pts with mTNBC. **Methods:** Available exposure efficacy and safety outcomes from the mTNBC cohort of the phase 1/2 IMMU-132-01 study (relapsed/refractory pts; n = 24) and mTNBC pts from the phase 3 ASCENT study who had received ≥2 prior therapies (> 1 in the metastatic setting; n = 253) were analyzed. Pts in IMMU-132-01 received 8 or 10 mg/kg SG and pts in ASCENT received 10 mg/kg SG on d1 and d8, of every 21d cycle. Effect of exposure on CR, ORR and the evaluated adverse events (AEs) of vomiting, diarrhea, hypersensitivity reactions, nausea, and neutropenia were analyzed using logistic (CR, ORR) or ordinal logistic (AE) regression models while OS, PFS, time to first dose reduction and time to first dose delay were analyzed using Cox PH models. Several exposure metrics related to the PK of SG, free SN-38, and tAB were evaluated as predictors of SG efficacy and safety and the most statistically significant exposure metric was retained in the model; effect of other covariates was characterized within the modeling framework. **Results:** Higher values of the average exposure over the treatment duration (CAVG) for SG ($CAVG_{SG}$) were significantly associated with an increase in the probability of CR and ORR and higher CAVG values for tAB ($CAVG_{tAB}$) were significantly associated with longer OS and PFS. The probability of Grade ≥1 evaluated AEs, the risk of dose reductions and dose delays were found to increase significantly with increasing $CAVG_{SG}$. Neutropenia was the only AE where the effect of exposure was significantly associated with the probability of Grade ≥3 evaluated AEs. No statistically significant associations between exposure and the probability of Grade 4 AEs were observed for any of the evaluated endpoints. The developed models were used to estimate the efficacy and safety outcomes for the 8 mg/kg vs 10 mg/kg SG dose levels and the results indicated a more favorable risk/benefit profile for the 10 mg/kg dose level driven by the higher estimated efficacy. Baseline Trop-2 expression level was not statistically correlated with magnitude of clinical response based on the limited available Trop-2 data. **Conclusions:** Exposure-response relationships were observed for all evaluated efficacy and safety endpoints for SG in patients with mTNBC, and the higher efficacy (as assessed by CR, ORR, OS and PFS) achieved with the exposures associated with the 10 mg/kg SG dose regimen and its manageable safety profile support the appropriateness of the approved regimen of SG. Clinical trial information: NCT02574455, NCT01631552. Research Sponsor: Gilead Sciences, Inc.

1077 **Poster Session**

A phase 3, multicenter, open, randomized controlled clinical study of gemcitabine plus capecitabine versus gemcitabine plus carboplatin in the first-line treatment for advanced triple-negative breast cancer. *First Author: Xiaodong Liu, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China*

Background: Gemcitabine plus capecitabine (GX) regimen is still lack of phase III clinical trial evidence for the first-line treatment of advanced triple-negative breast cancer (TNBC). We designed this phase III trial to compare the efficacy and safety of GX with gemcitabine plus carboplatin (GC) in patients with advanced TNBC. We also explored the correlation between tumor infiltrating lymphocytes (TILs) and the prognosis in TNBC treated with different chemotherapy regimen. **Methods:** Patients with advanced TNBC were randomly assigned to receive gemcitabine (1,000 mg/m^2) on days 1 and 8 plus oral capecitabine (1,000 mg/m^2 twice a day) on days 1 through14; or, to receive gemcitabine (1,000 mg/m^2) on days 1 and 8 plus carboplatin (AUC = 2) on days 1 and 8. The primary end point was progression free survival (PFS), and secondary end points were objective response rate (ORR), clinical benefit rate (CBR), overall survival (OS) and safety. Immunohistochemistry was performed with antibodies against CD3, CD4, CD8, and CD 19 antigens on tissue sections of 52 TNBC patients. The margin used to establish non-inferiority was 1.2. This study is registered on Clinical Trials.gov, number NCT02207335. **Results:** From Jan 2014, to Dec 2020, 187 patients underwent eligibility assessment and were randomly assigned (93 in GX and 94 in GC). The ORRs in GX arm and GC arm were 37.6%, and 39.4%, respectively (P = 0.808). The CBRs in GX arm and GC arm were 78.5% and 79.8%, respectively (P = 0.828). Median PFS was 6.1 months for GX arm compared with 6.3months for GC arm (log-rank P = 0.348; HR = 1.148, 95% CI: 0.856 to 1.539, P = 0.357). The median OS in GX arm and GC arm was 21.0 months and 21.5 months, respectively (log-rank P = 0.992; HR = 1.002, 95% CI: 0.717 to 1.400, P = 0.992). Hematologic adverse events (AEs) were commonly observed in both arms, especially in GC arm. Non-hematological AEs such as hand-foot syndrome, diarrhea, and peripheral sensory neuropathy were more common observed in GX arm, while alopecia, nausea, vomiting, fatigue, decreased appetite, infusion related reaction, and hyperglycemia were more common in GC arm. Patients with high $CD8^+$ TILs had a significantly longer PFS (HR = 0.559; 95% CI: 0.314 to 0.993, P = 0.047) and OS (HR = 0.436; 95% CI: 0.226 to 0.843, P = 0.014) compared with patients with low $CD8^+$ TILs. In the high $CD8^+$ group，patients treated with GC had prolonged PFS (HR = 0.322; 95% CI: 0.127 to 0.816, P = 0.017) and OS (HR = 0.300; 95% CI: 0.094 to 0.957, P = 0.042) compared with GX. **Conclusions:** The trial did not meet the prespecified criteria for the primary end point of PFS in the ITT population. Compared with GC, GX demonstrated lower toxicity. Compared to patients with low $CD8^+$ TILs, patients with high $CD8^+$ TILs showed better outcomes, and in these patients, GC regimen could improve survival compared with GX regimen. Clinical trial information: NCT02207335. Research Sponsor: Tianjin Key Medical Discipline (Specialty) Construction Project, Other Foundation, the Key Task Project of Tianjin Health anTianjin Medical University Cancer Hospital "14th Five- Year" Peak Discipline Support Program Project.

1078 **Poster Session**

Mechanisms of action and acquired resistance to atezolizumab plus *nab*-paclitaxel in metastatic triple-negative breast cancer (mTNBC). *First Author: Luciana Molinero, Genentech, Inc., South San Francisco, CA*

Background: In the IMpassion130 study (NCT02425891) first-line atezolizumab plus *nab*-paclitaxel (A+nP) provided clinical benefit compared with placebo plus nP (P+nP) in patients with mTNBC whose tumors were PD-L1+ (Schmid NEJM 2018). However, in many patients, disease that was initially controlled eventually progressed. The mechanism of action of A+nP and nP in the mTNBC tumor microenvironment (TME) and the biological changes associated with tumor progression with these therapies remain largely unknown. The goal of the current study was to evaluate biological changes in the TME induced by atezolizumab and nP early on treatment (OT) and at the time of progressive disease (PD) in IMpassion130. **Methods:** Paired tumor biopsies from IMpassion130 collected pre-treatment at baseline (BL), after 4 weeks OT, and at clinical PD were evaluated histologically for PD-L1 expression, CD8 content, stromal tumor infiltrating lymphocytes and immune phenotypes. RNA sequencing was also used to evaluate TNBC molecular subtypes and gene expression (hallmark gene sets, and immune cell and stromal gene signatures). Matched tumor pair samples from BL and PD were further analyzed by next-generation sequencing for genomic changes using the FoundationOne gene panel. Wilcoxon, Fisher, and McNemar's tests were used for statistical analysis. **Results:** OT A+nP (n = 24 pairs), but not P+nP (n = 18 pairs) increased PD-L1 in both tumor-infiltrating immune cells and tumor cells, and increased frequency of immune-inflamed tumors. RNA-based signatures for A+nP showed an increase in lymphocytes (T-, B-, and NK cell), as well as IFN-α and IFN-γ responses, driven mainly by responders. While P+nP increased RNA-based stromal signatures (cancer-associated fibroblasts, pericytes, and angiogenesis) and epithelial mesenchymal transition, these changes were not observed with A+nP. OT A+nP and P+nP both reduced cell proliferation but only A+nP reduced metabolic pathways. At PD there was a significant reduction of RNA-based immune and stromal signatures in both A+nP (n = 59) and P+nP (n = 55) arms. Cell proliferation and DNA repair signatures were increased with A+nP but not P+nP. Evaluation of genomic changes suggested that both A+nP and P+nP increased tumor mutational burden (TMB), but only A+nP increased genomic scarring. At PD, the tumor immune phenotypes changed at PD with no directionality, while TNBC subtypes remained stable. **Conclusions:** A+nP boosted tumor immune inflammation and decreased tumor cell proliferation and metabolism in mTNBC patients, particularly in responders. Addition of atezolizumab prevented early stromal recruitment induced by nP. While decreased immune and stromal components and increased TMB were observed with both nP and A+nP, A+nP tumor escape was characterized by increased cell proliferation and DNA scarring. Clinical trial information: NCT02425891. Research Sponsor: F. Hoffmann-La Roche Ltd.

1079 **Poster Session**

Comprehensive immune profiling unravels evolution of spatial distribution and immune repertoire in tumor microenvironment from primary to metastatic triple-negative breast cancer. *First Author: Weihua Guo, City of Hope National Medical Center, Duarte, CA*

Background: Immune checkpoint inhibitors (ICI) have improved PFS and OS in metastatic triple-negative breast cancer (mTNBC), but benefit is limited to PD-L1 positive tumors. Metastatic tumors are notorious for deficient immune cell infiltration and immunosuppressive features that may limit responses to ICI in mTNBC. However, the underlying mechanisms for the weak immunogenicity of the metastatic tumor immune microenvironment (TIME) and related poor ICI responses are still not well understood. The current study was designed to investigate the evolution of the TIME between paired primary and metastatic TNBCs. **Methods:** Spatial distribution of 37 key immune regulators using the NanoString digital spatial profiling (DSP) platform was analyzed. 452 regions of interests (ROIs) from 33 primary tumors (PT) and 29 metastatic tumors (MT) including 28 paired specimens, were selected based on CD45+ immune hotspots, and the protein expression levels of the key immune regulators were quantified within pan-cytokeratin (panCK) and CD45 masked regions, respectively. In parallel, we examined the clonality of tumor infiltrating B cell receptors by reconstructing the immune repertoire from bulk RNA-seq data. **Results:** Using the DSP platform, we confirmed reduced immune infiltration (e.g., CD3 and CD20) in both panCK and CD45 masked regions of MT, while CD8A and CD11c ($p_{adj} = 2.8\times10^{-7}$ and 2.1×10^{-6}) expression was only observed in panCK masked regions of MT compared with PT. A significant shift in myeloid composition between PT and MT as evidenced by increased CD68 signal ($p_{adj} = 5.8\times10^{-4}$) in CD45 masked regions of MT was identified. Within MT, PD-L1 signal was substantially higher ($p_{adj} = 0.030$) in CD45 masked regions only, while PD1 counts were lower ($p_{adj} = 0.035$) in panCK masked regions. This suggests the limited responses to ICI for MT may stem from relatively low expression of activated and targetable T cell subsets in MT islands. In support of the lower CD20 counts in MT, immune repertoire analysis revealed B cell receptor (BCR) repertoire diversity (represented by Gini index) was substantially lower in MT than PT (p = 0.041) suggesting that the ability of B cells to recognize a wide variety of tumor antigens in MT is greatly reduced in contrast to PT. **Conclusions:** Through comprehensive analysis of the TIME spatial organization within paired PT and MT, a significant reduction in dendritic cell/macrophage ratios (CD11c/CD68), reduced tumor localized T cell activation (CD8, PD1, PD-L1), and reduced B cell diversity (BCR clonality) are key features of the reduced immunogenicity of the metastatic TIME in TNBC. Further work to understand key mechanistic features driving the evolution of these differences in TIME between primary and metastatic tumors are ongoing. Research Sponsor: Genentech.

1080 **Poster Session**

Genomic landscape and peripheral blood biomarkers of advanced triple-negative breast cancer treated with immune checkpoint blockade: An exploratory analysis of the TQB2450-Ib-07 trial. *First Author: Yiqun Han, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China*

Background: Immune checkpoint inhibitor (ICI) has emerged as a novel therapeutic option for advanced triple-negative breast cancer (aTNBC). However, no robust biomarker indicative of clinical outcomes has been identified. Herein, we portraited the genomic landscape and explored the biomarkers for patients with aTNBC receiving ICI-based therapy. **Methods:** This is a prospective, multicenter, phase 1b clinical trial (NCT03855358) to assess the efficacy and safety profiles of TQB2450, a humanized monoclonal PD-L1 antibody, plus anlotinib in pretreated TNBC. Eligible patients undergo liquid biopsy at baseline and the timepoint of disease progression. NGS-based assay was performed based on circulating tumor DNA (ctDNA) in the bloodstream. Meanwhile, results of laboratory blood tests were dynamically collected and blood markers, including neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), and platelet to lymphocyte ratio (PLR), were successively evaluated. The primary endpoints were progression-free survival (PFS) and clinical efficacy assigned via guidelines for response criteria for use in trials testing immunotherapies (iRECIST). **Results:** Between May 29, 2019, and December 31, 2020, 34 patients with aTNBC were enrolled. Gene alternations primarily comprised mutation, amplification, or deletion of *TP53*, *MLL3*, *DNMT3A*, *PI3KCA*, *EP300*, *PTEN*, *LRP1B*, *MDM2*, and *NCOR1*. The median maximum somatic allele frequency (MSAF) was 9.97% significantly indicative of PFS, which was 3.58 months for the MSAF-high group and 13.34 months for the MSAF-low group (P = 3e-04), respectively. Else, a strong association was also signified between MSAF and tumor shrinkage (CR/PR vs. SD/PD, P = 0.012). For blood tumor mutation burden (bTMB), the median was 6.72 muts/Mb, which the bTMB-low group was suggestive of a better PFS (11.09 months vs. 5.52 months, P = 0.007), yet no obvious association existing in terms of clinical response. Dynamic analysis revealed that a decline in MSAF was significantly associated with a better PFS (7.10 months vs. 2.74 months, P = 0.018), while no correlations were detected between bTMB and PFS. Based on NLR week 2/0 of 0.95, PFS was significantly worse in the NLR-low group (11.0 months vs. 3.5 months, P = 0.006) and likely distinguished the clinical response (CR/PR vs. SD vs. PD, P = 0.049; non-PD vs. PD, P = 0.022). Moreover, NLR week 2/0 could notably foretell the clinical response for patients with aTNBC with the AUC of 0.82 (0.61-1.00). No comparable utilities were identified regarding LMR and PLR. **Conclusions:** For aTNBC treated with ICI, MSAF tended to be a robust indicator for both PFS and clinical response. NLR week 2/0 presented a favorable profile indicative of PFS as well as a strong predictor for clinical responsiveness of patients with aTNBC receiving immune checkpoint blockade. Clinical trial information: NCT03855358. Research Sponsor: Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

1081 **Poster Session**

Phase 1b/2 study of GX-I7 plus pembrolizumab in patients with refractory or recurrent (R/R) metastatic triple-negative breast cancer (mTNBC): The KEYNOTE-899 Study. *First Author: Joohyuk Sohn, Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea*

Background: GX-I7 (efineptakin alfa) is a hybrid Fc-fused long-acting recombinant human IL-7 which plays an essential role in the development and homeostasis of T-cells. GX-I7 can potentially enhance the anti-tumor effect of pembrolizumab via induction of T-cell activity. Here, we report results of phase 1b/2 study of GX-I7 plus pembrolizumab in patients with R/R mTNBC. **Methods**: Eligible patients had R/R mTNBC that failed up to 3rd lines of chemotherapy in the metastatic setting. Phase 1b patients received GX-I7 in 5 dose levels ranging from 360 μg/kg to 1,440 μg/kg every 9 (Q9W) or 12 (Q12W) weeks plus pembrolizumab 200 mg Q3W (n=51). Phase 2 is an expansion cohort where 33 patients were treated with the recommended phase 2 dose (RP2D). The primary objective was to determine the RP2D for phase 1b and to assess the objective response rate (ORR) for phase 2. **Results**: The study included 84 patients (phase 1b, n=51; phase 2, n=33) and 53.6% (45/84) of patients have received 2nd to 3rd lines of previous therapy. In phase 1b, one dose-limiting toxicity (DLT; grade 3 skin rash) was reported in the 1,440 μg/kg cohort and GX-I7 1,200 μg/kg Q9W was selected as RP2D. The ORRs were 15.7% [95% confidence interval (CI): 7.0 – 28.6] for phase 1b (n=51) and 21.2% [95% CI: 9.0 – 38.9] for phase 2 (n=33). Median PFS was 2.4 months (95% CI: 2.1 – 2.7) at the median follow-up of 10.4 months for all patients combined (n=84). GX-I7 induced up to 3.6-fold (range 1.2 – 8.1) increase in absolute lymphocyte counts (including CD4+ and CD8+ T cell) in all dose levels. The most common treatment-related adverse events (AEs) of any grade were injection site reaction (50.0%), ALT increased (39.3%), pyrexia (38.1%) and rash (35.7%). The additional correlative study data will be presented. **Conclusions**: GX-I7 in combination with pembrolizumab demonstrated a manageable safety profile with promising anti-tumor activity in patients with R/R metastatic TNBC. Clinical trial information: NCT03752723. Research Sponsor: Korea Drug Development Fund.

Baseline characteristics.

N(%)		Total N=84	Phase 1b N=51	Phase 2 N=33
Age, median(range)	-	50.0 (29.0-75.0)	49.0 (29.0–75.0)	51.0 (29.0–67.0)
ECOG PS	1	38 (45.2)	26 (51.0)	12 (36.4)
No. of metastatic organ sites	1	18 (21.4)	13 (25.5)	5 (15.2)
	2	29 (34.5)	17 (33.3)	12 (36.4)
	3	26 (31.0)	17 (33.3)	9 (27.3)
	≥4	11 (13.1)	4 (7.8)	7 (21.2)
Visceral metastasis	-	77(91.7)	45(88.2)	32(97.0)
PD-L1 (CPS Score)	<10	12 (70.6)	NA	12 (70.6)
	≥10	5 (29.4)		5 (29.4)
ALCs, median(range)	-	1175 (591–600)	1328 (591–4812)	1120 (631–2005)
Lymphopenia (≤1,000 cells/mm^3)		26 (31.0)	12 (23.5)	14 (42.4)
No. of previous lines of therapy	1	39 (46.4)	20 (39.2)	19 (57.6)
	2	27 (32.1)	16 (31.4)	11 (33.3)
	≥3	18 (21.4)	15 (29.4)	3 (9.1)

1082 **Poster Session**

Association of 27-gene IO score with outcome in a phase Ib trial of pembrolizumab (pembro) plus chemotherapy (CT) in metastatic triple-negative breast cancer (mTNBC). *First Author: David B. Page, Earle A. Chiles Research Institute at the Robert W. Franz Cancer Center, Portland, OR*

Background: The IO score is a is a 27-gene signature developed to classify the tumor immune microenvironment derived from the 101-gene TNBCtype genomic classifications. The IO score predicts clinical outcome following immune checkpoint inhibitor therapy in NSCLC and bladder cancer, and recently was shown to predict benefit by pCR of atezolizumab plus CT over neoadjuvant CT alone in early stage TNBC (NeoTRIPaPDL1 trial). The IO score has not yet been evaluated in mTNBC or with pembro in breast cancer. **Methods:** We report preliminary associations of IO score with response from a phase Ib trial (NCT02734290). mTNBC subjects received 1st/2nd line pembro (200mg IV q3wk) plus investigator's choice paclitaxel (80mg/m2 IV q1wk, n = 15) or capecitabine (2000mg PO BID x 7d, q2wk, n = 14). Baseline (n = 23) and on-treatment (at wk 6, n = 10) biopsies were analyzed for IO score and genomic subtype by RNA exome sequencing. Objective response rate (ORR, partial or complete response, 12 weeks) and survival was determined among response-evaluable subjects (n= 21). Tumor PD-L1 was assessed by IHC (combined positive score, CPS > 10%). The IO signature was analyzed as a binary classifier (IO+/IO-) and as a continuous variable (IO score). **Results:** 39% of evaluable subjects were IO+ (n =9/23). IO+ was associated with improved clinical outcome, including ORR (IO+ 43%, IO- 29%), median progression free survival (mPFS, IO+ 138d, IO- 79d), and median overall survival (mOS, IO+ 687d, IO- 305d). IO+/IO- classification and IO scores were stable across serial biopsies (Cohen's kappa = 0.74, r = 0.84). IO score was not strongly correlated with PD-L1 CPS (r = 0.27) or sTILs (r = .09). PD-L1-/IO+ tumors constituted 31% (n = 5/16) of PD-L1- cases and exhibited favorable outcome (ORR 40%, mPFS 162d, mOS 556d). IO score and ORR varied across TNBCtype classifications (BL1 subtype: 50% ORR, 66% IO+; BL2 subtype: 0% ORR, 66% IO+; LAR subtype: 50% ORR, 0% IO+, MSL subtype: 33% ORR, 60% IO+). **Conclusions:** IO score is associated with favorable outcome following pembro + CT, and may identify PD-L1-negative cases that respond to pembro + CT. Further investigation in larger datasets is warranted to ascertain the clinical utility of IO score in this setting. Funding: Drug support and funding provided by Merck Sharpe & Dohme as part of the Merck Investigator Studies Program. Clinical trial information: NCT02734290. Research Sponsor: Merck Sharpe & Dohme as part of the Merck Investigator Studies Program.

1083 **Poster Session**

Impact of steroid premedication on atezolizumab (atezo)-induced immune cell activation: A comparative analysis of IMpassion130 and IMpassion131 peripheral blood mononuclear cells (PBMCs). *First Author: Luciana Molinero, Genentech, Inc., South San Francisco, CA*

Background: The immune checkpoint inhibitor (ICI) atezo showed disparate outcomes as first-line therapy for metastatic TNBC when combined with nab-paclitaxel (nPac) in IMpassion130 [Schmid 2018] vs solvent-based paclitaxel (Pac) in IMpassion131 [Miles 2021]. A key difference between the trials was use of steroid premedication for Pac in IMpassion131 but not for nPac in IMpassion130. In patients (pts) receiving ICIs, prior steroid exposure has been linked to worse outcome [Drakaki 2020]. Further, IMpassion130 and IMpassion131 subgroup analyses suggested reduced atezo treatment effect in taxane-pretreated pts. This post hoc biomarker study explored the impact of: 1) steroids on systemic immune cell activation with atezo+taxane; 2) prior taxane exposure on atezo-induced immune cell activation. **Methods:** PBMCs collected at baseline and at day 1, cycle 2 (wk 4) were selected from matched pts (RECIST responders, PD-L1+, no liver metastases) from IMpassion130 and IMpassion131. Single-cell RNAseq was performed and the transcriptomic profile of immune cells was analyzed using GSEA pathway analyses, cell proportion and TCR clonality. **Results:** CITEseq from 695,851 single cells was generated from 39 IMpassion130 PBMC pairs (29 atezo+nPac; 10 placebo [Pla]+nPac) and 35 IMpassion131 pairs (26 atezo+Pac; 9 Pla+Pac). At wk 4, atezo+nPac resulted in increased IFNα and IFNγ responses across multiple cell types (CD4+ and CD8+ T cells, B cells, NK cells and monocytes) and proliferation in NK cells, but reduced TNF signaling across multiple cell types. In contrast, 4 wks of Pla+nPac increased TNF signaling but decreased IFNα and IFNγ responses. In the presence of steroids, 4 wks of atezo+Pac also increased IFNα and IFNγ responses mainly in NK cells and monocytes, but not T cells, and reduced proliferative pathways across B and T cells and TNF signaling. Pla+Pac increased TNF signaling only in NK cells, but reduced proliferative signatures across cell types. The only on-treatment change differing significantly between atezo+nPac vs atezo+Pac was the increase in proliferation pathways in NK, T and B cells with atezo+nPac. There were no significant changes in proportions of cell subsets or TCR clonality. PBMCs from taxane-pretreated pts had higher RNA-based metabolic profile (OxPhos, DNA repair and IFNα). Taxane-naive but not taxane-pretreated immune cells had increased IFNγ and IFNα response after atezo+taxane. **Conclusions:** Our results suggest that atezo+taxane promotes IFNα and IFNγ responses and that steroid co-administration reduces proliferation pathways across immune cells. Prior taxane exposure was associated with an increased metabolic status, possibly rendering immune cells less sensitive to atezo-induced activation. The immune context of taxane-naive TNBC may result in more potent immune activation with atezo. Clinical trial information: NCT02425891 and NCT03125902. Research Sponsor: F. Hoffmann-La Roche Ltd.

1084 **Poster Session**

Safety interim analysis (SIA) of atractib: A phase 2 trial of first-line (1L) atezolizumab (A) in combination with paclitaxel (P) and bevacizumab (B) in metastatic triple-negative breast cancer (mTNBC). *First Author: Maria Cortes, Hospital Ramon y Cajal, Madrid, Spain*

Background: A substantial benefit from adding an immune checkpoint inhibitor to chemotherapy (CT) was reported in mTNBC patients (pts) with PD-L1+ tumors. However, many pts still have a poor outcome. ATRACTIB is exploring the synergism between A (anti-PD-L1 antibody) and B (a VEGF-targeted antibody) with P in mTNBC irrespective of PD-L1 status. We report results from protocol-specified SIA. **Methods:** ATRACTIB is an open-label, single-arm, phase 2 trial (NCT04408118). Pts aged ≥18 years, with unresectable locally advanced or mTNBC, ECOG performance status of 0–1, who had received no prior systemic therapy or ≥12 months since (neo)adjuvant taxane-based CT are eligible. Pts receive A (840 mg IV, days 1, 15) with P (90 mg/m^2 IV, days 1, 8, 15), and B (10 mg/kg IV, days 1, 15) on each 28-day cycle until disease progression, unacceptable toxicity, or patient withdrawal. Primary endpoint is investigator-assessed progression-free survival (PFS) as per RECIST v.1.1. Secondary endpoints include objective response and clinical benefit rates, overall survival, and safety. The trial was designed to detect a treatment effect in terms of median PFS (H_0: ≤7 months; H_1: ≥9.5 months) and 100 pts are needed to attain 80% power at a nominal one-sided α level of 5%. One SIA was planned for evaluating safety as per CTCAE v.5.0 on the first 20 pts who had completed a 3-month follow-up or reached the end of study. **Results:** From Oct 5, 2020, through Nov 21, 2021, 34 pts were enrolled at 13 sites in Spain and Germany and received at least 1 dose of study treatment. Median age was 57.5 (range 40–84) years, 23 (67.6%) pts had received prior CT for early disease, and 19 (56.0%) had visceral disease. At data cutoff (Sep 30, 2021), 25 (71.4%) pts were still receiving the drug regimen. Adverse events (AEs) led to drug discontinuation in 3 (8.8%) pts. Mean relative dose intensity was 90.2% for A, 96.5% for P, and 95.7% for B. P dose reduction was reported in 7 (20.6%) pts. Five (14.7) pts required a dose delay due to AEs (11.8% for A, 11.8% for P, and 8.8% for B). The most common AEs of any grade (G) were fatigue (47.1%; 8.8% G≥3), diarrhea (38.2%; 0% G≥3), and neurotoxicity (35.3%; 8.8% G≥3). Anemia (20.6%; 0% G≥3) and neutropenia (17.6%; 8.8% G≥3) were the most frequent hematological AEs. AEs of clinical interest (AECI) for B were hypertension (17.6%; 5.9% G≥3) and pulmonary embolism (2.9%; 0% G≥3). AECI for A were pneumonitis (2.9%; 0% G≥3), autoimmune hepatitis (2.9%; 2.9% G≥3), and alanine aminotransferase increased (2.9%; 2.9% G≥3). No treatment-related deaths were reported. **Conclusions:** The addition of A to P and B as 1L therapy for mTNBC shows a tolerable safety profile which is consistent with known safety profile of each agent without a significant synergistic toxicity. Based on the independent data monitoring committee recommendation, patient recruitment is ongoing. Clinical trial information: NCT04408118. Research Sponsor: F. Hoffmann-La Roche Ltd.

1085 **Poster Session**

Targeting kinome reprogramming in ESR1 fusion-driven metastatic breast cancer. *First Author: Xuxu Gou, Baylor College of Medicine, Houston, TX*

Background: Genomic analysis has recently identified multiple *ESR1* gene translocations in estrogen receptor-alpha positive (ERα+) metastatic breast cancer (MBC) that encode chimeric proteins whereby the ESR1 ligand binding domain is replaced by C-terminal sequences from many different gene partners. Transcriptionally active ESR1 fusions promoted hormone-independent cell growth, motility and resistance to endocrine therapy. The diversity of partner genes creates a considerable diagnostic challenge and no targeted treatments exist for *ESR1* translocated tumors. Thus, we have established a transcriptional signature to diagnose the presence of an active ESR1 fusion (PMID: 34711608) and developed novel targeted therapies against ESR1 fusion-driven biology. **Methods:** Fifteen *ESR1* fusion cDNA constructs were expressed in ER+ breast cancer cell lines by lentiviral transduction. Cell growth was assayed by Alamar blue assay. A mass spectrometry (MS)-based Kinase Inhibitor Pulldown Assay (KIPA) and tandem mass tag-based proteomics were performed to identify ESR1 fusion-driven druggable kinases for subsequent pharmacological inhibition. **Results:** KIPA profiling demonstrated an increase of multiple receptor tyrosine kinases including RET in T47D cells expressing active ESR1 fusions. Inhibition of RET by repurposing an FDA-approved drug significantly suppressed ESR1 fusion-driven cell growth *in vitro*, suggesting that despite marked diversity in the 3' partners, common kinase activities were elevated and targetable. Proteogenomic profiling, including whole exome sequencing, RNA sequencing, and MS-based proteomics and phosphoproteomics were further performed on 22 ER+ patient-derived xenograft (PDX) tumors, which demonstrated different degrees of estradiol dependence. These integrated "omic" profiles defined targetable genes/pathways and predict tumor subsets that could be responsive to kinase inhibition therapy from this biologically heterogeneous panel of PDX tumors. WHIM18, a PDX naturally harboring the ESR1-YAP1 fusion showed elevated level of RET and CDK4/6 pathways. The tumor volumes were significantly reduced by the RET inhibitor. CDK4/6 inhibitor treatment showed similar tumor reductions to RET inhibition. Interestingly, WHIM9 PDX that expressed wild-type ESR1 conferred a comparable kinome profile to WHIM18. The tumor growth was significantly suppressed by RET or CDK4/6 inhibition. Therefore, pharmacological experiments validated proteogenomics-predicted drug response in two tested ER+ PDX models. **Conclusions:** Proteogenomics characterization of PDX tumors can drive clinical trial hypotheses. Here, we reveal therapeutic kinase vulnerabilities in ESR1 fusion-driven tumors as exemplified by RET inhibition, which will lay the framework for future clinical trials. Research Sponsor: Department of Defense, Other Foundation.

1086 **Poster Session**

Shedding of ctDNA, radiomics assessment of tumor disease volume (TDV), and concordance of mutations (mut) in synchronous liquid and tumor biopsies in metastatic breast cancer (MBC). *First Author: Andri Papakonstantinou, Department of Oncology-Pathology, Karolinska Institutet and Breast Cancer Group, Vall DHebron Institute of Oncology (VHIO), Barcelona, Spain*

Background: Genomic alterations driving MBC progression may be better captured by ctDNA reflecting clonal evolution, but it is currently unknow whether ctDNA analysis can replace tumor sequencing for clinical decision purposes. Aim: to study the concordance between mut in synchronous plasma and tumor samples prospectively collected from patients (pts) with MBC progressing on their last systemic therapy. **Methods:** MiSeq Amplicon-based NGS (custom panel of 60 cancer-related genes; *BRCA1/2* and *PALB2* not included) was performed in both tumor biopsy and plasma. The concordance of ESCAT Tier I and II mut (*PIK3CA, AKT1, ERBB2, ESR1, PTEN*) was determined and correlated with mutant allele fraction (MAF), TDV, and clinical features. Findings from liquid biopsies were classified as true positive (TP-ctDNA) if a given mut was detected in both tumor and plasma and false negative (FN-ctDNA) if only in the tumor. TDV: all metastasis volume assessed by CT scan (excluding sclerotic bone metastasis), and analyzed by an experienced radiologist using the 3DSlicer semiautomatic segmentation tool (TDV = pixel size x number of pixels). Non-shedding cases were those where any mut was detected in tumor but none in plasma. **Results:** 88 cases were collected (luminal 64, HER2+ 17, triple negative 7). Median age at diagnosis 49 years (range 28-80). Radiomics assessment could be performed in 78/88 cases. The plasma/tissue concordance at case level was 74%. Discordance came from 23 cases; in 15 cases mut was only found in tissue and in 8 cases it was only detected in plasma. At gene level, *PIK3CA* had the highest concordance (79%); in *ESR1* it was 52%. Higher concordance associated with non-luminal subtype (OR 0.08, 95%CI 0.002 – 0.59) and shorter interval between primary diagnosis and metastatic relapse (20.3 vs 51 months; p = .02), but not with MAF. FN-ctDNA occurred in 15/49 cases (31%) and associated with luminal subtype (p = .02), but not with other clinical variables. Non-shedding cases associated with older age (p = .03), luminal subtype (p = .007), low TDV (p = .0006) and < 3 metastatic sites (p = .05). In patients with visceral metastasis (n = 45), higher TDV associated with lower probability of FN-ctDNA (p = .03). All non-luminal subtypes were shedders and all but one were TP-ctDNA. In multivariate analysis, higher probability of TP-ctDNA in luminal tumors associated with tumor sampling from a progressing lesion (OR 10.8; 95% 1.5 – 122; p = .03) and shorter interval between diagnosis of metastatic disease and biopsy (OR 0.96, 95% CI 0.92 – 0.99; p = .03). **Conclusions:** Our results suggest that ctDNA can detect a significant proportion of clinically relevant mut in MBC. Patients' characteristics, tumor subtype, type of gene, and tumor volume should be integrated with ctDNA results to better inform clinical decisions. Research Sponsor: AP is supported by an ESMO Research Fellowship and ML is supported by a PERIS Grant-PIS Program.

1087 **Poster Session**

Retrospective study to estimate the prevalence of HER2-low breast cancer (BC) and describe its clinicopathological characteristics. *First Author: Giuseppe Viale, European Institute of Oncology, University of Milan, Milan, Italy*

Background: Approximately 50% of BCs traditionally categorized as HER2 negative (HER2-neg) express low levels of HER2 (IHC 1+ or IHC 2+/ISH-; Miglietta, *NPJ Breast Cancer* 2021). HER2-targeted therapies for HER2-low metastatic BC (mBC) are under investigation (eg, T-DXd in the phase 3 DESTINY-Breast04 study; NCT03734029), but HER2 assays currently used to select patients (pts) for approved anti-HER2 therapies are optimized for high HER2 expression and are not validated for HER2-low detection. A recent study found relatively poor agreement (<70% interrater agreement) in evaluation of IHC scores of 0 and 1+ using current HER2 assays (Fernandez, *JAMA Oncol* 2022). Our objectives were to assess the prevalence of HER2-low among HER2-neg based on rescored HER2 IHC slides after training on low-end expression scoring and to describe pt characteristics of HER2-low vs HER2 IHC 0 mBC. Preliminary results are reported for 233 of 1000 planned pts. **Methods:** This multicenter, retrospective study (NCT04807595) included pts with confirmed HER2-neg unresectable/mBC diagnosed between 2015 and 2017. Local laboratories, blinded to historical HER2 scores, rescored HER2 IHC-stained slides. HER2 was assessed using Ventana 4B5 and other assays. BCs were categorized as HER2-low or HER2 IHC 0. The prevalence of HER2-low BC among pts originally scored as HER2-neg was measured. Demographics (eg, age, country, race) and clinicopathological characteristics were examined via medical charts/electronic health records. Concordance between historical HER2 scores and rescores was assessed. **Results:** HER2 rescores were obtained for 233 pts (mean age, 54 y). HER2-low prevalence was 63.2% overall and numerically greater in hormone receptor (HR)–positive vs HR-negative subgroups (66.1% vs 54.8%; Table). No notable differences in prevalence were seen among different HER2 assays or in demographic/baseline disease characteristics between the HER2-low and HER2 IHC 0 groups. Concordance rate between historical and rescored slides for HER2-status classification was 82.3%. The presentation will include an expanded data set (≈400 pts) with additional results. **Conclusions:** Data on HER2-low prevalence in BC is limited. Preliminary data from this study of mBC samples suggest a somewhat higher prevalence estimate (≈63%) than a previous study of primary BC samples (≈50%). Concordance was 82%; ongoing analyses with updated data will clarify the concordance between rescored and historical HER2 slides. These data can support development of best practices for identifying pts with HER2-low expression who may benefit from HER2-targeted therapies. Clinical trial information: NCT04807595. Research Sponsor: This study is funded by AstraZeneca Pharmaceuticals and Daiichi Sankyo Inc. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201).

Prevalence of HER2-low in HER2-neg mBC population.

Assay, %	HR positive (n=167)	HR negative (n=62)	All pts (N=233)[a]
All (N=233)[b]	66.1	54.8	63.2
Ventana 4B5 (n=90)	67.6	50.0	64.4
Other (n=141)	64.9	56.8	62.4

[a]HR status missing, n=4. [b]HER2 score missing, n=2.

1089 **Poster Session**

Survival and prognostic factors in oligometastatic breast cancer. *First Author: Annemiek Van Ommen - Nijhof, The Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: Clinical guidelines for the treatment of oligometastatic breast cancer (OMBC) propagate multimodality treatment including polychemotherapy and ablative local therapy for all detected disease. The aim of this aggressive approach is prolonged disease remission, or even cure, but randomized data to support this strategy lack and long-term outcomes are not well known. We report prognostic factors, and event-free survival (EFS) and overall survival (OS) in a real world, single center cohort of patients with OMBC with long-term follow-up. **Methods:** Patients with breast cancer and 1-3 distant metastatic lesions who underwent treatment in the Netherlands Cancer Institute were identified via text mining of medical files. We collected patient, tumor and treatment characteristics as well as recurrence and survival data from the medical records. The Kaplan-Meier method was used to calculate EFS and OS estimates, and Cox regression analyses to assess potential prognostic factors. **Results:** The cohort included 239 patients (of whom two males), diagnosed between 1997 and 2020. Median follow-up was 75.0 months. Fifty-one percent had hormone receptor (HR)-positive/ human epidermal growth factor receptor 2 (HER2)-negative disease, 20.1% had HER2-positive disease, and 19.2% had triple negative (TN) disease. Median age at OMBC diagnosis was 49.0 years and 47.3% of patients had synchronous disease (metastases ≤6 months of primary diagnosis). Most patients (81.2%) received chemotherapy and local therapy (surgery, radiotherapy and/or radiofrequency ablation) of all metastatic lesions (83.7%). Of 239 patients, 134 experienced disease recurrence with a median EFS of 40.0 months (95% confidence interval (CI): 28.6-51.4); 97/239 died and median OS was 93.0 months (95% CI 74.5-111.5). The table shows factors associated with favorable OS in multivariable analysis. Cox regression analysis for EFS showed similar results. **Conclusions:** In this large real world cohort of OMBC patients, EFS and OS compare favorably to survival in the general MBC population. HR-positive and/or HER2-positive subtypes, synchronous disease or long DFI, favorable response to first-line systemic therapy and local therapy of all distant lesions are independently associated with better survival. Future studies should be directed at optimizing patient selection and therapy choices in this population with the potential for cure. Research Sponsor: None.

		HR	95% CI	p-value
Subtype (primary tumor)	Triple neg	ref	-	-
	HR-positive/HER2-neg	0.18	0.10-0.32	<0.001
	HER2-pos	0.11	0.05-0.23	<0.001
Disease-free interval (DFI)	DFI short (7-24 months)	ref	-	-
	DFI long (>24 months)	0.49	0.24-1.00	0.049
	No DFI (synchronous disease)	0.29	0.15-0.57	<0.001
Response to 1st line systemic therapy	Progressive disease	ref	-	-
	Any response, not complete	0.17	0.08-0.36	<0.001
	Complete response	0.05	0.02-0.14	<0.001
Local treatment of all metastases	(ref: no local treatment of all metastases)	0.52	0.28-0.98	0.042

1090 **Poster Session**

Quantitative proteomics landscape and association with BASP1 and breast cancer metastasis. *First Author: Jaspreet Kaur, Georgia State University, Atlanta, GA*

Background: Tumor recurrence and metastatic progression remain the leading cause for breast cancer related mortalities. The study aimed to identify differences in proteomics landscape in serum between (i) healthy controls and breast cancer patients, (ii) baseline samples at time of diagnosis from patients that later developed metastases versus those that did not and, (iii) baseline samples presented after completed treatment versus the samples collected before patients developed metastasis. **Methods:** We performed mass spectrometery-based proteome profiling of 100 serum samples from 51 breast cancer patients and 27 healthy donors. Of the 51-breast cancer patients, 29 patients did not metastasize, and 22 patients had a metastatic recurrence. Each of the 22 breast cancer patients with metastasis had 2 samples-one collected within a year of diagnosis and second one collected within a year before the patient developed metastases. Intensity-based absolute quantification (iBAQ) method was employed to convert recovered peptide information to quantificational gene protein product and then normalized to final quantificational value using an in-housed software. Protein values were normalized using z-score before differential expression analyses. FDR < 0.1 and a p-value < 0.05 was used as the cutoff to identify differentially expressed proteins. **Results:** We identified 1177 proteins in total from 100 serum samples of healthy women and breast cancer patients. PCA analysis revealed a complete separation of the breast cancer and healthy control samples. However, we found overlapping but distinct groups of metastatic and non-metastatic samples. We found 179 proteins to be differentially expressed between normal healthy control samples and baseline breast cancer samples irrespective of their metastatic status. Upon comparing baseline breast cancer samples that metastasized with breast cancer samples that did not metastasize, we found BASP1 as the top-ranked gene that was significantly upregulated in metastatic samples. We did not find any significant differences between paired baseline samples collected at diagnosis and pre-metastatic samples collected before the patient developed metastasis. **Conclusions:** Our results show distinct proteomic profiles exist between breast cancer and normal healthy control samples. Further studies are required to confirm if serum BASP1 can be used as a putative biomarker for predicting metastatic risk in breast cancer patients. Research Sponsor: U.S. National Institutes of Health.

1091 **Poster Session**

Efficacy and impact of SARS-CoV-2 vaccination on cancer treatment for patients with breast cancer: A multicenter, prospective, observational study. *First Author: Mitsuo Terada, Department of Breast Surgery, Nagoya City University Graduate School of Medical Sciences, Aichi, Japan*

Background: Vaccination is an essential strategy to prevent infection in the SARS-CoV-2 pandemic. However, there are concerns about vaccine efficacy and the impact of vaccination on cancer treatment. Additionally, the emergence of novel variants may affect vaccination efficacy. This multi-center, prospective, observational study investigated the efficacy and impact of vaccination against SARS-CoV-2 variants on treatment among breast cancer patients in Japan. **Methods:** Breast cancer patients scheduled to be vaccinated with the SARS-CoV-2 vaccine from May to November 2021 were included. They were stratified into five groups according to their cancer treatment: no treatment, endocrine therapy, CDK4/6 inhibitor, chemotherapy, anti-HER2 therapy. Serum samples were collected before the first vaccination and after the second vaccination. Immunoglobulin (Ig)G levels against the SARS-CoV-2 S protein and neutralizing antibody titers against wild-type (WT), alpha (α), delta (δ), kappa (κ), and omicron (o) variants were measured by ELISA assay. The effect of vaccination on cancer treatment was also investigated. **Results:** There were 85 eligible patients (no treatment, n = 5; endocrine therapy, n = 30; CDK4/6 inhibitor, n = 14; chemotherapy, n = 21; and anti-HER2 therapy, n = 15) with a median age of 65 years. The overall seroconversion rate of anti-SARS-CoV-2 IgG was 95.3%. The seroconversion rate of the chemotherapy group was 81.8%. The anti-SARS-CoV-2 IgG antibody concentration was positively correlated with the lymphocyte count before vaccination (r = 0.232, p = 0.039). Overall neutralizing antibody titers against each variant were significantly lower than for WT. Overall positive rates of neutralizing antibodies against WT, α, δ, κ, and o variants were 90.2%, 81.7%, 96.3%, 84.1%, and 8.5%, respectively. A downward trend of neutralizing antibody titers against each variant was seen in chemotherapy and CDK4/6 inhibitor groups compared with other groups. Significant decreases were detected in neutralizing antibody titers against WT, α, and κ variants in the chemotherapy group, and WT and α variants in the CDK4/6 inhibitor group compared with the no treatment group. Withdrawal or postponement of systemic therapy because of vaccination was only observed in one patient. **Conclusions:** Our data support SARS-CoV-2 vaccination for cancer patients being treated with systemic therapy. However, neutralizing antibody titers against the o variant were very low even after two vaccinations among patients with or without cancer treatment. Further, a decrease in neutralizing antibody titer was suggested during chemotherapy and CDK4/6 inhibitor, raising concerns about the impact on long-term infection prevention. For these patients, infection-preventive behaviors should be recommended even after vaccination. They will also be good candidates for booster vaccinations. Clinical trial information: UMIN000045527. Research Sponsor: None.

1092 **Poster Session**

Lurbinectedin in patients with pretreated *BRCA*1/2-associated metastatic breast cancer: Results from a phase II basket study. *First Author: Valentina Boni, NEXT Madrid, Universitario Hospital Quirónsalud Madrid (at the time of the study: START Madrid-CIOCC, Centro Integral Oncológico Clara Campal), Madrid, Spain*

Background: Lurbinectedin (L) is a selective inhibitor of oncogenic transcription that leads to cell apoptosis and shows antitumor activity against homologous recombination repair-deficient cell lines. A previous phase II study (Cruz *et al.* JCO 2018;36:3134-3143) demonstrated antitumor activity in patients (pts) with pretreated metastatic breast cancer (median of 1 prior advanced chemotherapy line) and *BRCA*1/2-mutated tumors with L 3.5 mg/m^2 or 7.0 mg flat dose (equivalent to 4.0 mg/m^2) every three weeks [q3wk]). This report focuses on the outcomes in the *BRCA*1/2-associated breast cancer cohort of a phase II Basket multitumor trial. **Methods:** This phase II study evaluated L 3.2 mg/m^2 1-hour intravenous (i.v.) infusion q3wk in a cohort of 21 female pts with pretreated *BRCA*1/2-associated breast cancer. The primary efficacy endpoint was ORR according to RECIST v1.1. Secondary endpoints included duration of response (DoR), progression-free survival (PFS), OS and safety. **Results:** Median age was 45 years (range, 29-73 years). Hormone receptor (HR)+ disease was observed in 76.2% of pts, triple negative disease in 19.0% and HER2+ in 9.5%. *BRCA1* and *BRCA*2 were reported in 47.6% and 52.4% of pts, respectively. Median number of prior lines of chemotherapy for advanced disease was 2 (range, 0-3 lines). Prior poly(ADP-ribose) polymerase inhibitors and platinum compounds had been administered to 23.8% and 47.6% of pts, respectively. Confirmed partial response (PR) was observed in six pts (ORR = 28.6%; 95% CI, 11.3-52.2%). Lurbinectedin was active in both BRCA mutations: four PRs in 11 pts (36.4%) in *BRCA*2 and two PRs in 10 pts (20.0%) in *BRCA*1. Median DoR was 8.6 months, median PFS was 4.1 months and median OS was 16.1 months. Stable disease (SD) was observed in ten pts (47.6%), including three pts with unconfirmed response in a subsequent tumor assessment (ORR unconfirmed = 42.9% [95%CI, 21.8-66.0]). Clinical benefit rate (PR + SD≥4 months) was 76.2% (95% CI, 52.8-91.8%). The most common grade 3/4 toxicity was neutropenia (42.9%; grade 4, 23.8%; with no febrile neutropenia). **Conclusions:** This phase II study met its primary endpoint and confirmed the activity of L in pretreated *BRCA*1/2-associated breast cancer pts. L 3.2 mg/m^2 1-hour i.v. infusion q3wk showed an acceptable, predictable and manageable safety profile. Considering the exploratory aim of this trial as well as previous results in other phase II study, further development of L in this indication is warranted. Clinical trial information: NCT02454972. Research Sponsor: PharmaMar.

1093 **Poster Session**

CK+/CD45+ (dual-positive) circulating cells are associated with prognosis in patients with advanced breast cancer.

First Author: Carolina Reduzzi, Northwestern University - Feinberg School of Medicine, Chicago, IL

Background: Circulating tumor cells (CTCs) expressing epithelial markers (EPCAM, cytokeratin (CK)) and lacking CD45 (a leukocyte marker) have been associated with poor outcome in many cancer types. Nonetheless, the presence of cells expressing both CK and CD45 (CK+/CD45+), circulating in the blood of cancer patients (pts) have also been reported, but not widely investigated. Early evidence indicates that circulating dual-positive cells (DPcells) are hybrids deriving from the fusion of tumor cells and macrophages. We previously reported that it is possible to detect DPcells in the blood of pts with metastatic breast cancer (BC) and that they are associated with shorter progression-free survival (PFS), in pts with <5 CK+/CD45- CTCs. Here, we investigated the impact of DPcells on overall survival (OS) in pts with advanced BC (aBC). **Methods:** Blood samples (7.5 ml) were collected from aBC pts before starting a new therapy and processed with the FDA-approved CellSearch platform for CTCs and DPcells enumeration. The prognostic role of CTCs and DPcells was assessed through the Kaplan-Meier method using the log-rank test. Single DPcells were isolated using the DEPArray platform and underwent whole genome amplification and lowpass whole genome sequencing (Ampli1 WGA and Ampli1 Lowpass kits). **Results:** Blood samples from 341 pts with luminal (n=168), HER2+ (n=76) and triple negative (n=88) BC were analyzed. Of these, 131 samples (38.4%) contained ≥5 CTCs (CTC^{pos}), whereas DPcell were detected in 152 samples (44.6%, range 0-53), of which 66 (43.4%) were CTC^{pos} and 86 (56.6%) CTC^{neg}. Overall, DPcells were associated with a shorter OS: median OS 24.5 vs 35.0 months, p=0.046. However, when analyzing CTC^{pos} and CTC^{neg} separately, only the latter group showed a difference in OS according to DPcells presence. In particular, among CTC^{neg} pts, those with ≥4 DPcells showed a 2.3-fold shorter OS (26.7 vs 60.6 months, p=0.025). Moreover, pts with ≥4 DPcells were less likely to experience a 6-months PFS clinical benefit (p=0.015). Interestingly, in the analysis by BC subtype, DPcells were confirmed to be associated with worse OS only in pts with triple negative BC (median OS 11.5 vs 16.9, p=0.048). To explore the exiology of DPcells, 2 out of 3 cells analyzed after single-cell isolation from 1 patient were confirmed to have copy number alterations (CNA) consistent with malignant cells. CNA and mutational profiling of additional single DPcells and CTCs are ongoing. **Conclusions:** DPcells are associated with worse OS in aBC pts, with the prognostic impact primarily in pts with <5 CTCs and triple negative BC. This suggests that DPcells might be an alternative way of tumor dissemination in specific pts, in which CK+/CD45- CTCs are less prevalent. More studies are needed to better elucidate DPcell clinical significance in BC, and to confirm their fusion-hybrid origin. Research Sponsor: Lynn Sage Breast Cancer Foundation, Other Foundation, Pharmaceutical/Biotech Company.

1094 **Poster Session**

Eribulin mesylate versus eribulin plus anlotinib in patients with advanced or metastatic breast cancer: Results of a phase II study.

First Author: Liping Liu, Department of Breast Cancer Medical Oncology, Hunan Cancer Hospital / The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, China

Background: Eribulin mesylate is a structurally simplified, synthetic, macrocyclic ketone analogue of Halichondrin B. We investigated the efficacy and safety of eribulin monotherapy versus eribulin plus the oral anti-angiogenesis inhibitor anlotinib in patients with advanced or metastatic breast cancer. **Methods:** This Phase II study included adult Chinese patients with locally advanced or metastatic breast cancer previously treated with at least two chemotherapy regimens, including both anthracycline- and taxane-based therapy (NCT05206656). Patients were randomized (1:1) to receive eribulin (1.4 mg/m^2, intravenously, on days 1–8), alone or in combination with anlotinib (12 mg orally once daily), in 21-day cycles. The primary endpoint was investigator-assessed disease control rate (DCR), per RECIST version 1.1. Key secondary endpoints included objective response rate (ORR), progression-free survival (PFS) and safety. **Results:** Between February 12, 2020, and July 22, 2021, 56 patients were randomized to eribulin (n=32) or eribulin plus anlotinib (n=24) (Table). Sites of metastasis were: bone (60.7%), lung (52.7%), liver (53.6%), lymph nodes (73.2%) and soft tissue (7.1%). Among all patients, the DCR was 66.7% versus 100% (treatment difference, 33.3%; P=0.007), the ORR was 37.0% versus 38.9%, and the median PFS was 3.7 months versus 9.7 months (adjusted hazard ratio, 0.20; 95% CI, 0.04 to 0.91; P=0.04) for patients receiving eribulin versus eribulin plus anlotinib, respectively. Among 36 (64.3%) patients with triple-negative breast cancer, the DCR was 55.6% versus 72.2% (treatment difference, 16.7%; P=0.300) and the median PFS was 3.6 months versus 9.7 months (log rank P=0.030) with eribulin alone versus eribulin plus anlotinib, respectively. The most frequent grade 3-4 adverse events in the eribulin and eribulin plus anlotinib groups were decreased neutrophil count (25.0% [n=8] vs. 29.2% [n=7]) elevated transaminase (6.3% [n=2] vs. 0.0%) and decreased thrombocyte count (3.1% [n=1] vs. 0.0%), respectively. **Conclusions:** Eribulin plus anlotinib was associated with a significantly better DCR, ORR and PFS than eribulin monotherapy in patients with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes. Clinical trial information: NCT05206656. Research Sponsor: None.

Patient clinical characteristics.

Variable	All patients (N=56)	Eribulin (n=32)	Eribulin plus anlotinib (n=24)
Mean age at eribulin usage ± SD (years)	48.9 ± 8.1	49.0 ± 8.2	48.8 ± 8.0
Time from diagnosis to relapse or metastasis ± SD (months)	28.2 ± 35.3	31.8 ± 40.3	23.5 ± 27.3
Surgery, n (%)	49 (87.5)	29 (90.6)	20 (83.3)
Neoadjuvant chemotherapy, n (%)	12 (21.4)	6 (18.7)	6 (25.0)
Adjuvant chemotherapy, n (%)	47 (83.9)	28 (87.5)	19 (79.2)
ER positive, n (%)	18 (32.1)	13 (40.6)	5 (20.8)
PR positive, n (%)	10 (17.9)	7 (21.9)	3 (12.5)
HER2 positive, n (%)	2 (3.6)	2 (6.2)	0 (0.0)

1095 **Poster Session**

Historical redlining and breast cancer survival in the United States: Evidence from the 2010-2017 SEER Medicare linked dataset.

First Author: Jean C. Bikomeye, PhD Program in Public and Community Health, Division of Epidemiology and Social Sciences, Institute for Health and Equity, Medical College of Wisconsin, Milwaukee, WI

Background: Cancer is the second leading cause of morbidity and mortality in the US. Systemic racism is a critical cause of health disparities and historically disadvantaged people experience poor outcomes including poor breast cancer (BC) survival. This study aims to investigate the impact of historical redlining on all-cause and BC-specific survival among older women in the US. **Methods:** Historic 1930's Homeowner's Loan Corporation (HOLC) boundaries and grades were linked to 2010 Census tracts and the 2010-2017 SEER Medicare BC cohort. Women were included if they were 66+ years old at diagnosis, diagnosed with invasive BC, enrolled in Medicare Part A and Part B for 12 months prior to diagnosis to calculate comorbidity, and a Census tract match for HOLC grade. The independent variable was HOLC grade in two categories: A and B(not redlined), and C and D(redlined). The outcomes were all-cause and BC-specific survival, determined by Kaplan Meier Survival curves and both unadjusted and adjusted Cox regression models. End point for censoring was 12/31/2019 (all-cause) and 12/31/2018 (BC-specific). The final models were stratified by age and tumor stage at diagnosis; and adjusted for comorbidity, race and ethnicity, hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) status, and interaction term between comorbidity and race. **Results:** Among 10,113 women, 62.8% resided in historically redlined Census tracts. At a mean (+SD) follow-up time of 48.5 (+28.8) months, 28.9% were deceased; 41.6% of which died of BC. Women residing in historically redlined census tracts experienced poorer BC survival (49.8 +28.2 months) than those residing in non-redlined Census tracts (57.8 +30.7 months). After controlling for covariates, residing in a historically redlined Census tract remained an independent predictor of higher mortality: HR (95%CI) = 1.11 (1.02, 1.20) and 1.24 (1.011, 1.39) for all-cause mortality and BC-specific mortality, respectively. **Conclusions:** Residing in a formerly redlined Census tract at the time of BC diagnosis is associated with worse all-cause and BC-specific mortality, even after stratifying/adjusting for important patient and tumor characteristics. Public health and government agencies stakeholders should consider historical contexts when designing and implementing equity-focused community and clinical interventions targeted at mitigating and reducing BC disparities and improving health equity. Research Sponsor: This study is part of the National Cancer Institute (NCI)–funded R01 research project (R01CA214805) led by Dr. Beyer at the Medical College of Wisconsin.

1096 **Poster Session**

Comprehensive whole-exome and transcriptome profiling to identify actionable alterations associated with response to PARP inhibitors in breast cancer.

First Author: Susan M. Dombrowski, Exact Sciences, Phoenix, AZ

Background: The use of targeted therapies identified using genetic and genomic approaches is now routine in breast cancer (BC). In this clinical lab experience study the frequency of actionable somatic alterations in DNA repair pathway genes associated with the use of PARP inhibitors (PARPi) is described. **Methods:** BC samples were sequenced with the Oncomap ExTra assay, which uses whole-exome DNA sequencing with germline subtraction to detect somatic single base substitutions, indels, and copy number alterations, and RNA sequencing to detect gene fusions. Clinically actionable alterations were defined as associated with FDA approved drugs or clinical trial enrollment. Here, the focus is on 49 repair genes associated with PARPi response: *ARID1A, ATM, ATR, ATRX, BAP1, BARD1, BLM, BRCA1/2, BRIP1, CDK12, CHEK1/2, EPCAM, ERCC1/2/3/4/5, FANCA/C/D2/E/F/G/I/L/M, MLH1, MRE11A, MSH2/6, MUTYH, NBN, PALB2, PMS2, PPP2R2A, PTEN, RAD21/50/51/51B/51C/51D/52/54L, XRCC1/2/3*. **Results:** Of 1103 BCs, 246 (22.3%) had mutations in repair genes; 69 (6.3%) were in *BRCA1/2*. Repair gene mutations were less common in $HER2^+$ cancers (n=27, 14.3%) compared to HR^+HER2^- (n=156, 23.9%) or TN cancers (n=49, 26.1%) (p<0.01). Across subtypes, the top four most commonly mutated of the repair genes were *PTEN* (27.2%), *ARID1A* (22.8%), *BRCA2* (14.2%), and *BRCA1* (14.2%); 33 cancers (13.4%) had mutations in multiple (≥2) repair genes. For the 69 cancers with *BRCA1/2* mutations, 11 (15.9%) carried other repair gene mutations (9 of 35 *BRCA1*; 3 of 35 *BRCA2*). RNA sequencing found 19 fusions in repair genes in 17 patients (1.5%); *CDK12* was involved in 13 (68.4%), and *RAD51C* in 3 (15.8%). Fusion incidence was more frequent in $HER2^+$ cancers (p<0.01) (Table). **Conclusions:** PARPi therapy is FDA approved for $HER2^-$ germline *BRCA1/2* mutated BC patients. Recent evidence suggests somatic *BRCA1/2* mutations predict PARPi benefit (Tung, NM. J Clin Oncol 2020). In addition to BRCA1/2 alterations, our study also highlights the importance of alterations in other DNA repair genes associated with response to PARPi. Trials are ongoing to determine if these genes predict for PARPi benefit. Research Sponsor: Exact Sciences Corporation.

Alterations involving DNA repair genes.

BC subtype	Patients (% of total)	*BRCA1/2* genes (%[a])	Non-*BRCA1/2* genes (%[a])	≥2 genes (%[a])	gene fusions (%[a])
All Patients	1103	69 (6.3%)	177 (16.0%)	33 (3.0%)	17 (1.5%)
HER2-/HR+	652 (59.1%)	43 (6.6%)	113 (17.3%)	20 (3.1%)	2 (0.3%)
TNBC	188 (17.0%)	16 (8.5%)	33 (17.6%)	9 (4.8%)	2 (1.1%)
HER2+	189 (17.1%)	8 (4.2%)	19 (10.1%)*	2 (1.1%)	13 (6.9%)**
NS	74 (6.7%)	2 (2.7%)	12 (16.2%)	2 (2.7%)	0 (0.0%)

NS = Not specified.
[a]% within subtype.
*underrepresented / **overrepresented compared to other subtypes (Fisher's Exact test, p<0.05).

1097 **Poster Session**

Interplay between B cell and GABA metabolism (GABAm) and association with immune evasion in breast carcinoma (BC). *First Author: Frances Elaine Chow, Department of Neurosurgery, University of Southern California, Norris Cancer Center, Los Angeles, CA*

Background: GABAergic signaling has been reported to play a pivotal role in breast cancer (BC) tumorigenesis and metastasis, however, its role in immune modulation remains unclear. Recent *in vitro* and *in vivo* studies (Zhang et al., Nature, 2021) report the role of B cell-derived GABA metabolites in promoting anti-inflammatory macrophages (MM), thus limiting anti-tumor immunity. In this study, we aim to characterize the interplay between B cells and the GABAm pathway, as well as their associated immune infiltrates and cytokines. **Methods:** BC tumors (n = 9455) were analyzed by next generation sequencing (NextSeq, 592 Genes and WES, NovaSEQ) and whole transcriptome sequencing (WTS, NovaSeq) at Caris Life Sciences. Gene set variation analysis (GSVA) scores were used for GABAm pathway activity (GMPA). IFN score to test the likelihood of a tumor's response to anti PD1 therapy and Immune cell fraction (quanTIseq) were assessed by mRNA analysis. Wilcoxon-Mann-Whitney test was applied (p without, q with multiple comparison correction). Correlation coefficients were calculated using spearman correlation. **Results:** GMPA demonstrated a statistically significant positive correlation with B cells fraction ($r = 0.24$, $p < 0.0001$). When stratified by classical molecular subtypes, the positive correlations were exclusive to HR+ and HER2+ BC, and absent in TNBC. GMPA was the most enriched in HR+ BC, followed by HER2+ and TNBC. BC tumors with high B cell infiltration were then grouped into GMPA-high (B+G+, cutoff > median for both) or GMPA-low (B+/G-), which likely represented tumors with B cell-derived high and low GMPA group, respectively. The GMPA-high group demonstrated significantly less fractions of MM1 (2.8 vs 3.7) and CD8+ T cells (0.8 vs 1.2) but greater MM2 (5.3 vs 4.9). mRNA levels of the MM2 marker IL10, a proposed marker of immune evasion, was significantly overexpressed in the B+/G+ group compared to the B+/G- group (fold change, FC = 1.39). mRNA levels of GAD1, a GABA-generating enzyme, were higher in B+/G+ than B+/G- (FC = 7.19). B+/G+ group had notably less IFN score than B+/G- group (-0.37 vs -0.27). When further stratified into molecular subtypes, concurrent more MM2 (5.4 vs 5.2) and less CD8+ T cell (0.74 vs 0.91) fractions were found in B+/G+ compared to B+/G- in HR+ tumors, but not in HER2+ or TNBC tumors. B+/G+ group also demonstrated a lower IFN score (-0.38 vs -0.32) in HR+ tumors. Additionally, IL10 and GAD1 were consistently overexpressed in B+/G+ regardless of subtype, reaching FC 7.9 in HR+ tumors. $q < 0.0001$ for all comparisons. **Conclusions:** Our study is the largest clinical dataset to demonstrate the association of interplay between B cell and GABAm with immunogenicity. Our results support the potential role of B cell-derived GABAm metabolites in immune modulation in BC in a subtype-specific manner. Targeting small metabolites to modulate immune evasion in BC warrants further investigation. Research Sponsor: None.

1098 **Poster Session**

A phase IB/II study of nivolumab in combination with eribulin in HER2-negative metastatic breast cancer (KCSG BR18-16). *First Author: Se Hyun Kim, Division of Hematology and Medical Oncology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea*

Background: Combining immune checkpoint inhibitors with chemotherapy has become a promising therapeutic strategy in metastatic breast cancer. Eribulin is a potent microtubule inhibitor and modulates the immune microenvironment of tumor cells. Therefore, combining eribulin to nivolumab may synergize antitumor efficacy in metastatic breast cancer. **Methods:** Adult patients with histologically confirmed recurrent/metastatic HER2- breast cancer were enrolled prospectively from 10 academic hospitals in Korea (ClinicalTrials.gov Identifier: NCT04061863). Key eligibility criteria included prior treatment with taxanes and/or anthracyclines, ≥1 measurable disease, and ≤2 prior cytotoxic chemotherapies in the metastatic setting. Patients received nivolumab 200 mg intravenously (IV) on day 1 plus eribulin 1.4 mg/m^2 IV on day 1 and 8 of every 3 weeks until disease progression or intolerable toxicity. The dose level was determined from safety profile of three patients in run-in phase. The primary endpoint was investigator-assessed progression-free survival (PFS) rate at 6 months. Secondary endpoints included investigator-assessed objective response rate (ORR) per RECIST v1.1, disease control rate (DCR), overall survival (OS), and toxicity profile of the combination treatment. The association between PD-L1 expression by SP142 Ab and efficacy was analyzed. **Results:** From August 2019 to June 2021, 90 patients (HR+HER2- 45 pts/TNBC 45 pts), with a median age of 51 (range 31–71), were enrolled in the study. With a median study follow-up time of 16.3 months, 68 (75.6%) patients experienced progressive disease. PFS rate at 6-months was 49.6% and 24.1% in patients with HR+HER2- and TNBC group, respectively. Median PFS was 5.6 months (95% CI: 4.3-6.8) and 3.0 months (95% CI: 1.3-4.7) for HR+HER2- and TNBC group, respectively. ORRs were 53.3% (CR:0, PR: 24) for HR+HER2- and 21.8% (CR1, PR: 12) for TNBC. Patients with PD-L1+ tumors (PD-L1 expression ≥ 1% on TC or IC) had similar ORR compared to PD-L1- tumors (ORR 50% vs. 53.8% in HR+HER2-, 30.8% vs. 29.0% in TNBC). The most common grade 3/4 adverse event was neutropenia (15/90, 16.7%), and the most common immune-related adverse events were grade 1/2 hypothyroidism (19/90, 21.1%) and grade 1/2 pruritus (16/90, 17.8%). Five patients had discontinued study treatment due to immune-related adverse events (3 pneumonitis, 1 hepatitis, 1 skin rash). **Conclusions:** In this parallel phase II clinical trial, the addition of nivolumab to eribulin showed promising efficacy and tolerable safety profile in previously treated HER2- MBC. Further survival and exploratory analyses to find predictive markers will be followed. Clinical trial information: NCT04061863. Research Sponsor: Ono Pharma (Nivolumab), Pharmaceutical/Biotech Company.

Objective response according to RECIST v1.1.

	ER+ (n)	(%)	TNBC (n)	(%)	Total (n)	(%)
CR	0	0	1	2.2	1	1.1
PR	24	53.3	12	26.7	36	40.0
SD	13	28.9	16	35.6	29	32.2
PD	8	17.8	16	35.6	24	26.7

1099 **Poster Session**

Is cure possible for breast cancer metastatic to the liver? *First Author: Rene Adam, AP-HP Hôpital Paul Brousse, Université Paris-Saclay, Villejuif, France*

Background: Metastatic breast cancer (MBC) is a lethal disease and is generally only amenable to systemic treatment. Although increasingly recommended on selected patients, local treatments, and particularly surgery, are seldom used in the therapeutic armamentarium for MBC and their long-term survival benefit is unknown. We hypothesized that combining surgery to systemic treatment for selected patients with breast cancer liver metastases could lead to long-term survival or even an option of cure. **Methods:** A retrospective study of prospectively gathered data from a surgical series of liver resections for MBC was conducted. Patients with no or limited and stable extra-hepatic disease were offered surgery after multidisciplinary discussion, if the liver metastases were responding to systemic treatment and were amenable to complete macroscopic resection. Five- and ten-year actual survivors were identified and their characteristics were explored. **Results:** From 1984 to 2020, 207 female patients underwent liver resections for MBC in our institution. There was no postoperative mortality. Postoperative complication rate was 23.3% and liver-specific complication rate was 19.0%. There was a total of 48 repeat hepatectomies. Median disease-free interval between initial breast cancer and liver metastasis was 36 ± 90.1 months. There was a median of 2 ± 1.8 liver metastases at diagnosis with a median size of 33.0 ± 18.3 mm and 73.1% of patients had radiological response before resection. Five- and ten-year overall survivals (OS) as well as 5- and 10-year disease-free survivals (DFS) were 39.6% and 12.7% as well as 14.2% and 6.4%, respectively. Median OS was 44.0 ± 47.2 months in the whole series. Focusing on the 5- and 10-year survivors, median OS were 89.5 ± 44.7 months and 144.0 ±42.6 months, respectively. In the 10-year survivors' group, median DFS was 98 ±62.3 months. Observed survivals in this study underestimate true actual survivals owing to censoring of patients lost to follow-up. **Conclusions:** Long-term survival (≥ 5 years) as well as a curative perspective (≥ 10 years survival) are achievable for selected patients with breast cancer liver metastases by combining surgery to systemic treatment. Considering the recent improvements in the results of systemic treatments, introducing surgical resection in the treatment sequences of MBC could play an even more beneficial role. Research Sponsor: None.

1100 **Poster Session**

Subgroup analysis of patients with no prior chemotherapy in EMERALD: A phase 3 trial evaluating elacestrant, an oral selective estrogen receptor degrader (SERD), versus investigator's choice of endocrine monotherapy for ER+/HER2-advanced/metastatic breast cancer (mBC). *First Author: Virginia G. Kaklamani, University of Texas Health Sciences Center, Houston, TX*

Background: EMERALD demonstrated significantly prolonged progression-free survival (PFS) and a manageable toxicity profile for elacestrant vs standard of care endocrine therapy (SOC) in patients with ER+/HER2- mBC following progression on prior endocrine and CDK4/6 inhibitor therapy. Benefit was observed in the overall study population and in patients with *ESR1* mutations *(mESR1)*. Here, we report a subgroup analysis from EMERALD in patients with no prior chemotherapy. **Methods:** EMERALD (NCT03778931) is a randomized, open-label, phase 3 trial that enrolled patients with ER+/HER2– mBC who had 1–2 lines of endocrine therapy, mandatory pretreatment with a CDK4/6 inhibitor, and ≤1 chemotherapy. Patients were randomized 1:1 to elacestrant (400 mg orally daily) or SOC (investigator's choice of fulvestrant or aromatase inhibitor). Primary endpoints were PFS in all patients and patients with *mESR1*. In this analysis, we compared PFS between elacestrant and SOC in patients without prior chemotherapy. **Results:** Among the 477 patients enrolled in the trial, 77.8% (n = 371) had not received prior chemotherapy for mBC (median age = 64). Among patients without prior chemotherapy, treatment with elacestrant was associated with significantly prolonged PFS compared to SOC in both the overall population (hazard ratio [HR] = 0.68 [95% CI, 0.52-0.89] P = 0.004; median PFS 3.7 vs 2.0; 6-mo PFS 38% vs 23%; 12-mo PFS 27% vs 12%), and patients with *mESR1* (HR = 0.54 [95% CI, 0.36-0.80] P = 0.002; median PFS 5.3 vs 1.9; 6-mo PFS 44% vs 24%; 12-mo PFS 31% vs 12%). Key treatment-related adverse events (AEs) in the no prior chemotherapy elacestrant group were nausea (25.9%), fatigue (12.7%), and hot flush (11.1%). There were no treatment-related deaths in either group. **Conclusions:** Among patients with ER+/HER2– mBC without prior chemotherapy, elacestrant significantly prolonged PFS compared to SOC endocrine therapy and showed favorable outcomes in this subgroup. Clinical trial information: NCT03778931. Research Sponsor: Radius Health, Inc and the Menarini Group.

1101 **Poster Session**

Clinical and radiographic characteristics of patients with metastatic breast cancer and pseudocirrhosis: A single-center retrospective cohort study. *First Author: Laura Ann Huppert, UCSF Helen Diller Comprehensive Cancer Center, San Francisco, CA*

Background: Pseudocirrhosis is a term used to describe changes in hepatic contour that mimic cirrhosis radiographically, but lack the classic pathologic features of cirrhosis. This radiographic finding is frequently found in patients with metastatic breast cancer (MBC); the pathophysiology and clinical consequences are poorly understood. The objective of this study is to describe the patient, tumor, and treatment characteristics associated with pseudocirrhosis, and to assess associated clinical outcomes. **Methods:** In this retrospective study, we identified patients with MBC and imaging findings consistent with pseudocirrhosis (diffuse liver contour abnormalities) who were treated at the University of California San Francisco from 2002-2021. We used chart extraction and radiology review to determine demographic characteristics, treatment history, response to treatment, imaging features, and complications of pseudocirrhosis. Comparisons between groups were made using the unpaired t-test or two-sided Fisher's exact test. **Results:** 120 patients with MBC and radiographic evidence of pseudocirrhosis were identified with the following BC subtypes: Hormone receptor (HR) positive, HER2 negative (n = 99, 82.5%), HR+/HER2+ (n = 14, 11.7%), HR-/HER2+ (n = 3, 2.5%), and triple negative (TNBC; n = 4, 3.3%). All patients with pseudocirrhosis had liver metastases (n = 120, 100.0%) and 82.5% (n = 99) had > 15 lesions. Median time from diagnosis of MBC to radiographic evidence of pseudocirrhosis was 29.2 months. Most patients received chemotherapy for MBC prior to the finding of pseudocirrhosis (n = 111, 92.5%) with median 2.0 lines. Pseudocirrhosis was observed in the setting of stable or responding disease in 50% of patients (n = 60). Patients received a median of 1.0 line of additional therapy after pseudocirrhosis diagnosis, with a median overall survival of 7.9 months from pseudocirrhosis to death. Sequelae of pseudocirrhosis included the radiographic finding of ascites (n = 97, 80.8%), gastric/esophageal varices (n = 68, 56.7%), splenomegaly (n = 26, 21.7%), GI bleeding (n = 12, 10.0%), or hepatic encephalopathy (n = 11, 9.2%). Radiographic evidence of ascites was associated with a shorter survival from MBC diagnosis compared to no ascites (42.8 vs. 76.2 months, p = < 0.001). GI/Hepatology consultation was uncommon (n = 9, 7.5%). **Conclusions:** To our knowledge, this is the largest reported case series of patients with MBC and pseudocirrhosis. Nearly all patients had HR+ disease and extensive liver metastases. Pseudocirrhosis was frequently observed in the setting of responding or stable disease, creating complexity in management. Survival was short in all patients, particularly patients with radiographic evidence of ascites. Further understanding of the pathogenesis of and risk factors for pseudocirrhosis could help improve outcomes for this condition. Research Sponsor: None.

1102 **Poster Session**

A multiple center, open-label, single-arm, phase II clinical trial of MRG002, an HER2-targeted antibody-drug conjugate, in patients with HER2-low expressing advanced or metastatic breast cancer. *First Author: Zefei Jiang, The Fifth Medical Center of Chinese PLA General Hospital, Beijing, China*

Background: MRG002 is a novel HER2-targeted ADC, composed of a sugar-modified trastuzumab, MMAE payload and a cleavable vc-linker. MRG002 was effective in HER2-low expressing breast cancer in preclinical studies. Hence, we conducted the phase II study to evaluate the safety and anti-tumor efficacy of MRG002 in HER-low breast cancer. **Methods:** HER2 low tumor expression was determined by a central lab and had to be immunohistochemistry (IHC)1+ or 2+/ISH-. Eligible patients had advanced/metastatic HER2-low expressing breast cancer that failed standard therapies. MRG002 was administered intravenously once every 3 weeks at the dose of 2.6 mg/kg, until disease progression or unacceptable toxicity which ever occurred first. The primary endpoint was objective response rate (ORR) assessed by independent review committee (IRC). The secondary endpoints were progression-free survival (PFS), disease control rate (DCR), and safety. **Results:** A total of 56 female patients with HER2-low advanced or metastatic breast cancer were enrolled at the time of data cut-off (Dec 31, 2021) and had received at least one cycle of MRG002. The median age was 55 (30-72) years. Most patients were HER2 IHC1+ (83.9%), hormone receptor positive (HR+) (85.7%), and with a ECOG PS of 1 (57.1%). Twenty-eight patients (50.0%) had received at least 2 lines of chemotherapy and the median treatment was 3. Forty-one patients (73.2%) had visceral metastasis and 31 patients (55.4%) had bone metastasis. The ORR and DCR in 49 evaluable patients were 34.7% and 75.5%, with 17 PR, 20 SD and 12 PD. Subgroup analysis indicated that the ORR was 39.5% (15/38) and DCR was 76.3% (29/38) among the evaluable patients with visceral metastasis. The tumor responses were similar in both the HER2 IHC 1+ and IHC 2+ subgroups, as is 34.1% and 37.5% respectively, which might be attributed to fewer IHC 2+ enrollment in this trial. Although only 8 HR- subjects enrolled in our study, the ORR (37.5%) and DCR (62.5%) is promising in these triple negative BC patients post to ≥2 line therapies. Most common treatment related adverse events (TRAEs) were grade 1 or 2. The most common TRAEs (≥20%) were neutrophil count decreased (53.6%), white blood cell count decreased (48.2%), AST increased (46.4%), alopecia and ALT increased (39.3%), blood lactate dehydrogenase increased(33.9%), GGT increased (32.1%), nausea (32.1%), vomiting (23.2%), constipation (23.2%), diarrhea(23.2%) and hyperglycemia (21.4%). Most common grade ≥3 TRAE(≥10%) was neutrophil count decreased(14.3%). No patients died due to MRG002. **Conclusions:** MRG002 shows promising efficacyand well tolerated in patients with HER2-low breast cancer. Further evaluation is underway. Clinical trial information: NCT04742153. Research Sponsor: Shanghai Miracogen Inc.

1103 **Poster Session**

Patient-reported outcomes for measuring the quality of life in advanced breast cancer treated with third-line and beyond chemotherapy-based regimens: A national cross-sectional study. *First Author: Xiuwen Guan, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: Prolongation of survival and maintenance of quality of life (QoL) are the primary therapeutic goals in advanced breast cancer. Around 10% of adverse events (AEs) in the CTCAE are symptomatic AEs (e.g., nausea, sensory neuropathy), which can severely and directly affect the QoL of patients. However, seldom evidence mapped the QoL and symptomatic AEs utilizing patient-reported outcomes (PROs) in heavily pretreated breast cancer patients. This study aimed to investigate the PROs for measuring the QoL and symptomatic AEs of advanced breast cancer treated with third-line and beyond chemotherapy-based regimens in China. **Methods:** This national survey enrolled patients with advanced breast cancer receiving third-line and beyond chemotherapy-based regimens in 59 centers all over China from March to April in 2021. Each patient filled out a questionnaire containing demographic information, medical history, EORTC-QLQ-C30, and symptomatic AEs. The symptomatic AEs included fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, alopecia, fever, and limb numbness. The range method was used for the linear conversion of the PRO scores, which were converted into standardized scores of 0 to 100. **Results:** This study enrolled 1015 patients with the median age of 52 years. The QoL of all patients were poor, with the global health status score of 52.4±17.7 (Table). All the symptomatic AE scores were low among the patients. However, no significant differences were observed in global health status and symptomatic AEs between mono-chemotherapy and multi-agent chemotherapy (All P>0.05). **Conclusions:** The QoL of advanced breast cancer patients treated with third-line and beyond chemotherapy were poor, especially in symptomatic AEs. In addition, the EOTRC-QLQ-C30 scale appears to underestimate the differences in symptomatic AEs between mono-chemotherapy and multi-agent chemotherapy, probably due to a lack of sensitivity of the scale, which fails to match the actual clinical observations of the PROs and QoL. Therefore, new scales need to be developed for the evaluation of symptomatic AEs and QoL in advanced breast cancer. Research Sponsor: Nature Science Foundation of China (82103634).

The comparation of the scores of QoL and symptomatic AEs between mono-chemotherapy and multi-agent chemotherapy.

Symptomatic AEs	All (n=1015)	Mono-chemotherapy (n=784)	Multi-agent chemotherapy (n=231)	*P* value
Global Health Status	52.4±17.7	52.0±17.8	53.8±17.4	0.319
Fatigue	43.0±25.8	42.8±26.3	43.8±24.2	0.622
Nausea and vomiting	47.7±28.7	48.4±28.9	45.4±27.9	0.155
Pain	48.2±27.8	47.9±28.2	49.5±26.3	0.503
Insomnia	42.8±30.7	43.1±30.4	42.0±31.6	0.518
Appetite loss	45.4±29.4	45.9±29.5	43.7±29.1	0.330
Diarrhea	55.9±32.6	55.6±32.4	57.0±33.6	0.567
Alopecia	37.0±31.6	36.5±31.1	38.4±33.3	0.534
Limb numbness	47.5±30.8	47.3±30.9	48.3±30.7	0.654

1104 **Poster Session**

A novel oral paclitaxel and HM10381 (oraxel)-treated metastatic breast cancer: A phase I study (KX-ORAX-CN-007). *First Author: Tao Qin, Sun Yat-sen University Sun Yat-sen Memorial Hospital, Guangzhou, China*

Background: This phase I study assessed the pharmacokinetics, safety, antitumor activity of oral paclitaxel and HM10381 (Oraxel) in patients with metastatic breast cancer. **Methods:** Oraxol (oral paclitaxel 205 mg/m^2 plus HM30181A 15 mg) daily for 3 consecutive days weekly for up to 16 weeks was administered to patients. The primary objective endpoint was pharmacokinetic analysis. The secondary endpoint were objective response rate (ORR) and safety. For pharmacokinetic analysis, timed blood samples were collected. **Results:** Twenty-four female patients were enrolled from Apr 2019 to Aug 2019. The median age was 53 years (range: 35 to 70 years). The mean lines and median line of treatment were 2.5 and 2, respectively. Previous breast cancer treatments included chemotherapy in 23 (96%) patients, hormonal therapy in 20 (83%) patients. Prior taxanes therapy was reported in 20 (83%) patients. There were 15 patients in efficacy dataset. The best ORR (Investigator) was PR in 40%, SD in 53%, and PD in 7%. The best overall response rate (ICRRC) was PR in 36%, SD in 57%, and PD in 7% of patients. There were no hypersensitivity-type reactions. Adverse events of interest neutropenia, neurotoxicity, and diarrhea were reported as 20 (83%) , 7 (29%) and 11 (46%), retrospectively. A total of 15 (63%) patients experienced Grade ≥3 TEAEs, including neutrophil count decreased in 11 (46%) patients, WBC count decreased in 8 (33%) patients. Treatment related SAE was reported in 1 (4.17%) patient experienced febrile neutropenia, pneumonia, and septic shock. The PK data indicated that the efficacy response is not associated with oral paclitaxel exposure parameters AUC or Cmax. **Conclusions:** The study showed that Oraxol as novel oral chemotherapy agent shows promising antitumor activity in patients with metastatic breast cancer, manageable toxicity, and no hypersensitivity-type reactions. Clinical trial information: NCT04993040. Research Sponsor: Athenex Pharmaceuticals (Chong Qing) Limited.

1105 **Poster Session**

Impact of an individualized counseling program on weight loss and quality of life in breast cancer survivors. *First Author: Iktej Singh Jabbal, Cleveland Clinic Florida, Weston, FL*

Background: Survivors of breast cancer who are obese have a greater than two-fold increase in mortality compared to their counterparts. We assessed the feasibility of an individualized nutrition counseling and exercise program with the goal of helping participants achieve a loss of 10% body weight. Secondary endpoints included impact on multiple metabolic parameters, cardiovascular health, and quality of life. **Methods:** We present preliminary data from a single-arm pilot trial (NCT04365569) whereby survivors of breast cancer with BMI ≥ 25 kg/m^2 participated in a 6-month, individualized counseling program. A registered dietitian (RD) counseled patients based upon recommendations by the American Cancer Society. The intervention included in-person (baseline, months 3 and 6) and telephone visits (months 1, 2, 4, and 5). The nutrition component included weight and body composition measures and blood work, including lipid panel and hemoglobin A1c. Cardiovascular fitness and extrapolated VO2 max were measured using SHAPE study. Quality of life was evaluated using: the Functional Assessment of Cancer Therapy – Breast Cancer (FACT-B), the Brief Pain Inventory (BPI), the Generalized Anxiety Disorder-7 (GAD-7), the Patient Health Questionnaire-9 (PHQ-9), and the NCCN Distress Thermometer. Paired statistics were used to compare changes in these aforementioned outcomes pre-and post-intervention. **Results:** A total of n=55 female breast cancer survivors (mean age 58.1± 9.13) were enrolled. N=28 completed the trial to date. While 14.3% of participants lost >10% of their baseline weight, 21.4% lost 5-10 % of their weight. Patients had a mean 45.30% drop in body fat composition overall (p<0.001). There was no statistically significant difference in lipids and hemoglobin A1c. In terms of cardiovascular function, a decline in mean VO_2 max of -4.71 (SD 4.71, p <0.001) was observed, accompanied by a decline in mean METS of -1.09 (SD 0.84, p <0.001). Higher compliance with the intervention was associated with losing weight (p 0.001). FACT-B scoring revealed improvements in Physical (mean +1.92, SD 3.82), Emotional (mean +1.03, SD 2.71), and Functional well-being (mean +2.70, SD 4.34) (p <0.05). This trial was also associated with lower indicators of depression, as evaluated by PHQ-9 scoring (mean -1.32, SD 3.19, p 0.038). Even in patients with weight gain, improvements in QoL surveys were observed, although not statistically significant, likely due to the small sample size in this subpopulation (n = 7). **Conclusions:** An individualized counseling program benefits survivors of breast cancer who are overweight by helping them reduce weight and improve their overall quality of life. While no improvements in VO2 max levels were observed, this may be partially explained by a decrease in effort on the part of participants. Further investigation into the utility of extrapolated VO2 max using the SHAPE study is ongoing. Clinical trial information: NCT04365569. Research Sponsor: Weston, Florida Internal Research.

1106 **Poster Session**

Optimal timing and interval of imaging for metastatic breast cancer. *First Author: Shruti Rajesh Patel, Stanford University, Stanford, CA*

Background: Breast cancer is a family of diseases with varying disease trajectories based on intrinsic biology of the tumor. The time of progression varies across & within subtypes, and with increasing rates of drug resistance depending on prior therapeutic exposure. There is no strong consensus about optimal surveillance and routine imaging in patients with metastatic breast cancer (mBC), but many oncologists report that monitoring strategies are based on strategies used in clinical trials. **Methods:** We reviewed 17 prior Phase III studies that led to FDA approval in mBC. We reviewed 8 studies for ER+ mBC, 5 studies for HER2+ mBC, 2 studies for triple negative (TNBC) mBC, and 2 studies for BRCA+ mBC. We calculated rates of progression or death (POD) per month for the first year on therapy using data from survival analysis tables and compared them across the different types and lines of therapy. **Results:** Risk of progression in mBC varies based on receptor status and line of therapy (Table). There was a significant difference in POD rates between ER+ therapies compared with all other disease types (HER2+, TNBC, BRCA) (p = 0.012). Patients with TNBC or receiving PARP inhibitors or later line HER2 therapies had higher POD rates than those with ER+ breast cancer or receiving first line HER2 therapy (6.9% vs 4.1% per month; p = 0.0004). No significant difference was seen in the monitoring frequency between ER+ and HER2+ disease (p = 0.39). **Conclusions:** These data suggest that shorter interval imaging should be performed for patients with TNBC or receiving PARP inhibitors or later line HER2 therapies. Surveillance imaging for patients with mBC should be based on disease biology, number of prior regimens, time since initiation of therapy, and regimen efficacy. Current imaging recommendations are not data-based and do not adjust for new agents that have been approved. Oncologists should integrate these into individualized estimates to determine optimum frequency of imaging in clinical practice and research. Research Sponsor: None.

Disease Type	Trial Name	Line of Therapy	Treatment	Treatment Arm: Risk of progression or death/month	Control	Control Arm: Risk of progression or death/month	Monitoring frequency (Every X Weeks)	Median PFS (months)
ER+	PALOMA2	First	Palbociclib + AI	3.10%	AI	4.20%	12	24.8
ER+	MONARCH3	First	Abemaciclib + AI	3.13%	AI	4.19%	8	28.2
ER+	MONARCH2	Subsequent	Abemaciclib + Fulvestrant	4.00%	Fulvestrant	5.30%	8	16.4
ER+	BOLERO2	Subsequent	Everolimus + AI	3.51%	AI	5.06%	6	6.9
HER2+	CLEOPATRA	First	Pertuzumab + Trastuzumab + Docetaxel	3.36%	Trastuzumab + Docetaxel	5.14%	9	18.5
HER2+	HER2CLIMB	Subsequent	Tucatinib + Trastuzumab + Capecitabine	7.29%	Trastuzumab + Capecitabine	8.02%	6-9	7.8
Triple Negative	KEYNOTE 355	First	Carboplatin + Gemcitabine + Pembrolizumab	6.60%	Taxanes + Platinum	7.18%	8	9.7
Triple Negative 5.6	ASCENT	Subsequent	Sacituzumab Govitecan	7.62%	Single Agent	Chemotherapy	8.27%	6
BRCA+ 7	OLYMPIAD	Subsequent	Olaparib	6.71%	Single Agent	Chemotherapy	7.65%	6

TPS1107 **Poster Session**

EPIK-B4: A phase 2, randomized study of metformin (MET) extended release (XR) +/- dapagliflozin (DAPA) to prevent hyperglycemia (HG) in patients (pts) with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-), *PIK3CA*-mutated (mut) advanced breast cancer (ABC) treated with alpelisib (ALP) and fulvestrant (FUL). *First Author: William John Gradishar, Northwestern University Feinberg School of Medicine, Chicago, IL*

Background: ALP (α-selective PI3K inhibitor and degrader) is approved with FUL for pts with *PIK3CA*-mut HR+, HER2– ABC. HG is a known on-target effect of PI3K inhibition, manageable with oral anti-HG agents such as MET and dose interruptions/modifications of ALP and reversible upon discontinuation of ALP. Although HG management guidelines were refined throughout the SOLAR-1 and BYLieve studies evaluating ALP + FUL/letrozole, there remains a need for optimized strategies beyond initial MET therapy that offers earlier and more sustained improvement of HG, particularly for pts at an increased risk for severe HG. In preclinical models, the addition of a SGLT2 inhibitor to ALP (+/– MET) reduced HG while maintaining ALP efficacy. The aim of this study is to evaluate the safety and efficacy of prophylactic MET XR +/– the SGLT2 inhibitor DAPA in reducing severe HG in pts with *PIK3CA*-mut HR+, HER2– ABC on ALP + FUL with an increased risk for severe HG (grade ≥ 3) on ALP. **Methods:** EPIK-B4 is a Phase II, randomized (1:1), open-label, active-controlled study assessing the efficacy and safety of MET XR +/– DAPA (starting at Cycle 1 Day 1 [C1D1]) with ALP (300 mg orally [PO], once daily [QD], starting at C1D8) + FUL (500 mg intramuscularly on C1D1, C1D15, and D1 of subsequent cycles) in pts (N ≈ 132) with HR+, HER2–, *PIK3CA*-mut ABC after progression on/after endocrine-based treatment (Tx). MET XR is administered PO starting at 500 mg QD (titrated up to 2 g QD) and MET XR + DAPA starting at 500 mg and 5 mg QD (titrated up to 2 g and 10 mg QD), respectively. Eligible pts include adult men or postmenopausal women with confirmed HR+, HER2–, *PIK3CA*-mut ABC and ≥ 1 risk factor for severe HG (diabetes [fasting plasma glucose (FPG) ≥ 126 mg/dL and/or HbA1c ≥ 6.5%], prediabetes [FPG ≥ 100 to < 126 mg/dL and/or HbA1c 5.7% to < 6.5%], obesity [BMI ≥ 30], age ≥ 75 years); prior endocrine-based Tx (eg, FUL or oral SERD) was permitted. Randomization is stratified by baseline diabetes status. Key exclusion criteria include > 1 line of Tx in the metastatic setting; prior chemotherapy (metastatic setting) or PI3K, mTOR, or AKT inhibitor; type I or II diabetes requiring Tx; or antecedent of pancreatitis or severe cutaneous reaction. The primary endpoint is the occurrence of severe HG (grade ≥ 3 [glucose > 250 mg/dL] based on laboratory assessments) over the first 8 weeks of ALP + FUL. Secondary endpoints include progression-free survival, overall response and clinical benefit rates with confirmed response, safety, and tolerability. A biomarker analysis is planned as an exploratory objective. Recruitment is ongoing with enrollment planned in 56 sites across 8 countries; completion of primary data collection is anticipated in 2023. Clinical trial information: NCT04899349; EUDRACT#2021-001908-15. Research Sponsor: Novartis Pharmaceuticals Corporation.

TPS1108 **Poster Session**

Phase 3 study of tucatinib or placebo in combination with trastuzumab and pertuzumab as maintenance therapy for HER2+ metastatic breast cancer (HER2CLIMB-05, trial in progress). *First Author: Erika P. Hamilton, Sarah Cannon Research Institute at Tennessee Oncology, Nashville, TN*

Background: The current first-line (1L) standard of care (SOC) for human epidermal growth factor receptor 2-positive (HER2+) metastatic breast cancer (MBC) is trastuzumab (T) plus pertuzumab (P) and a taxane. Despite advances in 1L SOC, most patients (pts) progress during maintenance therapy with T+P. Tucatinib is a tyrosine kinase inhibitor (TKI) approved in combination with T and capecitabine for adults with HER2+ MBC, with and without brain metastases (BM). In HER2CLIMB, the addition of tucatinib significantly prolonged progression-free survival (PFS) and overall survival (OS) in pts with HER2+ MBC and was well tolerated. Adding tucatinib also reduced the risk of disease progression or death in pts with untreated and/or active BM (Murthy et al. 2020, Curigliano et al. 2021). HER2CLIMB-05 investigates whether adding tucatinib to 1L SOC as maintenance therapy will extend PFS while maintaining quality of life (QOL). **Methods:** HER2CLIMB-05 (NCT05132582) is a phase 3, randomized, double-blind study evaluating tucatinib plus T+P as maintenance therapy for HER2+ MBC. Approximately 650 pts will be enrolled. Eligible pts will have advanced HER2+ disease, no progression on 4–8 cycles of prior 1L SOC, ECOG Performance Status of 0 or 1, and no or asymptomatic BM. Exclusion criteria include prior treatment with anti-HER2 and/or anti-epidermal growth factor receptor TKI (prior SOC for early BC is permitted) or inability to undergo contrast magnetic resonance imaging of the brain. Pts will be randomized 1:1 to receive either tucatinib or placebo twice daily, with T+P once every 21 days. Pts with HR+ disease may receive endocrine therapy. The primary endpoint is investigator-assessed PFS. Secondary endpoints include OS (key endpoint), time to deterioration of health-related QOL, central nervous system PFS, safety, and pharmacokinetic (PK) parameters. PFS and OS will be compared using a 2-sided stratified log-rank test between treatment groups. Time-to-event endpoints will be summarized using the Kaplan–Meier method. PK and safety data will be summarized using descriptive statistics. Enrollment is ongoing in the US, with additional sites planned. Clinical trial information: NCT05132582. Research Sponsor: Seagen.

TPS1109 **Poster Session**

EPIK-B5: A phase III, randomized study of alpelisib (ALP) plus fulvestrant (FUL) in patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-), *PIK3CA*-mutated advanced breast cancer (ABC) progressing on/after an aromatase inhibitor (AI) with a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i). *First Author: Michelino De Laurentiis, Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale"-Breast Oncology Unit, Naples, Italy*

Background: Endocrine therapy (ET) + CDK4/6i is standard of care for HR+, HER2– ABC; however, CDK4/6i resistance, in which the phosphatidylinositol-3-kinase (PI3K) pathway has a key role, remains challenging. Progression-free survival (PFS) for ≥ 2nd-line ET monotherapy post CDK4/6i is poor; prognosis may be worse in patients with a *PI3KCA* mutation. ALP (PI3K-α selective inhibitor and degrader) + FUL is approved by the European Medicines Agency (EMA) for HR+, HER2–, *PIK3CA*-mutated ABC after ET monotherapy. Outside the EMA, ALP + FUL approval includes post-CDK4/6i use. ALP + FUL has shown clinical activity and consistent safety in a small subpopulation in SOLAR-1 with prior CDK4/6i treatment (n = 9) and in BYLieve Cohort A (CDK4/6i + AI as immediate prior treatment; n = 121). The EPIK-B5 study aims to confirm the efficacy and safety of ALP + FUL in a larger population with HR+, HER2–, *PIK3CA*-mutated ABC with prior CDK4/6i + AI treatment. **Methods:** EPIK-B5 is a Phase III, randomized (1:1), double-blind, placebo-controlled study assessing the efficacy and safety of ALP (300 mg/d orally starting Cycle 1 Day 1 [C1D1]) + FUL (500 mg intramuscularly on C1D1 and C1D15, and D1 of subsequent cycles) in patients (N ≈ 234) with HR+, HER2–, *PIK3CA*-mutated ABC progressing on/after CDK4/6i + AI. Patients randomized to placebo + FUL can cross over to ALP + FUL after progression. Randomization is stratified by presence of lung and/or liver metastasis and prior CDK4/6i setting. Adult men or postmenopausal women with confirmed HR+, HER2–, *PIK3CA*-mutated ABC and ≥ 1 measurable lesion are eligible. The primary endpoint is PFS per blinded independent review committee assessment. Secondary endpoints include overall survival, overall response and clinical benefit rates, duration of and time to response, PFS by *PIK3CA*-mutation status in circulating tumor DNA, PFS on next-line treatment, time to definitive deterioration of ECOG status, quality of life (QoL), and safety and tolerability. Exploratory endpoints include biomarker analyses, additional QoL endpoints, and time to subsequent chemotherapy. Recruitment is ongoing, with enrollment planned over 2 years in 18 countries; completion of primary data collection is anticipated in 2026. Clinical trial information: NCT05038735; EUDRACT2021-001966-39. Research Sponsor: Novartis Pharmaceuticals Corporation.

TPS1110 **Poster Session**

A randomized, multicenter, placebo-controlled, phase III study to evaluate the efficacy and safety of HER2/neu peptide GLSI-100 (GP2 + GM-CSF) in patients with residual disease or high-risk PCR after both neo-adjuvant and postoperative adjuvant anti-HER2 therapy, Flamingo-01. *First Author: Snehal Patel, Greenwich LifeSciences, Stafford, TX*

Background: GP2 is a biologic nine amino acid peptide of the HER2/*neu* protein delivered in combination with Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) that stimulates an immune response targeting HER2/neu expressing cancers, the combination known as GLSI-100. In a prospective, randomized, single-blinded, placebo-controlled, multicenter Phase IIb study, no recurrences were observed in the HER2+ population after 5 years of follow-up, if the patient was treated with GLSI-100, survived and was followed from more than 6 months ($p = 0.0338$). Immunotherapy elicited a potent response measured by skin tests and immunological assays. Of the 146 patients that have been treated with GLSI-100 over 4 clinical trials, GLSI-100 was well-tolerated and no serious adverse events were observed considered related to the immunotherapy. **Methods:** This Phase 3 trial is a prospective, randomized, double-blinded, multi-center study. After 1 year of trastuzumab-based therapy, 6 intradermal injections of GLSI-100 or placebo will be administered over the first 6 months and 5 subsequent boosters will be administered over the next 2.5 years for a total of 11 injections over 3 years. The participant duration of the trial will be 3 years treatment plus 1 additional year follow-up for a total of 4 years following the first year of treatment with trastuzumab-based therapy. Patients will be stratified based on residual disease status at surgery, hormone receptor status and region. Approximately 498 patients will be enrolled. To detect a hazard ratio of 0.3 in invasive breast cancer free survival (IBCFS), 28 events will be required. An interim analysis for superiority and futility will be conducted when at least 14 events have occurred. This sample size provides 80% power if the annual rate of events in placebo patients is 2.4% or greater. Up to 100 non-HLA-A*02 subjects will be enrolled in an open-label arm. Eligibility Criteria: The patient population is defined by these key eligibility criteria: HER2/neu positive and HLA-A*02; Residual disease or High risk pCR (Stage III at presentation) post neo-adjuvant therapy; Exclude Stage IV; Completed at least 90% of planned trastuzumab-based therapy. Trial Objectives: To determine if GP2 therapy increases IBCFS; To assess the safety profile of GP2; To monitor immunologic responses to treatment and assess relationship to efficacy and safety. Accrual: Site selection and study start-up is in progress at multiple sites. Target enrollment is 598 subjects. Clinical trial information: 05232916. Research Sponsor: Greenwich LifeSciences, Inc.

TPS1111 **Poster Session**

Phase 2 trial of tucatinib plus trastuzumab deruxtecan in patients with HER2+ locally advanced or metastatic breast cancer with and without brain metastases (HER2CLIMB-04, trial in progress). *First Author: Ian E. Krop, Dana-Farber Cancer Institute, Boston, MA*

Background: Tucatinib is an oral reversible small-molecule tyrosine kinase inhibitor highly selective for human epidermal growth factor receptor 2 (HER2). Tucatinib is approved in the US for use in combination with trastuzumab and capecitabine in adult patients with HER2+ metastatic breast cancer (MBC), with and without brain metastases, who have received ≥1 prior anti–HER2-based regimens in the metastatic setting. Trastuzumab deruxtecan (T-DXd), an antibody–drug conjugate (ADC) comprising a HER2-directed monoclonal antibody conjugated to a topoisomerase I inhibitor payload, is also approved in the US for patients with HER2+ MBC. In HER2+ breast cancer (BC) xenograft models, tucatinib increased the antitumor activity of a HER2-directed ADC comprising a HER2-directed monoclonal antibody conjugated with 8 exatecan moieties (T-Ex) when compared to T-Ex alone (Kulukian et al 2019). While significant advances have been made in the treatment of patients with HER2+ BC, treatment of metastatic disease remains a clinical challenge due to limited treatment options. **Methods:** HER2CLIMB-04 (NCT04539938) is a single-arm, open-label, multicenter, phase 2 study evaluating the efficacy and safety of tucatinib plus T-DXd in previously treated patients aged ≥18 years with unresectable, locally advanced, or metastatic (LA/M) HER2+ BC. Patients must have prior treatment with a taxane and trastuzumab (with or without pertuzumab) in the LA/M setting or progressed within 6 months after neoadjuvant or adjuvant treatment involving a regimen including a taxane and trastuzumab (with or without pertuzumab). Patients with brain metastases, including active brain metastases, may be enrolled. A safety lead-in portion of the study with 10 patients who were followed for at least 1 cycle has been completed. This portion of the study demonstrated a manageable safety profile so the trial will enroll approximately 60 response-evaluable patients (including the 10 patients from the safety lead-in), evenly distributed between patients with and without brain metastases. The primary endpoint is confirmed objective response rate (cORR) by investigator assessment per RECIST 1.1. Secondary endpoints are progression-free survival (PFS), duration of response (DOR), disease control rate (DCR) by investigator assessment per RECIST 1.1, overall survival, and safety. Exploratory endpoints will include cORR, PFS, DCR, and DOR by independent central review per RECIST 1.1, pharmacokinetic analyses, biomarker analyses, and changes in patient-reported outcomes. Efficacy and safety will be summarized with descriptive statistics. Enrollment in the US began in late 2020. Clinical trial information: NCT04539938. Research Sponsor: Seagen.

TPS1112 **Poster Session**

Targeting HER2-positive metastatic breast cancer with ARX788, a novel anti-HER2 antibody-drug conjugate in patients whose disease is resistant or refractory to T-DM1, and/or T-DXd, and/or tucatinib-containing regimens. *First Author: Janice M. Lu, University of Southern California, Los Angeles, CA*

Background: The overexpression and/or amplification of human epidermal growth factor receptor 2 (HER2) occurs in approximately 20% of breast cancers (BC) and is a major driver of tumor development and progression. This HER2 subtype confers aggressive tumor behavior and the HER2 receptor remains a valuable target for antibodies, bi-specifics, and antibody drug conjugates (ADC). With advances in targeted therapy, patients with HER2-positive breast cancer (HER2+ BC) may experience an improved prognosis, including survival. Novel HER2-targeted therapies are being investigated to overcome drug resistance and to help mitigate adverse events (e.g., cardiotoxicity). ARX788 is a next-generation ADC using a technology platform whereby a HER2 specific monoclonal antibody is conjugated with Amberstatin269 (AS269), a potent cytotoxic tubulin inhibitor. Site-specificity, high homogeneity, and stable covalent conjugation of ARX788 leads to its slow release and prolonged peak of serum pAF-AS269, which may contribute to the lower systemic toxicity and increased targeted delivery of payload to tumor cells at a lower effective dose compared to other HER2 ADCs. Clinical activity has been seen in Phase I HER2 breast and pan-tumor studies. **Methods:** Trial Design: ACE-Breast-03 (NCT04829604) is a global, phase 2 study designed to assess anticancer activity and safety of ARX788 in patients with metastatic HER2 positive breast cancer. Patients whose disease is resistant or refractory to T-DM1, and/or T-DXd, and/or tucatinib-containing regimens are eligible. Patients must have adequate organ function. Any brain metastases must be radiographically stable without steroid dependence. Efficacy will be assessed using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 by imaging every 6 weeks on study. Endpoints include objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), best overall response (BOR), duration of response (DOR), and time to response (TTR). The safety and tolerability profile will be evaluated. Blood samples will be collected at specified time points to determine serum concentrations of ARX788, total antibody, and metabolite pAF-AS269. Potential predictive and/or prognostic biomarkers at baseline and on-treatment will be analyzed for exploratory purposes. Descriptive statistics will be used to evaluate anticancer activity, safety, and tolerability. The study is currently recruiting patients. Please contact breast03trialinquiry@ambrx.com for additional information. Clinical trial information: NCT04829604. Research Sponsor: Ambrx, Inc.

TPS1113 **Poster Session**

Targeting insulin feedback to enhance alpelisib (TIFA): A phase II randomized trial in metastatic, *PIK3CA*-mutant, hormone receptor–positive breast cancer. *First Author: Sherry Shen, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Breast cancer is the most common malignancy among women in the U.S. and is a leading cause of cancer-related death. Among women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer, 45% harbor activating mutations in the *PIK3CA* gene, which induces hyperactivation of phosphatidylinositol 3-kinase (PI3K) and drives cell growth and survival. The SOLAR-1 trial found that the combination of alpelisib, a PI3K inhibitor, and fulvestrant, an endocrine therapy, significantly improved progression-free survival compared to fulvestrant alone, leading to Food and Drug Administration approval in *PIK3CA*-mutated metastatic breast cancer. While PI3K inhibition induces apoptosis of cancer cells, inhibition of this pathway in the liver and skeletal muscle impairs physiologic insulin signaling leading to hyperglycemia. This affects > 60% of patients, results in grade 3-4 hyperglycemia in 36% of patients, and is a major cause of interrupted/reduced dosing or discontinuation. In preclinical models, application of a very low carbohydrate (ketogenic) diet or a sodium-glucose cotransporter 2 inhibitor (SGLT2i), a commonly used diabetes medication, minimized hyperglycemia and improved the anti-tumor efficacy of PI3K inhibition. These interventions are safe and feasible in cancer patients but have not been studied for the prevention of PI3K inhibitor-associated hyperglycemia. **Methods:** We are conducting a multicenter phase II clinical trial (NCT05090358) in patients receiving standard-of-care alpelisib plus fulvestrant to test the efficacy of three interventions (n = 106): 1) ketogenic diet, 2) low-carbohydrate diet, or 3) canagliflozin (a SGLT2i) in preventing alpelisib-associated hyperglycemia. The goal of this study is to mitigate a major toxicity of PI3K inhibitors and maximize their clinical efficacy. Eligible patients must be postmenopausal and have histologically confirmed HR-positive, HER2-negative metastatic breast cancer, ≥1 activating *PIK3CA* mutations, measurable disease per RECIST v1.1 or at least one predominantly lytic bone lesion, recurrence or progression during or after endocrine-based therapy, ECOG performance status of 0-1, hemoglobin A1c < 8%, and fasting blood glucose < = 140mg/dL. Prior CDK4/6 inhibitor use is allowed. The primary endpoint is the grade 3-4 hyperglycemia-free rate at 12 weeks. Secondary endpoints include the 6- and 12-month overall response rate, 6- and 12-month progression-free survival, alpelisib adherence, changes in systemic hormones and metabolites related to glucose homeostasis, changes in body composition, and quality of life. The first patient was enrolled on October 15, 2021. Participating sites include Memorial Sloan Kettering Cancer Center, Weill Cornell Medical Center, and the Ohio State University Wexner Medical Center. Clinical trial information: NCT05090358. Research Sponsor: Novartis.

TPS1114 **Poster Session**

A phase II, single-arm, non-randomized study of alpelisib (BYL719) in combination with continued endocrine therapy following progression on endocrine therapy in hormone receptor–positive, HER2-negative, *PIK3CA*-mutant metastatic breast cancer: A Big Ten Cancer Research Consortium Study (btcrc-BRE19-409). *First Author: Cristina I. Truica, Penn State Health Milton S. Hershey Medical Center, Hershey, PA*

Background: The PI3K pathway is frequently altered in hormone receptor positive (HR+) breast cancer (BC) and 40% of patients have *PIK3CA* mutations. The PI3Kα-specific inihibitor, Alpelisib, is FDA-approved in combination with fulvestrant for treatment of patients with HR+ HER2 negative (HER2-) *PIK3CA* mutated, advanced BC following progression on or after a non-fulvestrant endocrine therapy (ET) based regimen. We hypothesized that the benefit seen in the seminal SOLAR-1 study that compared alpelisib plus fulvestrant to placebo with fulvestrant, was due to the addition of alpelisib, rather than the change to fulvestrant, such that addition of alpelisib to ongoing ET at time of progression could lead to similar outcomes. Unlike SOLAR-1, our study continues prior ET at time of progression and requires prior CDK4/6 inhibitor therapy. **Methods:** We designed a phase II single arm study that tests the efficacy of adding alpelisib to ongoing ET at time of progression on ET. The primary objective is to estimate the progression–free survival (PFS) of alpelisib with continued ET (aromatase inhibitor or fulvestrant) following progression in patients with HR+ HER2-, *PIK3CA* mutant advanced BC. Secondary objectives are to estimate overall response rate, clinical benefit rate, duration of response, overall survival and safety/tolerability. Correlative studies include evaluation of PIK3-CA activity in circulating tumor cell liquid biopsy at baseline, C1D15, C2D1, C4D1 and at progression and correlation with primary and secondary objectives. Eligibility: Men and postmenopausal female patients with histologically confirmed ER and/or PR ≥1%, HER2- metastatic or unresectable BC with *PIK3CA* mutation and either measurable disease or at least one predominantly lytic bone lesion. No more than two lines of ET and no chemotherapy in the metastatic setting is allowed and patients must have received treatment with a CDK4/6 inhibitor and have progressed on ET as last line of therapy. Exclusions include prior *PIK3CA, mTOR* or *AKT* inhibitors in the metastatic setting, symptomatic active CNS metastases or CNS metastases that require therapeutic interventions. Statistical Analysis. The sample size calculation is based on testing the null hypothesis that the median PFS is at most 5 months against the alternative that the PFS is greater than 5 months (based on data from SOLAR-1). An increase of at least 3 months in the median PFS will be considered a sufficient efficacy signal. A sample size of 44 subjects is required to detect an anticipated increase in the median PFS from 5 to 8 months at the one-sided 0.10 significance level with 90% power, assuming a uniform accrual period of 24 months. Clinical trial information: NCT04762979. Research Sponsor: NOVARTIS, The Kerry Taylor Memorial fund.

TPS1115 **Poster Session**

A multicenter, open-label, phase 2 study of odetiglucan (IMPRIME PGG) and pembrolizumab in patients with metastatic breast cancer (mBCA) who have progressed through prior hormonal therapy. *First Author: Alison Stopeck, Stony Brook Cancer Center, Stony Brook University, Stony Brook, NY*

Background: Hormone receptor (HR) positive/ human epidermal growth factor receptor 2-negative (Her2-) breast cancer is generally considered 'immunologically cold' in comparison to TNBC or Her2+ breast cancer. Keynote-028 results showed a modest ORR of 12% to anti-PD1 antibody, pembrolizumab (PEM) in previously treated HR+/ HER2-/programmed death ligand 1-positive (PD-L1-positive) advanced breast cancer patients (pts). With limited options available, there is significant unmet need to expand clinical benefit from ICI. Odetiglucan, a novel beta glucan, acts as a pathogen-associated molecular pattern (PAMP) that drives a cascade of immune activating events. It repolarizes the immunosuppressive microenvironment, activates the maturation of antigen presenting cells and significantly enhances efficacy of ICI therapy in preclinical tumor models. In a Ph2 trial (IMPRIME 1) of odetiglucan + PEM in 44 pts with heavily pretreated metastatic TNBC, an ORR=15.9%, DCR=54.5%, mDOR=12.7mo, mPFS=2.86 mo, 12 mo OS rate=57.6%, and mOS=16.4 mo were observed. Clinical benefit was particularly evident in a subset of pts, mTNBC "converters" (12/44 pts) who were originally diagnosed with ER/PR+ disease and progressed through endocrine therapies +/- CDK4/6 inhibitors. In these 12 pts, an ORR=50%, DCR=83%, mDOR=11.2, mPFS=5.6 mo, 12-mo OS rate=64.8%, and mOS=17.4 mo were observed. **Methods:** Odetiglucan + PEM is now being explored in pts with hormone-resistant metastatic breast cancer (MBC). This is a phase 2, Simon's 2-Stage study of MBC pts who have progressed through prior hormonal therapy with >1 CDK4/6 inhibitor. Pts will receive odetiglucan 4 mg/kg/wk + PEM 200 mg Q3wk. Stage 1 will enroll 23 pts. If >4 pts have an objective response after 12 wks of treatment, the study will proceed to Stage 2 enrolling an additional 24 pts (N=47). Rejection of the null hypothesis requires >10 objective responses. Main eligibility criteria include: MBC having failed prior hormonal therapy with >1 CDK4/6 inhibitor, <2 chemotherapies, serum ABA ≥20 µg/mL, and no prior ICI exposure. Primary endpoint is ORR (RECIST v1.1); secondary endpoints are PFS, OS, DCR, DoR, and safety. Exploratory objectives assess impact of the treatment combination on immune activating events in peripheral blood and tumor biopsies, and correlate tumor microenvironmental changes with clinical benefit Select subpopulations may be explored. Point estimates with 95% confidence intervals (CIs) of ORR and DCR will be computed. Medians, first, and third quartiles with 95% CI will be estimated using Kaplan-Meier method for other secondary endpoints. Safety parameters will be summarized. The trial is sponsored by HiberCell, Inc. in collaboration with Merck & Co. ~25 US sites will participate. Clinical trial information: NCT05159778. Research Sponsor: HiberCell, Inc.

TPS1116 **Poster Session**

DOLAF: An international multicenter phase II trial of durvalumab (MEDI4736) plus olaparib plus fulvestrant in patients with metastatic or locally advanced ER-positive, HER2-negative breast cancer selected using criteria that predict sensitivity to olaparib. *First Author: Severine Guiu Lahaye, Institut de Cancerologie de Montpellier, Montpellier, France*

Background: PARP inhibitors have documented clinical activity in patients with HER2 negative breast cancer (BC) and a germline pathogenic variant (PV) in *BRCA1* or *BRCA2*. Defects in other genes involved in homologous recombination DNA repair (HRR) or mismatch repair pathway (microsatellite instability MSI) have been associated with preclinical cellular sensitivity to PARP inhibitors. Several preclinical and clinical studies have suggested synergy between immune checkpoint blockade and PARP inhibitors. Indeed, tumors with deficiency in HRR have higher mutagenic potential and produce a larger number of neoantigens. Around 60% of BC with a germline PV in *BRCA1/2* are ER+/HER2- tumors, and the ER-pathway remains a key target of their therapy. The combination of PARP inhibitors with endocrine therapy has shown to be superior to monotherapy. **Methods:** DOLAF is an open-label, international, multicentric, phase II trial assessing the combination of olaparib, fulvestrant, and durvalumab in ER+/HER2- metastatic or locally advanced BC with somatic or germline PV in *BRCA1, BRCA2* or other genes implicated in the HRR pathway *(ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCA, FAND2, FANCL, MRE11A, NBN, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D and RAD54L)* or in MSI status or other actionable genes (*AKT1, ESR1, FGFR1, FGFR2, FGFR3, and PIK3CA)* all based on central tumor NGS. Further an amendment in May 2021, patients with only alterations in these other actionable genes can no longer be included. Patients must have received 1 prior line of endocrine therapy for their metastatic BC, including CDK4/6 inhibitor and maximum of 1 line of chemotherapy in the metastatic setting. Patients receive olaparib (twice daily at 300 mg), fulvestrant (2 intramuscular injections of 250 mg every 28 days) and durvalumab (1500 mg intravenous every 4 weeks). The primary objective is to evaluate the progression-free survival rate at 24 weeks. Secondary endpoints include safety, overall survival, objective response rate, in the overall population and in the germline *BRCA* mutated population. With an optimum two-stage Simon design, $\alpha = 2.5\%$, $\beta = 5\%$, p0 (probability of inefficiency maximum) = 50%, p1 (probability of minimum efficiency) = 65%, it is necessary to include 158 patients. The strategy could be considered sufficiently effective if there are at least 87 patients without progression at 24 weeks. Given the lack of safety data from this association, a safety run-in phase including 6 patients has been completed without DLT. As of December 31, 2021, 266 patients have been screened of whom 102 have been treated. The first interim analysis occured in November 2021 after the inclusion of 64 evaluable patients. IDMC suggested that the trial continue as planned. Clinical trial information: NCT04053322. Research Sponsor: Astrazeneca.

TPS1117 **Poster Session**

postMONARCH: A phase 3 study of abemaciclib plus fulvestrant versus placebo plus fulvestrant in patients with HR+, HER2-, metastatic breast cancer following progression on a CDK4 & 6 inhibitor and endocrine therapy. *First Author: Kevin Kalinsky, Emory University at Winship Cancer Institute, Atlanta, GA*

Background: The use of cyclin dependent kinase 4 and 6 (CDK4 & 6) inhibitors plus endocrine therapy (ET) has transformed the management of hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC). However, most patients will experience disease progression. Identification of treatment options following progression is an unmet medical need. Additionally, as CDK4 & 6 inhibitors are now being deployed in the adjuvant setting, determination of optimal therapy following metastatic relapse is an important question. In patients with disease progression following a CDK4 & 6 inhibitor-based regimen, continuing CDK4 & 6 inhibition with abemaciclib while switching the ET backbone may provide benefit and delay the need for cytotoxic chemotherapy. Abemaciclib is an oral, selective, and potent CDK4 & 6 inhibitor administered continuously and approved as monotherapy or with ET for treatment of HR+, HER2- ABC. Abemaciclib has also been approved with ET for the adjuvant treatment of HR+, HER2-, node-positive, early breast cancer at high risk of recurrence and a Ki-67 score ≥20%. Fulvestrant is a selective ER degrader (SERD) approved for treatment of HR+, HER2- ABC. The postMONARCH study investigates whether abemaciclib plus fulvestrant will improve outcomes in patients with HR+, HER2- ABC after disease relapse or progression after adjuvant or first-line treatment with a CDK4 & 6 inhibitor plus ET. **Methods:** postMONARCH is a Phase 3, global, multicenter, randomized, double-blind, placebo-controlled study in patients with HR+, HER2- ABC and with disease progression on treatment with a prior CDK4 & 6 inhibitor plus an aromatase inhibitor as initial therapy for ABC or recurrence on/after treatment with a CDK4 & 6 inhibitor plus ET in the adjuvant setting. Eligible patients are randomized 1:1 to receive abemaciclib 150 mg twice daily or placebo, plus fulvestrant. Stratification factors include geography, presence of visceral metastasis, and duration of prior CDK4 & 6 inhibitor-based regimen. The study is powered at 80% with a cumulative Type I error of 0.025 to detect the superiority of abemaciclib plus fulvestrant versus placebo plus fulvestrant in terms of investigator-assessed progression free survival. Key secondary endpoints include overall survival, PFS by blinded independent central review, objective response rate, safety, patient-reported outcomes, and pharmacokinetics. This study opened in Jan 2022, plans for approximately 122 centers in 18 countries, and anticipates enrolling ~350 patients. Clinical trial information: NCT05169567. Research Sponsor: Eli Lilly and Company.

TPS1118 **Poster Session**

KEYNOTE-B49: A phase 3, randomized, double-blind, placebo-controlled study of pembrolizumab plus chemotherapy in patients with HR+/HER2- locally recurrent inoperable or metastatic breast cancer. *First Author: Hope S. Rugo, Department of Medicine, University of California San Francisco, Helen Diller Family Comprehensive Cancer Center, San Francisco, CA*

Background: HR+/HER2– advanced breast cancer that progresses on endocrine therapy is treated with chemotherapy (chemo). The phase 1b KEYNOTE-028 trial showed durable activity with pembrolizumab (pembro) monotherapy in previously treated HR+/HER2–, PD-L1–positive (combined positive score [CPS] ≥1) advanced breast cancer. KEYNOTE-B49 (NCT04895358) is a phase 3, randomized, double-blind study of pembro + chemo vs placebo (pbo) + chemo in centrally assessed PD-L1–positive, HR+/HER2– locally recurrent inoperable or metastatic breast cancer (mBC) after progression on prior endocrine therapy. **Methods:** ~800 patients (pts) with HR+/HER2– locally recurrent inoperable or mBC who are candidates for chemo (no prior chemo for metastatic disease) with PD-L1 CPS ≥1 and documented progression on prior endocrine therapy will be enrolled. Prior endocrine therapy comprises ≥2 lines (≥1 in combination with a CDK4/6 inhibitor) in the metastatic setting or 1 line with CDK4/6 inhibitor treatment for mBC in pts who had a relapse within 24 mo of primary surgery. Pts without prior CDK4/6 inhibitor treatment may enroll if they had progressed within 6 mo of starting endocrine therapy for metastatic disease and had previously relapsed within 24 mo of primary tumor surgery while on adjuvant endocrine therapy. Pts are randomized 1:1 to receive pembro 200 mg IV or pbo Q3W, each in combination with investigator's choice of chemo: paclitaxel 90 mg/m^2 IV on days 1, 8, and 15 Q4W; nab-paclitaxel 100 mg/m^2 IV on days 1, 8, and 15 Q4W; liposomal doxorubicin 50 mg/m^2 IV on day 1 Q4W; or capecitabine 1000 mg/m^2 PO BID on days 1–14 Q3W. Randomization is stratified by tumor PD-L1 (CPS 1–9 vs ≥10), presence of visceral metastases (yes vs no), and chemo on-study (taxanes vs liposomal doxorubicin vs capecitabine). Treatment is continued until disease progression, unacceptable toxicity, withdrawal, or, for pembro/pbo, completion of 35 cycles (~2 years); chemo can be continued per investigator discretion. Tumor PD-L1 status is determined centrally using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies; Carpinteria, CA, USA). Radiologic assessments are performed Q9W for 54 wk and then Q12W thereafter. AEs occurring from randomization until 30 d after treatment discontinuation (90 d for serious AEs) are graded per NCI-CTCAE v 5.0. Primary endpoints are PFS per RECIST v1.1 by BICR and OS in pts with PD-L1 CPS ≥10 and ≥1 tumors, separately. Enrollment is ongoing at 204 international sites. Clinical trial information: NCT04895358. Research Sponsor: Merck & Co., Inc., Kenilworth, NJ, USA.

TPS1119 **Poster Session**

Neoadjuvant survivin-targeted immunotherapy maveropepimut-S (MVP-S) to increase Th1 immune response in Ki67-high hormone receptor-positive (HR+) early-stage breast cancer (ESBC). *First Author: Sasha E. Stanton, Providence Cancer Center, Portland, OR*

Background: HR+ ESBC is associated with suboptimal pathologic complete response rate (pCR, ~10%) following neoadjuvant cytotoxic chemotherapy. Neoadjuvant anti-endocrine therapy with aromatase inhibitors (AI) may serve as an effective alternative. Efficacy can be gauged using the surrogate Ki67 cell proliferation histologic marker. Patients with poor Ki67 response (defined as Ki67 > 10%) following neoadjuvant AI exhibit poor prognosis and therapeutic resistance to both anti-endocrine therapy and chemotherapy. In a genomic analysis among Ki67-high HR+ tumors, we identified 8-fold upregulation of BIRC5 (survivin), a gene that regulates apoptosis and the cell cycle and that is associated with poor clinical outcome. Maveropepimut-S (MVP-S, previously named DPX-Survivac) leverages the non-aqueous, lipid-based DPX delivery platform to educate a specific and persistent T cell-based immune response to 5 HLA-restricted peptides from Survivin, a cancer-associated protein commonly upregulated in several cancers. Treatment with MVP-S and intermittent, low-dose cyclophosphamide (CPA) has shown tumor infiltration of survivin-specific T cells. Previous clinical trials have shown that MVP-S is well-tolerated, immunogenic, and could lead to clinical response in several cancer indications. Further exploration of the regimen in breast cancer could extend the application of this immunotherapy for this unmet medical need. **Methods:** NCT04895761 is phase I trial evaluating the safety and immunologic effects of neoadjuvant MVP-S plus letrozole (arm A, n = 6), with/without tumor-directed MR-guided radiotherapy (arm B, n = 6), or intermittent low-dose cyclophosphamide or CPA (arm C, n = 6). Postmenopausal patients with T1c+ HR+HER2- breast cancer with Ki67 > 10% will receive two doses of MVP-S and 7 weeks of neoadjuvant letrozole prior to surgery (all arms), whereas arm B will be treated additionally with concurrent 10Gy x 2 tumor boost radiation to facilitate immunogenic cell death, and arm C (n = 6) will be treated additionally with intermittent low-dose CPA (50mg BID) to facilitate regulatory T cell depletion. The primary objective is safety. Biomarker objectives are to evaluate for each treatment arm: 1) systemic type I survivin-specific immune response, as measured by IFN-γ ELISPOT; 2) changes in immune environment by GeoMx digital spatial genomic profiling; 3) and changes in tumor infiltrating lymphocytes (TILs) and Ki67. These data will be used to identify the most immunogenic MVP-S combination therapy for study in phase II trial powered to assess clinical outcome (pCR). Clinical trial information: NCT04895761. Research Sponsor: IMV INC.

TPS1120 **Poster Session**

ARV-471, an estrogen receptor (ER) PROTAC degrader, combined with palbociclib in advanced ER+/human epidermal growth factor receptor 2–negative (HER2-) breast cancer: Phase 1b cohort (part C) of a phase 1/2 study. *First Author: Erika P. Hamilton, Sarah Cannon Research Institute/ Tennessee Oncology, Nashville, TN*

Background: ARV-471 is a novel, potent, orally bioavailable PROteolysis TArgeting Chimera (PROTAC) protein degrader that selectively targets the ER. In xenograft models, ARV-471 demonstrated substantially greater ER degradation and antitumor activity compared with the selective ER degrader fulvestrant. In the phase 1 dose escalation portion (Part A) of the first-in-human phase 1/2 study, ARV-471 monotherapy was well tolerated and showed antitumor activity in patients with ER+/HER2- locally advanced or metastatic breast cancer who had previously received endocrine therapy and a cyclin-dependent kinase (CDK)4/6 inhibitor; the clinical benefit rate (rate of confirmed complete or partial response or stable disease ≥24 weeks) was 40% (95% CI: 26%–56%) in 47 evaluable patients. The phase 2 VERITAC expansion cohort (Part B) is further evaluating ARV-471 monotherapy in this patient population. Palbociclib, a CDK4/6 inhibitor, plus fulvestrant is a standard treatment option for patients with ER+/HER2- breast cancer who have had disease progression on endocrine therapy. ARV-471 plus palbociclib resulted in substantially greater tumor growth inhibition in xenograft models compared with palbociclib plus fulvestrant, supporting further investigation of the ARV-471 plus palbociclib combination in patients with ER+ breast cancer. Here we describe Part C of the phase 1/2 study, which evaluates the safety and clinical activity of ARV-471 plus palbociclib in patients with breast cancer who previously received endocrine therapy. **Methods:** Eligible patients (aged ≥18 years) have histologically or cytologically confirmed ER+/HER2- advanced breast cancer and have received ≥1 prior endocrine therapy and ≤2 prior chemotherapy regimens for advanced disease; prior CDK4/6 inhibitor therapy is permitted. Patients with known symptomatic brain metastases requiring steroids are excluded. ARV-471 and palbociclib will be administered orally once daily in 28-day cycles; ARV-471 will be given continuously and palbociclib for 21 days followed by 7 days off treatment. Primary objectives are to evaluate the safety and tolerability of ARV-471 plus palbociclib and select the recommended phase 2 dose and schedule of the combination (based on the incidence of dose-limiting toxicities during the first cycle and the frequency and severity of adverse events and laboratory abnormalities). Secondary objectives are to assess preliminary antitumor activity of ARV-471 plus palbociclib (based on overall response rate per Response Evaluation Criteria in Solid Tumors v1.1, clinical benefit rate, progression-free survival, and duration of response) and pharmacokinetic parameters. Clinical trial information: NCT04072952. Research Sponsor: Arvinas, Inc.

TPS1121 **Poster Session**

Phase 3 ENABLAR-2 study to evaluate enobosarm and abemaciclib combination compared to estrogen-blocking agent for the second-line treatment of AR+, ER+, HER2- metastatic breast cancer in patients who previously received palbociclib and estrogen-blocking agent combination therapy. *First Author: Elgene Lim, Olivia Newton John Cancer & Wellness Centre, Heidelberg, Australia*

Background: Targeting the androgen receptor (AR) may be the next important endocrine therapy for advanced breast cancer. The AR has been demonstrated to be a tumor suppressor when activated. Enobosarm is an oral selective AR targeting agonist that activates the AR in breast cancer. Preclinical studies in CDK4/6 inhibitor resistant PDX models demonstrated combinatorial synergistic activity of enobosarm plus CDK 4/6 inhibitors. An open-label, Phase 2 study, was conducted in 136 women with heavily pretreated ER+ HER2- metastatic breast cancer that were randomized to oral daily enobosarm at a dose of 9 or 18 mg. The efficacy evaluable (EE) group were patients that were AR positive (> 10% AR nuclear staining). In the EE population with measurable disease at baseline, 10 patients had received prior endocrine therapy + a CDK 4/6 inhibitor. Subsequent treatment with enobosarm resulted in a clinical benefit rate of 50% and the best overall response rate (ORR) was 30% (2CRs and 1 PR). Of the 10 patients, 7 had AR nuclear staining ≥40%. None of the patients with AR nuclear staining < 40% responded to enobosarm. Although a small subset of the study, it appears that enobosarm has activity in patients who had ≥40% AR staining and who had progressed on standard endocrine therapy with a CDK 4/6 inhibitor. Overall, treatment with enobosarm was well tolerated with significant positive effects on quality-of-life measurements. **Methods:** The ENABLAR-2 trial is an ongoing Phase 3, randomized, open-label, efficacy and safety study in patients with AR+ ER+ HER2- MBC with AR nuclear staining of ≥40%, who have progressed after one line of systemic therapy comprising estrogen blocking agent and palbociclib. The planned sample size is 186 patients randomized 1:1 to enobosarm + abemaciclib OR fulvestrant if the first line of therapy for MBC was a non-steroidal AI plus palbociclib, until disease progression, toxicity, or loss of clinical benefit. If first line therapy for metastatic breast cancer was fulvestrant plus palbociclib, then the patient will be randomized 1:1 to either enobosarm + abemaciclib OR an AI. Randomization will be stratified by AR% nuclear staining, ≥60% versus < 60%, as well as by estrogen blocking agent such that each cohort will have the same number of subjects previously receiving fulvestrant + palbociclib in first line therapy. The key objectives are to determine the safety and efficacy of enobosarm and abemaciclib combination versus an alternative estrogen blocking agent with the primary endpoint of PFS. Secondary endpoints include ORR, duration of response, overall survival, change from baseline in Short Physical Performance Battery (SPPB), change in EORTC Quality of Life Questionnaire (EORTC-QLQ) and change in body composition as measured by DEXA. Clinical trial information: NCT05065411. Research Sponsor: Veru Inc.

TPS1122 **Poster Session**

Phase Ib/II study of BCL-2 inhibitor lisaftoclax (APG-2575) safety and tolerability when administered alone or combined with a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor in patients with estrogen receptor-positive (ER^+) breast cancer or advanced solid tumors. *First Author: Kevin Kalinsky, Department of Hematology and Medical Oncology, Glenn Family Breast Center and Breast Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, GA*

Background: Various cancers evade apoptosis by overexpressing BCL-2 proteins. Investigational agent lisaftoclax (APG-2575) is a novel, potent, selective BCL-2 inhibitor, while palbociclib inhibits cyclin-dependent kinases (CDK) 4 and 6. In preclinical studies, palbociclib decreased proliferation of ER^+ breast cancer cell lines by arresting them in the G1 cycle phase. Preclinical data demonstrate favorable, complementary effects of palbociclib when combined with a BCL-2 inhibitor and support this combination in patients with ER^+/ human epidermal growth factor receptor 2-negative ($HER2^-$) metastatic breast cancer. **Methods:** This global multicenter open-label dose escalation and dose expansion study is assessing the safety of lisaftoclax monotherapy in patients with histologically or cytologically confirmed advanced solid tumors that have progressed on standard therapy or when combined with CDK4/6 inhibitor palbociclib in physiologically postmenopausal women with ER^+/ $HER2^-$ metastatic breast cancer that has progressed or relapsed after treatment with a CDK4/6 inhibitor. This trial consists of 2 parts: a phase Ib dose escalation phase using a standard 3+3 design to determine the maximum tolerated dose (MTD) of lisaftoclax as a single agent in patients with solid tumors, as well as both the MTD and recommended phase 2 (RP2D) dose of lisaftoclax when combined with palbociclib in women with ER^+/ $HER2^-$ metastatic breast cancer. Phase II of this study is a signal-seeking expansion of lisaftoclax at RP2D when combined with palbociclib in women with ER^+/ $HER2^-$ metastatic breast cancer. This phase is being conducted using Simon's Minimax two-stage design. The primary objective for phase II is to determine clinical benefit response, and secondary efficacy endpoints include overall response rate, duration of response, time to response, and progression-free survival. Lisaftoclax is being administered orally once daily in a 28-day cycle at the assigned dose. Clinical trial information: NCT04946864. Research Sponsor: Ascentage Pharma Group Corp. Ltd (Hong Kong).

TPS1123 **Poster Session**

TWT-203: Phase 1b/2 dose-confirming study of CFI-402257 as a single agent in advanced solid tumors and in combination with fulvestrant in patients with ER+/HER2- advanced breast cancer after disease progression on prior CDK4/6 and endocrine therapy. *First Author: Robert Wesolowski, The Ohio State University Comprehensive Cancer Center, Division of Medical Oncology, Columbus, OH*

Background: TTK (Threonine Tyrosine Kinase also known as Monopolar spindle 1 [Mps1]), is a dual-specificity serine-threonine kinase critical for anaphase promoting complex/cyclosome inhibition at the spindle assembly checkpoint, and is required for chromosome alignment and error correction. Inhibition of TTK causes cells to prematurely exit mitosis with unattached chromosomes, resulting in aneuploidy and cell death. Higher TTK tumor levels correlate with worse prognosis and may contribute to the survival and proliferation of aneuploid cells. CFI-402257, a potent and selective inhibitor of TTK inhibits the growth of a variety of human cancer-derived cell lines with IC50 of 8-40 nM. A first-in-human phase 1 study of CFI-402257 administered orally as a single agent, demonstrated a tolerable safety profile and evidence of clinical activity in patients with advanced solid tumors. The MTD was 168 mg daily, and the study expanded to 3 cohorts: solid tumors, HER2-negative breast cancer, and hormone receptor positive (HR+/HER2-) breast cancer in combination with fulvestrant. The dose limiting toxicity was manageable and reversible dose-dependent neutropenia. Investigator-confirmed partial responses (cPR) were observed in 5 patients (10.6%) with 25 (53.2%) exhibiting disease control. In the HR+/HER2- breast cancer population previously treated with cyclin dependent kinase 4/6 inhibitors (CDK4/6i) and aromatase inhibitors, there were 4 cPR's with a median duration of response of 256 days, with responses emerging after 2 cycles of therapy. Responses were observed with CFI-402257 as a single agent and in combination with fulvestrant. Based on these data, study TWT-203 will focus on advanced solid tumors and advanced HR+/HER2- breast cancers in combination with an approved endocrine therapy. **Methods**: Safety and clinical activity of CFI-402257 monotherapy will be evaluated in patients with advanced solid tumors (Part A) or in combination with fulvestrant in patients with HR+/HER2- advanced breast cancer (Part B). Part A will confirm the RP2D using a 3+3 design with a starting dose of 126 mg daily. Part B evaluates CFI-402257 in combination with fulvestrant in patients with HR+/HER2- advanced breast cancer following progression on prior CDK4/6i and endocrine therapy. Initially 6 patients will be treated with CFI-402257 and fulvestrant, and safety, tolerability, and PK evaluated, with further expansion to confirm the RP2D and characterize CFI-402257 activity. Efficacy endpoints include overall response rate and disease control rate. Safety endpoints include incidence of treatment emergent adverse events. Exploratory objectives include characterization of protein and molecular alterations relevant to the cell cycle and CFI-402257 response. Research Sponsor: Treadwell Therapeutics.

TPS1124 **Poster Session**

First-in-human global multi-center study of RLY-2608, a pan-mutant and isoform-selective PI3Kα inhibitor, as a single agent in patients with advanced solid tumors and in combination with fulvestrant in patients with advanced breast cancer. *First Author: Cesar Augusto Perez, Sarah Cannon Research Institute at Florida Cancer Specialists, Orlando, FL*

Background: Targeting constitutively active mutant kinases with selective small molecule inhibitors is a key therapeutic pillar of precision oncology. *Phosphatidylinositol-4,5bisphosphate-3 kinase, catalytic subunit alpha* (*PIK3CA*) mutations leading to oncogenic activation of PI3Kα represent the largest opportunity for this approach in solid tumors. However, there is no selective inhibitor that targets mutant PI3Kα in the clinic. Toxicity related to non-selective inhibition of WT PI3Kα (hyperglycemia) and other PI3K isoforms limits the tolerability, dosing and efficacy of the orthosteric inhibitor, alpelisib, the only approved solid tumor PI3K inhibitor. RLY-2608, a novel oral allosteric PI3Kα inhibitor, is uniquely designed to overcome these limitations via mutant- and isoform-selective PI3Kα inhibition for greater target coverage, improved tolerability and antitumor activity. We initiated a first-in-human (FIH), study to evaluate the clinical activity of RLY-2608 as a single agent in advanced solid tumor patients (pts) with *PI3KCA* mutations and in combination with fulvestrant in pts with *PIK3CA*mutant, HR+, HER2- metastatic breast cancer (MBC). **Methods:** This is a global, multi-center, dose escalation/expansion study (NCT05216432) of RLY2608 as a single agent in adults who have advanced solid tumors and are refractory, intolerant, or declined standard therapy and RLY-2608 in combination with fulvestrant in previously treated pts with HR+/HER2- MBC. Eligibility criteria include presence of *PI3KCA* mutation (blood or tumor) per local assessment, ECOG performance status 0-1, measurable or evaluable disease per RECIST 1.1 and no prior PI3K inhibitor (except combination group 2). RLY-2608 is administered on a continuous schedule with 4-week cycles. Adverse events (AEs) per CTCAE v5, PK, biomarkers (mutant ctDNAs and insulin pathway markers) and anti-tumor activity are assessed serially. Dose escalation employs a Bayesian Optimal Interval design to identify MTD and RP2D. Following dose escalation, pts will be treated with RLY-2608 at the MTD/RP2D in a monotherapy dose expansion with 5 groups (N = 75, 15 each): 1. Clear cell ovarian carcinoma 2. Head and neck squamous cell carcinoma 3. Cervical cancer 4. Other solid tumors 5. *PI3KCA* double mutations. In addition, two expansion cohorts will enroll patients with HR+/HER2- MBC treated with RLY-2608 and fulvestrant combination (N = 30, 15 each): 1. No prior PI3K therapy 2. Intolerant to PI3K inhibitors. The primary endpoints are MTD/RP2D and AE profile for single agent and combination; key secondary endpoints are *PI3KCA* genotype in blood and tumor, PK, biomarkers, and overall response rate. US enrollment began December 2021 and ex-USA startup is underway. Clinical trial information: NCT05216432. Research Sponsor: Relay Therapeutics.

TPS1125 **Poster Session**

Phase I trial of an alpha-lactalbumin vaccine in patients with moderate- to high-risk operable triple-negative breast cancer (TNBC). *First Author: George Thomas Budd, Department of Hematology/Oncology, Cleveland Clinic, Cleveland, OH*

Background: Triple-negative breast cancer (TNBC) is the subtype of breast cancer with the worst prognosis and is the subtype most often associated with germline mutations of BRCA1 and certain other genes. Alpha-lactalbumin (aLA) is a milk protein that is expressed in lactating breasts but not at other times or in other normal tissues. Expression of aLA is found in approximately 70% of TNBC (Cancers PMID: 27322324) so is an attractive immunologic target for TNBC based on the "retired protein hypothesis" (Semin Immunol PMID: 31926646). Pre-clinical studies have shown that vaccination with aLA provides treatment of established and, more potently, protection from development of autochthonous tumors in transgenic murine models of breast cancer and against 4T1 transplantable breast cancer in BALB/c mice (Nat Med PMID: 20512124). We are conducting a Phase I trial in patients with early stage TNBC to demonstrate the safety of this approach and to document the ability to produce a meaningful immunologic response to aLA. **Methods:** Patients with ER-negative, PR-negative, HER2-negative breast cancer of pathologic stage I-III or who had residual disease after standard pre-operative systemic therapy are being entered into a Phase I trial of alpha-lactalbumin with a GMP-grade zymosan adjuvant in Montanide ISA 51 VG vehicle. Participants must be within 3 years of initiation of treatment and have no evidence of recurrence. Patients receive a total of 3 vaccinations administered once every 2 weeks with doses escalated using a 3+3 trial design. Toxic events of Common Terminology Criteria for Adverse Events (CTCAE) grade 2 or greater are considered dose-limiting. Dose levels being tested are alpha-lactalbumin/zymosan 0.01 mg/0.01 mg, 0.1 mg/0.1 mg, and 1 mg/1 mg. Patients are being monitored for toxicity until 84 days after the first vaccination or resolution of toxicity, whichever is later. Blood is being drawn prior to therapy and 14, 28, and 56 days after the first vaccination to assess cellular response using enzyme-linked immunosorbent spot (ELISpot) assays of interferon-gamma and interleukin-17 production in response to aLA. Humoral response to aLA vaccination is being assessed by enzyme-linked immunosorbent assay (ELISA). After identification of the Maximum Tolerated Dose we will expand the dose levels associated with effective tumor immunity and enroll a cohort of patients without cancer planning to undergo prophylactic bilateral mastectomy. Funding Source: Department of Defense (W81XWH-17-1-0592 and W81XWH-17-1-0593). Clinical trial information: NCT04674306. Research Sponsor: Department of Defense.

TPS1126 **Poster Session**

Phase 1 pilot study with dose expansion of chemotherapy in combination with CD40 agonist and Flt3 ligand in metastatic triple-negative breast cancer. *First Author: Sangeetha M. Reddy, University of Texas Southwestern Medical Center, Dallas, TX*

Background: Only a subset of patients with metastatic triple-negative breast cancer demonstrate response to currently approved PD-1 immune checkpoint blockade, and few have durable responses. Antigen presentation defects may be a reason for this low response because deficiency of antigen-presenting DC1 dendritic cells is associated with poor anti-tumor immunity. CD40 agonists are a class of agents that activate antigen presenting cells including dendritic cells and B cells and also repolarize macrophages. Flt3 ligand is a growth factor that increases dendritic cells. In line with this, we recently demonstrated in pre-clinical models that the combination of liposomal-doxorubicin chemotherapy, a CD40 agonist, and a Flt3 ligand improves outcomes of breast cancer compared to alternate combinations. **Methods:** This is a single arm phase I pilot study of liposomal-doxorubicin, CDX-1140 (CD40 agonist), and CDX-301 (Flt3 ligand) combination therapy in patients with metastatic or unresectable locally advanced metastatic triple-negative breast cancer. Patients will be randomized to 3 lead-in arms (triplet therapy, doublet immunotherapy only, liposomal-doxorubicin only) prior to receiving full triplet therapy with fresh tissue biopsies before and after the lead-in treatment. CDX-301 will be discontinued after 2 cycles; liposomal-doxorubicin and CDX-1140 will be continued until disease progression or clinically limiting toxicities. Primary endpoint is determination of a recommended phase 2 dose based on treatment-related adverse events including dose-limiting toxicities. Secondary endpoints include anti-tumor immune response after triplet therapy, after immunotherapy alone, and after liposomal-doxorubicin alone; median progression-free survival, overall response rate, duration of response, and clinical benefit rate. Key eligibility criteria are unresectable stage III or stage IV triple-negative breast cancer (ER ≤10%, PR ≤10%, HER2/neu negative), 1st to 3rd line metastatic treatment setting (1st line patients need to be PD-L1 negative by 22C3 assay), measurable disease by RECIST 1.1 criteria, consent for pre-treatment and on-treatment biopsies of amenable soft tissue tumor lesions, no prior treatment with an anti-CD40 antibody or a Flt3 ligand, no anthracycline treatment in the metastatic setting, no prior progression while on anthracycline-based therapy or within 6 months of completing neoadjuvant chemotherapy, and no history of non-infectious pneumonitis or current pneumonitis. This trial will enroll up to 45 patients across multiple sites. Clinical trial information: NCT05029999. Research Sponsor: Celldex Therapeutics, Other Foundation.

TPS1127 **Poster Session**

Phase 1b/2 study of ladiratuzumab vedotin (LV) in combination with pembrolizumab for first-line treatment of triple-negative breast cancer (SGNLVA-002, trial in progress). *First Author: Jane Lowe Meisel, Winship Cancer Institute, Atlanta, GA*

Background: Patients with metastatic triple-negative breast cancer (mTNBC) have a poor prognosis. Treatment combinations of anti-programmed death ligand 1 (anti–PD-L1) agents with chemotherapy have shown promise in mTNBC. LV is an investigational antibody–drug conjugate directed to LIV-1, a protein highly expressed on breast cancer cells, via a humanized IgG1 monoclonal antibody conjugated to monomethyl auristatin E (MMAE) by a protease-cleavable linker. LIV-1–mediated delivery of MMAE disrupts microtubules and induces cell cycle arrest and apoptosis. LV has also been shown to drive immunogenic cell death (ICD) to elicit an immune response. LV + pembrolizumab may result in synergistic activity through LV-induced ICD, creating a microenvironment favorable for enhanced anti–PD-L1 activity. Preliminary results show LV delivered once every 3 weeks (Q3W) + pembrolizumab was tolerable with encouraging antitumor activity in patients with mTNBC (Han 2019). Additionally, interim results of weekly LV monotherapy at doses up to 1.5 mg/kg were clinically active and generally well tolerated (Tsai 2021). Based on pharmacokinetic and pharmacodynamic modeling and simulation analysis, an intermittent LV + pembrolizumab dosing regimen is being evaluated to further enhance efficacy and improve the tolerability profile. Due to an unmet medical need for patients with mTNBC who are PD-L1 low or negative, Part D will focus on this patient population. **Methods:** SGNLVA-002 (NCT03310957) is an ongoing global single-arm, open-label phase 1b/2 study of LV + pembrolizumab as 1L therapy for patients with unresectable locally advanced/mTNBC. Part D is currently enrolling ~40 patients. Eligible patients must have advanced disease with no prior cytotoxic/anti–PD-L1 treatment, PD-L1 combined positive score < 10, measurable disease per RECIST v1.1 and an ECOG score ≤1. Patients with Grade ≥2 pre-existing neuropathy or active central nervous system metastases are not permitted. Patients will receive LV at 1.5 mg/kg on Days 1 and 8 plus pembrolizumab 200 mg on Day 1 Q3W. The primary objectives are to evaluate the safety/tolerability and objective response rate of LV + pembrolizumab. Secondary objectives include duration of response, disease control rate, progression-free survival, and overall survival. Safety and efficacy endpoints will be summarized with descriptive statistics. Global enrollment is ongoing in the US, EU, and Asia. Clinical trial information: NCT03310957. Research Sponsor: Seagen Inc.

TPS1128 **Poster Session**

A phase I/II trial evaluating the safety and efficacy of eribulin in combination with copanlisib in patients with metastatic triple-negative breast cancer (TNBC). *First Author: Nusayba Ali Bagegni, Washington University in St. Louis School of Medicine, St. Louis, MO*

Background: Metastatic (met) TNBC remains a clinical challenge with limited treatment options and inevitable chemoresistance. Aberrant PI3K pathway signaling is frequently observed in TNBC. Increasing evidence shows PI3K pathway activation maintains the stemness and chemoresistance of BC stem cells (CSCs), and PI3K inhibition sensitizes CSCs to chemotherapy (chemo). Eribulin (E), a non-taxane microtubule dynamics inhibitor, showed survival benefit in met HER2 negative BC. Preclinically, E impacts tumor vascular remodeling, inhibits epithelial-to-mesenchymal transition and metastasis – key mechanisms implicated in PI3K inhibition resistance. Copanlisib (C), a potent pan-class I PI3K inhibitor (*i*), improved anti-tumor effect in E-sensitive and resistant TNBC patient-derived xenograft models, irrespective of PIK3CA/PTEN mutation (mut) status, when combined with E. This phase I/II study is aimed to determine the safety and efficacy of E+C in pts with met TNBC. **Methods:** This trial includes a phase I portion with the primary objective to determine the dose limiting toxicity (DLT) and recommended phase 2 dose (RP2D) of E+C, followed by a phase II randomized portion of E+C (at RP2D) versus (*vs*) E with the primary objective of progression-free survival (PFS). Key secondary objectives include objective response rate (ORR) and clinical benefit rate (CBR) [phase I]; and ORR and CBR, by arm and by PIK3CA/PTEN mut status and assessment of treatment induced target engagement [phase II]. Key exploratory objectives include analysis of genomic, proteomic and metabolomic changes as potential response biomarkers in tumor tissue and blood. Key eligibility criteria include pts with: met TNBC who progressed on ≤5 chemo lines, including anthracycline/taxane (unless contraindicated), ECOG 0-1, adequate organ function and known archival tumor PIK3CA/PTEN mut status. Key exclusions: prior E or PI3K/mTOR/AKT*i*, grade ≥2 neuropathy, tumor AKT mut, congenital QT prolongation, and uncontrolled diabetes or hypertension. Phase I portion will follow a 3+3 design for E+C dose escalation to enroll 18 max pts, starting at E 1.1 mg/m^2 IV and C 45 mg IV on days (D) 1/8 of 21-D cycle (C) (to E 1.4 mg/m^2 and C 60 mg max). RP2D will be defined as the highest dose level at which at most 1 of 6 pts experience DLT during C1. 88 pts will be randomized (1:1) in the phase II portion to E+C *vs* E (1.4 mg/m^2 D 1/8), stratified by PTEN/PIK3CA mut status. Response assessment by Response Evaluation Criteria in solid tumors (RECIST) v1.1 will occur every 9 weeks (+/-7 D). Tumor biopsy is required at baseline and C2D1-2, and optional at progression. A sample size of 88 achieves 80% power to detect PFS difference of median PFS 6.95 *vs* 4 months (corresponding to a hazard ratio of 0.5755) between the 2 arms, based on 1-sided two-sample log rank test at 0.1 α level. The phase I study is actively enrolling pts. Clinical trial information: NCT04345913. Research Sponsor: U.S. National Institutes of Health.

TPS1129 **Poster Session**

Evaluation of a three-part equity intervention for women of color with breast cancer. *First Author: Jamil Rivers, The Chrysalis Initiative, Philadelphia, PA*

Background: Women of color (WOC) with breast cancer miss and fail key points in care due to racial disparities in cancer services. Conscious and unconscious bias means that these women are not treated in a timely way or as rigorously. They are offered fewer options, and the patient navigation and education needed for them to self-advocate is ignored. Black women in particular have the highest breast cancer death rates. Care delivery differs even independent of such variables as literacy, income, and education. Separately and incrementally, findings to date have shown the potential oof patient navigation, equity assessment, and mobile support to reverse these disparities. In pilot investigations — partnering with academic cancer centers — The Chrysalis Initiative (a nonprofit patient advocacy and research organization) has validated the potential of combining these approaches in a three-part intervention. Based on preliminary work, it is hypothesized patients will: experience significantly greater adherence to the recommended continuum of care, without disruption or barriers; more often seek second opinions and additional supportive resources, and engage in clinical trials; demonstrate less co-morbidities, through more preventive measures and healthful lifestyle; suffer fewer interactions perceived to be influenced by racism; undergo less financial distress, with guidance on managing and planning costs; feel more confident and more optimistic in their outlook; and achieve better clinical results and lower costs. **Methods:** To determine and document the full impact, both quantitatively and qualitatively, of the experimental three-part intervention, the trial is: delivering navigation/coaching services to the study population, using counselors who are predominantly WOC who have experienced the challenges of breast cancer care. Surveys and interviews pre- and post-intervention will add to impact measures; providing the experimental group with the BC Navi App on both iOS and Android devices. Developed in partnership with InTouch, the app supports engagement and tracking. It provides a dashboard for care evaluation to supplement EMR data; conducting an equity assessment of breast cancer services of partnering clinical programs through use of focus groups with staff, patients, and community; procedural checks; and data collection from center EHR systems. The review audits 40 domains of care based on NCCI, NCI, ASCO, ACR, and other standards. The assessment team works closely and collaboratively with each cancer center's clinical and administrative staff to reveal disparities and find consensus on ways to close gaps. This trial in progress is randomizing 200 subjects to the coaching/mobile app intervention arm and 100 to benefits of the equity assessment only, with comparison to nonWOC with breast cancer. The trial aims to disseminate the three-part intervention in easily reproducible form. Research Sponsor: Pfizer (in partnership with MD Anderson - Cooper), Conquer Cancer Foundation of the American Society of Clinical Oncology.

TPS1130 **Poster Session**

Phase I/II first-in-human CAR T–targeting MUC1 transmembrane cleavage product (MUC1*) in patients with metastatic breast cancer. *First Author: Cynthia Carol Bamdad, Minerva Biotechnologies, Waltham, MA*

Background: Metastatic breast cancer (MBC) remains incurable and novel immunotherapy for durable response remains an unmet need. Chimeric antigen receptor (CAR) T-cell therapy, an innovative form of immunotherapy wherein autologous T-cells are genetically modified to target tumor specific cell-surface markers, has been developed for treatment of solid tumors. huMNC2-CAR44 recognizes the growth factor receptor form of MUC1, which is the transmembrane cleavage product called MUC1*. MUC1* is a Class I growth factor receptor that is activated by ligand-induced dimerization of its truncated extra cellular domain, which activates the MAP kinase signaling pathway as well as survival pathways. Onco-embryonic growth factor $NME7_{AB}$ binds to an ectopic site on MUC1* that is only unmasked after MUC1 is cleaved and the tandem repeat domain is shed from the cell surface. The targeting head of the CAR, huMNC2, competes with $NME7_{AB}$ for binding to this ectopic site. huMNC2 does not bind to full-length MUC1, hence highly tumor-selective. 70% of solid tumor cancers express a huMNC2 reactive MUC1* and huMNC2-scFv bound robustly to 93% of the breast cancers with minimal staining of normal tissues. huMNC2-CAR44 T cells completely obliterated a variety of MUC1* positive solid tumors in NSG mice in vivo. IND enabling animal studies demonstrated that huMNC2-CAR44 T potently inhibited MUC1* positive tumors xenografted into female NSG mice, whether the tumor cells were MUC1 negative cells stably transduced with MUC1* or breast cancer cells such as T47D that naturally express MUC1*. In one study, huMNC2-CAR44 T treated mice survived tumor-free for over 12 weeks, whereas control group had to be sacrificed at 3 weeks due to disease progression. **Methods:** This is a first-in human, phase I/II trial evaluating the safety and efficacy of huMNC2-CAR44 T in patients with MBC. Key inclusion criteria include age ≥18 years, ECOGPS 0-1, available FFPE tumor sample, tumor IHC ≥30% MUC1* and preserved organ function. Dose escalation is standard 3+3 design with dosing levels ranging from 3.3x10^5 to 1.0x10^7 CAR+ cells/kg, and fludarabine/cyclophosphamide lymphodepletion pre-treatment. Phase I accepts patients with MBC that has progressed through at least 3 previous lines of therapy. The primary objective of Phase I is to determine safety and determine a recommended Phase II dose (RPIID), with the exploratory objectives of assessing CAR T cell expansion, persistence, tumor penetration and potential tumor escape. Six (6) patients have been enrolled and five (5) patients have been treated to date. Phase II will be comprised of 3 cohorts of 15 patients in each arm of luminal, HER2+ and triple negative breast cancers for a total of 45 patients in Phase II. Clinical trial information: NCT04020575. Research Sponsor: Minerva Biotechnologies.

1500 **Oral Abstract Session**

Changes in cancer mortality by race and ethnicity following the Affordable Care Act implementation in California. *First Author: Elena Martinez, University of California San Diego Wertheim School of Public Health, La Jolla, CA*

Background: Implementation of the Affordable Care Act (ACA) has resulted in improvements in cancer outcomes but the extent to which these apply to specific racial and ethnic populations is unknown. We examined changes in health insurance distributions pre- and post-ACA and assessed cancer-specific mortality rates by race and ethnicity. **Methods:** The population included 167,181 newly diagnosed breast (n = 117,738), colorectal (n = 38,334), and cervix cancer (n = 11,109) patients younger than 65 years and 141,026 patients 65 years or older in the California Cancer Registry. Hazard rate ratios (HRRs) and 95% confidence intervals (CIs) were calculated using multivariable Cox regression to estimate associations with risk of 5-year cancer-specific death for each cancer site pre- (2007-2010) and post-ACA (2014-2017), and by race and ethnicity (American Indian/Alaska Natives, AIAN; Asian Americans; Hispanics; Native Hawaiian/Pacific Islanders, NHPI; non-Hispanic Blacks, NHB; and non-Hispanic whites, NHW). Difference-in-difference analysis was conducted to compare changes over time between younger (< 65 years) and older (65 years and older) patients. **Results:** Cancer-specific mortality for patients age < 65 was significantly lower post- vs. pre-ACA for colorectal cancer among Hispanic (HRR = 0.83; 95% CI: 0.74-0.93), NHB (HRR = 0.69; 95% CI: 0.58-0.81), and NHW (HRR = 0.90 95% CI: 0.84-0.97) but not Asian American (HRR = 0.95; 95% CI: 0.82-1.10) patients. The HRR for younger NHB colorectal cancer patients was significantly lower than that for patients 65 years of and older (HRR = 1.09; 95% CI, 0.95-1.25, p-interaction < 0.0001). A significantly lower risk of dying from cervix cancer was observed in the post- vs. pre-ACA period among younger NHB women (HRR = 0.68; 95% CI: 0.47-0.99), but this was not significantly different than that for older women (HRR = 0.41; 95% CI, 0.16-1.01, p-interaction = 0.30). No significant differences in breast cancer-specific mortality were observed for any racial or ethnic group. **Conclusions:** Findings show decreases in cancer-specific mortality for colorectal and cervix cancers for some racial and ethnic groups following ACA implementation in California. These results shed light on ongoing discussions as additional states consider Medicaid expansion. Future studies should assess shifts between health insurance plans resulting from the economic impact of the 2019 novel coronavirus (COVID-19) pandemic. Research Sponsor: U.S. National Institutes of Health.

1501 **Oral Abstract Session**

Association between state Medicaid policies and accrual of Black participants to cancer clinical trials. *First Author: Samuel U Takvorian, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA*

Background: Black individuals remain underrepresented in U.S. cancer clinical trials, partly due to financial barriers to participation. While coverage of the routine costs of trial participation has long been mandatory for Medicare and the commercially insured, only 16 states have enacted similar mandates for Medicaid enrollees. Given the disproportionate representation of Black individuals in state Medicaid programs, we hypothesized that such mandates may have led to improved accrual of Black participants to cancer clinical trials. **Methods:** We conducted a retrospective, quasi-experimental study using de-identified data from the ECOG-ACRIN Cancer Research Group to evaluate changes in the accrual of Black participants to cancer clinical trials associated with state-mandated Medicaid coverage of routine trial costs. The study population included non-elderly adults enrolled in therapeutic clinical trials for breast, colorectal, lung, or prostate cancer from 2000-2019. We employed a difference-in-differences approach with event-study specification to compare outcomes in states that mandated Medicaid coverage of routine trial costs relative to states that did not, before and after mandates were enacted. Outcomes included the proportion of trial participants who had Medicaid insurance (vs. non-Medicaid) and the proportion who were Black (vs. non-Black). Models adjusted for age, sex, cancer type, cancer stage, study phase, and study site (community vs. academic). **Results:** Among 24,321 trial participants (mean age 52.0 [SD 8.2] years, 82.8% female), 7.2% had Medicaid coverage and 10.5% were Black. Compared to states without Medicaid coverage mandates, states with mandates had a statistically significant increase in the proportion of Black trial participants in the first year following the mandate (+6.4 percentage points [95%CI 1.8% to 11.0%]) but not in subsequent years. There was no association between state mandates and the proportion of trial participants enrolled in Medicaid (effects ranged from -0.7 percentage points [95%CI -4.6% to 3.3%] in the first year after mandates to -3.9% [95%CI -8.6% to 0.8%] in the third year). **Conclusions:** State-mandated Medicaid coverage of the routine costs of trial participation was associated with a short-term increase in the proportion of Black trial participants. These findings suggest that Medicaid policies have the potential to improve representation of racial minority groups in cancer clinical trials, and support recent federal legislation mandating state Medicaid programs to cover trial participation costs as of January 2022. Our study was limited by use of data from only one large cancer research group, focus on only four common cancers, and limited power to analyze the policy impact for other racial and ethnic minority groups. Additional work is needed to replicate these findings in larger cohorts of trial participants. Research Sponsor: Leonard Davis Institute of Health Economics Pilot Award, Weill Cornell Ritu Banga Healthcare Disparities Research Award.

1502 **Oral Abstract Session**

Association between the Affordable Care Act Medicaid expansion and survival in young adults newly diagnosed with cancer. *First Author: Xu Ji, Emory University and Children's Healthcare of Atlanta, Atlanta, GA*

Background: Medicaid expansion through the Affordable Care Act (ACA), implemented by 26 states in January 2014 and 13 more states in later years, has been shown to improve insurance coverage and early diagnosis of cancer in young adults (YAs). Little is known about whether these improvements translate to a survival benefit in this population. We evaluated the association between the ACA Medicaid expansion and 2-year overall survival among YAs newly diagnosed with cancer. **Methods:** Using the National Cancer Database, we identified 345,414 YAs aged 18-39 years diagnosed with cancer between 2010 and 2017. YAs diagnosed pre-expansion were followed through September 30, 2013 or three months before Medicaid expansion implementation for late-expansion states, and YAs diagnosed post-expansion were followed through December 31, 2019. We applied the difference-in-difference (DD) method to estimate changes in 2-year overall survival before and after Medicaid expansion, in expansion- versus non-expansion states, controlling for key sociodemographic factors. DD analyses were performed for YAs overall, and stratified by cancer type, stage at diagnosis, race/ethnicity, comorbidity, and facility type. **Results:** Among all YAs, 2-year overall survival increased more in expansion states (90.39% pre-expansion to 91.87% post-expansion) than in non-expansion states (88.98% pre-expansion to 90.05% post-expansion), resulting in a net increase of 0.53 percentage points (ppt; 95% confidence interval [CI] = 0.11 to 0.95 ppt). The increase in 2-year overall survival in expansion states versus non-expansion states was greatest among subgroups of patients with female breast cancer (DD = 1.20 ppt; 95% CI = 0.28 to 2.13 ppt) and patients with stage IV disease at diagnosis (DD = 2.51 ppt; 95% CI = 0.28 to 4.74 ppt). Additionally, greater improvement in 2-year overall survival associated with the expansion was seen among racial/ethnic minority YAs (including Hispanic, non-Hispanic Black, and non-Hispanic others; DD = 0.98 ppt; 95% CI = 0.10 to 1.86 ppt) than their non-Hispanic White peers (DD = 0.41 ppt; 95% CI = -0.06 to 0.89 ppt), among patients treated in community cancer programs (DD = 1.10 ppt; 95% CI = 0.32 to 1.88 ppt) than academic comprehensive cancer programs (DD = 0.12 ppt; 95% CI = -0.52 to 0.77 ppt), and among patients with two or more comorbidities (DD = 6.37 ppt; 95% CI = 0.68 to 12.06 ppt) than patients with no comorbidity (DD = 0.48 ppt; 95% CI = 0.04 to 0.91 ppt). **Conclusions:** We provide the first evidence on the association between ACA Medicaid expansion and improved overall survival among YAs newly diagnosed with cancer. Survival benefits are notable among racial/ethnic minority patients and patients with high healthcare needs, and by patients' treatment facility type. Research Sponsor: U.S. National Institutes of Health.

1503 **Oral Abstract Session**

Impact of oncology clinical pharmacist intervention on clinical trial enrollment in The U.S. Oncology Network's MYLUNG Consortium. *First Author: Elizabeth Koselke, McKesson / US Oncology Network, The Woodlands, TX*

Background: The Molecularly Informed Lung Cancer Treatment in a Community Cancer Network: A Pragmatic Consortium (MYLUNG) clinical trial platform aims to advance the use of precision medicine in non-small cell lung cancer patients through a series of prospective and iterative clinic trials. "Protocol 2" is evaluating the patient and tissue journey of newly diagnosed lung cancer patients presenting for care. Timely patient accrual to oncology clinical trials is a known practice challenge. The US Oncology Network recently implemented a clinical pharmacist (ClinReview) to provide remote clinical services to support Protocol 2 enrollment. **Methods:** An oncology-trained clinical pharmacist remotely reviewed chemotherapy regimen orders and a weekly custom recruitment report within six community network practices (n = 149 physicians). The ClinReview pharmacist identified, screened, and assisted with recruitment of eligible patients for enrollment in the MYLUNG study. Relevant and concise patient data were provided to the on-site research team to facilitate ease of enrollment. Enrollments and intervention data were tracked to monitor the impact of the pharmacist intervention. The primary outcome of monthly enrollment was evaluated using a paired t-test. **Results:** Over a 6-month period, the ClinReview pharmacist screened 367 potentially eligible patients, 325 patients were recommended for enrollment, and 103 patients (32%) were consented and enrolled. Enrollment due to this ClinReview intervention increased monthly and ranged from 5 in first month to 33 enrollments in month 6. Average monthly enrollment was significantly greater after ClinReview intervention (3.4 patients/month vs. 6.8 patients/month; p = 0.008). Of the 154 patients recommended for enrollment that were not enrolled, 104 (68%) exceeded their eligibility window allowed by the trial, 15 (10%) were deceased or enrolled into hospice care, 10 (6%) declined trial participation, and 25 (16%) transferred care or were treated at outside facilities. **Conclusions:** We demonstrate that incorporation of an oncology clinical pharmacist in clinical research teams significantly enhanced clinical trial enrollment. The remote pharmacist easily adapted into clinic workflows in community practices. Validation across a broader spectrum of differentially resourced oncology practices will be conducted as the MYLUNG clinical trials platform is executed. Research Sponsor: Amgen, AstraZeneca, Eli Lilly, Genentech, Mirati.

Average monthly patient enrollment by practice, before and with ClinReview intervention.

	Average enrollment before ClinReview intervention	Average monthly enrollment with ClinReview	Change after intervention (%)
Practice 1	2.2	6.0	177%
Practice 2	3.4	6.8	101%
Practice 3	0.7	1.7	150%
Practice 4	3.4	10.0	194%
Practice 5	5.8	7.5	30%
Practice 6	4.8	8.5	78%
Total	3.4	6.8*	101%

*(p = 0.008).

1504 **Oral Abstract Session**

Operational metrics for the ELAINE II study combining a traditional approach with a just-in-time model. *First Author: Sibel Blau, Rainier Hematology Oncology/Northwest Medical Specialties, Seattle, WA*

Background: Trial recruitment that requires specific actionable mutations based on next-generation sequencing (NGS) is challenging. Barriers can include competing studies, physician study awareness, site proximity, mutation incidence, among other concerns. **Methods:** This study (NCT04432454) opened clinical sites using two methods during the COVID-19 pandemic. The "Traditional" approach included site selection, IRB and contract approval, and trial activation prior to a patient being identified for enrollment. The second approach used the Tempus "TIME" Trials network that would only open a site after identifying a patient with a mutation of interest and eligible for the trial. **Results:** The first patient enrolled was on 10/12/20 and the last patient was on 6/24/21. A total of 16 sites (6 Traditional and 10 TIME) participated. All Traditional sites, and none of the TIME sites, were affiliated with major academic institutions. Duration for full CTA execution for Traditional sites averaged 200.5 days (range 142 to 257) and for TIME sites averaged 7.6 days (range 2 to 14). IRB approval time average for Traditional sites was 27.5 days (range 12 to 71) and TIME sites was 3.0 days (range 1 to 12 days). Days from site selection to activation letter for Traditional sites was on average 250.0 days (range 187 to 281) and for TIME sites was 131.6 days (range 22 to 248). Time from study activation to first consent was 33.3 days (range 18 to 58) for Traditional sites and 8.8 days (range 1 to 35) for TIME sites. The first patient on-study was at a TIME site 115 days prior to a Traditional site and the first 7 patients enrolled were at TIME sites. Traditional sites consented 23 and enrolled 16 patients while the TIME sites consented 16 and enrolled 13. The trial enrolled all 29 patients in 8 months with the anticipated enrollment duration being 12 to 18 months. **Conclusions:** Although the Traditional and TIME programs had different operational models, they both contributed a significant number of patients and reduced the projected enrollment timeline. TIME sites enrolled the initial patients. These results demonstrate that the "Just-in-Time model," in conjunction with a Traditional model, can reduce projected overall time to enrollment in biomarker-driven studies. Research Sponsor: Sermonix Pharmaceuticals.

Number of patients enrolled at clinical sites by month.

	TIME	Traditional	Total
October 2020	2	0	2
November 2020	3	0	5
December 2020	0	0	5
January 2021	2	0	7
February 2021	1	2	10
March 2021	1	4	15
April 2021	0	4	19
May 2021	0	3	22
June 2021	4	3	29

1505 **Oral Abstract Session**

Impact of broadening trial eligibility criteria on the inclusion of patients with brain metastases in cancer clinical trials. *First Author: Joseph M. Unger, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: On October 2, 2017, the American Society of Clinical Oncology, Friends of Cancer Research, and the U.S. Food and Drug Administration (ASCO/FoCR/FDA) issued a joint research statement recommending that certain eligibility criteria in cancer clinical trials, including those related to brain metastases, be broadened to make trials more inclusive. We examined whether patterns of exclusions regarding patients with brain metastases changed over time in relation to these recommendations. **Methods:** We used data from ClinicalTrials.gov to evaluate patterns of trial eligibility criteria in phase I-III U.S.-based interventional clinical trials for patients with advanced breast, colorectal, or lung cancers from January 2013 through October 2021. Trial inclusion and exclusion criteria were abstracted; to enhance validity, reviewers were blinded to the year of trial activation. For each trial, we determined whether patients with brain metastases were not excluded, conditionally excluded (i.e., excluded in some circumstances), or wholly excluded. Trial registrations between October 2, 2017-December 31, 2018 were excluded to allow 1 year for newly conceived trials to adopt the recommendations, plus 3 months to account for the lag time between loading trial records and trial activation dates; thus, the independent exposure variable was January 1, 2019. An interrupted time series analysis with multinomial logistic regression was used to assess whether the ASCO/FoCR/FDA recommendations were associated with changes in brain metastases eligibility criteria. **Results:** We evaluated N = 1998 trials. Patients with brain metastases were not excluded in 307 trials (15.4%); conditionally excluded in 1459 trials (74.8%); and wholly excluded in 196 trials (9.8%). In the post-recommendation period, we found a 92% increase in the odds of trials with brain metastases not excluded compared to conditionally excluded (OR = 1.92, 95% CI, 1.08-3.45, p = .03). The estimated proportion of trials in which patients with brain metastases were not excluded increased from 9.2% had the recommendations not been made to 15.6% (p = .04). Conversely, the proportion of trials in which patients with brain metastases were conditionally excluded (76.9%) was lower than expected (85.3%, p = .02). We found no difference in the proportion of trials in which patients with brain metastases were wholly excluded (7.5% vs. 5.4%, p = .28). **Conclusions:** The ASCO/FoCR/FDA recommendations were associated with a shift in patterns of brain metastases exclusion criteria from conditionally excluded to not excluded. To our knowledge, this is the first evidence that cancer clinical trials have become more inclusive of a broader set of patients in response to the ASCO/FoCR/FDA recommendations. More inclusive eligibility improves trial access and representativeness, increasing trial validity and the pace at which trials enroll. Research Sponsor: Public Health Sciences Division of the Fred Hutchinson Cancer Research Center.

1506 **Oral Abstract Session**

Remote patient-reported symptoms and passive activity monitoring to improve patient-clinician communication regarding symptoms and functional status: A randomized controlled trial (PROStep). *First Author: Christopher Manz, Dana Farber Cancer Institute, Boston, MA*

Background: Oncologists suboptimally assess patient symptoms and functional status, possibly leading to poor symptom management or over-treatment. Remote patient-reported symptoms and passive activity monitoring may provide objective measures of symptoms and functional status to improve patient-clinician communication and symptom understanding. We assessed the impact of a clinician-centered dashboard of longitudinal patient-reported symptoms and step counts on patient-clinician communication regarding symptoms and functional status. **Methods:** This randomized trial enrolled 108 patients with incurable GI or lung cancers treated with chemotherapy at a large academic health center. Patients were randomized to either of Arms A) control, B) weekly patient-reported symptoms via text message + step tracking from a wearable activity monitor, with summary dashboards given to clinicians at each visit, or C) arm B plus text message-based prompts to patients encouraging discussion of symptoms and functional status prior to each visit. We used Kruskal Wallis tests to compare co-primary outcomes (patient-reported perceptions of clinician symptom and functional status understanding at 6 months after enrollment) between control (A) and intervention (B+C) arms on a 5-point scale (1 = Not at all; 2 = Slightly; 3 = Moderately; 4 = Considerably; 5 = Completely). **Results:** 33, 37, and 38 patients were enrolled in arms A, B, and C, respectively. Patients were 54.6% male, mean age was 58.9 years, 77% had GI cancer, and 23% had lung cancer. At six months, there was no difference between control and intervention arms in patient perception of clinician understanding of symptoms (Arm A: 4.5, Arm B/C: 4.5, p = 0.85) or functional status (Arm A: 4.5, Arm B/C: 4.3, p = 0.59). Patients reported that their oncology team seldom discussed PROstep data during appointments (mean 2.3 on 5-point scale where 2 = seldom). Hospitalization rates were 42% and 45% for Arms A and B/C (p = 0.8), respectively, and new palliative care referrals were 9% and 10% (p = 0.8), respectively. Mean adherence to weekly patient reports and Fitbit data (at least 4 of 7 days in a week) was 64% and 53%, respectively. Net promoter score was 8.3 on a 10-point scale. **Conclusions:** Clinician and patient-directed dashboards based on patient-generated health data did not lead to higher patient-perceived clinician understanding of symptoms and functional status, although this was limited by moderate adherence to remote symptom and step count collection and low frequency of clinician discussion of PROStep data with patients, highlighting challenges to clinical application of these data sources. Further efforts are needed to improve patient-clinician communication about symptoms and functional status. Clinical trial information: NCT04616768. Research Sponsor: Penn Institute of Translational Medicine and Therapeutics.

1507 **Oral Abstract Session**

Evaluating mass implementation of digital health solutions to improve quality and reduce disparities in a large multisite community oncology practice. *First Author: Amila Patel, Navigating Cancer, Seattle, WA*

Background: There is a priority to accelerate the delivery of digital health solutions (DHS) to provide patients with enhanced means for accessing care, but lack of understanding of their utility in certain populations. There are concerns that equitable adoption translate into disparities. We sought to implement a portfolio of DHS across a large practice and characterize engagement across populations to enhance clinical informatics solutions that support care delivery. **Methods:** This is a retrospective evaluation of cancer patients who engaged with a portfolio of DHS between March 1, 2019 and January 15, 2022. We included four tools with opt-in and opt-out functionality: (1) a care management (CM) platform utilized by clinical staff to manage patient activities, (2) an electronic patient-reported outcomes (ePRO) remote monitoring program for tracking symptoms and oral adherence, (3) a patient portal (PP) for securely accessing patient health records, and (4) digital education (DE) for patients regarding disease and treatments. The engaged population was defined as the number of enrolled patients with at least one (1) record of triage activity, (2) completed ePRO assessment, (3) PP login, and (4) DE read activity, for each tool, respectively. The start of the index period was adjusted based on the first go-live date of each tool. We evaluated factors (age, gender, race/ethnicity, preferred-language, marital status, and distance from clinic) associated with patient engagement using Chi-Square test and multivariate logistic regression. **Results:** This analysis included a total of 267,375 unique patients. Of the enrolled population per tool, 172,840 (73.6%), 9,938 (67.7 %), 49,771 (79.2%), and 12,044 (56.9%) patients were engaged in CM, ePRO, PP and DE, respectively. The majority (>50%) of engaged patients were female, White and non-Hispanic/Latino, English-language, and aged 61-80 yrs. After adjusting for covariates, we observed that White and non-Hispanic/Latino [(CM: OR 1.15, ePRO OR 1.46, PP: OR 1.48, and DE: OR 1.36) and English-language (CM: OR 1.2, ePRO OR 1.67, PP: OR 1.8 and DE: OR 1.89) patients were significantly (p-value <0.001) more engaged compared to their counterparts. Male patients were less likely to be engaged in CM (OR: 0.79) and ePRO (OR: 0.65) but more engaged in PP (OR: 1.1) compared to females. No significant difference was observed in engagement between non-rural (<20 mile) vs. rural (≥ 20 miles) and in all age groups 21-40, 41-60, 61-80 and >80 years as compared to reference age of 0-20 years for any digital tools except CM. **Conclusions:** DHS can be used to support the cancer patient journey and we demonstrated high utilization in an array of sociodemographic variables in our population. However, tools designed and implemented with different populations in mind to reduce staff burden and lessen the digital divide should be further explored. Research Sponsor: None.

1508 **Oral Abstract Session**

ePRO-based digital symptom monitoring in a community oncology practice to reduce emergency room and inpatient utilization. *First Author: Michael A. Kolodziej, ADVI, Washington, DC*

Background: We have previously reported on the successful implementation of an electronic patient-reported outcomes (ePRO)-based symptom monitoring tool in a community oncology practice. Basch et al reported that use of such a tool in the academic trial setting reduced ER visits and hospitalizations. We have examined the impact of the tool on ER and inpatient utilization in this real world patient population. **Methods:** Highlands Oncology Group (HOG) is a 21 physician oncology group located in Northwest Arkansas. Beginning in June 2020, HOG offered patients receiving parenteral cancer therapy enrollment onto Expain, an EMR-integrated ePRO system which enables remote symptom monitoring during therapy. EMR data were linked with the Arkansas State Health Alliance for Records Exchange (SHARE), the state's Health Information Exchange (HIE), to obtain ER visits/hospitalization data. All patients at HOG treated between September 30, 2020 and November 30, 2021 were included in this analysis. Clinical and demographic characteristics were compared in patients who enrolled on Expain versus those who did not, and corresponding p-values were calculated using Mann-Whitney and Chi-square tests. Crude rates for ER visits / hospitalizations were calculated as the total number of events per total person-time. **Results:** There were 855 patients enrolled on the ePRO system. Concurrently, in the same practice, 1773 patients were treated but not enrolled. Reasons for non-enrollment included patient's choice to not participate and patient not yet offered enrollment due to rolling enrollment. The non-ePRO cohort was slightly older (66.7 vs 63.3 yrs, $p < .001$), more commonly male (47.3% vs 39.3%, $p < .001$) and less likely to be White (85.3% vs 89.4%, $p = 0.003$). The cohorts were comparable with respect to cancer site distribution and included a diverse and representative distribution of common malignancies receiving systemic therapy in a community practice. The proportion of patients with metastatic disease was comparable (ePRO 52.9% vs non-ePRO 51.6%, $p = 0.55$). Health resource utilization rates were lower for patients in the ePRO cohort: ER visits: 1.72 vs 2.34 per 100 patient-months, rate ratio and 95% CI = 0.74 (0.60, 0.92), p-value = 0.005; hospitalizations: 4.76 vs 5.41 per 100 patient-months, rate ratio and 95% CI = 0.87 (0.77, 0.99), p-value = 0.04. **Conclusions:** Our findings confirm the substantial benefits of using an ePRO tool in reducing health care resource utilization, and extend the initial findings of previous publications in the academic, clinical trial setting to the real world setting. This observational data is subject to confounding factors and we are evaluating the robustness using various methods to address non-comparability of the cohorts. We are further examining the benefits in specific patient subsets and attempting to correlate these benefits with improved survival. Research Sponsor: None.

1509 **Poster Discussion Session**

Disparities in NCI and nonprofit organization funding and effect on cancers with high incidence rates among Black patients and mortality rates. *First Author: Suneel Deepak Kamath, Cleveland Clinic, Taussig Cancer Institute, Cleveland, OH*

Background: National Cancer Institute (NCI) and nonprofit organization (NPO) funding is critical for research and advocacy, but may not be equitable across cancers or racial and ethnic groups. **Methods:** This study evaluated funding from the NCI and NPOs supporting lung, breast, colorectal, pancreatic, hepatobiliary, prostate, ovarian, cervical and endometrial cancers, leukemia, lymphoma and melanoma from 2015-2018. The primary objectives were to assess for disparities in NCI and NPO funding across different cancers compared to their incidence and mortality and their incidence rates across age, racial and ethnic groups. We also investigated if underfunding correlates with fewer clinical trials. Correlations between NCI and NPO funding for each cancer and its incidence, mortality and number of clinical trials were analyzed using scatter plots and Pearson correlation coefficients (PCCs). **Results:** Diseases with the largest combined NCI and NPO funding were breast cancer ($3.75 billion) and leukemia ($1.99 billion). Those with the least funding were endometrial ($94 million), cervical ($292 million), and hepatobiliary cancers ($348 million). Disease-specific funding correlated well with incidence, but correlated poorly with mortality (PCCs: 0.74, $p = 0.006$ and 0.30, $p = 0.346$, respectively). Breast cancer, leukemia and lymphoma were consistently well-funded, while colorectal, lung, hepatobiliary and uterine cancers were consistently underfunded. These data are summarized in the Table. NCI and NPO funding increased proportionately as incidence increased for White patients (PCC: 0.73, $p = 0.007$), Hispanic patients (PCC: 0.66, $p = 0.02$), Asian/Pacific Islanders (PCC: 0.77, $p = 0.003$) and Native Americans and Alaskans (PCC: 0.72, $p = 0.008$) while cancers with higher incidence in the Black population were underfunded (PCC: 0.52, $p = 0.08$). The amount of combined NCI and NPO funding for a particular cancer correlated strongly with the number of clinical trials for that disease (PCC: 0.91, $p < 0.0001$). **Conclusions:** Many cancers with high incidence and mortality are underfunded, including those with higher incidence among Black patients. Underfunding strongly correlates with fewer clinical trials, which could impede future advances in underfunded cancers. Research Sponsor: None.

	Leukemia	Lymphoma	Breast	Lung	Colon	Pancreas	Liver	Melanoma	Uterine	Cervix	Ovary	Prostate
NCI+NPO Funding (millions)	$1,997	$1,299	$3,746	$1,595	$971	$942	$348	$660	$94	$292	$505	$1,215
Funding/Incidence	$33,162	$16,041	$14,852	$7,140	$7,191	$17,645	$6,757	$8,072	$1,555	$22,529	$22,669	$7,030
Funding/Deaths	$81,762	$61,616	$91,411	$10,165	$19,418	$22,191	$10,948	$67,089	$8,825	$70,359	$35,713	$44,765

1510 **Poster Discussion Session**

Impact of a shared-care model between community and academic centers for facilitating access to allogeneic and autologous stem cell transplantation. *First Author: Joshua Fein, Hartford Healthcare, Hartford, CT*

Background: Despite curative or disease-controlling roles in AML/MDS and MM, access to allogeneic (allo) and autologous (auto) hematopoietic stem cell transplantation (SCT) remains far from universal. Socioeconomic status (SES) and geographic distance from SCT centers have been shown to be barriers to SCT access. In 2016, Hartford HealthCare (HHC) and the Memorial Sloan Kettering Cancer Center (MSK) pioneered a Shared-Care Model (SCM) to streamline access to allo and auto SCT at MSK, featuring a dedicated nurse SCT coordinator, shared hematology tumor boards, MSK-led didactics for HHC providers, and an electronic health record sharing pipeline. We sought to determine if this has improved access to SCT for HHC patients. **Methods:** A retrospective chart review was conducted of HHC patients aged 18-70 with new diagnoses of AML, MDS, and MM between 2016 and 2020. Socioeconomic status (SES) was estimated by 9-digit zip-code using the Area Deprivation Index (ADI), shown to be a surrogate for healthcare access. Referral or not to a SCT center, referral to MSK through the SCM, and reasons for non-referral were abstracted from the medical record. For patients referred for SCT at MSK, we also captured the number of peri-SCT days in New York City (NYC) and number of subsequent MSK and HHC clinic visits/hospitalizations within 1-year post-SCT. **Results:** A total of 126 patients was included, with 81 (64%) treated for AML/MDS and 45 (36%) for MM. The median age was 60 years (interquartile range [IQR]: 53-66). The majority were white (n = 101, 80%) followed by 10% (n = 13) Black/African American; 10% (n = 12) were of Hispanic ethnicity. The median ADI percentile was 38 (IQR: 20-51; higher percentiles reflect decreased SES). The median ADI for MSK SCT referrals from New York, New Jersey, and Connecticut 2016-2020 for the same indications was 19 (IQR: 10-30, $p < 0.001$). A total of 90 patients (71%) were referred to SCT centers. Leading reasons for no referral were favorable-risk disease (n = 10), goals of care (n = 9), and death prior to referral (n = 5); 3 patients were not referred due to comorbidities/performance status. No differences were found between patients referred to MSK vs. other centers. Thirty-four HHC patients were referred to MSK (21 AML/MDS, 13 MM), vs. 3 between 2010 and 2015. Twelve patients underwent allo SCT, with median 97 days in NYC (range: 68-247); 8 underwent auto SCT, with median 21 days in NYC (range: 15-48). **Conclusions:** Our findings show the feasibility of a shared-care model between a non-SCT-providing large regional hospital system and a major academic transplantation center. Close collaboration between institutions may minimize time patients spend away from home. The SES of HHC referrals was lower than the general MSK population, suggesting that a shared-care model may facilitate access to SCT for patients with previous barriers for this potentially curative therapy. Research Sponsor: None.

1511 **Poster Discussion Session**

Time to biopsy of screening mammography-detected abnormalities: Evaluating the impact of same-day services implemented during the COVID-19 pandemic. *First Author: Kimberly Klinger, Massachusetts General Hospital, Boston, MA*

Background: Screening mammography programs often require patients undergo multiple visits (screening exam, diagnostic exam, and biopsy) before tissue diagnoisis of screen-detected abnormalities. During the COVID-19 pandemic, same-day breast imaging services were leveraged to decrease the number of visits following abnormal screening exams. Specifically, in May 2020, we implemented an immediate-read screening mammography program to synergize with our pre-existing same-day breast biopsy program, such that every effort was made to perform diagnostic imaging during the same visit after an abnormal screening mammogram. This study aims to evaluate the impact of these same-day breast imaging services on time and number of patient visits to undergo breast biopsy after an abnormal screening mammogram. **Methods:** Consecutive screening mammograms performed during normal business hours pre- (6/1/16 to 5/30/17) and post-implementation (6/1/20 to 5/30/21) of same-day services were identified. Patient demographics, imaging and biopsy results, and visit dates were extracted from the medical record. Multivariable logistic, linear, and ordinal regression models estimated with generalized estimating equations were fit to assess the association of period (pre- versus post-implementation), patient age, and race and ethnicity (White versus races other than White) with having a same-day biopsy (biopsy on the same day as the abnormal screening exam), number of days to biopsy, and number of visits. Adjusted odds ratios (aOR) and beta estimates (aBeta) of each covariate and corresponding 95% confidence intervals (CI) were estimated. **Results:** A total of 409/25,922 (1.6%) of patients (median age 61, IQR 50-70) pre-implementation and 221/20,452 (1.1%) patients (median age 62, IQR 49-71) post-implementation had screen-detected abnormalities leading to diagnostic breast imaging and biopsy. Median number of days from screening to biopsy decreased from 16 days pre-implementation to 5 days post-implementation ($p < 0.001$). Pre-implementation, 86.8% of patients required 3 visits between screening and biopsy, while post-implementation only 23.1% required 3 visits ($p < 0.001$). Compared to pre-implementation, the post-implementation period was associated with increased odds of undergoing same-day biopsy (aOR 20.7, 95% CI 8.3-51.7), $p < 0.001$), fewer days from abnormal screening mammogram to biopsy (aBeta -13.3, 95% CI -15.7 to -10.9, $p < 0.001$), and fewer visits (aOR 0.05, 95% CI 0.02-0.09), $p < 0.001$), controlling for age and race and ethnicity. **Conclusions:** Same-day breast imaging services decreased time and patient visits between abnormal screening mammogram and breast biopsy. Same-day services implemented out of necessity during the COVID-19 pandemic should be continued after the pandemic has subsided to improve timeliness of care. Research Sponsor: The 2021 Ralph Schlaeger Fellowship Award.

1512 **Poster Discussion Session**

Patient- and provider-level factors associated with telehealth utilization across a multisite, multiregional cancer practice. *First Author: Joshua Pritchett, Mayo Clinic, Rochester, MN*

Background: In response to the COVID-19 pandemic, many cancer practices adopted telehealth, including telephone and video appointments. Following a period of initial expansion that began in March 2020, sustained telehealth integration has emerged across the Mayo Clinic Cancer Practice (MCCP) in 2021. The primary objective of this study was to identify factors associated with utilization of telehealth appointments. **Methods:** A cross-sectional, multi-site, retrospective analysis was conducted across MCCP – a multisite, multiregional cancer practice with tertiary referral campuses in Minnesota, Florida, and Arizona, as well as rural, community-based hospitals and clinics throughout the Upper Midwest. Multivariable models were used to examine the association of patient- and provider-level variables with telehealth utilization. **Results:** Outpatient appointments conducted in July – August 2019 (n = 32,932) were compared with those from 2020 (n = 33,662) and 2021 (n = 35,486). The rate of telehealth appointment utilization increased from <0.01% in 2019 to 11.0% in 2020 and 14.0% in 2021. The strongest provider-level predictor of telehealth utilization was female physician provider type (OR 1.06, 95% CI 1.01 to 1.11; P = 0.0297), a trend consistently observed across career stages, practice locations and settings in 2020 and 2021. Additionally, while the rate of telehealth utilization was not significantly different at referral and community-based campuses in 2020, providers at referral campuses were significantly more likely to utilize telehealth than community-based campuses in 2021 (OR 1.1, 95% CI 1.01 to 1.12; P = 0.0289). Regarding patient-level factors, rural residence (defined by Rural-Urban Commuting Area codes), which accounted for 44.2% of the patient population, was significantly associated with lower telehealth utilization as compared to patients with urban residences, particularly for video appointments (OR 1.04, 95% CI 1.02 to 1.07; P < 0.0001). Notably, the disparity in telehealth utilization between rural and urban populations was found to be less pronounced in 2021 as compared to 2020. **Conclusions:** Multivariable analysis across a multi-site, multi-regional cancer practice identified several factors associated with increased telehealth utilization. These included female physician provider type, referral-based campuses, and patients residing in urban settings. A detailed understanding of the factors that influence telehealth utilization – a method of care delivery which represents a "new normal" across many cancer practices – will be essential to enable continued equitable access to high-quality, high-impact, patient-centered cancer care. Research Sponsor: Wohlers Family Foundation.

1513 **Poster Discussion Session**

Association between telehealth and adherence with patient-reported outcomes (PRO)-based remote symptom monitoring among adolescent/young adults (AYA), middle age, and older adults with cancer. *First Author: Ishwaria Mohan Subbiah, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: PRO-based remote symptom monitoring favorably impacts quality of life, healthcare utilization, and overall survival in patients (pts) with cancer. However remote PRO completion rates outside of a clinical trial remained widely varied. With the wide adoption of telehealth in cancer care during the pandemic, telehealth's impact on health behaviors such adherence w remote PROs is not fully characterized. To that end, we investigated PRO completion patterns in routine cancer care, pre- and during the pandemic. **Methods:** We queried a prospectively maintained institutional database of all PROs remotely delivered to pts at our institution from 1/1/18 to 12/31/21. Pts were divided into 2 time cohorts ("pre-pandemic" 1/1/18 to 3/31/20, "during pandemic" 4/1/20 to 12/31/21) and 3 age cohorts (AYA 15-39y, midage 40-64y, older adults 65y+). We calculated descriptive statistics and compared (t-test, ANOVA) between time and age cohorts and independent variables. **Results:** Overall 93,875 unique patients over 4 years received 1+ remote PROs as a part of their routine cancer care. PRO response rate increased from 35% prepandemic (12011 of 34742 pts responding) to 67% during pandemic (p <0.00001). To understand patient-level response patterns, we selected one representative global health PRO tool used widely across clinics in our institution and analyzed completion in a representative month over 4 years, 2 before (Oct '18, '19) and 2 mid-pandemic (Oct '20, '21). Overall 2738 pts (median age 60y, range 17-94y; 290 AYA 15-39y, 1444 midage 40-64y, 1004 older adults 65y+) were sent 3249 PROs during these 4m, 1378 PROs to 1075 pts in 2 pre-pandemic months & 1871 to 1663 pts in 2 mid-pandemic months. Overall, PRO response rate increased from 52% pre-pandemic to 81% during, non-responders dropping from 48% to 19%, and response rate without any reminder from the team increasing from 13% pre-pandemic to 79% during. Across all 3 age cohorts, overall PRO response rates increased (AYA up 21%, midage up 27%, seniors up 35%, p 0.012), PRO non-response rate decreased (AYA by 21%, midage by 27%, seniors by 35%, p 0.01), and PRO response rate without reminders from clinic team increased significantly (AYA, by 71%, midage by 78%, senior by 61%, p <0.00001). When further analyzing by visit type during pandemic, the improvements in overall PRO response rates are driven almost exclusively by telehealth where in-person PRO completion decreased by 19% (pre-pandemic 52%, during 33%) while pts who had an upcoming virtual visit had 94% PRO response rate (p < 0.00001). **Conclusions:** Substantially higher adherence with PRO-based remote symptom monitoring was seen during the pandemic with virtual visits accounting substantially for this broad adherence and the highest increases seen in older adults, highlighting the implications of telehealth on cancer care. Research Sponsor: American Cancer Society, the Andrew Sabin Family Foundation, Cancer and Aging Research Group (CARG) R21/R33 Infrastructure Grant.

1514 **Poster Discussion Session**

Electronic research consents for complex early-phase I-II clinical trials integrated with telemedicine visits compared with in-person encounters. *First Author: Michael T. Buckley, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Based on our previous research with patient satisfaction for electronic consenting (95% of 940 respondents would recommend it another patient), we hypothesized that telemedicine (telemed) would be received as well as or better than in-person clinical research (CR) consent encounters for complex early-phase clinical trial (Phase I-II) and clinical genetic consent discussions by patients. Oncologist experiences to date have shown that telemed works well for uncomplicated clinical scenarios, but its performance alongside increased care complexity is less clear from the patient perspective. **Methods:** We conducted a one-time survey of adult patients having a telemed consent visit between 8/31/21 and 2/13/22 and an in-person clinic visit. Nine CR specific questions covered visit preference and empowerment across 6 high value consent agency domains. **Results:** 513 patients completed the survey and consented across 96 Clinical trials (CT), including genetic, therapeutic, diagnostic, and quality of life. Consent discussions were performed by 75 clinicians and 41 non-clinicians, with the majority (64%) for clinical genetic and Phase I-II CTs. Most patients (52%) preferred telemed over in-person clinic visits (19%) when all visit related factors (time, cost, convenience, quality of care, healthcare team interaction) were considered (P<.05) (Table). Comparing their last in-person visit with telemed, patients reported feeling either less stressed/overwhelmed (16%) for their consent discussion or about the same (39%) using telemed, and 6% were more stressed (P<.05). Patients expressed equal comfort taking agency-supported action across 6 domains regardless of consent setting. **Conclusions:** Electronic consenting via telemed is the preferred method for consent in complex early-phase clinical trials when all visit factors are considered and performs as well across 6 key agency domains when compared with in-person visits. Telemed does not contribute additional stress to consent appointments for most patients and performs well across complex clinical genetic and Phase I-II clinical trial discussions. Our findings suggest telemed and electronic consent should be offered as an option for patients throughout their treatment continuum. Beyond MSK, our data support a broader call for organizations to offer telemed platforms for CT discussions to increase overall patient satisfaction and potentially increase participation. Research Sponsor: None.

Question	Prefer Telemedicine (%)	No Difference (%)	Prefer in Person (%)
Considering All Factors About Your Visit	52	29	19
Saying a CT is not right for me	9	82	9
Requesting time to decide about CT participation	12	79	9
Looking information up online	14	79	7
Sharing a concern about taking part in a CT	12	79	9
Asking for more information to better understand a CT	13	73	14
Include friends, family, or care givers to join the CT discussion	17	72	11

1515 **Poster Discussion Session**

Preliminary analysis of an expanded access study of the fixed-dose combination of pertuzumab (P) and trastuzumab (H) for subcutaneous injection (PH FDC SC) for at-home administration (admin) in patients (pts) with HER2-positive (HER2+) breast cancer (BC) during the COVID-19 pandemic. *First Author: Chau T. Dang, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Standard of care for HER2+ early/first-line metastatic BC (EBC/MBC) is P + H and concurrent chemotherapy (CT); PH FDC SC offers faster, more convenient admin vs intravenous (IV) P + H. COVID-19 has caused unprecedented strain on healthcare systems and disruption to cancer care; treatment (Tx) at home may: enable pts to continue cancer Tx; reduce exposure to COVID-19; free up hospital resources. This study's main objectives: to enable continuity of care during COVID-19; to assess safety of PH FDC SC given at home. **Methods:** This is an ongoing single-arm, hybrid, decentralized clinical trial (NCT04395508). Pts with HER2+ EBC/MBC who completed concurrent CT with P + H IV and are receiving/about to receive maintenance P + H IV, PH FDC SC, or H SC are switched to PH FDC SC given at home by a home health nursing provider (HHNP) until disease progression, unacceptable toxicity, pt withdrawal, or physician recommendation (pts with EBC will complete ≤18 cycles). The study endpoint is safety. A subset of pts took part in HARRIET, a substudy of at-home cardiac surveillance with artificial intelligence-guided cardiac ultrasound and optional 6L ECG acquired by an HHNP. **Results:** Data for 114 pts (1 male) were available at cutoff (Jan 19, 2022): 18 (16%) completed Tx; 20 (18%) discontinued; 76 (67%) remain on study; 79 (69%) had a COVID-19 vaccine while on study. Median age was 49 years; pts were balanced between EBC (n = 55, 48%) and MBC (n = 59, 52%); received a median of 6 (EBC) and 8 (MBC) cycles; and were from metropolitan (n = 109), urban (n = 4), and rural (n = 1) areas. 11 pts tested COVID-19-positive during the Tx phase: 8 continued Tx after appropriate COVID-19 Tx and/or quarantine. Safety is summarized in the table. No new adverse events (AEs) emerged due to home admin. AEs of special interest were grade (gr) 1–2: admin-related reactions (n = 76, 67%), hypersensitivity (n = 5, 4%), cardiac dysfunction (n = 4, 4%), except 1 case of gr ≥3 diarrhea. AEs leading to study Tx discontinuation or interruption/dose reduction occurred in 3 (3%) and 15 (13%) pts. A subset of 7 pts completed at-home cardiac surveillance testing; quantitative assessment of left ventricular ejection fraction was feasible in 3 (43%); 5 (71%) preferred at-home surveillance to clinic. **Conclusions:** In this preliminary analysis, safety of PH FDC SC at home was consistent with the established P + H safety profile, indicating that PH FDC SC at home is a viable option for continuing BC care during and beyond COVID-19. Clinical trial information: NCT04395508. Research Sponsor: Genentech, Inc.

AEs	Pts, n / %
Most common, any grade	
Injection site reaction	67 / 59
Diarrhea	17 / 15
Fatigue	10 / 9
Nausea	8 / 7
Injection site pain	6 / 5
Gr ≥3	4 / 4
Serious*	5 / 4
Fatal	0

*Not Tx-related: COVID-19 pneumonia, cystitis, acute kidney injury, diarrhea, seizure, sepsis, transient ischemic attack (gr 2).

1516 **Poster Discussion Session**

Outcomes following off-site remote chemotherapy administration. *First Author: Abram Arnold, VA Nebraska Western Iowa Health Care System, Omaha, NE*

Background: The Veteran Affairs Nebraska Western Iowa Health Care System (VA-NWIHCS) utilizes teleoncology and remote chemotherapy services to expand care to veterans in rural Nebraska who have difficulty accessing the primary campus in Omaha. Remote sites in Lincoln (60 miles) and Grand Island (GI) (150 miles) facilitate remote chemotherapy administration with oversight from oncologists in Omaha. This study compares clinical outcomes in patients receiving care at these remote sites to those in Omaha. **Methods:** Data were retrospectively reviewed for 151 patients receiving first-line chemotherapy at VA sites in Omaha, Lincoln or GI between 1/1/2018-12/31/2020. Data collected included age, gender, performance status, comorbidities, overall survival (start of treatment to death/last contact), malignancy type and stage, number of delayed or missed treatment cycles, chemotherapy-related toxicities, and emergency room (ER) visits or hospitalizations. SAS version 9.4 was used for analysis. **Results:** The study population included 108 patients who received their chemotherapy infusions in Omaha, while 43 received their infusions at the remote sites. The demographics of the patients at both Omaha and remote sites (Lincoln/GI) was predominantly male, 96% vs 91% respectively; median age was 69 years in each group; 82% vs 93% (p = 0.24) had an ECOG PS of 0-1. The two groups were comparable in terms of common comorbidities: chronic obstructive pulmonary disease (36% vs 37% p = 0.90); chronic kidney disease (38% vs 28% p = 0.24); coronary artery disease (41% vs 19% p = 0.01). Groups had a similar proportion of patients with stage IV disease (39% vs 33%; p = 0.54), treatment with curative intent (60% vs 51%; p = 0.32), and most prevalent cancers: head/neck (14% vs 12% p = 0.80), lung (25% in each p = 0.99), and gastrointestinal (10% vs 14% p = 0.57). There was no difference in median OS between the on-site treatment and remote treatment groups [96.8 (n = 84) vs 92.4 (n = 32) months (p = 0.92) for patients with solid tumors; 67.7 (n = 24) vs 94.3 (n = 11) months (p = 0.73) for hematologic malignancies]. Chemotherapy-related toxicities were noted in 61% vs 53% of patients (p = 0.39) in Omaha vs remote sites, including febrile neutropenia (6% vs 2% p = 0.99), neutropenia (6% vs 5% p = 0.67), other cytopenia (11% vs 14% p = 0.59), dehydration (9% vs 2% p = 0.18), nausea (5% vs 7% p = 0.69), and neuropathy (3% vs 7% p = 0.35). At least one hospitalization occurred in 33% vs 21% (p = 0.13) of patients and at least one ER visit in 42% vs 26% (p = 0.07). A delay in at least one treatment cycle occurred in 29% vs 21% (p = 0.32) of cases and at least one cycle of treatment was missed in 15% vs 19% (p = 0.59). **Conclusions:** The evaluated outcomes in oncology patients treated in Omaha versus remote sites via telemedicine under the same providers were similar. Effective oncology care, including parenteral chemotherapy administration, can be provided via telemedicine and this model can help mitigate issues with access to care. Research Sponsor: None.

1517 **Poster Discussion Session**

Remote symptom monitoring after hospital discharge. *First Author: Robert Michael Daly, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Strategies to improve transitions from the hospital to home for patients with cancer are considered an important component of quality, patient-centered care in oncology. CMS evaluates cancer hospital performance based on the 30-day unplanned hospital readmission rate, and this measure has been endorsed by the National Quality Forum. Nationally, the 30-day readmission rate for oncology patients ranges from 19%-27%. These readmissions come at high psychosocial, physical, and financial costs for patients and caregivers. A remote monitoring intervention that includes frequent contacts with the patient is likely to be effective in improving this transition. **Methods:** We evaluated the feasibility, acceptability, and perceived value of a mobile health intervention to monitor and manage symptoms of adult medical and surgical oncology patients discharged from an NCI-designated cancer center to home. Patients were monitored for 10 days, which is the median time to readmission for an oncology patient. The technology supporting the program included: 1) a patient portal enabling daily electronic patient-reported outcomes assessments; 2) a pulse oximeter to provide data on blood oxygen level and heart rate; 3) alerts for concerning symptoms; 4) an application to allow staff to review and trend symptom data; 5) a secure platform to support communications and televisits between staff and patients; 6) an advanced feedback report to provide just-in-time patient symptom education. Feasibility and acceptability were evaluated through engagement (goal: > 50% response rate) and symptom alerts and perceived value was measured through a patient engagement survey that included a net promoter score (how likely the patient is to recommend the program to similar patients; goal > 0.7). **Results:** Between September 27, 2020 to December 31, 2021, the program enrolled 1,091 medical oncology (median age: 63 years, 55% female) and 4,222 surgical oncology patients (median age: 63 years,55% female). Of those enrolled, 65% of medical and 74% of surgical oncology patients participated in home remote monitoring by self-reporting symptom data. This resulted in 2,869 completed symptom assessment from medical and 16,009 completed assessments from surgical patients. Sixty-three percent of medical oncology assessments resulted in a yellow (moderate) or red (severe) symptom alert compared with 26% for surgical oncology patients. Pain was the predominant symptom generating red alerts for medical oncology patients (17%). Fifty-two percent of patients completed the engagement survey, and the net promoter score was 0.82. **Conclusions:** A remote monitoring program after discharge was feasible, acceptable, and perceived to be of value by oncology patients discharged from a cancer center. Surgical and medical patients have similar response rates but differ in symptom burden. Future work will evaluate the value of a remote symptom monitoring platform in decreasing readmissions. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

1518 **Poster Discussion Session**

A pragmatic cluster-randomized trial of a standing physician order entry intervention for colony stimulating factor use among patients at intermediate risk for febrile neutropenia (SWOG S1415CD). *First Author: Dawn L. Hershman, Columbia University College of Physicians and Surgeons, New York, NY*

Background: Primary prophylactic colony stimulating factors (PP-CSF) are prescribed to patients undergoing chemotherapy to reduce the risk of febrile neutropenia (FN) but their benefit for regimens with intermediate FN risk is uncertain. Within a pragmatic, randomized trial of a standing order entry (SOE) intervention for prescribing PP-CSF, we designed a substudy to evaluate the effectiveness of PP-CSF for patients receiving therapy with intermediate FN risk. **Methods:** TrACER was a cluster randomized trial where NCI community Oncology Research Program practices were randomized to usual care (UC) or a guideline-based SOE intervention. In the primary study, sites were randomized 3:1 to a SOE of automated PP-CSF orders for NCCN-designated high FN risk chemotherapy regimens and alerts against PP-CSF orders for low FN risk regimens (intervention) versus usual care. A secondary randomization assigned intervention sites to a SOE intervention either to prescribe or not prescribe PP-CSF for patients receiving intermediate FN risk regimens. Clinicians were allowed to override the SOE. Patients age ≥18 with either breast, colorectal or non-small cell lung cancer were enrolled and followed for 12 mo. PP-CSF was defined as initiation within 24-72 hours after systemic chemotherapy. Sample size calculations were based on an FN risk reduction from 15% to 7.5%, and provided 80% power at a planned enrollment of 90 patients per site. Mixed effect logistic regression models were used to test differences between sites randomized to prescribe or not prescribe PP-CSF. **Results:** Between January 2016 and April 2020, 24 sites (2,287 patients) were randomized to the intervention. Among intervention sites, 12 were randomized to either SOE to prescribe or an alert to not prescribe PP-CSF for the 542 patients receiving intermediate FN risk regimens. Rates of PP-CSF use were higher among sites randomized to prescribe PP-CSF (37.1% vs 9.9%, OR = 5.90 (95% CI 1.72-20.20; p = 0.0048)). Overall, the rates of FN were low and identical between PP-CSF and no PP-CSF arms (3.7% vs 3.7%). Among patients who did not receive PP-CSF, rates of FN were also low and similar between arms (3.8% vs 4.1%). **Conclusions**: While implementation of a SOE intervention for PP-CSF significantly increased PP-CSF use among patients receiving intermediate risk regimens, FN rates did not differ between arms. Despite SOE, 63% of patients assigned to receive PP-CSF did not receive it. FN rates overall were lower than expected and did not differ between patients that did or did not receive PP-CSF. Although this guideline-informed SOE influenced prescribing, the results suggest that neither the SOE nor PP-CSF itself provide sufficient benefit to justify their use for persons receiving intermediate FN risk regimens. Clinical trial information: NCT02728596. Research Sponsor: U.S. National Institutes of Health, Other Government Agency.

1519 **Poster Discussion Session**

Cluster-randomized trial to evaluate the implementation of reproductive health care in cancer care delivery in community oncology practices: Results from ECOG-ACRIN E1Q11. *First Author: Ashlesha Patel, Cook County Health, Chicago, IL*

Background: Reproductive health (RH) needs of women newly diagnosed with cancer have been poorly addressed. RH management must be aligned with cancer treatment to optimize cancer survivorship. The primary objective of the EROS trial is to evaluate the effectiveness of implementing RH programming to improve RH care among reproductive aged women with cancer. **Methods:** E1Q11 used a cluster randomized design with 17 NCI Community Oncology Research Program (NCORP) Sites randomized to intervention (n = 8) or usual care (n = 9). Intervention sites received study-specific training delivered via webinar and tools to support RH care implementation. Pre-menopausal women aged 15-55 years newly diagnosed with cancer and pre-initiation of treatment were eligible. The primary endpoint was defined as the delivery of RH goal-concordant management within the first 3 months since enrollment. Data were obtained through patient completed questionnaires and medical record abstraction forms at baseline and 3 months. The management rate was analyzed using generalized estimating equations (GEEs) method. **Results:** From 7/2016 - 4/2021, 434 women enrolled (156 intervention, 278 usual care) and 392 were analyzable. The median age was 41 years. Patients self-identified as White 67.5%; Black 21.1%; Hispanic 15.9%. Most patients had breast cancer (83.5%) and local/regional disease (69.5%). A higher proportion of patients at intervention sites (77.1%, 108/140, 90% CI: 0.71-0.83) received goal-concordant RH care compared to patients enrolled from usual care sites (61.5%; 155/252, 90% CI: 0.56, 0.67). A total of 263/392 (67.1%) patients received goal-concordant RH care within the first 3 months of enrollment. The GEE analysis demonstrated patients enrolled from intervention sites were approximately twice more likely to receive goal- concordant RH care than patients at usual care sites (odds ratio, OR = 2.11, 95% CI: 1.30, 3.44, p = 0.003). Younger age (< / = 35 years vs. > 35 years) and better ECOG performance status (PS 0 vs. PS 1-3) were statistically associated with the adoption of RH goal-concordant management (OR = 2.85, 95% CI: 1.59, 5.12, p = 0.0004 and OR = 1.94, 95% CI: 1.04, 3.63, p = 0.04, respectively). The intervention effect on the primary endpoint remained after age and PS were adjusted in the model (adjusted OR = 2.23, 95% CI: 1.30, 3.84, p = 0.004). **Conclusions:** The EROS trial demonstrated significant improvement of goal-concordant reproductive health management amongst racially diverse women newly diagnosed with cancer treated in community oncology practices. Sites randomized to intervention more frequently delivered reproductive care compared to usual care sites. Findings support wider implementation of this intervention to improve reproductive health care delivery, improving cancer care quality for pre-menopausal women diagnosed with cancer. Clinical trial information: NCT01806129. Research Sponsor: This study was conducted by the ECOG-ACRIN Cancer Research Group (Peter J. O'Dwyer, MD and Mitchell D. Schnall, MD, PhD, Group Co-Chairs) and supported by the National Cancer Institute of the National Institutes of Health.

1520 **Poster Discussion Session**

Improving supportive care for patients with thoracic cancer. *First Author: Lakedia Banks, VA, Palo Alto, CA*

Background: Improving lung cancer care among Veterans is a priority within the Veterans Affairs due to higher rates of lung cancer incidence, morbidity, and mortality among Veterans compared to non-veterans. Unaddressed symptom burden is common due to many factors including complex comorbidities, psychosocial challenges, smoking history and limited social support networks. Additionally, complications from social determinants of health can obstruct successful discussions of symptom-burden between Veterans and their clinical care teams which can limit compliance with recommended symptom management strategies. To overcome these barriers, we conducted a randomized controlled trial to test the effectiveness of a lay volunteer-led proactive symptom assessment and symptom intervention. The objective was to determine if the intervention improved clinician documentation from baseline to 6-months post-enrollment compared to usual care. Secondary outcomes included change in patient activation, health-related quality of life (HrQOL), and symptom-burden. **Methods:** Patients were randomized into the lay volunteer proactive symptom assessment intervention plus usual cancer care (intervention group) or usual cancer care alone (control group). We conducted electronic health record review to assess primary cancer-clinician symptom documentation of Veterans' symptoms identified as moderate-to-severe at baseline and 6-months using the Edmonton Symptom Assessment Scale. Patient surveys with validated assessments were used to assess patient activation, HrQOL and symptom burden at baseline (time of enrollment) and 6-months post-enrollment. We used regression models to evaluate differences in our primary and secondary outcomes. **Results:** 60 Veterans were consented and randomized into the study (29 control; 31 intervention). There were no differences in demographic or clinical factors across groups. The median age was 70 years (range 56-85), 95% were male, 70% identified their race as White, 53% were married and 48% had a 2-year or 4-year college degree. The majority had at least 3 comorbidities (54%), diagnosed with stage 3 or 4 (62%) and received systemic treatment with chemotherapy and/or radiation (77%). At 6-months post-enrollment as compared to baseline, the intervention group had greater improvements in symptom documentation (56% from 12.5% vs. 29% from 43%, p = 0.01), greater improvements in patient activation (p<0.001), HrQOL (<0.001), and lower symptom burden (p<0.001) than the control group. **Conclusions:** Integration of proactive symptom assessment by lay volunteers has a significant and meaningful effect on symptom documentation, patient activation, quality of life, and reducing symptom burden among Veterans with lung cancer. Clinical trial information: NCT03216109. Research Sponsor: Carevive, Inc, U.S. National Institutes of Health.

1521 **Poster Session**

The initial outcome of deploying a mortality prediction tool at community oncology practices. *First Author: Ping Ye, The U.S. Oncology Network, McKesson, The Woodlands, TX*

Background: Hospice improves the quality of life and care for cancer patients and reduces the likelihood of unwanted death in the hospital . Advance Care Planning (ACP) allows physicians to proactively initiate hospice and end-of-life discussions with identified patients, promoting timely hospice care enrollment. We developed a machine learning (ML) model to predict 90-day mortality risk for patients with metastatic cancer. The tool was designed to enable earlier ACP discussions leading to increased hospice enrollment. This study assesses the ML tool usage on ACP documentation in a community oncology setting. **Methods:** Twelve practices across the nation were included in the study, all participating in the Oncology Care Model. Five practices implemented the ML tool during 10/26/2020-9/30/2021, with patients scored every two weeks to provide insights on mortality risk. Patients identified as high-risk were evaluated for ACP utilization, obtained from timely EMR data and historical claims. Seven practices did not implement the ML tool and served as the control for the study. **Results:** A total of 1,663 patients were predicted to have a high risk of mortality at the 12 practices during the timeframe. The median age was 74 years. 53% of patients were males, and 47% were females. ACP documentation varied among the practices. The range was 19.4%-55.8% among ML tool participating practices and 7.4%-31.0% among non-participating practices. The weighted mean of ACP utilization was 34.4% for participating practices and 14.0% for non-participating practices. Compared with non-participating practices, the ACP rate increased significantly by 2.5-fold for participating practices (p-value = 0.03, two-sided T-test). **Conclusions:** This initial outcome study showed improved ACP documentation after deploying a mortality prediction tool in a community oncology setting. We are currently working on propensity score matching and regression analysis to reduce the effect of confounding factors such as practices, patient demographics, diagnosis, and treatment. Future studies will evaluate the impact of mortality tool use on other outcomes, including hospice enrollment, emergency department visits, and hospital admission. Implementing the mortality prediction tool is an ongoing effort with more practices planned to adopt. Research Sponsor: None.

1522 **Poster Session**

Imaging and physician visits at cancer diagnosis: COVID-19 pandemic impact on cancer care. *First Author: Rui Fu, University of Toronto, Toronto, ON, Canada*

Background: Understanding how cancer system responded to the first wave of the COVID-19 pandemic has crucial implications to de-escalation measures in future waves. Here we examined the pandemic impact on the provision of diagnostic imaging (MRI, CT, and ultrasound) and physician visits (virtual and in-person) at cancer diagnosis in Ontario, Canada. **Methods:** For each week of June 26, 2016–September 26, 2020, we identified cancer diagnoses whose time around diagnosis (91 days +/- the date of diagnosis) fell into this week and restricted those diagnoses to be one per person-day and to patients aged 18+ at the beginning of that week. For these cancer patients, we used physician claims database to identify diagnostic imaging and visits received around cancer diagnosis. In separate segmented negative binomial regression procedures, we assessed the trends in weekly volume of these services per thousand cancer patients in pre-pandemic (June 26, 2016 to March 14, 2020), the change in mean volume at the start of the pandemic, and the additional change in weekly volume in the pandemic (March 15, 2020 to September 26, 2020). **Results:** Among 403,561 cancer patients in the cohort, 41,476 (10.3%) were diagnosed in the pandemic. As COVID-19 arrived, mean diagnostic imaging volume decreased by 12.3% (95% CI: 6.4%-17.9%) where ultrasound decreased the most by 31.8% (95% CI: 23.9%-37.0%) and MRI did not change (p-value = 0.27). Afterwards, the volume of all scans increased further by 1.6% per week (95% CI: 1.3%-2.0%), where ultrasound increased the fastest by 2.4% for each week (95% CI: 1.8%-2.9%). Mean in-person visits dropped by 47.4% when COVID-19 started (95% CI: 41.6%-52.6%) while virtual visits rose by 5515% (95% CI: 4927%-6173%). In the pandemic era, in-person visits increased each week by 2.6% (95% CI: 2.0%-3.2%), but no change was observed for virtual visits (p-value = 0.10). **Conclusions:** Provision of diagnostic imaging and virtual visits at cancer diagnosis has been increasing since the start of COVID-19 and already exceeded pre-pandemic utilization levels. These findings imply the feasibility of combining virtual consultations with diagnostic imaging to manage new cancer patients and highlight the need to monitor the quality of these services. Research Sponsor: Sunnybrook Research Institute and Sunnybrook Foundation COVID-19 Response Grant.

1523 **Poster Session**

The promising use of hospital at home in an oncology setting. *First Author: Melanie Wain Kier, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: Hospitalization at Home (HaH) is an emerging clinical model that delivers the essential elements of acute hospital-level care in the home and has demonstrated efficacy largely for inpatient medical conditions. Few programs have implemented HaH for patients with active cancer diagnoses. There is little data evaluating the impact of HaH on cancer outcomes, patient experience or cost effectiveness. In 2019, the Mount Sinai Health System (MSHS) expanded its HaH program to include oncology patients. Here, we describe our institution's experience of HaH in oncology. **Methods:** We performed a retrospective chart review for solid tumor, myeloma and lymphoma patients at MSHS from August 2019 to November 2021 enrolled in HaH. Patient eligibility for HaH required meeting established institutional HaH admission criteria. Demographics, cancer diagnosis, social situation, indication for antecedent ED or inpatient stay, and HaH admission were extracted from the electronic medical record. Our primary endpoint was rate of successful HaH admission, with success defined as discharge from HaH for complete recovery from the acute condition or transition to hospice. We also evaluated patient social support and home resources. **Results:** We enrolled 19 patients with multiple myeloma (n = 7), lymphoma (n = 1), and solid tumor (n = 11). Sixty-three percent (n = 12) were male, 74% (n = 14) were age 65 or older, and 42% (n = 8) were white. Patients were enrolled in HaH either from an inpatient service (n = 15) or from the emergency room (n = 4). While on the inpatient service, 6 of the 15 patients had received chemotherapy. Post-chemotherapy monitoring was the primary reason for HaH admission. Successful HaH admissions occurred for 79% (n = 15) of patients. The mean duration of HaH admission was 4.5 days (range 1-10 days). Three patients opted to re-enroll in HaH planned care at a later point. There were no significant issues with provider home visits, access, medication delivery, lab draws, or social support. **Conclusions:** The MSHS Oncology HaH program successfully cared for 79% of our cohort demonstrating the functionality of expanding the program to patients with cancer. We continue to increase enrollment for oncology patients. Further studies to assess patient outcomes, cost savings, and re-hospitalization rates when compared to the standard in hospital only care for oncology patients will help determine the benefits and preferred population to utilize oncology HaH. Research Sponsor: None.

1524 **Poster Session**

Reducing inpatient mortality in patients with cancer through multidisciplinary review and targeted interventions. *First Author: Manan P Shah, Stanford Health Care, Stanford, CA*

Background: Excess inpatient mortality is a marker of poor quality in cancer care. We developed a multidisciplinary mortality review committee to review each inpatient death to determine key drivers of mortality and develop targeted interventions to reduce our inpatient mortality index. **Methods**: Through retrospective review, inpatient deaths were identified at Stanford Health Care for patients with an ICD10 cancer diagnosis regardless of inpatient service. Details of each hospitalization were reviewed by a quality consultant and subsequently reviewed by a physician quality team member to identify opportunities for improvement. Most cases were then discussed in a monthly multidisciplinary committee meeting. The committee analyzed key drivers of inpatient mortality, communicated suggestions to the patient's outpatient and inpatient attending physicians, and/or identified opportunities for systemic change. The resulting targeted interventions were tracked using the observed versus expected mortality ratio for inpatient deaths over time. **Results**: From May 2017 through August 2021 we reviewed 528 inpatient oncology deaths. Patients' median age was 65 years, and the median length of stay was 8 days. 73% of patients had metastatic cancer, and 28% received chemotherapy within 14 days of death. 25% of patients had a prior ED visit, and 35% had a prior hospitalization within 30 days of admission. Only 26% of patients had an advanced directive on record at time of death. Opportunities for improvement were identified for 60% of cases (Table). Interventions have aimed to increase advance care planning conversations and documentation, develop predictive models for cancer-related readmissions and mortality, expand outpatient services for urgent symptoms, and expedite transitions to hospice. **Conclusions**: Understanding key drivers for preventable inpatient mortality through a multidisciplinary review process identified targeted interventions that have successfully contributed to reduction of the inpatient cancer mortality index. Research Sponsor: None.

Opportunities for improvement identified by physicians through secondary review of inpatient deaths (n = 528).

Opportunities for improvement identified in mortality review	% of cases
Lack of outpatient advance care planning conversations and documentation	24
Delay in transition to hospice	13
Delayed or inadequate incorporation of palliative care service	9
Medical futility or aggressive treatment with unlikely clinical benefit	9
Goals of care discordance between providers and patient/family	5

1525 **Poster Session**

A pragmatic cluster-randomized trial of a computerized clinical decision support system to improve colony stimulating factor prescribing for patients with cancer receiving myelosuppressive chemotherapy (SWOG S1415CD). *First Author: Scott David Ramsey, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: Primary prophylactic colony stimulating factors (PP-CSF) are prescribed to patients undergoing chemotherapy to reduce the risk of febrile neutropenia (FN). Prior studies have shown that 55-95% of CSF prescribing is inconsistent with practice guidelines. We conducted a cluster randomized trial to determine if guideline-informed standing orders for PP-CSF improved prescribing and reduced the incidence of FN. **Methods:** Patients age ≥18 with breast, colorectal or non-small cell lung cancer initiating first cancer-directed therapy with NCCN-recommended regimens were eligible. The intervention consisted of automated PP-CSF orders for high FN risk chemotherapy regimens and an alert not to use PP-CSF for low FN risk regimens. Regimen FN risk was based on NCCN guidelines. Clinicians could override the orders. Primary and secondary outcomes were PP-CSF use among patients receiving high and low risk regimens FN incidence within 6 months of initial therapy. Sample size estimates assumed an FN risk of 25% for high-risk chemotherapy. 32 NCI Community Oncology Research Program (NCORP) practices randomized 3:1 to the order entry system (intervention) versus usual care (UC) provided 90% power to detect a 50% reduction in FN at a planned enrollment of 90 patients per site. Mixed effect logistic regression models were used to test differences among randomized sites. 13 practices with pre-existing PP-CSF order sets enrolled in a parallel cohort study. Patients and other stakeholder groups informed study design, conduct and reporting. **Results:** Between January 2016 and April 2020, 2,946 patients were randomized (2287 intervention, 659 UC); 718 were enrolled in the cohort. Mean age across arms was 58.1. 77% of patients were female; 61% diagnosed with breast cancer. Among patients receiving high-risk regimens, PP-CSF use did not differ between arms (89.2% intervention; 95.8% UC, adjusted p = 0.21) and was similar to the cohort patients (93.0%). The FN rate for high-risk patients was 5.7% in intervention clinics and 4.2% in UC clinics (adjusted p = 0.26); FN was 14.9% among high-risk patients who did not receive PP-CSF. Among patients receiving low-risk regimens, PP-CSF use did not differ between arms (intervention 6.3%, UC 5.5%, adjusted p = 0.74) and was slightly lower than the cohort (8.3%). FN rates did not differ between low risk groups (intervention 1.5%, UC 0.8%, adjusted p = 0.51). **Conclusions:** Guideline-informed standing orders did not increase PP-CSF use in high-risk patients, nor did it decrease use in low-risk patients. Adherence to guidelines in both risk groups exceeded historical reports. FN rates among patients not receiving PP-CSF were substantially below those reported in CSF guidelines. Automated standing orders for PP-CSF do not appear to be helpful or necessary. Clinical trial information: NCT02728596. Research Sponsor: PCORI, U.S. National Institutes of Health.

1526 **Poster Session**

Breast cancer screening and diagnosis in a community health system during the COVID-19 pandemic. *First Author: Andrew Rudberg, University of Minnesota Medical School - Duluth Campus, Duluth, MN*

Background: Following the onset of the COVID-19 pandemic in March 2020, there was a drastic reduction in elective procedures, including screening mammograms. This was accompanied by a precipitous drop in the number of breast cancer diagnoses in 2020 compared with other years. The first aim of this study was to determine the extent of reduced mammogram screening during the first year of the COVID-19 pandemic. Secondary aims of this study were to determine the effect of reduced screening on breast cancer staging at initial diagnosis and to determine if there was a significant difference in screening patterns between rural and urban settings. **Methods:** This was a retrospective study. Mammogram data and cancer diagnosis data was collected from the time periods of March 2019 - Feb 2020 (Year 1) and March 2020 - Feb 2021 (Year 2). The patient data was selected from the Duluth/Essentia Cancer registry and through the Essentia Breast Imaging registry. Patient records were reviewed for cancer diagnosis and stage. Data on the number of mammograms performed was collected from Essentia sites across northern Minnesota that offer mammography services, including Duluth First Street, West Duluth, Virginia, and International Falls. **Results:** The demographics of patients diagnosed with breast cancer were similar between the two years. The total number of screening mammograms between March – May 2019 was 3,124. The total from March – May 2020 was 1,016, which is a reduction in the number of screenings of 2,108. Comparing June 2019 – Feb 2020, the total was 10,102, as compared to 10,459 in June 2020- Feb 2021, a total of 357 higher. This translates to a reduction of 1,751 screenings in Year 2 compared with Year 1. Between Year 1 and Year 2, we saw an increase in the proportion of stage III/IV breast cancers diagnosed, from 9.6% in Year 1 to 16.9% in Year 2, accompanied by a decrease in stage I/II cancers from 90.4% to 83.1% (p = 0.06). The total diagnoses between Year 1 and Year 2 also decreased from 211 to 185. We saw a significant decrease in the proportion and number of residents that were diagnosed via screening mammograms from urban settings during COVID, while rural patients had a significant increase in proportion and number. **Conclusions:** There was a remarkable reduction in the total number of screening mammograms and breast cancers diagnosed during the first year of the COVID-19 pandemic compared with the year prior. Patients were lost to screening, and potential diagnoses were not made. Those that did come in were more likely to present with an advanced stage cancer. Patients from rural settings were more likely than those from urban settings to be diagnosed via screening mammogram during COVID, but more investigation should be done to determine screening patterns among these populations.Providers should emphasize the importance of screening mammograms with patients and should be attentive to higher-staged cancers due to missed screenings. Research Sponsor: University of Minnesota Medical School.

1528 **Poster Session**

Time on treatment is prolonged in patients utilizing an ePRO based digital symptom monitoring platform in the community setting. *First Author: Christina Parrinello, Expain, New York, NY*

Background: Earlier and more effective management of cancer-related symptoms and treatment-related toxicities might improve the survival of patients receiving systemic anti-cancer therapy. One potential mechanism for improved outcomes could be prolonging time on therapy. We have previously reported on the successful real-world implementation of an electronic patient-reported outcomes (ePRO) tool in a community oncology practice. We now report on the impact of the tool on time on therapy for common anti-cancer treatments. **Methods:** We evaluated time on treatment across three community oncology practices that have implemented Expain, an EMR-integrated ePRO system which enables remote symptom monitoring during therapy. We compared drug-specific cohorts of patients that had been enrolled on the ePRO tool with a concurrent cohort of patients not enrolled on the ePRO platform. We examined time on treatment using a Kaplan Meier (KM) approach. Analysis was confined to patients with no prior administration of the parenteral therapeutic agent or a 90-day treatment-free washout period; and to patients with at least three months of potential follow-up. Analysis was only conducted for drugs with at least 80 patients in the Expain arm. **Results:** In each drug-specific cohort, the distribution of age, sex, and primary cancer diagnosis was similar in patients enrolled vs not enrolled on the ePRO (Mann-Whitney and Chi-square p > 0.05 except for the rituximab cohort which had more males in the ePRO cohort [67 vs 52%]). The impact of the ePRO-based symptom monitoring system on time on therapy was statistically significant for 5 agents. **Conclusions:** We confirm in the community setting the observation that digital symptom monitoring can increase time on therapy. We believe this is due to more effective management of treatment related toxicities, as well as more effective management of malignancy related or comorbid medical emergencies which might interrupt or lead to the discontinuation of therapy. We are evaluating the robustness of these results after using various methods to address any potential non-comparability of the cohorts. We are also examining the impact of prolonging time on treatment on survival. Research Sponsor: None.

Drug	ePRO (n)	Non-ePRO (n)	log-rank p value	% on therapy at 3 months (ePRO vs Non-ePRO)
bevacizumab	80	257	0.06	70.1 vs 57.4
carboplatin	254	616	0.02	49.1 vs 37.8
oxaliplatin	121	305	0.02	66.7 vs 52.1
pembrolizumab	117	357	< 0.01	79.5 vs 65.2
rituximab	112	472	< 0.01	65.9 vs 45.6

1529 **Poster Session**

FDA analysis of expanded access use in pediatric patients from 2015 to 2020. *First Author: Elizabeth Duke, US Food and Drug Administration, Silver Spring, MD*

Background: Expanded Access is a regulatory mechanism that enables patients with a life-threatening condition or serious disease to receive treatment with an investigational drug outside of a clinical trial when no comparable or satisfactory alternative options are available. FDA has decades of experience with expanded access, but little has been reported about its use in pediatric cancer patients. **Methods**: FDA's central electronic database was queried for single-patient investigational new drug (spIND) applications submitted to the Office of Oncologic Diseases between January 2015 through December 2020. Data collection included IND receipt date, IND type/status, drug name, and patient demographics. Duplicate or exempt INDs, those cancelled by the physician-sponsor before initiating therapy, and those requested for indications that occur almost exclusively in adults (e.g. lung cancer) or were missing patient age were excluded. **Results**: Of 2,901 unique spINDs granted, 534 (18%) were for patients less than 18 years of age. The pediatric population was 57% male, median age 6.0 years (range 0.1 to 17); race/ethnicity were reported in <1%. Patients were treated in 132 zip codes across 39 states; one-quarter of submissions were from 5 large academic hospitals. Central nervous system tumors were the most common indication (Table 1). A total of 98 unique drugs were requested, with 1 to 73 spINDs for each drug; approximately 50% were for tyrosine kinase inhibitors, 25% for other small molecules, and the remainder for immunotherapies and other drug types. Median time for FDA to grant was 1 day. Follow-up information was provided for 75% (annual report or withdrawal letter); 1/3 were withdrawn within 1 year. Over the last 2 years, utilization of the program increased by 120%. **Conclusions**: While approximately 1% of all cancers per year are diagnosed in children under 17 years of age, 18% of spINDs over the last five years were for pediatric patients. Although utilization of this program for children is robust, efforts are needed to assess its impact on patient outcomes and ensure its availability to patients, families, and institutions more widely. These data highlight interest within the pediatric oncology community in accessing innovative therapies, which supports early investigation of promising new drugs in children. Research Sponsor: None.

Tumor types for pediatric spINDs (n = 534).

Class	N (%)	Tumor Type (N)
Nervous System	229 (43)	High-Grade Glioma/Diffuse Intrinsic Pontine Glioma (59); Low-Grade Glioma (67); Embryonal/Other brain tumor (68); Plexiform neurofibroma (35)
Hematologic	102 (19)	Acute Lymphoblastic Leukemia (25); Acute Myeloid Leukemia (36); Lymphoma (9); Other (32)
Sarcoma	90 (17)	Osteosarcoma (58); Ewing (6); Rhabdomyosarcoma (7); Other (19)
Neuroendocrine	30 (6)	Neuroblastoma (28); Paraganglioma (1); Neuroendocrine carcinoma (1)
Liver	7 (1)	Hepatoblastoma (5), Hepatocellular carcinoma (1), Wilm's tumor (1)
Other	76 (14)	Multiple

1530 **Poster Session**

Evaluation of outcomes in patients (pts) with stage 4 non-small cell lung cancer (NSCLC 4) harboring actionable oncogenic drivers (AOD) when treated prior to report of mutation without tyrosine kinase inhibitors (TKI): An Integra Connect Database (ICD) retrospective observational study. *First Author: Robert E. Smith, Integra Connect, West Palm Beach, FL*

Background: In a prior analysis, we identified 525 pts with newly diagnosed NSCLC 4 harboring AOD in the ICD. Of these, 141 were treated prior to the reporting of AOD with chemotherapy (C), immune checkpoint inhibitor (ICI), or both. This report details the clinical outcomes of these 141 compared to the 384 treated after AOD reported. **Methods:** Real world data (RWD) were obtained from a curated ICD for pts with NSCLC 4 diagnosed 1/1/2018-12/31/2020 with cutoff of data 3/31/2021. Pts with EGFR, ALK, ROS1, BRAF, MET, RET, HER2, and NTRK were included if their treatment record were captured. Also included were demographics, ECOG score, date of first report of AOD and dates of initiations of first and any second line of therapy and date of apparent death (AD). Outcome measures were time to next treatment or apparent death (TTNT) and apparent survival (AS) (ICD model does not allow date of death per HIPAA de-identified Expert Determination). Descriptive statistics were used with Kaplan-Meier (K-M) estimates and Hazard Ratios (HR) by Cox regression. 3 cohorts were defined: Group (Gr) A with 384 pts treated after AOD reported and used as the comparator; the 141 pts treated before AOD with C, ICI or both were divided into Gr B (n = 51) who subsequently switched to TKI within 35 days and Gr C (n = 90) who did not switch. **Results:** As shown in data table, AS was significantly worse in Gr B and Gr C, TTNT was significantly worse in Gr C and with worsening trend in Gr B. Two potential confounders were identified: higher ECOG scores might indicate more urgency to assign treatment, but pts with ECOG ≥ 2 were similar in all 3 groups; also, difference in proportion of EGFRm by Group (Gr A 62%, Gr B 57%, and Gr C 29%), but separating cohorts by EGFR mutation status did not alter results. **Conclusions:** While subject to the limitations of a retrospective observational RWD study, this study strongly suggests outcomes are significantly compromised in pts harboring AOD but who are treated initially with C, ICI or both, even in pts quickly switched to TKI. Since a prospective clinical trial is not ethically feasible, these findings may stimulate review of current guidelines, fuel optimization of universal testing in NSCLC 4, and encourage utilization of liquid or ultra-fast NGS with their rapid turnaround times in order to improve survival in this setting. Research Sponsor: Thermo Fisher.

Cohort	n	ECOG ≥ 2	Median TTNT (range) in days	TTNT HR (p-value)	Median AS (range) in days	AS HR (p-value)	HR (p-value) adjusted for EGFR %
Group A	384	31%	706 (631-762)	-	Not reached	-	-
Group B	51	50%	656 (433-658)	1.35 (0.08)	672 (433-1010)	1.72 (0.008)	TTNT 1.32 (0.10); AS 1.69 (0.012)
Group C	90	29%	435 (350-560)	1.52 (0.002)	437 (358-580)	2.36 (< 0.0001)	TTNT 1.43 (0.009); AS 2.23 (< 0.0001)

1531 **Poster Session**

Oncologists' perspectives on individualizing dose selection for patients with metastatic cancer. *First Author: Rachel Jimenez, Massachusetts General Hospital, Boston, MA*

Background: The goal of treatment for patients with metastatic cancer (MC) is to prolong and maintain quality of life. Patients and oncologists have questioned the current paradigm of initial dose selection for systemic therapy and want additional information about the potential trade-offs between efficacy and toxicity. However, empirical data on oncologists' dose selection strategies and beliefs is lacking. **Methods:** ASCO conducted an international survey of medical oncologists who treat patients with metastatic breast or gastrointestinal cancers. Survey questions addressed experience with and attitudes towards reducing the standard dose of the first cycle of systemic therapy to minimize potential toxicity. The survey was open November 14 to December 13, 2021. **Results:** Among 3,099 eligible ASCO members, 367 completed the survey (response rate 12%), including 117 general oncologists (GO), 142 breast specialists (BRS), and 108 GI specialists (GIS). 77% of respondents practice in the US, 94% had experience leading a clinical trial, and 50% had been caregivers or patients themselves. Most respondents (52%) reported reducing the first dose of systemic agents at least 10% of the time in patients with MC to minimize toxicities. GIS were more likely to report reducing the first dose at least 10% of the time (72% vs. 50% of GO and 51% of BRS, $p < .005$). Of those who dose reduce, 89% reported discussing potential tradeoffs between efficacy and toxicity with patients. Among 10 common breast cancer drugs, capecitabine (76%) was the most likely to be dose reduced at initiation while tamoxifen (4%) was the least likely. Among 10 common GI cancer drugs, regorafenib (78%), capecitabine (71%) and sorafenib (66%) were most commonly dose reduced at initiation, while bevacizumab (7%) and panitumumab (8%) were the least likely. Overall, 65% of respondents agreed it is acceptable to lower starting doses to reduce side effects even at the potential expense of efficacy, with younger clinicians more likely to agree vs. older clinicians (72% age < 50 vs. 55% age > 50, $p < .005$). While the majority (53%) believe that oncologists should start with the recommended dose and lower it in response to side effects, GIS were more likely to disagree with this approach compared to BRS or GO (57% vs. 37% and 36% respectively, $p < .005$). In contrast, 45% of respondents believe that oncologists should start at a lower dose and consider increasing the dose for future cycles if the drug is well tolerated. There was strong support (89%) for future trials that seek to determine the minimal effective dose as opposed to the maximum tolerated dose. **Conclusions:** Oncologists frequently dose reduce to avoid toxicity in patients with MC but practices and attitudes regarding dose reduction vary considerably. Further research is needed to establish optimal dosing during drug development and to support oncologists and patients in selecting the starting dose in clinical practice. Research Sponsor: American Society of Clinical Oncology.

1532 **Poster Session**

Will COVID-19 directives to reduce regularly scheduled physical examinations affect recurrence detection in patients with early breast cancer? *First Author: Ana-Alicia Beltran-Bless, Division of Medical Oncology, Department of Medicine, University of Ottawa, Ottawa, ON, Canada*

Background: The COVID-19 pandemic has significantly reduced routinely scheduled in person assessment and examination of early breast cancer patients (EBC). To assess if this is likely to impact the detection of recurrent disease, we reviewed recurrence patterns of EBC patients enrolled in a survivorship program that adheres to ASCO guidelines. **Methods:** Charts of EBC patients transferred through a single center Wellness Beyond Cancer Program (WBCP) and who subsequently had a breast cancer recurrence between February 1, 2013 and January 1, 2019 were reviewed. Patient, tumor and treatment characteristics were evaluated. **Results:** Of 206 patients eligible for the current study, 41 patients had ipsilateral breast recurrences (19.9%), 135 had distant recurrences (65.5%) and 30 had contralateral new breast cancers (14.6%). Ipsilateral breast recurrences were detected by the patient in 53.7% (22/41) and by routine imaging in 41.5% (17/21). The majority of distant recurrences (125/135, 92.6%) were detected via patient-reported symptoms. Contralateral breast primaries were detected by patients 16.7% (5/30) or by routine imaging (83.3%, 25/30). Only 2/206 (1.14%) recurrences/new primaries were detected by healthcare providers at routinely scheduled follow-up visits. There was a statistical difference in recurrence detection between image detected vs. self-detected in the following factors: grade 3 (26.5% vs 51%, $p < 0.007$), triple negative breast cancer (3.9% vs. 15.1%, $p = 0.03$), HER2 disease (18.4% vs. 9.8%, $p = 0.04$). **Conclusions:** Despite following ASCO follow-up guidelines for routinely scheduled follow-up appointments with physical examination, healthcare providers rarely detect recurrence disease. While reduced in person visits may affect other aspects of follow-up (e.g., toxicity management), it appears unlikely, provided patients attend regular screening tests, that reduced in-person follow-up is associated with worse breast cancer-related outcomes during the COVID-19 pandemic. Research Sponsor: None.

		Local	Distant	Contralateral
N		41	135	30
How was recurrence detected	N (%) Patient	22 (53.7)	125 (92.6)	5 (16.7)
	Imaging	17 (41.5)	9 (6.7)	25 (83.3)
	Health Care Provider	1 (2.4)	1 (0.7)	0
Most common sites of metastases	N (%) Bone	0	78 (57.8)	0
	Lung	0	9 (18.5)	0
	Liver	0	27 (20.0)	0
Most common symptoms	N (%) Bone Pain	0	44 (32.6)	1 (3.3)
	Respiratory Symptoms	0	27 (20)	0
	Abdominal Symptoms	0	22 (16.3)	0

1533 **Poster Session**

Ancillary treatment referrals and visits after breast cancer surgery in a sociodemographically diverse population. *First Author: Vernice Hui Yan Chan, The University of Hong Kong, Pokfulam, Hong Kong, Hong Kong*

Background: Ancillary therapies by rehabilitative, palliative, and survivorship specialists mitigate breast cancer surgery's physical and emotional effects. Existing data suggest that patients from disadvantaged backgrounds may be less likely to receive such care. We investigated provider referrals and patient visits at a high-volume urban cancer center to identify associated sociodemographic factors and characterize which populations may not be maximally benefiting from ancillary services. **Methods:** Data was culled from electronic health records of surgically-treated breast cancer patients at Yale-New Haven Health System between 2010-2017. Postoperative provider referrals to Physical/Occupational Therapy, Palliative Medicine, and Survivorship Program were evaluated for associations with demographic and disease variables in univariable and multivariable logistic regression analyses. Patient utilization of referrals, defined as attending at least one consultation, were analysed similarly. **Results:** Among 5,496 patients identified, 2,288 (41.6%) were referred for ancillary treatments and 1,572 (28.6%) attended at least one consultation. Provider referrals were highest among patients of Hispanic and Black ancestry (57.5% and 54.9%, respectively), no health insurance (57.6%), lowest percentage high school degree for zip code (50.5%), and lowest median income for zip code (50.7%). These associations remained significant in multivariable analysis [all p<0.050]. In contrast, referral utilization was greatest among patients with private insurance (70.7%), highest percentage high school degree (72.8%), and highest median household income (72.2%), in addition to Hispanic ethnicity (73.5%). In multivariable analysis, highest median household income (OR 1.45, p = 0.019) and Hispanic ethnicity (OR 1.50, p = 0.048) remained associated. **Conclusions:** In a large urban health system serving a diverse population, traditional markers of poor healthcare access were positively associated with provider referral for ancillary services after breast cancer surgery. However, referral did not translate to utilization, suggesting that access remains a critical barrier to therapies that target post-operative morbidity and elevate quality of life. Research Sponsor: None.

Multivariable analysis of demographic factors associated with referrals and visits to ancillary services after breast cancer surgery.

VARIABLE	REFERRAL OR	REFERRAL P-value	VISIT OR	VISIT P-value
RACE	-	***0.001**	-	**0.167**
White	Ref	Ref	Ref	Ref
Black	1.35	*0.011	1.30	0.131
Hispanic	1.53	*0.002	1.50	*0.048
INSURANCE	-	***0.020**	-	**0.933**
None	Ref	Ref	Ref	Ref
Government	0.83	0.649	1.04	0.948
Private	0.65	0.298	0.99	0.978
MEDIAN HOUSEHOLD INCOME (USD)	-	***<0.001**	-	**0.138**
<65,000	Ref	Ref	Ref	Ref
65,000-79,999	0.74	*0.001	1.20	0.205
80,000-99,999	0.65	*<0.001	1.24	0.169
≥100,000	0.80	*0.026	1.45	*0.019

*Indicates statistical significance.

1534 **Poster Session**

CONTINUUM: A pilot care transition intervention for hospitalized patients with advanced cancer. *First Author: Daniel E Lage, Harvard Medical School, Boston, MA*

Background: Patients with advanced cancer are frequently hospitalized and experience burdensome transitions of care after discharge. Interventions to address patients' symptoms, support medication management, and ensure continuity of care after discharge are lacking. We sought to demonstrate the feasibility and acceptability of CONTINUUM (CONTINUity of care Under Management by video visits) for this population. **Methods:** We conducted a single-arm pilot trial (n = 54) of CONTINUUM at Massachusetts General Hospital (MGH). The intervention consisted of a video visit with an oncology nurse practitioner (NP) within 3 business days of hospital discharge to address symptoms, medication management, hospitalization-related issues, and care coordination. Prior to discharge, we enrolled English-speaking adults with advanced breast, gastrointestinal, genitourinary, or thoracic cancers experiencing an unplanned hospitalization who were receiving ongoing oncology care at MGH and being discharged home without hospice services. We defined the intervention as feasible if ≥70% of approached and eligible patients enrolled and if ≥70% of enrolled patients completed the intervention within 3 business days of discharge. At 2 weeks after discharge, patients rated the ease of use of the video technology and stated whether they would recommend the intervention. NPs completed post-intervention surveys to assess fidelity to the intervention protocol. **Results:** From 01/07/21 to 05/28/21, we enrolled 54 patients (77.3% of patients approached). Of the enrolled patients (median age = 65.0 years; 59.3% and 22.2% had advanced gastrointestinal or thoracic cancers, respectively), 83.3% of enrolled patients received the intervention within 3 business days of discharge. Patient rating of the ease of use of video technology was a mean of 7.8 out of 10, with 71.4% stating they "agreed" or "strongly agreed" that they would recommend the intervention. NP post-intervention surveys revealed that visits focused on symptom management (85.7%), followed by addressing post-hospital care issues (69.0%). At 30 day follow up, 38.8% were readmitted within 30 days of discharge, and 12.2% died within 30 days of discharge. **Conclusions:** We found that CONTINUUM, which consists of an NP-delivered video visit soon after hospital discharge addressing patients' symptoms, medications, and care coordination, represents a feasible and acceptable approach to provide post-discharge care for hospitalized patients with advanced cancer. Future studies will test the efficacy of the intervention for reducing hospital readmissions. Clinical trial information: NCT04640714. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

1535 **Poster Session**

Oncology hospital at home in rural communities: The Huntsman at Home rural experience. *First Author: Kathi Mooney, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT*

Background: Oncology hospital at home programs have shown promise in decreasing unplanned health care utilization while improving quality of life. While most hospital at home programs serve local urban areas, we extended our oncology hospital at home program, Huntsman at Home, to provide equitable distribution of program services for cancer patients living in rural communities at a distance from our cancer center. **Methods:** Utilizing a community engagement approach we redesigned our urban Huntsman at Home program for 3 rural communities in Southeastern Utah, a 2 to 5 hour one-way drive from Huntsman Cancer Institute. We systematically collected patient data and program modifications required for rural community delivery during the program's first 6 months. Care was delivered by on-ground and telehealth nurse practitioner visits and on-ground registered nurse and physical therapy visits. Cardiovascular remote monitoring was utilized during acute care episodes. **Results:** A total of 47 cancer patients (31 men; 16 women; mean age 69 years) were admitted to the rural program during the first 6 months. Seven patients had 9 acute illness episodes of care. The average length of acute episode care was 6.1 days for treatment of infection, respiratory distress/ hypoxia, cardiac instability (hypotension, tachycardia), and dehydration/electrolyte imbalance and uncontrolled vomiting. Forty patients received subacute management aimed to prevent acute episodes and escalation to the emergency department (ED) or hospitalization. Subacute patients were in the program an average of 15.8 days. There were 4 appropriate escalations (2 hospitalizations, 1 ED visit returned to home and 1 ED visit with hospitalization) for symptoms related to disease progression requiring imaging and hospital-based procedures and one for diagnosis of a post-surgical PE. We found geographic and social determinates of health impacted rural patients' cancer burden, most notably transportation barriers (44.7%). Secondarily, we found food insecurity impacted nutritional status in 14.9% of patients. A significant number of patients experienced financial toxicity (29.8%) related to lost wages, co-pays and/or out of pocket expenses for care. Lack of health literacy impacted 48.9% of patients effectively navigating their health care and self-management at home. Robust communication and coordination between the hospital at home clinical team, local primary care providers, the rural hospital, community resources and the patients' cancer center oncology team were keys to improving care pathways. **Conclusions:** Rural oncology hospital at home is feasible and addresses geographic disparities in equitable access to acute and subacute cancer care in local communities. It requires adaptation to rural needs and culture, coordinated escalation procedures and a focus on addressing geographic and social determinates of health that impact cancer burden. Research Sponsor: Rita and Alex Hillman Foundation, Huntsman Cancer Foundation, Cambia Health Foundation.

1536 **Poster Session**

The impact of an oncology-specific shared savings agreement. *First Author: Edward Thompson, CVS Health, Lincoln, RI*

Background: In response to rising healthcare costs, several innovative payment strategies have emerged to improve the value and efficiency of healthcare spending. One of these strategies is a shift from volume-based to value-based care (VBC), resulting in the introduction of alternative payment models, innovative provider contracting and new value frameworks. The purpose of this study is to evaluate the impact of a VBC arrangement on total cost of care for chemotherapy patients, specifically cancer-related drug costs, daily hospital inpatient admissions and emergency room visits. **Methods:** This is a cohort study of chemotherapy patients, in a single state, enrolled in a large national insurer from January 18, 2021, to September 30, 2021. Oncology patients were divided into two groups; the study group consisted of chemotherapy patients receiving care in a VBC arrangement; the control group consisted of chemotherapy patients receiving care at oncology practices not engaged with the insurer in a VBC agreement. The following levers were employed to improve value: digital symptom tracking, biosimilar or lower-cost drug options and NCCN regimen concordance. We defined cancer-related drug costs as the sum of allowed costs paid for medical and pharmacy claims during the study period. Additionally, we averaged the cost per hospital inpatient day and emergency room visit and compared these by group. **Results:** This study included 1,574 patients, 733 patients in the study group and 841 in the control group. A reduction of 5.1% (a difference of $441) in cancer-related drug costs per member per treatment month (PMPTM) was observed among patients in the study group. Patients in the study group reported 27.8% fewer inpatient days resulting in a savings of $194 PMPTM. Similarly, patients in the study group reported 70.0% fewer emergency room visits resulting in a savings of $59 PMPTM. **Conclusions:** In this study, chemotherapy patients participating in a shared savings VBC spent less on cancer-related drug costs, hospital inpatient days and emergency room visits through three value levers. Further studies are needed to assess if these results are similar all types of healthcare coverage and to what degree additional value levers further reduce costs. Additionally, the long-term health outcomes of these patients should be assessed. Research Sponsor: None.

1537 **Poster Session**

Impact of cancer diagnosis, stage, and systemic therapies on immunogenicity after COVID-19 vaccination in patients with cancer: A systematic review and meta-analysis. *First Author: Guilherme Nader Marta, Academic Trials Promoting Team, Institut Jules Bordet and l'Université Libre de Bruxelles (U.L.B), Brussels, Belgium*

Background: Patients (pts) with cancer are at increased risk of severe COVID-19. Both underlying malignancy and anti-cancer treatments influence the immune system, potentially impacting the level of vaccine protection achieved. **Methods:** A systematic literature search of PubMed, Embase, CENTRAL and conference proceedings (ASCO annual meetings and ESMO congress) up to 28/09/21, was conducted to identify studies reporting anti-SARS-CoV-2 spike protein immunoglobulin G seroconversion rates (SR) at any time point after complete COVID-19 immunization (mRNA- or adenoviral-based vaccines) in cancer pts. Complete immunization was defined as 1 dose of JNJ-78436735 vaccine or 2 doses of BNT162b2, mRNA-1273 or ChAdOx1 nCoV-19 vaccines. Subgroup analyses were performed to examine the impact of cancer diagnosis, disease stage, and anti-cancer therapies on the SR. Overall effects were pooled using random-effects models and reported as pooled SR with 95% confidence intervals (CI). **Results:** Of 1,548 identified records, 64 studies were included in this analysis reporting data from 10,511 subjects. The Table shows the SR in the overall population and specific subgroups. In pts with solid malignancies (SM), disease stage and primary site did not significantly impact the SR. In pts with hematologic malignancies (HM), SR were significantly lower in pts with chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL) compared to acute lymphoblastic leukemia (ALL), Hodgkin lymphoma (HL), and multiple myeloma (MM). Concerning the impact of cancer therapies on SR, pts with SM undergoing chemotherapy had numerically lower SR (N = 1,234, SR 87%, CI 81-92) compared to those treated with immune checkpoint inhibitors (N = 574, SR 94%, CI 88-97) or endocrine therapy (N = 326, SR 94%, CI 86-97) with or without another targeted therapy. Pts with HM treated with anti-CD20 therapy (within the last 12 months: N = 360, SR 7%, CI 2-20; or more than 12m: N = 175, SR 59%, CI 35-80), immune-modulating agents (BTK or BCL2 inhibitors) (N = 462, SR 47%, CI 32-64%) or other immunotherapies (anti-CD19/CART or anti-CD38) (N = 293, SR 37%, CI 23-53) had lower SR compared to pts treated with autologous (N = 353, SR 77%, CI 67-85) or allogenic stem cell transplantation (N = 509, SR 77%, CI 68-84). **Conclusions:** SR varies between cancer types and anticancer therapies with some cancer pts having low protection against COVID-19 even after complete vaccination. Research Sponsor: None.

Variable	Category	N of pts (N of studies)	Overall SR % (95% CI)	Hematologic SR % (95% CI)	Solid SR % (95% CI)
Overall		10,511 (64)	78 (73-82)	74 (68-80)	93 (91-95)
Stage	Non-metastatic	368 (7)			85 (77-91)
	Metastatic	1,084 (8)			88 (82-92)
Primary site (SM)	Non-lung	833 (7)			87 (84-89)
	Lung	180 (6)			88 (82-92)
Type of HM	ALL	37 (4)		67 (28-91)	
	CLL	1,462 (12)		45 (37-54)	
	HL	126 (6)		83 (31-98)	
	NHL	912 (9)		44 (30-58)	
	MM	1,235 (14)		80 (72-86)	

1538 **Poster Session**

Characteristics associated with functional resilience versus functional decline among adult patients with advanced non–small cell lung cancer. *First Author: Joy Tang, Ohio State University, Columbus, OH*

Background: As more treatment options become available for advanced non-small cell lung cancer (NSCLC), oncologists still have difficulty predicting functional resiliency versus functional disability throughout treatment. Functional resiliency refers to the ability to recover baseline functional status in the face of an intervening health care event. This study aims to identify characteristics associated with resilience among adults with advanced NSCLC. **Methods:** In a prospective cohort of participants with newly diagnosed stage IV NSCLC, resilience was evaluated based on three functional disability items in the EQ-5D-5L (modified: mEQ-5D-5L) through 12 months of follow-up compared to baseline scores. This included patients treated with chemotherapy, immunotherapy, targeted agents and no treatment. Participants were classified into four groups: functional decline, maintenance, resilient, or variable. Resilience was determined based on improvement in disability scores, with a 1-point increase in functional status score representing a 0.5 standard deviation change on the mEQ-5D-5L. Patient characteristics included demographics, comorbidities, ECOG performance status, presence of brain or bone metastases, mood (GAD-7, PHQ-9), and lung cancer-specific symptoms (QLQ-LC13). Treatment toxicity and toxicity grades were also recorded. Differences between groups were determined through Fisher's exact test or ANOVA. **Results:** Among 207 participants, 87 (42.0%) maintained functional status, 78 (37.7%) experienced functional decline, 22 (10.6%) were classified as resilient and 20 (9.7%) were variable. Characteristics associated with higher resilience ($p < 0.1$) included being employed ($p = 0.02$) and living in a metro setting ($p = 0.10$). Characteristics not associated with resilience included age, education level, smoking status, presence of brain metastases, ECOG performance status, or psychological symptoms. Approximately half the participants (n = 105, 50.7%) who received treatment experienced toxicities. One third (33.8%) experienced ≥ grade 3 toxicities. There was no significant association between toxicity grade and resilience grouping. **Conclusions:** Characteristics associated with functional resilience included employment status and living setting. At least half of adults with advanced NSCLC experience treatment-related toxicities. It is important to determine characteristics of resilience to better understand which patients will tolerate cancer treatments. Research Sponsor: None.

1539 **Poster Session**

Impact of provider education on hepatitis B screening practices prior to patients receiving cancer treatment. *First Author: Michael Adashek, St. Joseph Mercy Hospital IHA Hematology Oncology, Ypsilanti, MI*

Background: Hepatitis B virus (HBV) reactivation is a known side effect of CD20 targeted therapies with complications ranging from transient hepatitis to fulminant hepatic failure and death. In 2020 the American Society of Clinical Oncology (ASCO) expanded its provisional clinical opinion (PCO) to recommend HBV screening for all patients prior to receiving non-hormonal systemic anti-cancer therapies and if positive, offer viral prophylaxis or treatment. We assessed in a single-institution prospective study if a provider-led educational session on the 2020 ASCO PCO was effective in increasing HBV screening among patients receiving systemic non-hormonal anti-cancer therapies. **Methods:** An educational session for 30 minutes on the benefits outlined in the ASCO 2020 PCO discussing hepatitis B screening was held at a community-based hematology/oncology practice in Michigan. HBV screening panel was added to pre-chemotherapy lab order sets. Provider compliance with HBV screening recommendations was assessed monthly. Patients with positive HBV serology were identified and referred to Hepatology for monitoring and anti-viral treatment/prophylaxis as indicated. Data from 1,984 patient encounters for cancer treatment utilizing either chemotherapy or rituximab among 12 providers from March of 2020 to December 2021. Multivariate and logistic regression analysis was performed. **Results:** The educational intervention on the best practices of screening for Hepatitis B was effective in raising screening. Prior to intervention, 79.3% of all patients receiving rituximab (N = 140) and 15.7% of all patients receiving chemotherapy (N = 1277) had documentation for Hepatitis B before cancer treatment. Post-intervention hepatitis B testing increased both among patients receiving rituximab to 95.8% (N = 48) and chemotherapy to 29.9% (N = 519). In summary, prior to intervention, just 22.0% of 1,417 patient encounters had documentation for Hepatitis B screening before undergoing a treatment regimen. Post-intervention this level was raised to 35.45% (= 37.41,). In this study, 3 cases (0.5%) of acute and 12 cases (2.0%) of chronic HBV were identified from the 603 tested patients. A mixed effects logistic regression model controlling for treatment type and provider found patient encounters occurring post-intervention were 2.30 times more likely to be screened (OR = 2.30, 95% CI = [1.81, 2.93], $p < 0.001$). **Conclusions:** Our single educational session discussing the 2020 ASCO PCO and testing techniques for HBV was effective at increasing the odds of screening 2.3 times among patients receiving non-hormonal systemic anticancer therapies adjusting for therapy and provider. This may serve as a model for other implementations of PCOs. Further research will assess long-term oncologic outcomes of those identified with HBV and effects of anti-viral interventions. Research Sponsor: None.

1540 **Poster Session**

Long COVID-19 in patients with cancer: Report from the National COVID Cohort Collaborative (N3C). *First Author: Noha Sharafeldin, Department of Hematology & Oncology, School of Medicine, University of Alabama at Birmingham, Birmingham, AL*

Background: Post-acute sequelae of SARS-CoV-2 or long COVID, is characterized by persistence of symptoms and/or emergence of new symptoms post COVID-19 infection. As evidence accumulates and national initiatives arise to address this increasingly prevalent syndrome, characterization of specific patient groups is still lacking including patients with cancer. Using a nationally representative sample of over 4.3M COVID-19 patients from the National COVID Cohort Collaborative (N3C), we aim to describe characteristics of patients with cancer and long COVID. **Methods:** We employed two approaches to identify long COVID patients within N3C: i) patients presenting to a long COVID clinic at four N3C sites and ii) patients diagnosed using the recently introduced ICD-10 code: U09.9 Post COVID-19 condition, unspecified. We included patients with at least one positive COVID-19 diagnosis between 1/1/2020 and 2/3/2022. Patients had to survive at least 90 days from the date of their COVID-19 diagnosis. Analyses were performed in the N3C Data Enclave on the Palantir platform. **Results:** A total of 1700 adult patients with long COVID were identified from the N3C cohort; 634 (37.3%) were cancer patients and 1066 were non-cancer controls. The most common represented cancers were skin (21.9%), breast (17.7%), prostate (8.3%), lymphoma (8.0%) and leukemia (5.7%). Median age of long-COVID cancer patients was 64 years (Interquartile Range: 54-72), 48.6% were 65 years or older, 60.4% females, 76.8% non-Hispanic White, 12.3% were Black, and 3% Hispanic. A total of 41.1% were current or former smokers, 27.7% had an adjusted Charlson Comorbidity Index score of 0, 18.6% score of 1 and 11.2% score of 2. A total of 57.2% were hospitalized for their initial COVID-19 infection, the average length of stay in the hospital was 9.6 days (SD: 16.7 days), 9.1% required invasive ventilation, and 13% had acute kidney injury during hospitalization. The most common diagnosis among the non-cancer long COVID patients was asthma (26%), diabetes (17%), chronic kidney disease (12%), heart failure (9.4%), and chronic obstructive pulmonary disease (7.8%). Among long COVID patients, compared to non-cancer controls, cancer patients were more likely to be older (OR = 2.4, 95%CI: 1.1-5.4, $p = 0.03$), have comorbidities (OR = 4.3, 95%CI: 2.9-6.2, $p < 0.0001$), and to be hospitalized for COVID-19 (OR = 1.3, 95%CI: 1.0-1.7, $p = 0.05$), adjusting for sex, race/ethnicity, body mass index and smoking history. **Conclusions:** In a nationally representative sample of long COVID patients, there was a relative overrepresentation of patients with cancer. Compared to non-cancer controls, cancer patients were older, more likely to have more comorbidities and to be hospitalized for COVID-19 warranting further investigation to identify risk factors for long COVID in patients with cancer. Research Sponsor: U.S. National Institutes of Health.

1541 **Poster Session**

Enabling community-led integrated women health care models for women cancers screening and early detection through EMPOWER (Enabling and Motivating Partnerships Owned by Women who Engage and Reclaim their lives) project. *First Author: Dorothy Nyongo, County first ladies association, Nairobi, Kenya*

Background: With the growing burden of Women cancers in East Africa, integrating cancer screening and prevention to optimize horizontal care delivery models is a paramount approach to strengthening women-centered and cost-effective primary healthcare. EMPOWER is a unique partnership with the government of Kenya, County referral hospitals, County First Ladies Association, International Cancer Institute, Patient organizations and Roche Kenya to demonstrate integrated cancer prevention and treatment within primary healthcare shared across the Kenyan Health system. **Methods:** EMPOWER clinics were launched with over 300 community health workers (including women living with disabilities) and HCPs were identified and trained to provide facility and community-based screening and early detection for breast cancer, cervical cancer, hypertension and diabetes through an integrated health systems strengthening approach. Mentorship was provided to HCPs through routinely held joint screenings and clinics, weekly Tumor Boards, Teleclinics, Telemedicine and Digital Pathology platforms. In addition, training support was provided through virtual preceptorships, skills-training workshops, hub-and-spoke oncological services provision and robust patient navigation. **Results:** 14 EMPOWER clinics have been launched across Kenya to increase community awareness of breast, cervical, and NCDs, strengthen capacity to deliver integrated Women cancer management services in County health clinics. In Kenya out of 25,502 people screened, 13,192 were screened for breast cancer with 97 abnormal findings identified; 10,349 screened for cervical cancer with 200 abnormal cervical screenings identified and 1,664 screened for prostate cancer with 32 abnormal findings. In addition, an integrated approach in Non Communicable Disease (NCD) care, diabetes and hypertension screening; 4,298 screened for diabetes and 6,116 screened for hypertension. All those diagnosed with cancers were linked to existing cancer care delivery systems and continuous support offered through the strengthened health care systems. Prostate cancer was added as more men turned up for screening events. **Conclusions:** This model is replicable and scalable across LMIC and recently the model inspired health providers' from Tanzania and Nigeria to adopt the same for women's cancers. EMPOWER has demonstrated a scalable care model in Kenya contributing to investments in pathology training and clinical treatment to improve challenges in referrals and updating guidelines to enable multi-disease tissue testing and handling and treatment with Standard of Care. Research Sponsor: Public Private Partnership.

1542 **Poster Session**

Does the 4R oncology model improve clinicians' effectiveness in patient-facing planning of complex cancer care? *First Author: Julia R. Trosman, Center for Business Models in Healthcare, Chicago, IL*

Background: The 4R Oncology model was proposed within the NCI ASCO Teams Project as an approach to facilitate patient-facing care planning, team-based delivery and patient self-management. 4R (Right Info/Care/Patient/Time) enables care teams and patients to manage complex care with a novel 4R Care Sequence plan. We previously reported that 4R significantly improved patient self-management, namely patients' ability to organize and manage their care (Trosman JCO OP 2021). Here we report the impact of 4R on effectiveness of clinicians to plan and deliver complex multidisciplinary care. **Methods:** We surveyed clinicians (physicians and nurses) from 8 cancer centers (4 academic, 4 community) participating in a 4R adoption program. The survey was conducted Mar 2019 to Sep 2019 prior to 4R launch (Baseline cohort), and Nov 2021 to Jan 2022 post-4R launch (4R cohort). Baseline cohort included clinicians conducting care planning with patients. 4R cohort included clinicians who used 4R in care planning with new patients. The survey focused on clinicians' self-reported effectiveness in planning and management of guideline-based care. Descriptive statistics and Fisher's 2-sided test were used in analyses. **Results**: Baseline cohort's response rate was 79% (66/83); 4R cohort's response rate was 86% (62/72). 4R implementation was associated with significant improvement in all 5 metrics of effective care planning between the baseline and 4R cohorts (Table). Within the 4R cohort, 87% (54/62) clinicians found 4R Care Sequences useful or very useful for care planning and management. The majority, 79% (49/62), spent 10 minutes or less on average developing and administering 4R Care Sequence to a new patient, and 58% (36/62) reported decreased overall volume of post-visit inquiries about care plan from patients who received 4R. When asked about 4R delivery format, 65% (40/62) preferred paper, 23% (14/62) electronic delivery and 12% (8/62) had no preference. **Conclusions:** The 4R Oncology model is a promising approach to improving clinicians' effectiveness in patient-facing care planning and reducing the workload associated with patient inquiries. An ongoing 4R research and implementation program continues efforts to identify optimal implementation methods and integrate 4R into clinical practice across the U.S. Research Sponsor: The Coleman Foundation.

	Baseline cohort, n = 66 %	4R cohort, n = 62, %	P value
I am satisfied with ability to create and provide patients with individualized cancer care plans	50%	90%	< 0.0001
I am able to include multiple aspects of comprehensive care in a care plan (surgery, systemic therapy, radiation, supportive care, health maintenance, etc.)	41%	66%	0.005
I am able to effectively discuss a comprehensive care plan with new patients	22%	77%	< 0.0001
My patients can effectively manage their care across specialties	32%	61%	0.001
My practice effectively enables patients to manage their care across specialties	49%	88%	< 0.0001

1543 **Poster Session**

Demographic and laboratory determinants of humoral immune responses and impact of different anti-SARS-CoV-2 vaccine platforms in patients with cancer: A systematic review and meta-analysis. *First Author: Diogo Martins-Branco, Academic Trials Promoting Team, Institut Jules Bordet and l'Université Libre de Bruxelles (U.L.B), Brussels, Belgium*

Background: Patients (pts) with cancer have increased mortality from COVID-19 and their vaccination is crucial to prevent severe infection. We aimed to identify demographic and laboratory determinants of humoral immune responses to COVID-19 vaccination in pts with cancer and investigate differences in responses based on the vaccine platform. **Methods:** We searched for records in PubMed, Embase, and CENTRAL up to 28/09/21, as well as conference proceedings from ASCO and ESMO 2021. We included studies of pts ≥16 yr with a cancer diagnosis, who were vaccinated against SARS-CoV-2. Studies were excluded if ≥10% of the participants had other causes of immunosuppression or baseline anti-SARS-CoV-2 spike protein antibodies (Ab)/previous COVID-19 (PROSPERO ID: CRD42021282338). For this subgroup analysis of studies that reported a proportion of pts with cancer and positive Ab titers at any timepoint following complete vaccination, a random-effects model was used to estimate the humoral response rate (HRR) with 95% confidence intervals (CI). **Results:** We included 64 records, reporting data from 10,511 cancer pts. The HRR in the overall population and by subgroup are shown in Table. Elder patients with hematologic cancers (59%, CI 47-70%, N = 667) and patients with lymphopenia (50%, CI 25-75%, N = 111) or hypogammaglobulinemia (36%, CI 19-57%, N=226) were the subgroups with lower HRR. Male (77%, CI 69-84%, N = 2,659) and Asian (84%, CI 54-96%, N = 37) pts showed a trend to lower HRR when compared with females and other races, respectively. Pts vaccinated with mRNA vaccine platforms (79%, CI 74-83%, N = 9,404) had numerically higher HRR than those receiving the adenovirus vaccines (28%, CI 19-40%, N = 74). **Conclusions:** This study highlights demographic and laboratory determinants of weaker immune responses to SARS-CoV-2 vaccination, permitting better identification of more vulnerable pts. Despite the small number of pts included receiving adenovirus vaccines, these data also suggest prioritizing mRNA platform vaccination in pts with cancer. Research Sponsor: None.

Proportion of pts with anti-SARS-CoV-2 spike protein Ab.

Determinant	Subgroups (N of studies; pts)	Overall % (95% CI)	Solid cancers % (95% CI)	Hematologic cancers % (95% CI)
Overall	(64; 10,511)	78 (73-82)	95 (89-95)	64 (58-69)
Age	Younger (13; 1,240) vs Elder (13; 1,127)	79 (67-88) vs 71 (57-82)	93 (85-97) vs 93 (85-97)	71 (58-80) vs 59 (47-70)
Sex	Female (26; 2,840) vs Male (25; 2,659)	81 (73-87) vs 77 (69-84)	89 (84-93) vs 89 (84-93)	66 (55-75) vs 61 (51-69)
Race	White (4; 1,675) vs Black (4; 83) vs Asian (3; 37)	91 (81-96) vs 91 (75-97) vs 84 (54-96)		
Lymphocytes	Lymphopenia (3; 111) vs No lymphopenia (3; 369)	50 (25-75) vs 81 (60-93)		
Gammaglobulins	Hypogamma (4; 262) vs Non-hypogamma (4; 520)	36 (19-57) vs 66 (46-81)		
Vaccine platform	mRNA (59; 9,404) vs Adenovirus (4; 74)	79 (74-83) vs 28 (19-40)		

1544 **Poster Session**

Analysis of the likelihood of depression versus distress screening to identify need for intervention. *First Author: Valerie Pracilio Csik, Sidney Kimmel Cancer Center, Philadelphia, PA*

Background: Psychosocial assessments are increasingly used to evaluate a patient-centered approach to quality cancer care delivery. Value-based oncology programs endorse screening metrics at every encounter. To comply with expectations of these programs, our cancer center utilizes two standardized tools: Patient Health Questionnaire (PHQ) to screen for depression at every encounter; National Comprehensive Cancer Network Distress Thermometer (NCCNDT) to screen for acute distress at clinically meaningful intervals. In 2021, oncology patients completed, on average, 5 annual appointments at Sidney Kimmel Cancer Center (SKCC), with a median appointment frequency of once every 19 days. Given the high encounter-per-patient ratio, we aimed to assess utility of frequent screening leading to supportive intervention. **Methods:** A retrospective analysis was conducted of medical oncology patients seeking care at SKCC with a completed depression and/or distress screening, as recorded in the patient's electronic health record, between 1/1/2021 and 12/31/2021. This analysis intended to evaluate the percentage of patients whose scores indicate need for intervention. Patients who received more than one screening were attributed the highest score recorded during the measurement period. **Results:** A total 13,342 patients were screened at least once for either depression (n = 7,433), distress (n = 1,325), or both (n = 4,584). 3% of all patients screened ever met the intervention threshold (IT) for depression; 33% met the IT for distress. Of the patients who received both types of screenings, 31% met the IT for distress without meeting the threshold for depression. Those 1,418 patients would not have been referred for intervention through depression screening alone. **Conclusions:** This analysis highlights routine depression screening among a cancer population with a high encounter-per-patient ratio may not be sensitive in identifying need for supportive intervention. It also suggests that distress screening is more likely to lead to a supportive intervention than depression screening alone. This analysis combined with the anecdotal assessment by social workers supports the value of distress at clinically meaningful intervals over depression screening at each encounter. Research Sponsor: None.

Depression versus distress screening results.

		Depression	
		Below IT (<10)	*Meets IT (≥10)*
Distress	*Meets IT (≥4)*	1418 (31%)	145 (3%)
	Below IT (<4)	2964 (65%)	57 (1%)

1545 **Poster Session**

Impact of proactive symptom monitoring on quality of life (QoL) and treatment toxicity in patients with cancer receiving chemotherapy: A meta-analysis of randomized clinical trials. *First Author: Faris Tamimi, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Early recognition and management of symptoms can improve outcomes in cancer patients receiving treatment. A number of randomized trials have investigated the effects of adding proactive symptom monitoring to usual care (UC). These include web-based, application-based, or telephone-based assessments. Results have been variable, and the impact of proactive symptom monitoring on QoL, treatment toxicity and utilization of unscheduled acute care remains unclear. **Methods:** A systematic search of MEDLINE identified prospective, randomized trials that studied the effect of proactive monitoring and intervention versus UC in cancer patients receiving chemotherapy. The difference between proactive symptom monitoring and UC on the mean and SD for QoL using validated scales was collected for each study and pooled in a meta-analysis. Analysis was performed using the standardized mean difference (SMD) using random-effects modeling. The effect size was reported as the Hedges' adjusted g. We also calculated the odds ratios (OR) for the occurrence of several common symptoms of any grade in the individual trials and pooled them in a meta-analysis. Statistical significance was defined as $P < 0.05$. Quantitative significance was defined as a difference in QoL score exceeding the minimal clinically important difference (MCID) based on previous studies for each QoL framework. **Results:** Of the 17 trials which met eligibility criteria, FACT-G and EORTC QLQ C30 were the most consistently utilized QoL tools. The mean difference in score between intervention and control at the last evaluation visits was 2.82 (95% CI -0.57 to 6.21; P = 0.10) in FACT-G and 2.33 (95% CI -0.29 to 4.96; P = 0.08) in EORTC QLQ C30, neither of which met quantitative or statistical significance. There was a statistically significant reduction in fatigue (OR 0.67, 95% CI 0.46 to 0.97; P = 0.04), but no difference in constipation (OR 0.63, 95% CI 0.34 to 1.17; P = 0.15), nausea (OR 1.03, 95% CI 0.72 to 1.47; P = 0.89), pain (OR 0.83, 95% CI 0.62 to 1.10; P = 0.19), or diarrhea (OR 1.41, 95% CI 0.40 to 5.01; P = 0.60). SMD for symptom severity was calculated for fatigue, diarrhea, and nausea. Severity of fatigue was statistically lower with proactive symptom monitoring (SMD -0.45, 95% CI -0.69 to -0.22; $I^2 = 0\%$, $P < 0.001$), however, magnitude of effect was modest. **Conclusions:** Proactive symptom monitoring in cancer patients receiving treatment is not associated with significant or meaningful QoL improvement. Similarly, there is limited impact on individual toxicity. Research Sponsor: None.

1546 **Poster Session**

Cancer health disparities in the state of Georgia: African American oncology care. *First Author: Nabin Raj Karki, Augusta University, Medical College of Georgia, Augusta, GA*

Background: Approximately 58,970 new cancer diagnoses are projected for 2022 in Georgia (GA), contributing to 18,750 deaths. African Americans (AA) make up about one-third of Georgia's population compared to 14% of the national population. Cancer survival rates are lower for AA than non-AA for almost all cancer types. Biological factors do not account for all these differences. We explore the impact of racial disparities on cancer care in Georgia. **Methods:** We used 2020 behavioral risk factor surveillance system (BRFSS) data to capture patient-reported data on various demographic and health coverage variables. Oncology patients in the stage of Georgia were selected for our analysis. We evaluated the effect of racial disparities on clinical services received. **Results:** In the state of GA, 9,090 participants responded to the 2020-BRFSS, of which 400 partcipants had a history of cancer diagnosis other than skin cancer. Males and females comprised 37% and 63%, respectively. AA represented 15.8% of the respondents. The majority of the oncology respondents reported having health care coverage (96%) and having insurance coverage for all cancer treatments (96.8%) despite having 81.9% of the participants unemployed. Compared to non-AA, AA participants reported lower rates of health insurance payment for cancer treatment (84% v 99.3%, P = 0.0022) and lower levels of annual incomes (percentage of annual income <50,000$/year was 72.3% vs 51.5%, P = 0.0151). AA participants were four times less likely to have full coverage for cancer-related treatment than non-AA (odds ratio=4.31). There was no statistically significant difference in secondary education rates, health care coverage, the inability to see a physician due to cost, receipt of summary of treatment or written instructions, denial of insurance coverage due to cancer, and clinical trial participation. Participants with at least secondary education were more likely to have full insurance coverage for all cancer treatment expenses (P = 0.0206). **Conclusions:** Among cancer patients in Georgia, income rates were lower in AA than in non-AA. They were also less likely to have full coverage for cancer-related treatment. Analysis suggests secondary education increases the likelihood of having full insurance coverage. Education and income disparity may have a bearing on the accessibility and quality of cancer care. Addressing these inequities on a societal level will be key in ensuring high-quality oncology care for all. Research Sponsor: None.

Differences in socioeconomic and health coverage for AA and non-AA respondents to the 2020 BRFSS survey: State of Georgia.

	Factor	African American (%)	Non-African American (%)	P-value
Health care coverage	Yes	95.2	96.1	0.7012
	No	4.8	3.2	
Participated in cancer clinical trial	Yes	0	6.1	0.2411
	No	100	93.9	
Health insurance paid for all cancer treatment	Yes	84	99.3	0.0022
	No	16	0.7	
Annual income	Less than 25k	40.4	23.3	0.0151
	25 – 50 k	31.9	28.5	
	More than 50 k	27.7	48.1	

1547 **Poster Session**

Machine learning (ML)–enabled, circulating tumor cell–based classification of patients for non-prerequisite adjuvant therapy. *First Author: Gowhar Shafi, Indx Technology, Mumbai, India*

Background: Oncology implicates highest precision using next generation diagnostics and progressive therapies assisted by predictive tools. If validated clinically, machine learning (ML) can provide better insights in precision oncology. Furthermore, it longitudinally may stratify the progression of cancer disease burden in a real time. We have developed, Circulating Tumor Cells (CTCs) driven ML model as a predictor for the treatment decision strategy for both surgery and adjuvant therapy in head and neck squamous cell carcinoma (HNSCC) patients. **Methods:** In this study, a total of 380 HNSCC patients who underwent either surgery alone or surgery plus adjuvant therapy were accounted for. CTCs in patients were stratified based on clinicopathological parameters and using OncoDiscover platform having anti EpCAM antibody system regulated by the Drug Controller of India. Following this, we explored the predictive performance of the ML model on the usefulness of adjuvant therapy in HNSCC patients after the surgery. The available data was randomly divided into two subsets. First, 75%, of the original data was applied for Training the ML, and rest 25% of the data was used as a Test set. Survival curves were generated by Kaplan–Meier method and calculated through the Log rank test. **Results:** XGBoost machine learning classifier was superior to Random Forest and SVM-based analyses in predicting the usefulness of adjuvant therapy post-surgery using CTC alone or in combination with other clinical parameters in HNSCC patients. Machine learning algorithms were compared for predicting the accuracy of patients stratification. The results for each model were: XGBoost model (Accuracy = 0.84, ROC value = 0.73, Kappa = 0.43); Random Forest model (Accuracy = 0.81 ROC value = 0.70, Kappa = 0.41); SVM model (Accuracy = 0.76, ROC value = 0. 69, Kappa = 0.40). The ROC value of the XGBoost model was highest (0.73) while the ROC value for the SVM model was lower (0.69). We observed that when CTCs were combined with clinicopathological parameters, the accuracy, kappa values and AUC-ROC drastically improved in predicting the usefulness of adjuvant therapy post-surgery. A similar trend was observed when CTCs were combined with clinicopathological parameters in predicting the line of chemotherapy, post-surgery. **Conclusions:** ML-enabled, CTCs driven predictions can be highly accurate and ascertain the patient treatments. CTCs can be a positive predictor for selecting patient's treatment regimen in both surgery as well in type of treatment (e.g. surgery alone or surgery + adjuvant therapy). It can also implicate to classify the patients and determine who necessitates an additional adjuvant therapy. Further investigations in this direction are necessary to predict the treatment options based on ML that may improve the overall survival of cancer patients. Research Sponsor: iNDX.Ai.

1548 **Poster Session**

Applicability of a web app for lung cancer risk calculation and personalized recommendations for screening in Mexico. *First Author: Jose Felipe Muñoz Lozano, Centro Universitario Contra el Cancer, Monterrey, NL, Mexico*

Background: Lung cancer screening continues to be an area of great opportunity in public health, especially in developing countries. In Mexico, about 10,000 new cases of lung cancer are detected annually, of which less than 5% are diagnosed in early stages. There are no national programs for timely detection of lung cancer in our country, so it is essential to seek accessible measures to prioritize resources for high-risk people. **Methods:** We developed a web app that consisted of a short survey to stratify patients according to their risk of lung cancer (https://cuccuanl.com/tamiz_pulmon/). The questions were based on Nelson's criteria to categorize high-risk subjects who are deemed candidates for screening. The program contained automated logic programmed using JavaScript to guide people to the low or high-risk page if they met standard risk criteria in those age 50 and older. The high-risk page alerted people of their risk, displaying general information about lung cancer as well as contact information to make an appointment at our cancer center. An appointment could be also scheduled within the app if the person so wished. The web app was launched and distributed through social media. **Results:** After a period of 2 months, 939 people completed the survey. The median age of the responders was 40 years, and 61% were men. Of the total, 185 participants were 50 years of age or older. 268 people (29% of the total) were sent to the high-risk page, including persons under 50 years of age with symptoms highly suggestive of lung cancer. According to their smoking status, 80% of the subjects reported active smoking, while 9% reported heavy smoking, considered as more than 20 pack-years. Among all the people evaluated, 44 high-risk subjects scheduled a specialized medical appointment within the web app. **Conclusions:** This pilot study showed a high response of Mexican population seeking lung cancer risk evaluation, especially among the persons who smoke regularly. The use of web apps can result in mass diffusion which will help reach people with less medical access, a common scenario in many developing countries. Further analysis should be made to measure the real impact on lung cancer diagnosis and oncological outcomes. Our study shows how effective social media is as a means of diffusion on health topics. Research Sponsor: None.

Patients with high-risk features (n = 268)	**Percent**	**Absolute #**
Suggestive symptoms (all ages)	81%	218
Suggestive symptoms (≥50 years)	15%	41
≥20 pack years + ≥50 years	13%	35
Presence of EPOC	1%	2
Radon Exposure	0%	0
Laboral exposure to contaminated air	9%	25
≥100 wood smoke years	0%	0

Tobacco smoking status		**Absolute #**	**Percent**
<50 years old n = 754	Have never smoked	148	20%
	<20 pack-years	555	74%
	≥20 pack-years	51	7%
≥50 years old n = 185	Have never smoked	40	22%
	<20 pack-years	110	59%
	≥20 pack-years	35	19%

*None of the surveyed with ≥20 pack years had abandoned smoking for ≥20 years.

1549 **Poster Session**

Development of an electronic health record registry to facilitate collection of Commission on Cancer (CoC) metrics for patients undergoing surgery for breast cancer. *First Author: Heather G. Lyu, MD Anderson Cancer Center, Houston, TX*

Background: Accurate and efficient data collection is a challenge for quality improvement initiatives and clinical research. We describe the development of a custom electronic health record (EHR) based registry to automatically extract structured Commission on Cancer (CoC) axillary surgery specific metrics from a custom synoptic note template included in the operative reports for breast cancer patients undergoing surgery. **Methods:** The "Smart" functionality of our enterprise-based EHR system was leveraged to create a custom Smart phrase to capture axillary surgery specific variables. A multidisciplinary team developed structured data elements correlating to each axillary surgery-specific variable. These data elements were then included in a note template for the operative report. Each variable could be aggregated and converted into a single flat database through the EHR's reporting workbench and serve as a live, prospective registry for all users within the EHR. **Results:** The final axillary surgery-specific note template in a synoptic format allowed for efficient and easy entry and automatic collection of breast cancer specific metrics. From initial adoption in February 2021 through December 2021, there were 1,254 patients who underwent breast surgery with axillary surgery. The operative notes allowed for automatic capture of metrics from 60.5% (n = 759) of patients. Data capture improved from 37.6% in the initial adoption period of six months to 86.2% in the last five months. Capture rate in December 2021 was 98%. **Conclusions:** We were able to demonstrate successful implementation of provider driven structured data entry into EHR systems that permits automatic data capture. The end result is a custom synoptic note template and a real-time, prospective registry of breast cancer-specific CoC metrics that are robust enough to use for quality improvement initiatives and clinical research. Research Sponsor: None.

1550 **Poster Session**

Using machine learning on real-world data to predict metastatic status. *First Author: Foad H. Green, Syapse, San Francisco, CA*

Background: Real world data (RWD) is increasingly used to inform research, patient care, and population health in oncology; however, using RWD at scale requires accurate methods to identify clinically-relevant attributes. Metastatic status is a highly relevant clinical attribute in cancer patients but it is not routinely captured in structured formats and its determination conventionally requires review and interpretation by certified tumor registrars (CTRs). Clinical diagnoses, treatments, imaging procedures and other clinical variables documented in electronic health records (EHRs) can be used to differentiate metastatic from non-metastatic patients. This study describes an effective machine learning approach in utilizing prevalent and standardized data elements from EHRs across multiple health systems. **Methods:** 28,043 lung cancer and breast cancer patients from two large health systems within the Syapse Learning Health Network with data sources from CTR abstraction and EHRs were analyzed. Patients were labeled for reference metastatic status by CTRs and split into training (n = 22,434) and testing (n = 5,609) cohorts, with proportionate distribution of cancer type and metastatic status between cohorts. A regularized gradient boosting algorithm, XGBoost, was trained using over 750 variables from the patient records collected at the time of or after the initial cancer diagnosis. **Results:** Integration of ICD-10-CM codes with antineoplastic treatment history and radiologic imaging procedure orders achieved metastatic status prediction with increases to precision and recall in lung cancer (21% and 32% respectively) and breast cancer (39% and 9% respectively), when compared to the use of only ICD-10-CM diagnosis codes for secondary malignant neoplasms (Table). The addition of treatment and procedure data from different cancer types improved the model classification within individual cancer types. **Conclusions:** One of the biggest challenges in using RWD for precision oncology is identification of clinically-relevant phenotypes at scale. Here we demonstrate a scalable evidence-based method utilizing structured data for imputing metastatic status with high predictive power from two separate health systems. With further validation, this approach may be generalized to other cancer types, applied to temporal slices of data to identify changes in metastatic status, as well as provide a high-confidence designation of metastatic status for other use cases such as staging. Research Sponsor: None.

Model performance metrics.

	Precision	Recall
Lung and bronchus (ICD-10-CM only)	0.67	0.50
Lung and bronchus (Predictive model)	0.88	0.82
Breast (ICD-10-CM only)	0.56	0.82
Breast (Predictive model)	0.95	0.91

1551 **Poster Session**

Performance of an artificial intelligence-based annotation algorithm for reporting cancer genomic profiling tests. *First Author: Hidenori Kage, Department of Next-Generation Precision Medicine Development Laboratory, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan*

Background: Cancer genomic profiling (CGP) tests have been approved in Japan since June 2019, with the requisite that all test results be discussed by molecular tumor boards (MTBs). More than 20,000 patients in over 200 designated hospitals have taken CGP tests by December 2021. As CGP tests have entered clinical practice, streamlining decision making by MTBs and standardizing interpretation of test results and treatment recommendations have become urgent issues. Here, we evaluated the utility of Chrovis, an annotation algorithm for reporting CGP tests to support MTBs make their recommendations. **Methods:** We retrospectively reviewed the reporting process of all approved CGP tests done at The University of Tokyo Hospital between December 2019 and November 2021. Chrovis provided annotation for each genetic variant by incorporating biologic, clinical, and therapeutic information by referencing several public knowledge databases and using natural language processing, and generated reports using the automated program. The MTB reviewed and made any necessary changes before finalizing the report. Changes in disclosure of germline findings were made according to the recommendations of a national guideline with consideration of past and family history. **Results:** Of the 243 tests, 91 changes in 81 Chrovis reports (33% of all reports) were made by the MTB. The most common type of change was germline disclosure with 26 changes (29%), followed by clinical trial information in Japan (18 changes, 20%) and recommendation of the patient-proposed national basket trial with multiple targeted agents (17 changes, 19%). Changes in germline disclosure increased from June 2021, when an update to a national guideline was released, while the proportion of changes in the latter two types remained unchanged. Gene alterations that led to the highest number of changes was *TP53*, with 13 changes. Changes in therapeutic recommendations were frequently observed in the RAS/MAPK pathway (*BRAF*, *KRAS*, *NF1*, *NRAS*) with 12 changes. More changes were required with a tumor-only tissue CGP panel (57 of 149) compared with a matched tumor/normal tissue CGP panel (24 of 94, p = 0.04), mostly due to germline disclosure (24 vs. 2 changes). **Conclusions:** We observed that automated algorithm-based reporting was sufficient in 67% of reports. Recommendation for germline disclosure still requires manual supervision, particularly with tumor-only tissue CGP panels if algorithms do not incorporate medical history. The process of recommending clinical trials needs improvement, e.g., standardizing database formats for inclusion and exclusion criteria. Research Sponsor: Xcoo, Inc.

1552 **Poster Session**

Can an artificial intelligence-based platform reduce physician burden and increase access to clinical trials? *First Author: Limor Gortzak Uzan, Trialjectory, Closter, NJ*

Background: Clinical trials for cancer patients are an important treatment option and a resource for drug development. Although patients are more actively searching for treatment options through various approaches, the national average of cancer patients accrued to clinical trials remains static at only 2-4%. The most widely recognized resource is clinicaltrials.gov, which does not offer direct trial matching, is geared toward healthcare professionals and uses complex medical terms that are challenging for many patients. For clinicians, the absence of real-time access and insight into all relevant oncology trials, forms a burden on their already-limited time. Alleviating this burden could reduce barriers to clinical trial accrual. **Methods:** Using AI and an unsupervised natural language process approach, the Trialjectory platform monitors, analyzes and matches patients to clinical trials. Matching is achieved by patient response to a dynamic set of questions curated based on the eligibility criteria of available trials. The online questionnaire (www.trialjectory.com) collects detailed clinical data that include disease characteristics (histological, molecular and mutational status), treatment history, general health and comorbidities. All collected data points are incorporated into the matching process, yielding a high-quality actionable matched-trial list. A skilled support team is available to answer questions and concerns via email, text or phone calls. The platform enables patients to share the matched trial list with their oncologist for discussion. **Results:** from July 2019 - December 2021, 49,906 cancer patients completed Trialjectory's questionnaire. Patient accrual grew rapidly since the second half of 2019 with 1462, 2201, 9364,12685, and 24194 new questionnaire completions in each consecutive 6-month period from the 2nd half of 2019 through December 2021. 49,199 (98.6%) of registered patients were found eligible for available trials. Of the matched patients, 4428 patients (9%) applied to a clinical trial. Our matching engine identifies each specific trial match to each patient profile with a sensitivity of 90% and a specificity of 95%. When aggregated to a patient level, the chance that a patient will be matched for at least one trial from those that he is eligible to is 99.9%. Metrics are validated by automatically matching multiple artificially-created patient profiles and manually verifying the quality of the match. **Conclusions:** TrialJectory is an effective AI-based tool that offers cancer patients and their oncologists direct, precise and quick access to relevant clinical trials. Our data show a high adoption and growing registration rates and well-above average clinical trial application rate. By democratizing the access to clinical trials, increased opportunities are noted that might lead to increased trial participation. Research Sponsor: Trialjectory.

1553 **Poster Session**

Machine learning models for accurate pretreatment prediction of chemotherapy associated LV dysfunction in patients with breast cancer and lymphoma receiving chemotherapy (WF-98213 PREVENT and CCCWFU9912 DETECT IV). *First Author: Suditi Shyamsunder, Virginia Commonwealth University, Richmond, VA*

Background: Cancer survivors receiving potentially cardiotoxic chemotherapy are at increased risk for developing left ventricular (LV) dysfunction. We implemented machine learning (ML) models to predict future LV dysfunction in patients with breast cancer or lymphoma scheduled to receive potentially cardiotoxic chemotherapy. **Methods:** We utilized prospectively collected data from NIH studies R01HL118740 (supported by the Wake Forest NCORP Research Base (UG1CA189824)) and R01CA167821. Data included measurements of LV function and demographic factors before, during, and 24 months after initiating potentially cardiotoxic chemotherapy. The two datasets were used both separately and collectively in the development of multiple ML models including penalized linear regression, support vector machine, and random forest (RF). A data preprocessing step properly handled missing information, data imbalance, and encoding. Hyperparameter tuning was performed using cross validation of training data. The final models were assessed with a 20% hold-out test dataset. Cardiotoxicity was defined as a pre- to 24-month post cancer treatment decline in LV ejection fraction (LVEF) of > 10% or to an absolute value of < 50%. **Results:** 276 patients were included in ML models (7% men, 93% women; age 52±13 years). The RF model based on the combined dataset had the best performance with a prediction accuracy, sensitivity, and specificity of 0.94, 0.81, and 0.98, respectively. The most important variables assessed pre-treatment as measured by the Gini impurity factor were in descending order, LVEF, global LV circumferential strain, LV end-systolic volume, body mass index, LV stroke volume, LV end-diastolic volume, and LV mass. **Conclusions:** Prior to cancer treatment, supervised ML methods such as RF models predicted declines in LVEF of > 10% and/or to absolute values below 50% would occur 24 months after initiating chemotherapy for breast cancer or lymphoma. With further improvement and validation using larger datasets, these models may play an important role in cardio-oncology care during and following cancer treatment. Research Sponsor: U.S. National Institutes of Health.

1554 **Poster Session**

Feasibility of an explainable AI-based therapeutic recommendation-tool utilizing tumor gene expression profiles in advanced and refractory solid tumors. *First Author: Ouissam Al Jarroudi, Department of translational medicine, Centre Léon Bérard, Lyon, France*

Background: Precision oncology aims to guide patient (pts) treatment decisions by matching biological features with available drugs. Extensive genomic analysis allows to identify an actionable alteration in 40-60% of patients. In a recent study of 50 pts with advanced refractory diseases included in PROFILER (NCT01774409), whole exome and fusion transcripts had a limited value over a 90-tumor gene panel (TGP) to increase molecular-based treatment recommendations (MBTR). Herein, we evaluated the feasibility, in the same cohort of pts, of the AI-transcriptional-based therapeutic recommendation-tool OncoKEM to guide treatment recommendations. **Methods:** 77 fresh frozen (FF) and/or FFPE samples including paired specimens for 53 pts with available RNA-Seq gene expression profiles were included. For each pts, a tumor transcriptional profile (TTP) was generated by identifying differentially expressed genes between the pts tumor and a cohort of matched healthy tissue. A large database of drug transcriptional signatures (DTS) was queried in order to identify a "reversal relationship" between the TTP and a DTS. A total of 205 drugs were ranked, including a subset of 61 FDA and/or EMA approved targeted therapies (aTT). **Results:** Most common diagnoses were breast cancers (21% of which 63% were TNBC), followed by ovarian cancers (OC, 18%) and soft-tissue sarcomas (STS, 13%). The median number of previous treatment lines was 4 (range: 1 - 10). Among the 77 tumor samples analyzed, 54 (70%) specimens led to the generation of an OncoKEM report, with no differences between FF and FFPE samples (p = 0.85). The overlap between the top 10 proposed drugs between paired FF and FFPE samples was 56% on average. All patients had at least 2 propositions (range: 2-9) of aTT among the top 10 ranked drugs in the Onco KEM reports. Most frequently proposed drugs among the top 10 were palbociclib, talazoparib, infigratinib in TNBC; bosutinib, sapanisertib, SAR125844 in OC; ipilimumab, cabozantinib, sapanisertib in STS. Among the 30 pts (79%) without any MBTR based on TGP/WES/fusion transcript analysis, all had at least 2 proposed aTT in the Onco KEM report (median: 4, range: 2-9). Top ranked drugs were MET (18%), VEGFR (12%), Abl (12%), FGFR (11%), PI3K/AKT/mTOR (11%), PARP (10%) and CDK4/6 inhibitors (7%). **Conclusions:** AI-transcriptional-based therapeutic recommendation-tool OncoKEM is feasible and has the potential to expand personalized cancer treatment in pts with advanced & refractory diseases without tractable genomic alterations. The clinical relevance assessment is planned in an upcoming clinical trial. Research Sponsor: OmiCure.

1555 **Poster Session**

Machine learning application to find patients with lower-risk myelodysplastic syndrome from real-world data. *First Author: Colden Johanson, Syapse, San Francisco, CA*

Background: It is a challenge to identify patients with myelodysplastic syndrome (MDS) using structured data from electronic health records (EHRs). Current claims-based algorithms incorporating diagnosis codes, clinical labs, and procedures have not been validated against an expert reference standard. A machine learning-based approach was investigated to identify erythropoietin-stimulating agent (ESA)-treated, lower-risk (LR)-MDS patients from structured EHR data. **Methods:** A sample of 1,549 patients from the Syapse Learning Health Network (SLHN) was identified as potential ESA-treated LR-MDS patients by a team of clinicians and epidemiologists based on diagnosis and medication data from multiple health systems' EHRs and cancer registries. Of these, 404 (25%) were confirmed as ESA-treated LR-MDS patients through a review of patient records by certified cancer registrars (CTRs). The sample was divided into training and validation sets at a ratio of 80/20, stratified by the outcome. Age, sex, diagnosis codes corresponding to MDS and chronic kidney disease, medication (ESA, luspatercept, lenalidomide), clinical lab tests (hemoglobin, absolute neutrophils, platelet, blast percentage), and evidence of bone marrow biopsy were included as the predictive variables for the models. Gradient boosting machines with a nested cross-validation scheme were adopted to build the optimal model on the training set. Model acceptance was evaluated based on precision and recall on the validation set. The optimal model was then applied to the remaining unscreened SLHN patient population. **Results:** The optimal model identified an additional cohort of 157 patients based on the predicted likelihood. Among these, 69 (44%) were CTR-confirmed ESA-treated LR-MDS patients, all of whom were previously missed by the initial expert-determined selection criteria, as shown in the table. **Conclusions:** The application of machine learning methods increased the rate of ESA-treated MDS patient identification even after the expertly-determined population was depleted. This suggests the application of machine learning models using EHR data may improve the efficiency of MDS patient identification and screening efforts for research, quality improvement, and clinical care. Research Sponsor: Bristol Meyers Squibb.

Criteria		SLHN patients screened	ESA-treated MDS
Expert-determined selection criteria	Two MDS diagnosis* dates ≥ 90 days apart + evidence of ESA treatment§†	239	122 (51%)
	MDS Registry evidence by ICD-O-3 Histology‡	1,229	270 (22%)
	Patients with suspected MDS based on manual review of clinician notes	41	1 (2%)
	Other small sample attempts	40	6 (15%)
	Total	1,549	404 (25%)
Machine learning model		157	69 (44%)

*MDS ICD-10 codes: C94.6 and D46. ‡MDS ICD-O-3 Histology: 9980, 9981, 9982, 9983, 9984, 9985, 9986, 9987, 9988, 9989, 9993. §ESA treatment: darbepoetin alfa or epoetin alfa. †The first code fell within the study window of 2016-01-01 to 2019-06-30.

1556 **Poster Session**

Natural language processing-optimized case selection for real-world evidence studies. *First Author: Jacob Koskimaki, CancerLinQ, Alexandria, VA*

Background: Much information describing a patient's cancer treatment remains in unstructured text in electronic health records and is not recorded in discrete data fields. Accurate data completeness is essential for quality care improvement and research studies on de-identified patient records. Accessing this high-value content often requires manual and extensive curation review. **Methods:** AstraZeneca, CancerLinQ, ConcertAI, and Tempus have developed a natural language processing (NLP)-assisted process to improve clinical cohort selection for targeted curation efforts. Hybrid, machine-learning model development included text classification, named entity recognition, relation extraction and false positive removal. A subset of nearly 60,000 lung cancer cases were included from the CancerLinQ database, comprised of multiple source EHR systems. NLP models extracted EGFR status, stage, histology, radiation therapy, surgical resection and oral medications. Based on the results, cases were selected for additional manual curation, where curators confirmed findings of the NLP-processed data. **Results:** NLP methods improved cohort identification. Successfully returned cases using the NLP method ranged from 75.2% to 96.5% over more general case selection criteria based on limited structured data. For all cohorts combined, 84.2% of the cases sent out for NLP curation were returned with curated content (Table). Each cohort contained a range of NLP-derived elements for curators to further review. In comparison, more general case selection criteria yielded a total of 3,878 cases returned out of 41,186 lung cancer cases sent for curation, for a success rate of only 9.6%. **Conclusions:** NLP-driven case selection of six distinct, complex lung cohorts resulted in an order of magnitude improvement in eligibility over candidate selection using structured EHR data alone. This study demonstrates NLP-assisted approaches can significantly improve efficiency in curating unstructured health data. Research Sponsor: AstraZeneca.

NLP-assisted cohort selection for the six pre-specified lung cancer cohorts.

Cohort	Cohort Description	Number of cases available from NLP-assisted identification methods	Number of cases sent to Tempus and ConcertAI for curation	Number of cases returned to CancerLinQ with curated content	Percent of successfully curated cases
1A	NSCLC, stage I, II, III, EGFR+, complete resection	408	408	341	83.6%
1B	NSCLC, non-squamous, stage I, II, III, EGFR wild type/unknown, complete resection	4313	1500	1285	85.7%
2A	NSCLC, stage III, unresectable, curative radiation to the chest total dose >= 50 Gy, did receive Imfinzi	852	620	466	75.2%
2B	NSCLC, stage III, unresectable, curative radiation to the chest total dose >= 50 Gy, did not receive Imfinzi	3050	750	724	96.5%
3	SCLC, received Imfinzi or Tecentriq	559	500	402	80.4%
4	NSCLC, received Tagrisso as first line treatment	971	812	647	79.7%
Total:		10153	4590	3865	

1557 **Poster Session**

Natural language processing of Veterans' electronic health records to confirm diagnoses of monoclonal gammopathy of undetermined significance. *First Author: Mei Wang, Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, Saint Louis, MO*

Background: The Veterans Health Administration (VHA) provides extensive electronic health records (EHRs) on Veterans nationwide. Our prior studies utilized VHA data to study the risk of progression from monoclonal gammopathy of undetermined significance (MGUS) to multiple myeloma. These studies relied on International Classification of Disease (ICD) codes and manual abstraction on clinical notes to both identify and verify MGUS patients. Diagnosis confirmation is necessary because many providers place a diagnosis on the clinical notes to order lab tests, which is often left in the EHR despite a negative test result. However, manual abstraction is labor intensive and time consuming. With the advancement in natural language processing (NLP), we developed a model to make MGUS confirmation more efficient. **Methods:** We randomly selected 700 patients within patients diagnosed with MGUS from 1999-2021 in the VHA identified via ICD codes. A random sample of 500 patients were selected and split into the training (80%) and the testing (20%) sets. The remainder (n = 200) served as the validation set. There were 32,708 unstructured hematology/oncology Text Integration Utility reports and 9,237 lab reports (including 2,322 discrete results and 6,915 unstructured comments). All reports were manually reviewed to confirm MGUS diagnoses and served as the reference standard. We compiled three lists of keywords suggestive of MGUS diagnosis, subtypes of immunoglobulins, and negation modifiers. We trained a symbolic NLP model to identify diagnoses using combinations of the lists along with M-protein levels from lab reports. The optimized combination that gave the highest recall and precision from the training set was used and evaluated on the testing and validation sets. **Results:** Among patients with ICD codes for MGUS, manual abstraction confirmed 84% MGUS diagnoses in the testing set and 80% in the validation set. Our NLP model in the training set confirmed 75% and achieved recall, precision, accuracy, and F1 score of 88.1, 98.7, 89.0, and 93.1%, respectively; in the validation set, our rule confirmed 76% patients and the recall, precision, accuracy, and F1 score were 89.4, 94.7, 87.5, and 92.0%, respectively. On average data abstraction took five minutes per patient (excluding data loading time), whereas NLP model completed 13 patients per minute. **Conclusions:** The developed NLP model to confirm MGUS diagnosis improves accuracy in diagnosis, compared to ICD codes alone. While the performance is similar to that of manual abstraction, our NLP model is an efficient and viable method in MGUS diagnosis confirmation. Research Sponsor: U.S. National Institutes of Health.

	Recall (%)	Precision (%)	Accuracy (%)	F1 score (%)
Dataset (patients/clinical reports/lab reports)				
Training (400/19,309/5,112)	86.52	94.85	85.50	90.49
Testing (100/4,907/1,437)	88.10	98.67	89.00	93.08
Validation (200/8,492/2,688)	89.38	94.70	87.50	91.96

1558 **Poster Session**

Impact of trial site selection on minority patient recruitment in prostate cancer trials. *First Author: Charles Lagor, ConcertAI, Cambridge, MA*

Background: Historically, minority patients have been underrepresented in clinical cancer trials. Despite recognition of this problem, trials in the early 2000's showed a decrease from 10.5% to 6.2% in African American trial participation when compared to trials from the early 1990's. The drop in trial participation is also reflected in prostate cancer trials, although Black men have a 1.76 higher prostate cancer incidence rate than White men. Using prostate cancer as an example, we investigated the impact of trial site selection on potential minority patient recruitment; thus, overcoming a major system-level barrier to trial access. **Methods:** We created a prostate cancer cohort by filtering our real-world data sources (CancerLinQ, Electronic Medical Office Logistics) for adult male patients with ICD10 CM code C61* or ICD9 CM code 185 on 1/1/2015 or later (cohort #1). As a pre-requisite for computing site level prostate cancer patient counts, we used claims data to attribute missing site information. Finally, to identify the most promising sites for minority trial recruitment, we ranked sites by the proportion of Black patients and the overall cohort patient count. We repeated the above steps for a subset of cohort #1, which was based on the criteria for trial NCT00887198 investigating the prostate cancer drug abiraterone (cohort #2). **Results:** The prostate cancer cohort (#1) had 151,261 patients, of which 99,152 (65.6%) were attributed to sites. The percentage of Black patients being treated at the top ten sites ranged from 33.0% to 66.4%, with a median of 45.2% (see table). All ten sites had participated in an interventional cancer trial, and eight had participated in prostate cancer trials. Half of them were community, and half were academic sites. The abiraterone cohort (#2) had 1,267 patients, of which 1,174 (92.7%) were attributed to sites. Among the top ten sites the Black patient percentages ranged from 23.8% to 85.7%, with a median of 39.3%. **Conclusions:** In an analysis of 17 recent FDA drug registration trials for prostate cancer, Black trial participation ranged from only 1.4% to 6.2%, with a median of 3.0%. In contrast, Black patients being treated at the top sites in our data ranged from 33.0% to 66.4%, with a median of 45.2% (cohort #1). The percentages for the abiraterone cohort (#2) were similar, suggesting that even after applying trial criteria the Black patient percentages remain in the double-digits at top sites. Our results demonstrate that informed trial site selection could have a substantial positive impact on minority patient recruitment. Research Sponsor: None.

Top ten sites.

Site	Black Patients (n, %)	Total (n)	PCa Trial Hist	Type
A	172 (66.4%)	259	Y	Ac
B	227 (57.8%)	393	Y	Co
C	836 (54.2%)	1542	Y	Co
D	438 (47.8%)	916	N	Co
E	329 (46.8%)	703	Y	Co
F	342 (43.5%)	786	Y	Ac
G	1013 (41.1%)	2462	Y	Ac
H	1053 (37.6%)	2798	N	Ac
I	318 (35.9%)	887	Y	Co
J	596 (33.0%)	1804	Y	Ac

PCa Trial Hist, Prostate Cancer Trial History; Y, Yes; N, No; Ac, Academic; Co, Community.

1560 **Poster Session**

A novel support vector machine to predict sentinel lymph node status in elderly patients with breast cancer. *First Author: Abbas Hassan, University of Texas MD Anderson, Houston, TX*

Background: Routine sentinel lymph node biopsy in older breast cancer patients with favorable tumor biology is not recommended. However, cases must be evaluated on an individual basis to avoid under or over-treatment. Many nomograms have been developed to calculate the risk of nodal positivity, but machine learning (ML) is a novel tool that may improve the accuracy of nodal prediction. In this study, we developed a support vector machine (SVM) model to delineate factors indicative of sentinel lymph node positivity and refine individualized nodal risk assessment for this heterogeneous patient population. **Methods:** We conducted a single-institution comprehensive retrospective review of patients 70 years or older diagnosed with unilateral stage I–III primary breast cancer from January 2005 to January 2016. Patient data was partitioned into training and testing sets. A SVM model was developed to predict lymph node status using patients' demographics, tumor stage, genetic profile, and imaging data. Primary outcome was model performance determined by area under the curve (AUC). Secondary outcomes were accuracy, sensitivity and specificity. Permutation feature importance (PFI) analysis and accumulated local effect (ALE) plots were used to evaluate significant predictors identified by the SVM. **Results:** We identified 1706 consecutive patients who met the study criteria with a mean age of 76±4.5 years. The plurality of patients were Caucasian (82%), had ER+ (86%), PR+ (70%), HER2- (87%) stage I (72%) breast cancer. Sixteen percent of patients (n = 271) had a positive sentinel lymph node biopsy. The SVM model demonstrated good discriminatory performance for predicting sentinel lymph node positivity with mean AUC of 0.70 (95%CI, 0.62-0.77), mean accuracy of 84% (95%CI, 80-88%), mean sensitivity of 61% (95%CI, 57-66%), and mean specificity of 62% (95%CI, 52-73%). PFI and ALE identified higher disease stage, younger age, family history of breast cancer, margin status, estrogen and progesterone receptor positivity as independently associated with high risk of sentinel lymph node positivity. **Conclusions:** The proposed ML model accurately identified sentinel lymph node status in older patients with breast cancer. This model holds promise for counselling patients as to the potential risk for node positive disease which may impact surgical and adjuvant therapy recommendations. Research Sponsor: None.

1561 **Poster Session**

Incidence and impact of proportional hazards violations in phase 3 cancer clinical trials. *First Author: Timothy Lin, Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins University School of Medicine, Baltimore, MD*

Background: Hazard ratio (HR)-based analyses used in oncology trials rely on the assumption of proportional hazards, i.e. a HR that is constant over time. Proportional hazards violations (PHVs) may lead to misinterpretation of trial results. Restricted mean survival time (RMST) is valid with non-proportional hazards and has received recent attention specifically for immunotherapy (IO) trials but has not been routinely adopted in oncology trial design as a whole. We aimed to comprehensively characterize the incidence and factors associated with PHVs among phase 3 oncology trials and assess RMST as an alternate measure of treatment effect in survival analysis. **Methods**: We used Clinicaltrials.gov to identify all superiority-design, 2-arm phase 3 cancer trials with time-dependent endpoints with published results through February 2020. We manually reconstructed patient-level data from published Kaplan-Meier (KM) curves, assessed PHVs with the Schoenfeld residual test ($p < .05$) and analyzed the RMST. To assess reconstruction accuracy, reported and reconstructed HRs were compared. Univariable logistic regression was used to assess the likelihood of PHVs by trial characteristic, with statistically significant factors ($p < .05$) included in a multivariable analysis. Concordance of RMST-based and HR-based analysis was established when both tests agreed as to the statistical significance of the comparison. **Results:** Of 342 KM comparisons eligible for reconstruction, 318 comparisons across 315 trials, enrolling 347,538 patients from 1989-2017, were accurately reconstructed and analyzed. PHVs were identified in 76/318 (23.9%) trials. There was no difference in likelihood of PHVs among IO vs non-IO trials (LR 2.31, 95% CI 0.30 17.85, P = .37), nor by disease site, year of trial initiation, or sample size. Few trials with PHVs (16/76) pre-specified a plan to account for non-proportional hazards in statistical design. Trials with an overall survival (OS) primary endpoint (PEP) were less likely to have PHVs than trials with a non-OS PEP (LR: 0.50, 95% CI 0.28 - 0.90, P = .02). Trials whose PEP was non-significant were more likely to have PHVs (LR 1.73, 95% CI 1.01 - 2.97, P = .047). No factor remained significantly associated with PHV in multivariable analysis. Overall, 291/318 (91.5%) KM comparisons were concordant. Among trials with PHVs, 5/76 were significant by RMST but not HR, and 5/76 were significant by HR but not RMST. Of these, 1 led to FDA drug approval, and 2 others are cited in NCCN guidelines. **Conclusions:** PHVs are common across all phase 3 cancer clinical trials. Attempts to account for PHVs in trial design are lacking despite the potential for trial misinterpretation in the event of non-proportional hazards. RMST-based analysis is broadly concordant with HR-based analysis and may aid in interpretation of trials with PHVs. Hence, we recommend that prospective trials include *a priori* a statistical plan to account for PHVs. Research Sponsor: Sabin Family Fellowship Foundation, Fund for Innovation in Cancer Informatics.

1562 **Poster Session**

Improving first-in-human and window-of-opportunity informed consent forms through participant feedback. *First Author: Anna Avinger, Emory Healthcare-Winship Cancer Institute, Atlanta, GA*

Background: Although patient advocates have created templates for standard consent forms, assessing patient preferences for First in Human (FIH) and Window of Opportunity (WO) trials consents is important given their unique risks. FIH trials are the first time a drug is tested in humans. In WO trials, treatment naïve patients receive a therapeutic agent in the window of time between diagnosis and standard of care (SOC) surgery. Our goal was to determine patient-preferred presentation of important information in FIH and WO consent forms. **Methods**: The study consisted of two phases: (1) analysis of consents for FIH and WO oncology trials open at a cancer center between 2019 and 2022; (2) interview patients who had reviewed consents for FIH or WO trials during the consent process. FIH consents were analyzed for the location(s) of information stating that the study drug has not been tested in humans (FIH info). The WO consents were analyzed for the location(s) of information stating the risk that trial may delay SOC surgery (WO info). Participants were asked about their preferred placement of the information in their own trial's consent form and whether the consent was clear. Interviews were audio-recorded and double coded. Consent form analysis was compared to patients' preferences. **Results**: 25 consents [20 FIH; 5 WO] were analyzed. 19/20 FIH consent forms included FIH info, and 4/5 WO consent forms included WO info. 42 patients were approached [19 FIH; 23 WO]; 34 [17 FIH; 17 WO] participated. 12/17 (71%) WO participants thought that the trial explanation in the consent form was clear. Conversely, only 9/17 (53%) FIH participants found it clear. **Conclusions**: Patients preferred that the important FIH and WO information be placed early in the consent, though exactly where varied. 82% of FIH participants wanted FIH information in the purpose, while only 19% of WO participants clearly preferred that WO information be in the purpose, and 41% preferred WO information to remain in the risks section. Using consent templates that reflect patient preferences accurately is essential for ethical informed consent; however, a one-size fits all approach may not accurately capture patient preferences, so multiple templates may be necessary. Research Sponsor: U.S. National Institutes of Health, U.S. National Institutes of Health, The Winship and Davidson Impact Fellowship and Winship Cancer Institute of Emory University.

Location of FIH and WO info in consent forms compared to patient preference.

Title	Purpose / Introduction	Title & Purpose	Purpose & Risks	Title, Purpose, & Risks	Title & Risks	Risks	
Location of FIH Info in consent forms (n = 20)	0	0	0	20% (5)	10% (2)	5% (1)	20% (4)
Patient preference for location of FIH info (n = 17)	0	18% (3)	6% (1)	29% (5)	29% (5)	6% (1)	6% (1)
	Introduction	**Purpose**	**End of risks section**	**Beginning of risks section**	**Treatment Schedule**	**"Early on" in consent form**	**Key Concepts**
Location of WO info in consent forms (n = 5)	0	40% (2)	40% (2)	0	0	0	20% (1)
Patient preferences for location of WO info (n = 17)	0	12.5% (2)	25% (4)	18.75% (3)	6.25% (1)	18.75% (3)	12.5% (2)

One FIH and one WO patient had no preference.

1563 **Poster Session**

Clinical development of new drugs for adults and children with cancer in 2010-2020: Longitudinal study of investigational drugs. *First Author: Andrea Arfe, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Many investigational drugs start clinical testing to evaluate potential therapeutic benefits for oncology patients, but few eventually receive FDA approval. Moreover, only a small number is evaluated in pediatric populations, potentially contributing to the paucity of new approved drugs for young patients with cancer. Limited information is available on the development pipeline of investigational drugs, including the range of drug types entering clinical trials, trial phases at which development stalls, or rate of regulatory approval. To inform current clinical development efforts, we characterized the development and outcomes for a comprehensive sample of New Molecular Entities (NMEs) that started clinical testing worldwide in 2010-2015. **Methods:** We performed a longitudinal study using AdisInsight, a commercial database of global pharmaceutical research and development. This is a comprehensive database of drug development activity, which collects and curates data from trial registries, conference proceedings, journal publications, and press releases. Using these data, we identified all NMEs starting their first clinical trial for an oncology indication in 2010-2015. We followed each NME from the start of its first phase I trial to the end of 2020, and identified all associated trials, final development status, and FDA deliberations. We classified trials as pediatric-eligible if patients aged < 18 years were eligible for participation. We used the Drugs@FDA website to identify all FDA actions, including marketing approvals and requests for pediatric trials under pediatric programs (i.e. BPCA requests or PREA requirements). **Results:** A total of 572 NMEs started initial phase I clinical trials in 2010-2015. Among these, the most studied classes were small molecules (N, %: 316, 55%), antibodies (148, 26%), and antibody-drug conjugates (44, 8%). Overall, the NMEs were studied in 6,141 clinical trials by the end of 2020, with a median of 3 trials per NME. The highest pre-approval development phase reached by an NME was phase I for 325 (57%), phase II for 153 (27%), and phase III for 94 (16%). Only 39 NMEs (7%) were approved by the FDA by the end of 2020. Among approved NMEs, the median time (range) from start of first phase I trial to date of first approval was 6 (3-10) years. Among all NMEs, only 67 (12%) were tested in pediatric-eligible trials by the end of 2020, and 5 (< 1%) were approved for use in selected pediatric populations. Three of these had been subject to BPCA requests, and all had PREA requirements waived. **Conclusions:** More efficient clinical development strategies are needed to accelerate the production of new cancer therapies, especially for children. Analyses such as this one should be conducted regularly to help identify areas in need of innovation and to assess the potential impact of regulatory initiatives (e.g. the RACE act, effective since August 2020). Research Sponsor: None.

1564 **Poster Session**

TBCRC 057: An online survey about anxiety and willingness to participate in breast cancer clinical trials during the COVID-19 pandemic. *First Author: Karen L. Smith, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins School of Medicine, Baltimore, MD*

Background: Enrollment in clinical trials has declined during the COVID-19 pandemic. Simultaneously, breast cancer patients have reported heightened anxiety. We assessed whether breast cancer patients' anxiety about the pandemic affects their willingness to participate in trials. **Methods:** English or Spanish-speaking US residents with breast cancer were eligible to complete the online REDCap survey 8/6/21 – 9/30/21. Respondents rated their anxiety about the pandemic on an 11-point scale from 0 (no anxiety) to 10 (worst anxiety possible). Anxiety scores were categorized as no/mild (0-3), moderate (4-6) or severe (7-10). Knowledge about trials was assessed with 11 true/false items and attitudes toward trials with the Attitudes Toward Cancer Trials Scales - Cancer Treatment Subscale (ATCTS-CTS). Respondents rated their willingness to participate in a breast cancer clinical trial before and during the pandemic on 5-point scales from 0 (not at all willing) to 4 (definitely willing). Trial participants were considered "definitely willing." Change in willingness to participate in trials during the pandemic compared to prior was defined as a binary outcome, "less willing" vs "no less willing." Means were compared via t-test and mean difference was tested via paired t-test. Multivariable logistic regression was used to model the association of anxiety and other factors with being less willing to participate in trials during compared to prior to the pandemic. **Results:** Among 385 respondents, median age was 52 (range 25-85), 271 (70%) were non-Hispanic White and 202 (53%) had metastatic disease. 154 (40%) received care at academic centers and 37 (10%) were current trial participants. Most rated their anxiety as moderate (43%) or severe (38%). Mean willingness to participate in a trial was lower during compared to prior to the pandemic (2.97 vs 3.10; $p < 0.0001$). Fifty (13%) respondents were less willing to participate in a trial during the pandemic compared to prior. After controlling for covariates, those with severe anxiety had 5.07 times odds of being less willing to participate during the pandemic compared to prior than those with no/mild anxiety ($p = 0.01$). For every 1-point increase in ATCTS-CTS score (indicating better attitude toward trials) there was a 3% decrease in the odds of being less willing to participate during the pandemic ($p = 0.006$). For every 1-point increase in the clinical trials knowledge score (indicating more knowledge) there was a 15% decrease in the odds of being less willing to participate during the pandemic ($p = 0.02$). **Conclusions:** Pandemic-related anxiety is common in breast cancer patients and is associated with being less willing to participate in trials during the pandemic compared to prior. Education about trials, including safety modifications implemented during the pandemic, may mitigate anxiety and improve willingness to participate. Research Sponsor: Metastatic Breast Cancer Network.

1565 **Poster Session**

Participation in cancer research in BNSSG, England: A Health Equity Audit 2021. *First Author: Kathryn Hamilton, South West England Public Health Training, Bristol, United Kingdom*

Background: Cancer is a cause of health inequalities, and nationally, patients from deprived communities have lower participation rates in cancer research. Equitable access to research benefits patients, healthcare organisations and improves applicability of research. **Methods:** We undertook a health equity audit of participation in cancer research (trials and non-trials based) in Bristol, North Somerset and South Gloucestershire (BNSSG), England from 1.4.2019-30.3.2020 using data from the Acute Trust patient datasets. Comparison cohorts were extracted from a regional primary care dataset (the system wide dataset). Firstly, an incident cancer cohort: diagnosed from 1.11.2019-1.10.2020. Secondly a "living with cancer" cohort: cancer flag in the 5 years prior to 1.7.2021. Deprivation is measured by IMD of home postcode small area (LSOA). **Results:** Results are presented for the audit in the table below, with 95% confidence intervals where appropriate. Compared to people newly diagnosed with cancer, adults aged 70 or older were 56% less likely to take part in research (OR 0.44, 95% CI 0.39-0.51), and adults aged 80 or older were 77% less likely to take part in research (OR 0.23, 95% CI 0.18-0.29). Compared to people newly diagnosed with cancer, people from the most deprived 20% of the population were 27% less likely to take part in research (OR 0.73, 95% CI 0.88-0.92). The most deprived research participants were more likely to be younger, have one or more comorbidities and a recent emergency admission. Patients from outside BNSSG (18%) appear similar in profile to those from within BNSSG, including for deprivation. Better data are needed for other factors relevant to equity, including ethnicity and Inclusion Health. **Conclusions:** This health equity audit confirms and quantifies inequities in access to cancer research in our region. Under-representation of deprived and older patients appeared multifactorial in this audit, but further work to understand facilitators and barriers to recruitment is needed. These results are a call to action. Research Sponsor: None.

Patient Group	Patients	Mean Age (95% CI)	Younger Patients (<18 years) N (%)	Teenagers and young adults (16-24 years) N (%)	Older patients (>70 years) N (%)	Older patients (>80 years) N (%)	Gender (% female)	Patients from Out of Area N (%)	Most deprived 20% population
BNSSG cancer research				participants	1,052	62y (61.0-63.0)*	36 (3.4%)*	12 (1.1%)	365 (34.7%)*
74 (7.0%)*				52.9%**	189 (18.0%)	11.4% *** (9.5-13.3)			
New Cancer diagnosis in BNSSG	5,193	69y (68.1-69.0)	46 (0.9%)	NA	2,827 (54.4%)	1,299 (25.0%)	55.7%	NA	15.0% (14.0-15.9)
Living with Cancer in BNSSG	14,214	67y (66.6-67.1)	107 (0.8%)	NA	7,036 (49.5%)	2,765 (19.5%)	48.1%	NA	12.9% (12.0-13.8)

*Significant difference to the New Cancer diagnosis and the Living with Cancer patient groups, $p < 0.0001$. **Significant difference to the Living with Cancer cohort, $p = 0.0026$. ***Significant difference to the New Cancer diagnosis cohort, $p = 0.0027$.

1566 **Poster Session**

A retrospective cohort analysis of return-to-work outcomes for cancer survivors using a digital coaching intervention. *First Author: Yuri Aung, Imperial College, London, United Kingdom*

Background: Return-to-work (RTW) is a key unmet need for working age cancer survivors, with up to 40% failing to RTW 1 to 2 years post-diagnosis. This study sought to evaluate RTW outcomes of a multidisciplinary digital coaching intervention provided as routine employee support. **Methods:** A retrospective cohort analysis was conducted from October 2018 to February 2020 where cancer patients with more than 3 months absent from work were provided by their insurance carriers with a multidisciplinary intervention comprising digital resources and telephone calls with a health coach. A logit regression model was used to calculate a propensity score using covariates of age, gender, insurance benefit type, cancer diagnosis date and time from diagnosis. Participants were then matched on a 1:1 basis using the nearest-neighbour method without replacement to create a matched control group out of 1,856 participants who did not receive the intervention. Primary outcomes, derived from insurance-claims data as standard business practice, included rate and time to RTW, along with death and other reasons for claim closure. **Results:** 220 participants enrolled in the intervention, of which 125 met the criteria for analysis (median age 53, IQR 45-58, 91% female). These participants were matched with 125 controls (median age 53, IQR 47-59, 94% female). Median follow-up from cancer diagnosis was 79 weeks (IQR 60-106). Of the matched controls, 22 returned to work (17.6%) compared with 38 (30.4%) in the intervention group (P = .02). 19 matched controls died prior to claim closure (15.2%) compared with 13 in the intervention group (10.4%; P = .26). Finally, Kaplan-Meier method estimated median time for the first 15% of participants to RTW was 87.1 weeks for controls (CI 60.0-109.1 weeks) compared with 70.6 weeks for the intervention group (CI 52.6-79.6 weeks; P = .08). **Conclusions:** This study evaluated the impact of a digitally delivered coaching program in a real-world setting for cancer patients, demonstrating a 12.8% increase in RTW rate over 18 months compared to matched controls. These findings corroborate and add to the literature on cancer as a chronic and manageable disease in the workplace. Research Sponsor: CancerAid.

1567 **Poster Session**

Applicability of a web app for breast cancer risk calculation and personalized recommendations for screening in Mexico. *First Author: Jose Felipe Muñoz Lozano, Centro Universitario Contra el Cancer, Monterrey, NL, Mexico*

Background: A minority of women with breast cancer in Mexico are being diagnosed through a screening program, which translates into late diagnosis and a worse prognosis. It is imperative to develop easy access and low-cost interventions to increase the screening rate. **Methods:** We developed a web app tailored to guide patients to seek medical consultation if they were at high risk for breast cancer or standard screening recommendations based on the predicted risk for age (https://cuccuanl.com/calcula-tu-riesgo-de-cancer-de-mama/). The web app consisted of an 8-question survey designed using object-based programming with HTML5, the additional logic was programmed on JavaScript. The program logic automatically guided patients to medical consultation if they were at high risk for breast cancer, or standard screening recommendations based on their predicted risk for age. On each confirmation page, the contact information of the hospital appeared, also, consultation at the clinic could be scheduled within the web app. The web app was distributed via social media on International Breast Cancer Awareness Day. **Results:** A total of 1,012 persons answered the survey after a follow-up period of two weeks. The median age of respondents was 34 years. Among participants, 10.8% were considered at very high risk for breast cancer due to symptoms, 22% were classified as high risk based on family history or more than 5 years of contraceptive use, and 19% were considered as average-risk population for whom age-based screening tests were recommended. The remaining 48% of participants were considered at low risk for breast cancer development and were directed to educational information about breast cancer awareness. Among all persons that answered our survey, 21 requested a specialized medical appointment within the web app. **Conclusions:** This pilot study showed a high response of Mexican population seeking breast cancer risk evaluation, 11% of women that responded to our survey had symptoms highly suggestive of breast cancer. The use of web apps can result in mass diffusion which will help reach people with less medical access, a common scenario in many developing countries. Further analysis should be made to measure the real impact on breast cancer diagnosis and oncological outcomes. This study shows how effective social media is as a means of diffusion on health topics. Research Sponsor: None.

Risk Category	% of Respondents (n = 1,012)
Low Risk (< 40 Years, No Risk Factors)	48%
Screening Recommendation (≥ 40 Years, No Other Risk Factors)	19%
High Risk (Oral Contraceptive Use for > 5 Years or Family History)	22%
Very–High Risk (Symptom Suggestive of Breast Cancer)	11%

1568 **Poster Session**

Assessing health electronically for adolescent and young adult oncology patients (AHEAD Study). *First Author: Tyler Garrett Ketterl, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: Screening and counseling for health risk behaviors (RB) are recommended but infrequently performed, particularly in individuals undergoing cancer therapy. Unmet needs among adolescents and young adults (AYAs) with cancer translate to poor physical and psychosocial outcomes. The authors aimed to 1) modify an existing RB electronic health assessment (eHA) and intervention tool and 2) determine the feasibility and acceptability of the RB eHA and intervention tool among AYAs with cancer and their oncology providers. **Methods:** The internally developed HRB eHA and intervention tool Check Yourself was adapted by a multidisciplinary healthcare professional panel for an AYA oncology population and informed by literature review and AYA stakeholder feedback. "Check Yourself Oncology" assesses risk and health domains including home, education, sexual health, safety, alcohol/drugs, mental health and medication adherence. Optional feedback is provided for sexual health, safety, alcohol/drugs and mental health domains. Eligible AYAs were 13 to 29 years old, diagnosed with cancer, receiving cancer directed therapy, follow-up scheduled with a Seattle Children's Hospital oncology physician or nurse practitioner, and fluent in English. 72 hours prior to their next oncology clinic visit, participants were text messaged or emailed a personalized link to the Check Yourself Oncology tool to be completed prior to their next visit. Upon completion, a detailed report was sent to the primary clinical oncology team prior to the patient's visit. Feasibility was defined as 1) ≥70% completion of the RB eHA and 2) a Feasibility of Intervention Measure (FIM) mean score >4. Acceptability was defined as an Acceptability of Intervention Measure (AIM) mean score >4 and qualitatively. The FIM and AIM were sent by REDCap survey following the clinical visit; verbal feedback from AYAs and clinicians was analyzed with qualitative content analysis. **Results:** Of 30 eligible, approached AYAs, 25 (83%) enrolled in the study and 23 (76%) completed the Check Yourself Oncology tool and follow-up assessments. The AYAs had a mean age of 17 years (SD = 2.9 years) and 50% identified as female. Four AYAs declined participation due to lack of interest, 1 due to declined parental consent, 1 passively declined after enrollment, and 1 declined further participation following the confidentiality terms. The mean FIM and AIM scores were 4.1 (SD=0.6) and 4.0 (SD =0.7) respectively. Seventeen AYAs (74%) felt that the feedback provided was relevant and useful. 74% of visits providers reported that they incorporated the results in the care of the patient and 87% reported the results positively impacted care. **Conclusions:** Risk behavior screening with motivational feedback though the modified eHA tool Check Yourself Oncology is feasible and acceptable in AYAs undergoing cancer directed therapy. Clinical trial information: NCT04484194. Research Sponsor: Seattle Children's Research Institute.

1569 **Poster Session**

Evaluating an AI-based nutrition expert platform delivered via SMS-text to support patients with cancer. *First Author: Marissa Lubin Buchan, Savor Health LLC, New York, NY*

Background: Interventions incorporating nutritional strategies can prevent and manage nutrition-related symptoms, however, due to a shortage of oncology dietitians (RD CSO) combined with healthcare access disparities, many patients do not receive the support they need, resulting in poor outcomes and quality of life (QoL). High rates of cell phone utilization among all demographics offers a unique opportunity to provide interventions using mobile technology. **Methods:** Launched to select groups in 2019, Ina (trademarked by Savor Health LLC) is a virtual nutrition assistant powered by an artificial intelligence (AI)-enabled expert platform, to facilitate self-management of cancer treatment side effects. The platform combines evidence, expertise, and unique patient data to deliver the personalized guidance patients would receive from an RD CSO, "on-demand" via text. This study applied the RE-AIM framework to evaluate the intervention from five dimensions. **Results:** Reach: The program reached 1,706 users as of 2021. Based on self-report among 1209 users, 78% are patients, 18% are caregivers, and 5% are healthcare professionals with 66% female and 34% male. Ina supports all cancer types, and top diagnoses among users are genitourinary (28%), lung (20%), gynecologic (16%), gastrointestinal (15%), and breast (11%). Disease burden is high, with 62% of users reporting they are experiencing nutrition-addressable symptoms at any given time. Effectiveness: Based on weekly patient reported outcome (PRO) surveys, 87% of respondents report Ina helps them manage symptoms, and 80% report that using Ina has improved their QoL. The cumulative likelihood to recommend is 4.1 on a 5-point scale. Adoption: Users are from over 18 cancer organizations, proving the feasibility and accessibility of this intervention. Implementation: Ina is accessible 24/7 via text, and is offered to patients in a B2B2C model. Users typically receive responses to nutrition-related questions within seconds from the AI platform (or 1-3 minutes with live RD oversight). Each active user (one that engages at least once in a given month) asks an average of 2.8 questions per month. Maintenance: The median time users remain on the platform is 156 days (range 0-884) and 57% of evaluable users stayed on the platform 6 months or longer. The platform's database, which includes over 54,000 referenced interventions, grows daily via supervised machine learning supported by RD CSOs. When surveyed on future feature development, respondents are most interested in tele-nutrition (57%), mental health (65%), and stress management (62%). **Conclusions:** Initial data suggests this is a feasible and accessible tool to support cancer patients' unique nutrition and symptom-management needs. Clinical trials are needed to validate feasibility and assess impact on clinical and QoL outcomes. Product development to integrate language and cultural preferences is ongoing. Research Sponsor: None.

1570 **Poster Session**

Impact of the COVID-19 pandemic on oral oncolytic adherence. *First Author: Elias Pittos, CVS Health, Lincoln, RI*

Background: COVID-19 has substantially decreased cancer screening, management visits and surgeries. CVS Health recently developed a best-in-class mobile app and website that enables oncology patients to start and stay on therapy. This study examined the impact of COVID-19 on adherence to oral oncolytic agents in a large health plan with a significant digital health platform. **Methods**: This retrospective cohort study included adult patients with chronic myelogenous leukemia (CML), ovarian cancer or prostate cancer initiating oral oncolytics between 3/1/19 and 3/1/2021. Patients were divided into two groups: pre-COVID oral oncolytic initiators before 3/1/20 and COVID initiators after 3/1/20 and were followed for 1 year after therapy initiation. The primary outcome was optimal adherence to oral oncolytic agents as defined by a medication possession ratio (MPR) $\geq$ 0.8. Percent of digital engagement, defined as the number of times a patient interacted with the CVS digital platform, was examined as a secondary endpoint and was considered as a binary and categorical endpoint (none, low (< 28), moderate (28-105) and high (> 105)). Descriptive statistics and logistic regression modeling were performed; p-values < 0.05 were significant. **Results:** In total, 15,494 patients were included in the study, with 8,067 (52.07%) in the pre-COVID initiator group. Patient demographics were similar across study groups, with the exception of pre-COVID initiators who were less likely to be male (75.32% vs. 77.34%; p < 0.01) and receive copay assistance (38.37% vs. 41.70%; p < 0.01). No difference in digital engagement pre and during COVID was noted (74.55% vs. 73.60%; p = 0.18). Pre-COVID initiators were less likely to be optimally adherent than COVID initiators (84.75% vs. 85.96%; p = 0.04). Therapy persistence was more common among COVID initiators, with greater number of fills (Median [quartile (Q) Q1-Q3]: 10 [4-12] vs. 9[4-12]; p < 0.01) and less changes to therapy (8.87% vs. 9.95%; p = 0.02). After regression, COVID initiation of oral oncolytics was not associated with optimal adherence (odds ratio (OR) = 1.06 [95% (confidence interval (CI) 0.96-1.16]). Adherence increased as digital engagement increased (low: OR 0.64 [95% CI 0.56-0.72]; moderate: OR 0.67 [95% CI 0.56-0.76]; high: OR 1.71 [95% CI 1.48-1.99]). Other factors associated with increased adherence were copay assistance, male gender and age between 65 and 84 (all p < 0.05). Factors associated with decreased adherence were therapy change, CML and age < 50 years (all p < 0.05). **Conclusions:** The onset of the COVID-19 pandemic did not significantly impact optimal adherence for new-to-therapy oral oncology patients. Patients with high digital engagement during the pandemic experienced significantly improved adherence than those not engaged. Additionally, persistence and number of fills were slightly improved in COVID initiators, suggesting that the current pandemic may have influenced adherence behaviors. Research Sponsor: None.

1571 **Poster Session**

Mobile app in oncology: A pilot survey on Latina patients with gynecological cancers and their perception on utilizing a mobile app. *First Author: Paulina Ramirez, Texas Tech University Health Sciences Center, El Paso, TX*

Background: Mobile applications have changed the way that users access information and revolutionized healthcare by allowing patients to educate themselves regarding their diagnosis and treatment. Challenges in developing a mobile health application include patient satisfaction and usage over time. Barriers to usage include trust, personalization, and accessibility. Investigating the patient population's preferences on app content and ease of use is imperative. The use of mobile applications specifically for Latina Gynecologic Oncology patients undergoing treatment has yet to be investigated. **Methods:** Fifty-six patients were recruited from the Gynecologic Oncology clinic at an urban academic health sciences center located on the Texas-Mexico border. Cross-sectional analyses were performed. Subjects were asked a series of 10-point Likert scale questions including how comfortable they would feel using medical applications on their smartphones. Linear regression models were fit with this scale score as the outcome. **Results:** The age of the 56 patients ranged from 28 to 77 years with a mean of 53.9 years (SD: 11.1). Spanish was the preferred language of 53.8% of the patients (28/52). Forty-four subjects were available for the regression analyses. Subjects were asked, "Would you feel comfortable using medical applications on your smartphone," where 1 represented "not at all comfortable" and 10 represented "very comfortable". The mean comfort scale score was 7.39 (SD: 2.85). Thirty of the 44 subjects (68.2%) replied "Multiple times per day" to the question about how frequently they use mobile apps on their phone. After controlling for the patient's age in a regression model, patients who used mobile apps multiple times per day had an average comfort scale score that was 1.75 points higher than that of women who did not use mobile apps on their phone multiple times per day (p = 0.03). After adjusting for the frequency of mobile app use, there was a reduction of 0.11 points (p = 0.002) in the comfort scale score for every one year increase in the patient's age. **Conclusions:** Our unique pilot study found a positive association between the frequency of current app use and anticipated comfort in using smartphone medical applications. Overall, patients demonstrated a considerable amount of comfort with the prospect of using a mobile app. These findings support the idea of creating a mobile app designed to monitor Latina Gynecologic Oncology patients in efforts to lessen patients' postoperative burden, improve mortality and morbidity outcomes, and decrease health care system costs. Research Sponsor: None.

Parameter estimates from the linear regression analyses in 44 patients.

Model	Frequency of mobile app usage:	Age: 1 year increase	Education: College vs. Less education	Adjusted R-squared
1	2.35 (p = 0.01)	-	-	0.13
2	1.68 (p = 0.046)	-0.10 (p = 0.003)	0.33 (p = 0.66)	0.28
3 (Final)	1.75 (p = 0.03)	-0.11 (p = 0.002)	-	0.30

1572 **Poster Session**

Association between remotely-monitored activity, patient-reported outcomes, and physical function in patients with advanced pancreatic cancer. *First Author: Gillian Gresham, Cedars-Sinai Medical Center, Los Angeles, CA*

Background: Patients with pancreatic ductal adenocarcinoma (PDAC) experience significant functional decline over the course of their treatment, which can negatively impact their quality of life (QOL) and clinical outcomes. There are currently no standardized methods to monitor physical function (PF) in PDAC patients outside the clinic setting. The use of wearable technology to obtain continuous and objective activity data combined with routine collection of patient-reported outcomes (PROs) provides an opportunity to monitor PF and intervene in a timely matter. **Methods:** We conducted a single-site, single-arm prospective study in advanced stage 3 and 4 PDAC patients between 2019 and 2/2022. Patients used a wrist-worn wearable activity monitor (Fitbit) continuously for 8 weeks and completed NIH PROMIS surveys (PF, pain, fatigue, sleep disturbance, and emotional distress) at baseline, week 4 and week 8. ECOG performance status (PS), hand grip strength, and timed 15-foot walk test were also assessed at each timepoint. Pearson correlation coefficients were calculated for activity data (step counts, distance, stairs, time spent sedentary and in light, moderate, or vigorous activity, sleep), PROs, and functional outcomes. Multivariable regression models, adjusted for age, sex, and cancer stage, were fit to evaluate associations between activity metrics, PROs, and functional outcomes. Multivariable cox proportional hazard models were fit to evaluate the impact of activity levels on survival. **Results:** A total of 40 patients consented onto study: 50% female, median age: 67 years (range 47-85), 92% ECOG 1. Baseline activity data are summarized in Table. Statistically significant correlations between step counts and PF T-scores (coeff: 0.6, p = 0.001) and lower pain scores (coeff: -0.53, p = 0.002) were observed. Increased stairs count and time spent in moderate and high physical activity were also positively correlated with increased PF (p<0.001). No statistically significant correlations were observed between hand grip strength, activity metrics or PROs. Fewer average step counts and worse PF scores were significantly associated with poor survival with hazard ratios (HR) of 1.44 per 1000 steps (95% CI 1.06, 1.97, p = 0.02) and 1.69 (95% CI 1.1-2.56, p = 0.017), respectively, after adjusting for age, sex, stage, and ECOG PS. **Conclusions:** Findings from this research suggest that the use of wearable technology for remote monitoring of daily activity is feasible and may be used to supplement functional assessment and predict outcomes in PDAC patients. Larger trials are needed to validate findings. Research Sponsor: Pancreatic Cancer Action Network.

Activity metric	Mean (SD)
Steps/Day	4627.7 (3144)
Distance/Day (miles)	2.0 (1.4)
Stair flights/Day	4.3 (6.9)
Sedentary times (Hours)	14.7 (3.76)
Active minutes	
Light	162.6 (79.6)
Moderate	9.9 (12.9)
High intensity	5.9 (9.3)
Sleep (hours)	5.3 (2.8)

1573 **Poster Session**

Interface software can markedly reduce time and improve accuracy for clinical trial data transfer from EMR to EDC: The results of two measure of work time studies comparing commercially available clinical data transfer software to current practice manual data transfer. *First Author: Maureen Thompson, NEXT Oncology, San Antonio, TX*

Background: Clinical studies and new drug approvals are delayed by slow data transfer and transcription errors from site entered data. These delays have been compounded by a shortage of data entry personnel at sites such that data entry approaches 10-30 days post visit. Data transfer is largely performed by manual keyboard entry from electronic medical records (EMR) into electronic case report forms (ECRF). **Methods:** We conducted two separate measure-of-work time studies to compare a commercially available interface software product, ProXimity to the current manual data entry. The clinical trial data from two different EMRs (ARIA and IKM G2) to an EDC (Medidata Rave). The EDC mirrored an IRB approved clinical study. Time to transfer data and error rates were the primary and secondary endpoints, respectively. For study 1 Aria EMR data from 3 subjects and 1497 data fields including demographics, vital signs, ECOG PS, physical findings, adverse events, and lab results including CBC, CMP, urinalysis, coagulation, serology were selected for visits from Screening and C2D1. For Study 2 IKM G2 data from 6 subjects and 834 data fields included demographics, vitals, and lab results. The data entry personnel were aware of the timed nature of the study. **Results:** Study 1 ProXimity took 13.2 min to transfer the data compared to 73.4 min for manual entry, with error rates of 0.8% compared to 3.5%, respectively. In Study 2 Proximity took 6.5 min compared to 29 min for manual entry, with error rates of 1.4% each due to non- conformant data (text). **Conclusions:** Software data transfer interfaces can markedly shorten the time for data entry, reduce error rates and reduce operational costs. Research Sponsor: None.

1574 **Poster Session**

PRECISE CURATE.AI: A prospective feasibility trial to dynamically modulate personalized chemotherapy dose with artificial intelligence. *First Author: Agata Blasiak, National University of Singapore, Singapore, Singapore*

Background: Most treatment guidelines recommend chemotherapy at maximum tolerated doses, which does not always lead to optimal efficacy, but implicitly results in toxicity. To overcome this challenge, we developed CURATE.AI, a small data, AI-derived platform that harnesses only a patient's own prospectively/longitudinally acquired data to dynamically identify their own optimal and personalized doses. We subsequently harnessed CURATE.AI to dynamically modulate individualized chemotherapy doses for patients in a prospective clinical trial. **Methods:** We conducted an open-label, multicenter, single-arm, prospective feasibility trial in patients diagnosed with advanced solid tumors and treated with single-agent capecitabine, XELOX or XELIRI (+/- biologics) (NCT04522284). The standard-of-care (SOC) capecitabine dose was 1000 mg/m^2, unless adjusted by clinician to account for patient's comorbidities and organ dysfunction. Using an AI-discovered second-order correlation between patient-specific variation of capecitabine doses and corresponding tumor marker (CEA, CA19-9 or CA-125) readouts for each cycle, CURATE.AI generated individualized patient digital avatars and recommended bespoke dose for the subsequent cycle. The clinicians were permitted to accept CURATE.AI dose recommendations, or reject the recommendations and dose based on clinical judgement. **Results:** Since August 2020 we recruited ten patients: single-agent capecitabine (n = 1), XELOX (n = 6), and XELIRI (n = 3). As of 20 Jan 2022, one patient remains on the trial. The prescribed dose was on average reduced by 20 % (± 13.8 %) as compared to the projected SOC dose. The nine reported patients completed 3.9 cycles (± 2.2 cycles), with the longest participation lasting 8 cycles. CURATE.AI recommendations were considered in 27 out of 40 total dosing decisions and accepted for prescription in 26 of those decisions. The reasons for not considering CURATE.AI included insufficient time from patient recruitment to the first dose administration and complex medical circumstances at the time of the dosing decisions. **Conclusions:** CURATE.AI has been successfully incorporated into the clinical workflow of dynamic dose selection in the treatment of solid tumors under a clinical trial. Prospective validation of CURATE.AI led to a reduction of an average prescribed capecitabine dose, which alongside additional preliminary findings may eventually play an important role in improving patient response rates and durations compared to SOC. Results from the PRECISE CURATE.AI trial support the initiation of a randomized clinical trial and potential expansion towards other oncologic indications. Clinical trial information: NCT04522284. Research Sponsor: Institute for Digital Medicine (WisDM) Translational Research Programme (R-719-000-037-733) at the Yong Loo Lin School of Medicine, National University of Singapore, Other Government Agency.

1575 **Poster Session**

Analyzing patient engagement with digital health tools to facilitate equity across a large statewide community oncology practice. *First Author: Debra A. Patt, Texas Oncology, Dallas, TX*

Background: Digital health solutions (DHS) allow for enhanced remote communication between patients and clinical staff and the COVID-19 pandemic has brought these tools to the forefront of care delivery. Once adopted, barriers to adequate utilization still exist. Given the important need to decrease digital divides, and the diversity of patients and care settings across our clinic's 220 sites of service, we sought to understand how utilization of oncology DHS may be limited among certain populations. **Methods:** We investigated utilization among cancer patients who enrolled and engaged with a portfolio of DHS between March 1, 2019 and January 15, 2022. This portfolio includes three tools: (1) an electronic patient-reported outcomes (ePRO) remote monitoring program for tracking symptoms and oral adherence, (2) a patient portal (PP) for securely accessing patient health records, and (3) digital education (DE) for patients regarding disease and treatments. ePRO completion rate, average number of PP logins, and DE read rate were used as measures of utilization for each tool, respectively, and compared among patients with different age (< 65 and ≥65 years), language preference [English (EL) or Spanish (SL)], and distance from clinic (non-rural: < 20 miles OR rural: ≥20 miles). Mann-Whitney U and Chi-Square tests were used to compare continuous and categorical variables, respectively. **Results:** This study included a total of 77,347 unique patients representing 651,004 digital encounters. 9,938 patients engaged in ePRO, 49,771 patients in PP, and 12,044 patients in DE. Engagement across all DHS was high in patients of age group < 65 (ePRO: 72.7%, PP: 79.67% and PE 54.7%) as compared to ≥65 years, but the ePRO completion rate is high in ≥65 age group (59.0% vs 55.6%), whereas no significant difference was observed in the PP login activity and DE read rate. EL patients were significantly (p-value < 0.01) more engaged (ePRO 68% vs. 54%, PP: 80% vs. 62%, DE: 57% vs. 37%) and had higher digital utilization (ePRO completion rate: 57.31% vs 53.23%, average PP logins: 7.48 vs 7.14 and DE read rate: 96.2% vs 90.8%) than SL patients across the DHS. Patients living in rural areas comprised roughly 25% of the population and participated across tools similarly as patients living in non-rural areas (ePRO 67% vs. 69%, PP: 79% vs. 79%, DE: 56.9% vs. 56.8%). Utilization of the portfolio was variable based on rural vs non-rural status (ePRO completion rate: 56.3% vs. 57.4%, average PP logins: 7.9 vs. 7.3, DE read rate: 96.02.7% vs 96.3%). **Conclusions:** Despite variable engagement based on age, language, and rural status across the portfolio, patients within these populations continue to utilize the DHS. How we understand and explore enhancements to DHS remain under investigation for tool optimization for patient-specific barriers to care. Research Sponsor: None.

1576 **Poster Session**

Comparative effectiveness of different interventions for cancer-related fatigue delivered digitally by online platforms. *First Author: Paris A. Kosmidis, Care Across, London, United Kingdom*

Background: As cancer treatments improve, patients' quality of life becomes even more important. In parallel, supportive care delivery is increasingly challenging, also due to resource pressures and COVID19. The effectiveness of digital and remote patient support tools as a complementary approach to improve patients' quality of life is under evaluation. Fatigue is considered among the most prevalent and persistent side effects regardless of tumour type; also, despite ongoing research, there is no single approach established. We compare the effectiveness of different self-care interventions delivered by online platforms to cancer patients in several countries. **Methods:** Patients report side effects (including Fatigue) on the CareAcross online platforms and receive tailored support to help them improve their quality of life. The supportive material encompasses many topics, and patients may receive several combinations. For Fatigue, different topics (nutrition, hydration, rest etc) were analysed to evaluate effectiveness based on prospectively collected patient reported outcomes. **Results:** 1456 breast, lung, colorectal or prostate cancer patients from 8 countries (mainly UK, Germany, France, Spain, Italy) reported Fatigue at least once. This analysis focuses on persistent fatigue: 1215 patients reported Fatigue more than once, receiving up to 7 permutations of topics (F1-F7; F4-7 consist of F1-3 combinations). All permutations include the "Physical Activity" topic (see Table). Overall, the "Hydration" topic stands out as consistently linked with the most effective material (all except F3). Comparative analysis between similar combinations shows that those with "Anemia warnings" and "Rest" tend to be more effective (F7>F6). Ambiguously, the "Physical activity before & after treatment", "Relaxation exercises" and "Fatigue diary" topics contribute to effectiveness (F5>F1), but do not counterbalance absence of the previous 3 (F1>F3). Food-related topics have unclear impact, too: "Food types" is absent from the top combination (F2) where "Food timing" is used; however, that topic is linked with a slightly inferior combination (F7>F5). **Conclusions:** Fatigue is a complex, multifactorial challenge; digitally delivered interventions can lower its incidence. Hydration appears effective, but the nature of these interventions complicates their thorough evaluation. Randomised studies may enhance these findings and enable additional personalisation towards further quality of life improvements. Research Sponsor: None.

Material (beyond "Physical Activity")	F1 (N = 65)	F2 (N = 77)	F3 (N = 79)	F4 (N = 213)	F5 (N = 200)	F6 (N = 205)	F7 (N = 376)
Physical activity before & after treatment			Y		Y	Y	Y
Relaxation exercises		Y	Y	Y	Y	Y	Y
Fatigue diary		Y	Y	Y	Y	Y	Y
Food types	Y		Y	Y	Y	Y	Y
Food timing		Y		Y		Y	Y
Hydration	Y	Y		Y	Y	Y	Y
Rest	Y			Y	Y		Y
Anemia warning	Y			Y	Y		Y
Effectiveness=reduced Fatigue incidence	27.7%	41.6%	21.5%	29.1%	34.0%	29.8%	32.2%

1577 **Poster Session**

Electronic capture of cancer-related distress in a community oncology program. *First Author: Amit Sanyal, SSM Health Cancer Care, Madison, WI*

Background: Cancer related distress can be seen in as many as one in two patients. Many organizations such as the Commission on Cancer require distress screening. National Comprehensive Cancer Network (NCCN) distress thermometer is a common tool used for screening. We studied feasibility of embedding the NCCN thermometer into oncology electronic health record (EHR) for routine patient care. We concurrently studied feasibility of using a mobile health tool for serial evaluation of cancer related distress. **Methods:** A flowsheet containing NCCN distress thermometer questions was created in Epic EHR (Epic Systems, Verona, WI). Oncology nurses used the flowsheet for routine patient assessment. Patients with distress level ≥ 4 answered additional questions. Ancillary care providers such as palliative care nurses or social workers addressed the identified needs by providing appropriate 'services'. A field to capture these interventions was created. We also adapted our previously reported web based mobile tool [1] for monitoring cancer distress. Patients rated their distress on a 1-10 scale and highlighted the distress domain (physical, emotional, practical, family). Distress level ≥ 4 generated a color-coded flag for provider review and intervention. Data from both electronic tools was periodically analyzed to inform patient care and quality improvement. **Results:** Between January and December 2021, Epic EHR based distress flowsheet collected 28,594 distinct responses in 911 patients. 57.4%, 14.9%, 14.1%, 9.4% and 2.3% of the responses were in the physical, emotional, practical, familial and spiritual domains respectively. 'Other' responses were 1.4%. Cumulative frequency of non-physical problems was 42.5%. 1819 'services' were provided with 357 emotional, 351 work, 351 housing, 350 transportation and 350 financial need-based interventions. Of 1231 patients who used the distress scale and provided additional comments, 315 (25.5%) had distress levels ≥ 4. The mobile tool captured 849 unique patient responses to the distress question between April 2020 and February 2022. Distress level ≥ 4 was flagged by 281 unique patients (33.09%). Average distress level was 2.7. Emotional domain problems generated the greatest distress level followed by family, physical and practical problems in decreasing order. **Conclusions:** We demonstrate feasibility of electronic capture of cancer related distress to facilitate holistic patient care in a community-based oncology program. EHR based and mobile tool distress evaluations generated concordant results. Distress caused by emotional, practical and familial domain problems was nearly as frequent and often more severe than distress caused by physical problems, underscoring the need for comprehensive cancer care. References:Sanyal, A. *Mobile health tool for monitoring cancer treatment complications*. 2020 ASCO Quality Care Symposium: American Society of Clinical Oncology. Research Sponsor: None.

1578 **Poster Session**

Association between remote monitoring and acute care visits in high-risk patients initiating intravenous antineoplastic therapy. *First Author: Robert Michael Daly, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Acute care visits (emergency department [ED] visits or inpatient admissions) for patients with cancer are growing disproportionately. Traditional oncology care models have not effectively identified and managed at-risk patients to prevent acute care. A next step is to harness advances in technology and mobile applications to enable patients to report symptoms any time, enabling "digital hovering" - intensive monitoring and management of high-risk patients. Our objective was to evaluate a digital platform that identifies and remotely monitors high-risk patients initiating intravenous antineoplastic therapy with the goal of preventing unnecessary acute care visits. **Methods:** This was a single-institution matched cohort quality improvement study conducted at an NCI-designated cancer center between January 1, 2019 and March 31, 2020. Eligible patients were those initiating intravenous antineoplastic therapy who were identified as high-risk for seeking acute care. Patients were identified as high-risk for an acute care visit by their oncologist with decision support from a web-based machine learning model. Enrolled patients' symptoms were monitored using a digital platform. The platform is integrated into the EMR and includes: 1) a secure patient portal enabling communication and daily delivery of electronic patient-reported outcomes symptom assessments; 2) clinical alerts for concerning symptoms; and 3) a symptom trending application. A dedicated team of registered nurses and nurse practitioners managed reported symptoms. These clinicians acted as an extension of the primary oncology team, assisting with patient management exclusively through the platform. The primary outcomes evaluated were incidence of ED visits and inpatient admissions within six months of intravenous antineoplastic initiation. **Results:** Eighty-one high-risk patients from the intervention arm were matched by stage and disease with contemporaneous high-risk control patients. Matched cohorts had similar baseline characteristics, including age, sex, race, and treatment. ED visits and hospitalizations within six months of treatment initiation were analyzed using cumulative incidence analyses with a competing risk of death. The cumulative incidence of an ED visit for the intervention cohort was 0.27 (95% CI: 0.17, 0.37) at six months compared to 0.47 (95% CI: 0.36, 0.58) in the control group (p = 0.01). The cumulative incidence of an inpatient admission was 0.23 (95% CI: 0.14, 0.33) in the intervention group versus 0.41 (95% CI: 0.30, 0.51) in the control group (p = 0.02). **Conclusions:** The narrow employment of technology solutions to complex care delivery challenges in oncology can improve outcomes and innovate care. This program was a first step in using a digital platform and a remote team to improve symptom care in the home for high-risk patients. Research Sponsor: U.S. National Institutes of Health.

1579 **Poster Session**

Lack of price transparency for prostate-directed radiation therapy relative to radical prostatectomy. *First Author: Rahul Neal Prasad, Department of Radiation Oncology, The Ohio State University Wexner Medical Center, Columbus, OH*

Background: For patients with low to favorable-intermediate risk prostate cancer (PC), management with active surveillance, radical prostatectomy (RP), external beam radiation therapy (EBRT), and brachytherapy (BT) are all National Cancer Center Network-supported definitive monotherapy options. Because therapy is non-urgent and choosing therapy can be complex, patients routinely seek second opinions and cost can be an important consideration. Recent federal price transparency (PT) guidance requires hospitals to provide payer-negotiated prices for ≥300 common services in a "shoppable," user-friendly, online format. 70 services, including RP, are specified, while the remainder are left to institutional discretion. Despite equipoise between radiation therapy (RT, inclusive of EBRT and BT) and RP in definitive treatment for PC, inclusion of prices for RT is optional. National Cancer Institute (NCI)-designated cancer centers (NCI-CC) are high volume referral centers who have the option to volunteer prices for RT; the rate at which NCI-CC choose to report payer-negotiated price estimates for prostate-directed RT is unknown. We hypothesize that reporting rates for BT and EBRT are significantly lower than for RP. **Methods:** Through online query, we identified "shoppable" price tools for NCI-CC in December 2021. Using billing codes and keyword searches, we queried these price tools for cost estimates for RP, EBRT (delivered using intensity modulated radiation therapy), and BT. Descriptive statistics, include frequency counts and proportions, were performed. The rate of reporting of "shoppable," negotiated prices for each therapy was assessed. These rates were compared using the chi-squared test (significance level of $\alpha = 0.05$). **Results:** Of the 63 NCI-CC offering clinical care, 58 (92%) published "shoppable" tools. 6 (10%), 7 (11%), and 51 (81%) published "shoppable" prices for EBRT, BT, and RP, respectively, demonstrating a significantly higher rate of publication of prices for RP than for EBRT or BT ($P < 0.001$). All of the published prices for BT were for high dose rate BT. The 11 Medicare Prospective Payment System–exempt NCI-CC had the highest rates of reporting "shoppable" prices at 91%, with 64%, 27%, and 36% including prices for RP, EBRT, and BT, respectively. **Conclusions:** Under existing regulations, patients with PC can obtain payer-negotiated price estimates for EBRT and BT from just roughly 10% of NCI-CC, while price estimates for RP are offered by > 80% of these institutions. This represents a potential obstacle to informed decision making, undermines the stated goals of US PT health policy, and the impact on utilization rates (or patient choice of therapy) is unknown. Moving forward, mandating the inclusion of common RT services (EBRT and BT) in "shoppable" price tools is a straightforward intervention that may be highly beneficial in this common cancer population. Research Sponsor: None.

1580 **Poster Session**

Pharmaceutical industry payments to physicians for the promotion of cancer drugs. *First Author: Aaron Philip Mitchell, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Personal financial payments from the pharmaceutical industry to oncologists are common and increasing. A prevalent view is that the purpose of industry payments to physicians is to facilitate education on new drugs. However, little is known regarding the distribution and trends in industry payments related to cancer drugs. The goal of this study was to characterize current patterns in industry payments related to cancer drugs, and test whether these patterns are consistent with an educational purpose. **Methods:** We included on-patent cancer drugs without generic/biosimilar competitors, and used publicly-available federal data sources to measure Medicare spending (proxy for overall drug revenue), number of prescribers, and industry payments (Open Payments, which includes data regarding which the drug[s] was the subject of each payment) for each calendar year from 2014-2018. We analyzed General Payments to individual physicians, which encompasses payment types such as meals, travel, consulting, and speaking fees. We tested two hypotheses implied by the claim that industry payments serve educational purposes. First, payment amounts should not be associated with drug revenue. To test this hypothesis, we used generalized estimating equations (GEE) to model the association between mean per-physician industry payments and Medicare spending. Second, payments related to a given drug should decline over time as physicians become educated. To test this hypothesis, we determined the relative year-to-year change in industry payments for all cases wherein consecutive years were observed, and used GEE to estimate the year-to-year change with respect to duration of time since initial FDA approval. **Results:** The sample included 89 drugs and 361 drug-year observations. The total amount of industry payments for oncology drugs increased during the study period, from $53,333,854 in 2014 to $90,343,731 in 2018. There was no association between log-transformed mean, per-physician industry payments and per-physician Medicare spending (estimate -0.001, 95%CI: -0.005, 0.004). In aggregate, Industry payments for cancer drugs were greatest immediately after FDA approval and trended downward over time; the estimated industry payments in the subsequent year for a drug with mean payments of $1,000 per-physician in the index year was: $681* for drugs 0-4 years since approval, $825 for drugs 5-9 years, and $679* for drugs≥10 years (*p<0.05). **Conclusions:** The absence of association between industry payments and Medicare spending and the decline in industry payments for drug subsequent to approval are consistent with claims that these payments function to facilitate physician education. Research Sponsor: U.S. National Institutes of Health.

1581 **Poster Session**

Exploring country priorities and contextual considerations for implementing national cancer control plans (NCCP) among participants of International Cancer Control Partnership (ICCP) ECHO. *First Author: Darya Aleksandrovna Kizub, UT MD Anderson Cancer Center, Houston, TX*

Background: Promoting NCCP implementation by low- and middle-income countries (LMICs) is key to addressing inequities in cancer outcomes and the global burden of cancer. We explored contextual factors that may influence implementation of NCCP priorities in LMICs. **Methods:** Seven countries participated in the 2021 International Cancer Control Partnership ECHO (R) geared toward creating a community of practice to inform NCCP implementation. Using qualitative methods, we conducted focus group discussions (FGDs) with country teams who were asked to identify NCCP priorities and provide contextual considerations around implementing these in the 12-months program. FGDs were audio-recorded, transcribed, double-coded, and underwent thematic analysis. **Results:** Thirty-three participants from 6 Sub-Saharan African countries and 1 country in Asia took part in 7 FGDs, including 14 physicians, 9 non-governmental organizations, 6 Ministry of Health/NCCP and 4 cancer registry representatives. All seven country teams (100%) prioritized cancer early detection, especially for cervical (71%) and breast (57%) cancer, including by educating primary care clinicians (57%) and general population (43%) about cancer signs and symptoms. Related contextual factors included late-stage diagnosis of cancer (43%) and low knowledge about cancer among primary care clinicians and the general population (29% each), respectively. Finding resources for implementation of NCCP priorities was important given lack of funding (57% each). Harmonizing programs and building partnerships for implementation (57%) was prioritized given perceived fragmentation of efforts and benefit of leveraging limited resources (29% each). Improving access to treatment (43%) was a priority given a lack of oncology specialists (29%) and unaffordable treatment (14%). Improving access to palliative care (43%), including by writing guidelines (29%), was prioritized due to late-stage diagnosis and insufficient access to palliative care (14% each). Improving cancer registry data was essential for NCCP program planning (43% each), while cancer research (43%) was key to answering specific questions related to cancer registry data (14%) and program impact (29%). Additional contextual considerations for making progress on these priorities dicussed by country teams included leveraging existing programs (100%) and learning from other countries and ICCP technical experts (57% each). **Conclusions:** There were similarities in country NCCP priorities and contextual factors affecting implementation. These results allow for future exploration of how LMIC country teams implement NCCPs and examine the value of communities of practice promoted by ICCP and facilitated by ECHO, towards improving cancer outcomes. Research Sponsor: None.

1582 **Poster Session**

Financial payments from the pharmaceutical industry to U.S. cancer centers, 2014-2019. *First Author: Aaron Philip Mitchell, Duke University, Durham, NC*

Background: Payments from the pharmaceutical industry to US health care providers were made public through Open Payments in 2013. Since then, industry payments to individual physicians have been studied extensively, but payments to hospitals remain uncharacterized. The goal of this study was to examine trends in industry payments to US cancer centers. **Methods:** We identified all US cancer centers that were National Comprehensive Cancer Network (NCCN) members or were National Cancer Institute (NCI) comprehensive cancer center as of 2019. Each institution was manually mapped to Open Payments, which contains industry payment data. Where applicable, subsidiary hospitals were included with the parent center. Among the NCCN centers, we used National Plan and Provider Enumeration System data to identify medical oncologists practicing there. Oncologists were linked to Open Payments by name and address. We analyzed "research payments" (RP), which include payments related to preclinical and clinical research, and "general payments" (GP), which include non-research-related payments in categories such as speaker fees, consulting fees, meals, grants, charitable contributions, and licensing fees. We ascertained public research support from NIH data, and included all research project grants. We used correlation analysis and linear regression models to assess the association between industry payments to a cancer center and to oncologists practicing at that center. All dollar values were inflation-adjusted to 2019 dollars using the Consumer Price Index for medical care from the US Bureau of Labor Statistics. **Results:** Overall industry RP to US cancer centers increased from $527 million in 2014 to $653 million in 2019, while GP increased from $346 million to $786 million. NCI research funding increased from $1,397 million in 2014 to $1,583 million in 2019 (13.3% increase) while overall industry payments (RP+GP) increased from $873 million to $1,439 million (64.8% increase). Industry payments were highest as a portion of total income (industry + NCI) at MD Anderson (64.2%) and lowest at St. Jude (0.1%). Among NCCN institutions, industry payments to cancer centers and the oncologists practicing at those centers were correlated (coefficient = 0.382). A $1,000 increase in GP to a cancer center from a given pharmaceutical company was associated with a $1.00 ($0.61 - $1.30) increase in GP from that company to oncologists at that cancer center. **Conclusions:** From 2014-2019, cancer center funding from industry sources grew quickly, driven by an increase in non-research payments, and now approaches the amount of public research funding cancer centers receive. Cancer center acceptance of industry payments is associated with increased industry payments to its employed physicians, which are known to sway prescribing practices. These trends raise concerns regarding the ability of these institutions to fulfill their public missions. Research Sponsor: U.S. National Institutes of Health.

1583 **Poster Session**

Disparity in initiation of checkpoint inhibitors among metastatic melanoma and lung cancer. *First Author: Meng Li, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Checkpoint inhibitors are transforming cancer care. However, the high prices of these medicines raise concerns over their affordability and disparity in use. The objective of this study is to describe the disparity in initiating checkpoint inhibitors and examine patient- and area-level factors associated with delayed initiation. **Methods:** This study is a retrospective cohort study using Optum data. We identified commercially insured patients newly diagnosed with metastatic lung cancer and melanoma since the introduction of checkpoint inhibitors in these cancers (lung cancer cohort: diagnosed between January 2015 and December 2020; melanoma cohort: diagnosed between January 2011 and December 2020). Time from metastatic cancer diagnosis to initiating checkpoint inhibitors was analyzed using Cox proportional hazard models. Independent variables included county-level measures (percentage of black population, percentage of Hispanic population, percentage of other minority, percentage of population living below poverty line, rurality, number of medical oncologist per population, and having a National Cancer Institute designated cancer center) and patient-level characteristics (age, sex, Charlson comorbidity index, any dual eligibility, Medicare Advantage, and year of diagnosis). We clustered standard errors at the county level. **Results:** The percentage of metastatic lung cancer and metastatic melanoma patients on checkpoint inhibitors increased from 23% to 52% from 2015 to 2020 and from 22% to 58% from 2011 to 2020. Counties with greater percentage of black, Hispanics, and other minorities were high urban with greater density of medical oncologists and NCI-designated cancer centers. However, greater percentage of Hispanic population in a county was associated with significantly slower initiation of checkpoint inhibitors for both the lung cancer and the melanoma cohorts (hazard ratios [HR]: 0.937 and 0.946, respectively; p-values: < 0.001 and 0.014, respectively). Percentage of other minority population in a county was associated with slower initiation for metastatic lung cancer (HR: 0.983; p-value: < 0.001). No other county-level factors had a significant coefficient from the multivariate Cox models. In terms of patient-level characteristics, older age, female, more comorbidities, any dual eligibility, and Medicare Advantage were associated with significantly slower initiation for the lung cancer cohort and older age and female were associated with significantly slower initiation for the melanoma cohort. **Conclusions:** Commercially insured metastatic lung cancer and melanoma patients who lived in counties with greater percentage of Hispanic population had slower initiation of checkpoint inhibitors after their cancer diagnosis, despite the fact that those counties had greater density of medical oncologists and NCI-designated cancer centers. Research Sponsor: None.

1584 **Poster Session**

The impact of physician-hospital integration on spending and quality of oncology care. *First Author: Pragya Kakani, Harvard University, Cambridge, MA*

Background: There has been increasing hospital and health system ownership of physician practices in recent years, particularly in oncology. However, relatively little is known about how this impacts care delivery for patients with cancer, who use many hospital-based services that may be impacted by integration. We evaluated the impact of physician-hospital integration in oncology on spending and quality of care for Medicare beneficiaries with cancer. **Methods:** We used Medicare Fee-for-Service claims from 2005-2019 linked with a unique Health System and Provider Database, developed by National Bureau of Economic Research and Harvard University researchers, to track practice ownership relationships over time. We used a stacked event study to assess outcomes for patients three years before and after oncologists move from independent practices to hospital- or system- owned practices. We compared outcomes to a control group with oncologists who shifted from independent to hospital- or system-owned practices in later years. We focused on two cohorts of patients. The first cohort included cancer patients with presumed incident or recurrent cancer based on $\geq$2 visits to an oncologist and no visit in the past year. For these patients, we evaluated the impact of physician-hospital integration on the likelihood of receiving chemotherapy following the visit. The second cohort included 6-month episodes for patients receiving chemotherapy. For these patients we evaluated the impact of physician-hospital integration on spending, utilization, and quality. Quality measures included receipt of timely chemotherapy (within 60 days) following surgery, inpatient readmissions, non-use of tamoxifen + strong CYPD26 inhibitors, and end-of-life intensity of care measures. **Results:** There was no change in the likelihood of receiving chemotherapy with an initial oncology consultation following an oncologist's transition to hospital-based employment. Total spending during six-month chemotherapy episodes increased by $1391 (95%CI: $465, $2316). The primary contributors to this growth were increases in spending on inpatient care, chemotherapy administration, and office visits. Spending growth, where observed, was driven primarily by higher Medicare prices for care in hospital outpatient settings. We found no positive impact of physician-hospital integration on timeliness of chemotherapy initiation, readmissions, concurrent use of tamoxifen+strong CYPD26 inhibitors, or intensity of end-of-life care. **Conclusions:** Physician-hospital integration resulted in higher prices and thus higher spending, but had limited impact on utilization and no detectable impacts on measures of quality. These results suggest that claims of quality improvements and concerns regarding overuse associated with physician-hospital integration may be overstated. Our results also support continued movement towards site-neutral payments. Research Sponsor: U.S. National Institutes of Health.

1585 **Poster Session**

Market determinants of commercial prices for intravenous chemotherapy infusions. *First Author: Michael Milligan, Harvard Medical School, Boston, MA*

Background: Recent price transparency legislation mandated that hospitals across the country report their individually negotiated prices with insurers. Using this data, we sought to characterize the prices paid for standard intravenous (IV) chemotherapy infusions, and determine the hospital, regional, and market factors associated with higher prices. **Methods:** We utilized a database of U.S. hospital-reported price transparency data to characterize prices for the most commonly billed chemotherapy drug administration Common Procedural Terminology (CPT) codes—*96413* (initial IV chemotherapy infusion) and *96415* (additional hour of IV chemotherapy). We obtained standard charges and commercial prices negotiated with private payers from hospitals that directly administer chemotherapy. To assess variation in prices, we calculated the ratio of the 90th percentile price to the 10th percentile price among private payers in each hospital and among hospitals in each Hospital Referral Region (HRR). We performed multivariable linear regressions to assess hospital, regional, and market factors associated with higher prices. **Results:** A total of 1,458 hospitals reported at least one price for CPT code *96413* or *96415*. Hospitals reported 1 chargemaster and a median of 18 (IQR: 8–35) commercial prices negotiated with different private payers. National median commercial prices for CPT codes *96413* and *96415* were $536.00 (IQR: $326.43-$784.63) and $175.06 (IQR: $98.28-$327.25), respectively. Within each hospital, the 90th percentile commercial price was 2.2 times higher, on average, than the 10th percentile price for CPT code *96413*, and 2.8 times higher for *96415*. Among different hospitals within each HRR, the median commercial price at the 90th percentile hospital was 1.5 times higher than at the 10th percentile for CPT code *96413*, and 2.3 times higher for *96415*. On multivariable analysis, higher prices for CPT code *96413* were observed at for-profit hospitals ($215.12 higher than government not-for-profit hospitals, 95% CI: $55.22-$429.61). Higher prices for CPT code *96415* were observed at hospitals with higher predicted practice costs ($35.79 for every 1% increase in the geographical practice cost index, 95% CI: $16.69-$54.87), and a lower disproportionate share percentage ($0.96 for every 1% decrease in DSH patient percentage, 95% CI: $0.08-$19.41). **Conclusions:** Commercial prices for commonly billed IV chemotherapy infusions demonstrate significant variability. Prices for identical infusions vary by a factor of 2 depending on which hospital or private payer a patient selects. While prices for CPT code *96415* are largely explained by the relative cost of care, prices for the more expensive *96413* appear to be driven by the profit-status of the hospital. Further study is required to characterize the implications of such high levels of price variability on access to care and overall healthcare costs. Research Sponsor: None.

1586 **Poster Session**

Time to access to novel anticancer drugs in Europe, a case study in seven European countries. *First Author: Colinda Post, AmsterdamUMC, Amsterdam, Netherlands*

Background: After European Medicines Agency Marketing Authorization (EMA-MA) different national reimbursement processes may contribute to unequal access throughout the EU. The aim of this study is to investigate the access time to new anticancer medicines in seven high-income Northern European countries and factors influencing the reimbursement process. **Methods:** We performed a retrospective database study. New anticancer medicines were included with a positive CHMP advice between January 2016 and January 2020, leading to EMA-MA followed by an application for national reimbursement approval in Germany, UK, France, The Netherlands, Belgium, Norway and Switzerland. The relevant Health Technology Assessment (HTA) - and reimbursement websites for each country were used to identify reimbursement dates. Time to access was defined as the time between EMA-MA and date of inclusion in the relevant reimbursement list. In addition we investigated the differences in national approval process and study-, medication- and patient- related factors which might influence the time to reimbursement. **Results:** We found that for the thirty-six new anticancer medicines, national reimbursement came on average 289 days after EMA-MA, with a variety of -125 in Switzerland (i.e. non EU-member) to 1415 days. Of these EMA-MA new anticancer medicines 42% were reimbursed in all countries. The average number of cancer medicines reimbursed in the examined countries was 27 (75%) , with a range of 24 (67%) in Belgium to 36 (100%) in Germany. The shortest average time from EMA-MA to reimbursement were in Germany, 2.33 days, France and Switzerland following with 207 days and 279 days respectively. The median time to reimbursement was 227 days with a range of 3 days in Germany to 553 days in Belgium. In Germany, where there is no pricing and reimbursement approval required when launching a pharmaceutical, 100% of the cancer medicines are reimbursed within five days. After one year, In the UK 56% of the medicines are reimbursed, followed by 53% in the Netherlands, France and Switzerland. Belgium and Norway have a one year reimbursement rate of 14% and 11% respectively. Access to anticancer medicines is dependent on regulatory procedures, HTA and price regulations. Germany has a fast market access for anticancer medicines with a price regulation one year after launching the medicines. In the other countries, price regulation is part of the launching process. Other factors which might accelerate the time to reimbursement we are examining are high clinical benefit score (ESMO-MCBS), (non-)orphan status of the medicines and submission by big pharmaceuticals. **Conclusions:** This study shows that after EMA-MA, except for Germany, on average it takes a long time for anticancer medicines to be reimbursed in Northern European countries. There is a considerably variety both within and among countries. Research Sponsor: None.

1587 **Poster Session**

Reliability of cancer registry primary payer information and implications for policy research. *First Author: Amy J. Davidoff, National Cancer Institute, Rockville, MD*

Background: Researchers commonly use "Primary Payer at Diagnosis" measured in cancer registry data to assess the impact of health policy, such as the Affordable Care Act, on insurance, and the impact of insurance on cancer care and outcomes. Measurement error may bias estimated effect size and significance. Little is known about patterns of Medicaid or Medicare misreporting in registry databases commonly used for policy analysis. **Methods:** We used the National Cancer Institute's Surveillance, Epidemiology and End Results registry data for adults aged 19-64 years at diagnosis with known cancer stage, linked to most recently available (2007-2011) CMS records on Medicaid and Medicare enrollment at diagnosis month. We recoded the registry Primary Payer variable into 6 categories: private/managed care, Medicare, Medicaid, other government, status unknown, uninsured. State-year policy data regarding Medicaid eligibility and managed care enrollment were also linked. We compared the registry data to Medicaid and/or Medicare enrollment data, and calculated underreporting rates by patient characteristics and state policy. **Results:** The linked sample (N = 896,031) was 68% non-Hispanic white, 49% male. Overall, the registry data reported 7.8% Medicare and 10.1% Medicaid, while enrollment was 5.5% Medicare, 10.4% Medicaid, and 3.4% dual Medicare-Medicaid. The registry data concordantly identified 61.4% and 57.7% of persons identified per enrollment data to be Medicaid-only and Medicare-only, respectively (Table). Most Medicaid-only enrollees without concordant registry information were reported to have private insurance or be uninsured. Medicaid underreporting (39% overall), was higher for males (43%) vs females (37%), in low (46%) vs high (38%) poverty areas, for Medicaid poverty expansion or waiver enrolled (50%) vs cash assistance related eligibility (33%), and in states with large managed care enrollment, all at p<.001. If Medicaid and Medicare enrollment data were used to edit the registry data, 8% of persons would switch insurance assignment. **Conclusions:** Primary Payer data reported by cancer registries are subject to measurement error and may result in biased estimates of insurance-related policy impacts. Enhancement with objective Medicaid and Medicare enrollment data will reduce measurement error and may result in unbiased estimates necessary to support policy assessment. Research Sponsor: None.

Distribution of CMS Medicaid & Medicare enrollment by registry primary payer (column %).

Registry Payer Data	Total (100%)	Medicaid only (10.4%)	Medicare only (5.5%)	Dual enrolled (3.4%)	Neither (80.7%)
Private	68.0	19.3	28.2	7.6	79.6
Medicare	7.8	3.7	57.7	80.2	1.9
Medicaid	10.1	61.4	1.4	6.5	4.3
Other government	3.3	1.2	6.1	1.0	3.5
Unknown insurance status	5.6	3.9	5.2	4.0	5.9
Uninsured	5.1	10.6	1.3	0.7	4.9

1588 **Poster Session**

Effect of immunotherapy and time-of-day infusion chronomodulation on survival in advanced cancers. *First Author: Blessie Elizabeth Nelson, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Emerging clinical studies report correlation of time-of-day infusion (TOI) to immunotherapy outcomes and the intricate interplay of the human circadian rhythm and cancer and immunotherapy exposure. Preclinical and clinical studies have shown cancer chronotherapy to play important role in transcriptional rhythmicity of oncogenic process. We evaluated the association of TOI and immunotherapy outcomes in a large cohort to determine impact of TOI on overall survival (OS) and progression free survival (PFS). **Methods:** We reviewed charts of patients with solid tumors who received immunotherapy, specifically anti programmed cell death protein 1 (PD1) and anti-programmed death-ligand 1 (PD-L1) agents at MD Anderson Cancer Center. Infusion times were divided into two hours cohorts from 8am-8pm and one overnight cohort from 8pm-8am. Accelerated failure time models were used to model OS (log-normal distribution) and PFS (Weibull distribution) with relation to TOI after adjusting for factors such as age, gender, tumor type and prednisone > 10mg daily use within 1 month of immunotherapy initiation to minimize confounding factors. **Results:** Of 6151 patients with advanced tumors, 4441 patients received immunotherapy therapy after adjusting for minimum 140 patients in each tumor cohort from 10/15/2016 until 10/15/2021. Tumor types included advanced lung cancer (31.4%), melanoma (28.7%), renal (14.4%), breast (7.6%), colon (6.2%), liver cancer (3.9%) and head and neck (H&N) cancers (2.8%). Median age was 63 (15-99) with 58% males and 42% female. 1894 (43%) patients received investigational agents and 2547 (57%) received standard of care therapies. Mechanism of action of various agents: anti PD1, anti-PDL1, TGF-βRII and anti-PDL1, anti-PD-1 with OX40+ T Cell activation, PD-1 / PD-L1 bispecific antibody, PD-L1 dependent 4-1BB agonist and anti PD-1 and CTLA-4 activity. Among all patients, median OS was 26.4 months while median PFS was 4.8 months. Preponderance of immunotherapy TOI occurred between 12-2pm and 2-4pm in all patients. Patients receiving overnight TOI with lung, renal and breast cancer demonstrated significantly ($p < 0.05$) poorer OS compared to TOI (10am-4pm) whereas in melanoma, significantly lower OS was seen with overnight, 8-10am and 6-8pm compared to 10am-4pm TOIs. Among H&N cancer patients, early TOI (8-10am) was associated with significantly lower OS compared to afternoon TOI (12pm-4pm). PFS trends were less distinct than for OS but showed a slighted inverted tendency towards lower PFS following daytime TOI. **Conclusions:** In this large cohort of patients treated with immunotherapy, clinically significant association of TOI with overall survival is seen. These intriguing findings warrant prospective validation in a future randomized trial to harness the role of chronomodulation of cancer therapies for improving outcomes. Research Sponsor: None.

1589 **Poster Session**

Novel use of clinical pathways to identify poor prognosis lung cancer patients: Implementation and outcomes. *First Author: David Michael Jackman, Dana-Farber Cancer Institute, Boston, MA*

Background: Cancer patients in the last year of life have different clinical needs and evolving goals of care. Using our oncology decision-support pathways to help clinicians consistently identify such patients in a systematic and prospective fashion, at a discrete moment in the care trajectory, may be an important step towards matching the care of these patients with their stated goals. **Methods:** Medical oncologists from each disease group at the Dana-Farber Cancer Institute (DFCI) were tasked with identifying clinical settings in each oncology care pathway associated with an expected median survival of < 12 months. This information was embedded into the underlying data model of the pathways platform, allowing us to determine how often clinicians navigated through each poor prognosis node. **Results:** From 3/1/20 – 6/30/21, there were 264 navigations in 205 unique lung cancer patients receiving standard of care (i.e., not on clinical trial) for a clinical condition associated with poor prognosis. Overall, the median overall survival from the time of a patient's first navigation through a poor prognosis node during the defined study period was 6.4 months. Table lists outcomes for each specific setting. Patients with squamous or small cell lung cancer being treated in or beyond the third-line setting had notably poor outcomes, with less than a third of these patients surviving 6 months from the time of navigation. **Conclusions:** A clinical pathways platform can be a key tool in designating clinical scenarios associated with poor prognosis and identifying patients who may be particularly at risk. Pathways analytics provide real-world evidence corroborating the expected poor prognosis based on published studies and can identify specific clinical subsets for whom specific resources are warranted. By embedding this into the pathways data model, we aim to alert physicians to conduct goals of care conversations, offer supportive care resources, and match patients to appropriate treatment options and clinical trials. Research Sponsor: None.

Setting	Navigations	Died/ censored	6-month survival, %	Median overall survival (OS) from date of pathway navigation, months (95% CI)
Metastatic NSCLC, non-squamous, targeted therapies inappropriate or exhausted, 3rd line or beyond	95	77/18	51%	6.6 (5.0-8.3)
Metastatic NSCLC, squamous, 2nd line	26	16/10	64%	9.0 (2.6-13.3)
Metastatic NSCLC, squamous, 3rd line and beyond	23	18/5	33%	3.5 (1.8-5.5)
SCLC, second line	62	47/15	47%	5.7 (3.9 – 7.5)
SCLC, 3rd line and beyond	58	49/9	32%	4.2 (3.2-5.2)

1590 **Poster Session**

Patient efficacy in telehealth is moderated by distress among patients with cancer: A cross-sectional survey study. *First Author: Joseph William McCollom, Wright State University, Dayton, OH*

Background: The COVID-19 pandemic increased the use of telehealth to reduce exposure, which was critical for patients with cancer. The extent to which patients with cancer view telehealth visits as meeting their medical needs was investigated using a cross-sectional survey. **Methods:** Patients currently receiving cancer treatment at a single cancer institute who had had at least one telehealth visit were emailed an online survey. Response rate was 5% (94/1944). The survey measured patients': 1) Emotional Thermometer (i.e. distress, anger, depression, anxiety, and need for help on a 0-10 scale); 2) Telehealth usability questionnaire (TUQ; 21-items with various subscales, like interaction quality; α=0.98).); and 3) Perceived Efficacy in Patient-Physician Interactions (PEPPI-5) scale (five items, e.g., "How confident are you in your ability to make the most of your visits with your doctors?"). Respondents completed the PEPPI-5 for in-person visits and for telehealth visits. Descriptive statistics were calculated for all measures. A generalized linear model was estimated predicting PEPPI-5 for telehealth visits from emotional thermometer and TUQ scores. The interaction between emotional thermometer and TUQ scores was estimated to test the hypothesis that emotional distress moderated the relationship between TUQ and efficacy in patient-provider interactions during telehealth visits. **Results:** Across all five thermometers, 30.8% (28/91) reported a high score on at least one metric. The most frequently reported high score was for anxiety, 23.3% (21/90) and least frequently reported high score was for anger, 12.2% (11/90). The mean TUQ score was 5.5 (SD=1.5) and mean PEPPI-5 score for telehealth visits was 8.1 (SD=2.4). As shown in Table, emotional thermometer scores did moderate the relation between TUQ and patient self-efficacy during telehealth visits. For high emotional thermometer scores, self-efficacy decreased as TUQ scores decreased. **Conclusions:** For patients experiencing high emotional distress, low comfort and ability with telehealth usability resulted in low patient self-efficacy in communicating with providers and getting medical needs met. Telehealth is a convenient and effective modality; however, in times of emotional distress for patients who are not familiar with telehealth, in-person clinic visits may result in greater patient self-efficacy. Research Sponsor: None.

Summary results from generalized linear model estimating patient efficacy during telehealth visits.

Parameter	Estimate	Standard Error	t-Value	P-value
Intercept	0.04	1.41	0.03	.97
TUQ	1.39	0.25	5.58	<.0001
Emotional Thermometer (low)	6.03	1.80	3.35	.001
TUQ X Emotional Thermometer	-1.00	0.32	-3.15	.002

1591 **Poster Session**

Responses to telehealth expansion for older adults with cancer during the COVID-19 pandemic. *First Author: Robin T. Higashi, University of Texas Southwestern Medical Center, Dallas, TX*

Background: Synchronous video visits ("telehealth") were rapidly adopted to facilitate provision of cancer care during the COVID-19 pandemic, with little time to comprehensively assess patient and provider needs. Attitudes toward telehealth use during active treatment (vs. survivorship care) were largely unknown, as were perceptions of, experiences with, and needed support for telehealth use among older adults with cancer. Older adults in particular may face increased vulnerability to inequities in access to care due to limited digital literacy. **Methods:** We conducted surveys and semi-structured interviews with providers, staff, and older patients (age ≥60) from a comprehensive cancer center. Data collection occurred between Dec 2020 - Nov 2021. **Results:** We completed a total of 106 provider/staff surveys, 128 patient surveys, 20 provider/staff interviews, and 15 patient interviews. A majority of surveyed providers/staff felt that telehealth should "definitely be offered" during treatment-phase encounters (55.9% treatment follow-up; 69.1% results communication; 70.2% discussing treatment side effects). Similarly, most patients indicated they would be willing to have video visits with a member of their care team for: discussing treatment side-effects (73.5%), results communication (69.6%), and treatment follow-up (65.7%). Patients reported experiencing challenges with joining video visits (29%) and understanding the telehealth process (28%). Similarly, less than a third (30.8%) of providers/staff agreed or strongly agreed that the institution did a good job of preparing patients for their first telehealth encounter. Patients felt the institution should do more to communicate the advantages of telehealth to older adults in handouts and videos, which included: engaging multiple family members in critical appointments (e.g., treatment decisions, end-of-life), seeing their doctor when they were too sick to travel, and reducing potential exposure to infectious disease at the clinic. Participants suggested several strategies to assist patients with limited digital literacy: offering video tutorials of the connection process, creating "fake appointments" to practice online connections, and hiring a digital navigator to assist with technical difficulties and setup of the online portal. Despite challenges, a majority of surveyed patients (65.7%) and providers/staff (76.9%) intend to continue using telehealth after the COVID-19 pandemic passes. **Conclusions:** Use of telehealth for cancer care was received positively by older patients and providers/staff. Taking targeted steps to enhance implementation could reduce barriers to care, including among older adults and other populations with limited digital literacy, thereby promoting greater equity of access to telehealth benefits beyond the pandemic. Research Sponsor: Simmons Comprehensive Cancer Center, Community-Engaged Research Pilot Award.

1592 **Poster Session**

Evaluation of a pharmacist-led video consultation to identify drug interactions among patients initiating oral anticancer drugs. *First Author: Morgan R.L. Lichtenstein, Columbia University Medical Center, New York, NY*

Background: The past decade has seen a dramatic increase in the number of oral anti-cancer drug (OACD) approvals in the United States. Though polypharmacy and drug-drug interactions (DDIs) likely contribute to OACD toxicity, the prevalence of these features in patients on OACDs remains largely unknown. We aimed to evaluate a one-time 30-minute pharmacist-led video consultation among metastatic cancer patients initiating OACDs to identify medication list inaccuracies as well as the prevalence, characteristics, and severity of OACD-related potential DDIs. **Methods:** We conducted a single-arm, prospective telehealth intervention study among 29 patients initiating OACDs to evaluate a one-time 30-minute pharmacist-led video consultation. The video visits focused on identifying and discussing polypharmacy and potential DDIs, and pharmacists then communicated recommendations to each patient's oncologist. We estimated the prevalence, characteristics (QTc prolongation, absorption interactions, etc.), and severity of OACD-related potential DDIs. Lexicomp and Micromedex were used to assess potential DDIs and measure severity on a standardized scale (A – D, X). In addition, we assessed the prevalence of medication list inaccuracies, polypharmacy, and patient satisfaction. **Results:** Twenty-five patients completed the intervention (86% completion rate) of whom 40% were 75 years of age or older and 60% were men. The majority were white (68%) and non-Hispanic (76%). Sixteen patients (68%) had a solid tumor diagnosis. Nearly half (48%) were insured by Medicare. The median number of medications per patient was 9 with a range of 4 – 21, and 96% of patients had at least 5 prescriptions listed. The median number of medication list errors was 2 with a range of 0 – 16, with at least 1 error for 76% and more than 1 error for 52% of patients. Pharmacists identified potential OACD-related interactions in 9 cases (40%). These included change in drug absorption or metabolism (7), QTc prolongation (1), hypotension (1), and bleeding (1). Interactions were classified as either category C (8) or D (2), requiring close monitoring or a change in treatment, respectively. All patients expressed a high level of satisfaction with the video visit. **Conclusions:** Polypharmacy, medication list errors, and potential DDIs are prevalent among patients initiating OACDs despite use of an electronic medical record requiring medication reconciliation. Our study suggests that a one-time remote 30-minute pharmacist-led video consultation can effectively identify and address OACD-related potential DDIs, which may decrease medication complexity and improve adherence in this population. Research Sponsor: American Cancer Society.

1593 **Poster Session**

Variation in telemedicine usage in gynecologic cancer: Are we widening or narrowing disparities? *First Author: Leslie Andriani, Penn Medicine Abramson Cancer Center, Philadelphia, PA*

Background: Telemedicine rapidly increased with the COVID-19 pandemic and may be a way to reduce care disparities. Our aim was to evaluate sociodemographic (race, insurance), patient, health system, and cancer factors associated with use of telemedicine in gynecologic cancers. **Methods**: We conducted a retrospective cohort study of patients with documented endometrial or ovarian cancer using the nationwide de-identified electronic health record-derived Flatiron Health data. We used multi-level regression models to analyze the association of telemedicine usage during COVID-19 pandemic (2020-2021) with sociodemographic, patient, health system, and cancer factors overall. **Results**: Of 13,450 patients with endometrial or ovarian cancer, 14.4 % (95%CI 14.0-16.1) used telemedicine during COVID-19 for their cancer care within the Flatiron Health network. Insurance was not associated with likelihood of telemedicine in any model. Region was significantly associated with telemedicine usage across models with patients living in the Northeast more likely to use telemedicine. **Conclusions**: In this large cohort study, we found regional disparities across cancer types and oncology settings. Expanding access to telemedicine may improve racial and geographic disparities in gynecologic cancer. Research Sponsor: American College of Obstetrics and Gynecology, University of Pennsylvania Basser Center for BRCA.

Predictors of telemedicine usage during COVID-19 in gynecologic cancer.

	Risk ratio	Risk ratio
	Endometrial cancer	Ovarian Cancer
Patient Race		
Black	0.79 (0.62-1.01)	0.83 (0.62-1.12)
Asian	0.94 (0.57-1.57)	1.44 (1.04-1.97)*
Other	0.83 (0.63-1.10)	1.11 (0.93-1.34)
Unknown race	0.95 (0.74-1.22)	1.06 (0.87-1.28)
White	Reference	Reference
Hispanic or Latino	1.39 (1.00-1.94)	0.77 (0.59-1.02)
Patient Insurance		
Medicaid	0.85 (0.61-1.18)	0.82 (0.62-1.08)
Medicare	0.86 (0.68-1.07)	1.02 (0.85-1.22)
Uninsured	0.92 (0.73-1.17)	0.85 (0.70-1.03)
Unknown	0.90 (0.071-1.15)	0.85 (0.68-1.05)
Private insurance	Reference	Reference
Region		
Southeast	0.29 (0.22-0.38)**	0.44 (0.36-0.53)**
Midwest	0.44 (0.33-0.58)**	0.48 (0.38-0.61)**
West	0.56 (0.44-0.72)**	0.67 (0.56-0.79)**
Unknown	1.05 (0.84-1.31)	0.86 (0.70-1.04)
Northeast	Reference	Reference
Recurrent cancer	1.11 (0.89-1.40)	1.70 (1.49-1.93)**

Risk ratios are adjusted for age, BMI, ECOG status, stage, and histology.
*p-value<0.05.
**p-value<0.001 (Bonferroni correction applied).

1594 **Poster Session**

Hematology/oncology outpatient perspectives on telehealth one year into the COVID-19 pandemic. *First Author: Anne Hudson Blaes, University of Minnesota, Minneapolis, MN*

Background: Telehealth use expanded during the COVID-19 pandemic, but few studies have explored patient perspectives on it after the initial months. Using mixed methods, we aimed to understand patient telehealth perspectives and to examine for whom telehealth is less optimal. **Methods:** A modified Telemedicine Satisfaction and Usefulness Questionnaire (TSUQ) for hematology/oncology outpatient care was sent to patients ≥18 years old within the M Health Fairview Masonic Cancer Clinic with ≥1 prior telehealth visit (phone and/or video). Two focus groups were also conducted. We summarized cohort characteristics and views on telehealth. We dichotomized selected TSUQ items (measured on a 1-5 scale) and evaluated them using logistic regression, adjusted for age (<65 years, ≥65 years), gender, race (White, other), income (<$50,000, $50,000-99,000, ≥$100,000, prefer not to say), education (no college degree, at least college degree), and having cancer (yes, no). Focus group data were analyzed qualitatively. **Results:** Of 7848 invitations, 588 surveys were completed (7.5% response rate). For respondents, 71% were female, 68.7% married/partnered, 90.6% identified as White, and 36.1% had a graduate/professional degree with an annual salary ≥$150,000 (21%). Most had cancer (73.3%) but were not currently receiving treatment (36.5%); 40% each had employer-based insurance or Medicare. Focus group members (n = 16) were chosen from a demographic mix of 121 volunteers. Most survey respondents found telehealth satisfactory [mean 3.8 ± standard deviation (SD) 0.9] and easy to use (mean 3.4 ± SD 0.9), 72.2% found it convenient, and 82.2% agreed that it saved time. Most (78.6%) would be happy with a combination of telehealth and in-person care going forward, but those with cancer were less likely to prefer future telehealth care (adjusted odds ratio [OR] 0.52, 95% confidence interval [CI] 0.34 - 0.81). Being male and having lower incomes were associated with greater telehealth satisfaction, (male vs. female, OR 1.68, 95% CI 1.00 - 2.83), income <$50,000 vs. ≥$100,000 (OR 2.47, 95% CI 1.16 - 5.28). Focus group members reported between 1 - 30 telehealth visits (overall care range 8 months - 30 years). Views on telehealth mirrored survey results. Time saved and reduced exposure risk were beneficial, especially for those in rural settings and for those seeing genetic counselors or palliative care. However, concerns were voiced about fewer in-person interactions, communication gaps, and provider style variability. **Conclusions:** Our findings show that oncology patients prefer care in person despite telehealth's benefits. Additional work is needed to ascertain the optimal, and possibly patient subgroup-specific, combination of in-person and telehealth in ambulatory hematology/oncology care to manage the needs of different populations. Research Sponsor: University of Minnesota Department of Medicine, Division of Hematology, Oncology, and Transplantation Grant.

1595 **Poster Session**

Utilization of telemedicine among patients newly diagnosed with cancer. *First Author: I-Wen Pan, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The use of telemedicine among cancer patients remains limited. Because of the COVID-19 pandemic, CMS expansion of telehealth with 1135 waiver was enacted in March 2020, broadening the opportunities to provide patient care using telemedicine. This study examined the impact of the CMS expansion on the use of telemedicine among cancer patients. **Methods:** We identified newly diagnosed patients with 5 common cancers (breast, prostate, lung, colorectal, and lymphoma) between 3/2019 and 12/2020 from Optum's de-identified Clinformatics Data Mart Database. Patients who had 6 months of full enrollment (3 months before and 3 months after the first [index] cancer diagnosis date), had cancer claims on 3 separate dates within 3 months of the index date for the specific cancer diagnosis, and no prior history of cancer were included. We defined telemedicine use as patients who had a telemedicine procedure code within 1 month of their index diagnosis and had the cancer diagnosis on the telemedicine claim. We conducted an interrupted time series analysis to examine the impact of CMS expansion on telemedicine use. A multivariable logistic regression model was used to identify factors associated with telemedicine use during the post-expansion period. **Results:** Of 96,632 patients included, the average crude rate of telemedicine use was 0.12% before and 14.2% after the expansion in March 2020 (see Table). There was a significant impact of expansion on telemedicine use (21% increase; p<0.001). The peak rate (adjusted) was 28% in April 2020, decreasing and plateauing in July/August 2020, with rates staying in the range of 10-12% between August and December 2020. During the post-expansion period, lymphoma, prostate, and lung cancer patients (adjusted rates: 14.6%, 15.7%, and 15.9%, respectively) were more likely to use telemedicine compared to patients who had breast (12.7%) or colorectal (12.3%) cancer. Patients who were older (adjusted rates: ≥65 years, 13.8%; 50-64, 14.2%; 20-49, 18.6%), Black (12.4% vs 14.4% for White, 15.5% for Hispanic and 16.6% for Asian), resided in East South Central census division (8.4% vs 23.5% in New England) and had Medicare (12.2% vs 20.3% for commercial insurance) were less likely to use telemedicine (all p<.001). **Conclusions:** After the CMS telehealth expansion, the use of telemedicine among newly diagnosed cancer patients increased significantly. Telemedicine use varied by patient age, geographic location, race/ethnicity, and payer. Further research is needed to understand the pattern of telemedicine use. Research Sponsor: U.S. National Institutes of Health.

Unadjusted rates of telemedicine use before/after March 2020 expansion by cancer site.

Cancer site	Before % (N)	After % (N)
Breast	0.15 (18688)	13.3 (13627)
Prostate	0.11 (15916)	15.1 (11609)
Lung	0.08 (9543)	15.0 (6962)
Colorectal	0.13 (6879)	12.3 (5077)
Lymphoma	0.13 (4704)	15.7 (3627)
Overall	**0.12 (55730)**	**14.2 (40902)**

1596 **Poster Session**

Telemedicine adoption and utilization among financially distressed patients with cancer during the COVID-19 pandemic: Insights from a longitudinal nationwide survey. *First Author: Abbas Hassan, University of Texas MD Anderson, Houston, TX*

Background: Telemedicine use during the COVID-19 pandemic among financially distressed patients with cancer, with respect to the determinants of adoption and patterns of utilization, has yet to be delineated. We sought to systematically characterize telemedicine utilization in financially distressed patients with cancer during the COVID-19 pandemic. **Methods:** We conducted an analysis of survey data assessing the use of telemedicine in patients with cancer during the COVID-19 pandemic collected by Patient Advocate Foundation (PAF) from May 2020 to December 2020. Primary study outcome was telemedicine utilization rate. Secondary outcomes were independent predictors of telemedicine utilization patterns, volume, and utilization preferences. Multivariate and poisson regression analyses were used to identify predictive factors. **Results:** Of the 1,390 respondents, 627 completed two survey waves and were included in this study. Telemedicine adoption during the pandemic was reported by 67% of patients, with most (63%) preferring video visits. Younger age (odds ratio, 6.07; 95% CI, 1.47-25.1), and higher comorbidities (odds ratio, 1.79; 95% CI, 1.13-2.65) were independent predictors associated with telemedicine adoption. Younger age (19-35 yrs.) (incidence rate ratios [IRR], 1.78; 95%CI, 24-115%) and higher comorbidities (≥3) (IRR; 1.36; 95%CI, 20-55%) were independent predictors associated with higher utilization volume. As area deprivation index increased by 10 units, the number of visits decreased by 3% (IRR 1.03, 95%CI, 1.03-1.05). **Conclusions:** The rapid adoption of telemedicine may exacerbate existing inequities, particularly among vulnerable financially under-resourced patients with cancer. Policy-level interventions are needed for the equitable and efficient provision of this service. Research Sponsor: None.

1597 **Poster Session**

The role of telemedicine in care of patients with cancer: A real-world experience from a Peruvian cancer institute during the COVID-19 pandemic. *First Author: Katia Roque Perez, Instituto Nacional de Enfermedades Neoplasicas, Lima, Peru*

Background: For patients with cancer, the COVID-19 pandemic has increased morbidity and mortality due to their bigger susceptibility to infection and to the discontinuity of treatment. In this context, telemedicine has become an invaluable tool for cancer care. The purpose of this study is to describe the impact of telemedicine in the care of cancer patients from a Latin American public institution. **Methods:** Retrospective, descriptive and cross-sectional study of cancer patients who received medical care through telemedicine from the Department of Medical Oncology of the Instituto Nacional de Enfermedades Neoplasicas (INEN) during the COVID-19 pandemic, from March 2020 to February 2021. Data collection was performed in real time by medical oncologists. Impact was mesuared with a comparison between the amount of cancer care during the COVID 19 pandemic vs the previous year. A modified version of the University of Kansas Cancer Center telephone satisfaction survey was conducted. Variables included the process of requesting an appointment by telemedicine, satisfaction with telemedicine service and distribution of drugs. **Results:** 16 456 telemedicine visits were carried out in one year time, 96.1% were conducted by telephone and only 3.9% used a video communication platform. 73% of patients were female and 62% were in the age group from 31 to 60 years old. 43% corresponded to solid tumors where breast cancer was the most frequent diagnosis. Patients in active treatment represented 70% (n = 11587), with 64% of patients being treated with curative intent and 36% within the palliative setting. Regarding the result of telemedicine visits, 62% (n = 10,281) had a medical prescription (40% corresponded to hormonal therapy; and 19%, to intravenous or subcutaneous systemic treatment). Overall, 8% (n = 56) of cases required an in-person visit. In the annual comparative analysis (against in-person visits during the previous year), the gap was 23% (60%, 20%, 8% and 13% during the first, second, third and fourth quarters, respectively). According to the type of medical care, telemedicine accounted for the 27.6% of the total medical care employed during in the year. The maximum level of usage was in May 2020 with 52% and in February 2021 with 48%, coinciding with the first and second waves of COVID in Peru. The satisfaction survey was applied to 5765 randomly chosen patients from July to October 2020. The mean scores for the 3 variables studied were: 4.6 / 5 points for the process of requesting an appointment, 4.58 / 5 points for telemedicine service and 4.33 / 5 points for the distribution of medicines and orders. **Conclusions:** Telemedicine is key to guarantee the continuity of care for cancer patients with an adequate level of satisfaction. If the Telemedicine service had not been implemented, the number of medical consultations would have dropped to 40% in comparison to the previous year. Research Sponsor: None.

TPS1598 **Poster Session**

Improving care coordination for adolescents and young adults with cancer. *First Author: Emily Ruth Haines, Wake Forest School of Medicine, Winston-Salem, NC*

Background: In the US, many of the 90,000 adolescents and young adults (AYAs) (i.e., individuals ages 15-39) diagnosed with cancer each year do not receive services to address the range of needs they experience during cancer treatment. AYAs' unmet needs are associated with higher distress, poorer health-related quality of life, and higher physical symptom burden. However, AYAs often do not use services available to them through their cancer programs, even when they face no access issues (e.g., cost, insurance status, local service capacity). AYAs report barriers to service use including lack of awareness, challenges navigating large volumes of information and complex health systems, and hesitance to broach needs with providers without prompting. To facilitate a systematic and patient-centered approach to addressing AYAs' unmet needs, we leveraged user-centered design to develop the AYA Needs Assessment & Service Bridge (NA-SB). NA-SB includes a patient-reported outcome measure assessing AYAs' physical, psychosocial, and practical needs, and a collection of referral pathways for connecting AYAs to services based on the needs they report. In this feasibility pilot study, we are evaluating the implementation of NA-SB in the University of North Carolina Lineberger Comprehensive Cancer Center (UNC) AYA Cancer Program. **Methods:** Eligible participants include AYAs ages 18-39 currently undergoing cancer treatment at UNC (n = 25-50). The needs assessment portion of NA-SB is administered electronically through REDCap during routine clinical encounters with the AYA team. After an AYA completes the needs assessment, an AYA provider (i.e., social worker/nurse practitioner) reviews their responses and initiates referral pathways. Six weeks following their completion of the needs assessment, AYAs complete a survey assessing their perceptions of (1) the usability of the NA-SB needs assessment, (2) the feasibility, acceptability, and appropriateness of implementing NA-SB, and (3) the extent to which their needs have been met. We are also assessing participating providers' perceptions of NA-SB's implementation through periodic check-in calls. Results: We will report descriptive statistics on participant demographics, needs reported, and quantitative outcomes. We will analyze data from provider check-in calls inductively to further elaborate on implementation experiences and determinants. Conclusion: By harnessing patient-reported data to facilitate care coordination for AYAs, NA-SB has the potential to improve processes of care and subsequent outcomes for AYAs, an underserved and understudied population. This pilot study represents a critical first step towards translating NA-SB into routine cancer care for AYAs. Clinical trial information: NCT04586127. Research Sponsor: U.S. National Institutes of Health.

TPS1599 **Poster Session**

Evaluating the feasibility of using an electronic patient-reported outcome (ePRO) smartphone application (app) and biosensor by patients with cancer undergoing systemic treatments. *First Author: Karma L. Kreizenbeck, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: Almost half of the nearly 370,000 patients with cancer who receive chemotherapy in the United States each year experience Emergency Department (ED) visits and unplanned hospital inpatient (IP) stays during treatment, largely due to poorly controlled symptoms. Recent studies have shown that utilizing PRO information in oncology practice can improve symptom management and patient outcomes. This study aims to examine the feasibility and usability of a PRO app paired with a biosensor to identify patients who are at high risk for ED and IP visits. **Methods:** This prospective, pragmatic, observational study will evaluate the feasibility and usability of a clinic-provided smartphone app and smartwatch biosensor for monitoring patients undergoing systemic cancer treatment. Eligible patients are 18–80 years old, ECOG PS 0–2, have a biopsy-proven solid tumor diagnosis of cancer (excluding non-melanoma skin cancer), and are scheduled to receive the first dose of intravenous (IV) or oral cancer therapy as an initial or new line of treatment. Patients should be able to provide informed consent, wear the biosensor daily, and complete the app ePRO survey and questionnaires in English. Study exclusion criteria include receiving radiation or hormone therapy only, residing in a skilled nursing facility, participating in another clinical trial, current pregnancy, and wearing pacemakers, implantable cardioverter defibrillators, cochlear implants, and/or neurostimulator devices. The app collects PROs (PRO-CTCAE), app usability and satisfaction (modified mHealth App Usability Questionnaire [mMAUQ]) and patient satisfaction with the biosensor (modified Quebec User Evaluation of Satisfaction with Assistive Technology [QUEST 2.0]). The study is divided into two phases: (1) vanguard (N = 30); (2) operational (N = 70). Patients will be asked to wear the biosensor and enter PROs into the app daily for a 2-week (vanguard) or 6-week period (operational). The vanguard sample size allows for the recruitment of ~10 patients at each of the three participating oncology community clinics as is standard for initial device and software testing and development. Study endpoints for feasibility include: (1) vanguard – patient recruitment and protocol adherence, completeness of data capture, app usability, user satisfaction of biosensor; (2) operational – validity of self-reported hospital visits, feasibility of using electronic case report forms. Data collected from the vanguard will inform modifications to the app for the operational phase. The operational phase sample size is sufficient to assess data capture completion and clinical trial recruitment procedures in diverse practice settings (e.g., low volume vs. high volume, rural vs. urban). Clinical trial information: ISRCTN25569053. Research Sponsor: Genentech, Inc.

TPS1600 **Poster Session**

Natural history study for children and adults with rare solid tumors. *First Author: Diana Grace Varghese, National Institutes of Health, Bethesda, MD*

Background: Rare cancers is defined as fewer than 15 cases per 100,000 people per year and account for 27% cancers diagnosed and lead to 25% of cancer-related deaths. Nearly 13% (1 in 8) of all cancers diagnosed in adults ages 20 and older are rare. All pediatric cancers are rare and approximately 12,600 children under the age of 20 years are diagnosed with cancer each year. Rarity of these diseases has caused a stagnation in understanding the tumor biology and developing newer therapies. Initiatives like Orphan Drug Act (1983) and Rare Disease Act (2002) has led to improvement in funding and research about these rare tumors. The Cancer Moonshot Research Initiative funded My Pediatric and Adult Rare Tumor (MyPART) network (cancer.gov/mypart) in the NCI Pediatric Oncology Branch and launched a longitudinal Natural History Study for Children and Adults with Rare Solid Tumors (NCT03739827). **Methods:** A prospective study to evaluate the natural history of rare pediatric and adult solid tumors comprehensively and longitudinally. Patients of any age with a rare solid tumor (<15 cases per 100,000 people per year) are eligible. Patients with germline mutation who are at risk of developing these tumors or relatives of participants are also eligible. Patients can participate from home or are are invited to NIH for annual evaluations. Participants complete individual medical history, family history, patient related-outcomes measurements (PROs) and provide samples (blood, saliva) for DNA analysis. Tumors are analyzed using a 500+ gene panel (TruSight500, Illumina Panel) and undergo a comprehensive genomic and epigenomic analysis. Participants invited to NIH undergo a clinical evaluation, genetic counseling, blood collection (standard clinical labs, germline DNA/RNA, immune phenotypes, cytokines, exosomes), and imaging studies, as indicated. The goals of this study are to 1) Estimate and define the clinical spectrum of rare cancers 2) Evaluate and follow biological relatives of patients with rare tumors or carriers of germline genetic variants that predispose to development of rare tumors 3) Develop a better understanding of these diseases in an effort to develop a) Novel therapeutic interventions, b) Preventive/screening guidelines, c) Endpoints for future clinical trials, and d) Relevant patient reported outcomes that can improve our understanding of patients psychosocial and functional needs. Subprotocols under this protocol for children and adults include adrenocortical cancer (NCT04447014), neuroendocrine neoplasms (NCT04488263) and Chordoma (NCT0391046) to gather tumor specific data. Study accrual is ongoing. Clinical trial information: NCT03739827. Research Sponsor: U.S. National Institutes of Health.

TPS1601 **Poster Session**

Addressing Latinx CANcer Care Equity (ALCANCE) randomized controlled trial: Precision medicine and community health workers. *First Author: Gladys M. Rodriguez, Division of Oncology, Stanford University School of Medicine, Stanford, CA*

Background: Cancer mortality has declined over the past decade due to clinical advances including precision medicine. Despite these clinical advancements, low-income and racial/ethnic minorities experience worse cancer morbidity and mortality. Specifically, these populations have lower rates of genomic testing and are significantly underrepresented in precision medicine research. Community-based, culturally tailored approaches are needed to address these ongoing disparities. The objective of this randomized controlled trial is to test whether a community health worker (CHW)-led intervention can improve patient understanding of precision medicine topics and delivery of evidence-based cancer care more than usual cancer care alone. **Methods:** We developed a county-wide cancer care initiative and a community advisory board (CAB) comprised of patient, caregiver, payer, clinician, and governmental stakeholders in Monterey County—comprised of 60% Latinx, non-English speaking, immigrant populations. As guided by the CAB, we developed a CHW-model to provide education on precision medicine and screen for complications of social determinants of health in 1:1 discussions with patients. In collaboration with a local community oncology clinic, we plan to randomize 110 patients with cancer who are receiving active treatment into usual care or usual care plus the CHW-led intervention. Inclusion criteria includes patients who are: 1) 18 years of age or older; 2) racial/ethnic minorities; 3) low-income; 4) uninsured or insured by Medicaid and/or local agricultural employers; and 5) speak English or Spanish. Exclusion criteria includes: 1) lack capacity to consent to study procedures; 2) plan to move from the area within a year. We will measure the effect of the intervention on patient knowledge of precision medicine using a survey adapted from Davies et al. Secondary outcomes include effect on health-related quality of life using the Functional Assessment of Cancer Therapy – General, patient activation using the Patient Activation Measure, satisfaction using the Satisfaction with Decision Scale, prognosis and treatment preferences using an adapted survey by Weeks et al., healthcare utilization, and receipt of evidence-based cancer care. We will administer surveys at baseline, 3-, 6- and 12-months post-enrollment. To date, 67 participants have been enrolled. This study will show if CHW-models increase knowledge of precision medicine in this population. Clinical trial information: NCT04843332. Research Sponsor: California Initiative to Advance Precision Medicine through grant #OPR18113, This work is also supported, in part, by the Lung Cancer Research Foundation.

TPS1602 **Poster Session**

Screening for high frequency malignant disease (SHIELD). *First Author: H.A. Nguyen, Guardant Health, Inc., Redwood City, CA*

Background: Implementation of asymptomatic cancer screening has yielded positive impacts on global cancer mortality rates. However, significant screening adherence gaps exist. A blood-based multi-cancer screening test with clinically significant performance in cancers where early detection and intervention can save lives, can address adherence gaps, especially by reducing access barriers inherent to current screening options. Effective evaluation of such a test in screen relevant populations requires studies designed to enroll individuals across multiple cancer types, taking into account prevalence rates for the cancers being evaluated, allowing for overlapping screen-eligible populations, and ensuring representation of individuals from diverse ethnicities and geographies. **Methods:** SHIELD (Screening for High Frequency Malignant Disease; NCT# 05117840) is a prospective, observational, multi-center basket study ongoing in the United States and Europe uniquely designed to recruit individuals across multiple cancer types. The study's primary objective is to evaluate the performance of a blood-based multi-cancer screening test (GuardantLUNAR-2, Guardant Health, USA) to detect cancer in screen-relevant individuals as compared to the reference standard cancer screening modality. The study will recruit eligible individuals into multiple separate cohorts with specified pathways for cancer screening. Within each cohort, eligible individuals consent to whole blood collection within 90-days of the standard of care screening method. Clinical diagnoses, including the diagnosis of cancer, are made per standard of care. Primary outcomes are sensitivity, specificity, negative predictive value, and positive predictive value of the test as compared to the standard of care screening modality. Secondary outcome is the number of screen-detected cancers, early- (stage I/II) and late-stage (stage III/IV), per 1000 screened individuals. Follow-up continues for 24 months with outcomes collected at one and two-years to investigate the possibility of incidental non-screen relevant cancer cases and interval screen-relevant cancer cases that had not reached clinical threshold for detection at initial screening. Additional cancer specific follow-up is designed per cohort. The first cohort to enroll screen-eligible individuals, cohort A, is focused on those who meet guideline criteria for lung cancer screening with low dose CT. Additional cancer-risk cohorts will begin enrolling as the study expands and are designated cohort B, C, etc. Cohort A: Eligibility criteria are aligned with lung cancer screening guidelines – age 50-80 years with > 20 pack-year smoking history who are current smokers or have quit < 15 years prior, without a cancer history, preinvasive lung lesions, or current treatment for pneumonia. Cohort A enrollment, targeting 9,000 subjects over 24 months at up to 120 global sites, began in January 2022. Clinical trial information: NCT05117840. Research Sponsor: Guardant Health.

TPS1603 **Poster Session**

Telehealth weight loss program for breast cancer survivors is feasible and acceptable: Preliminary results of pilot clinical trial. *First Author: Julia C. Tchou, University of Pennsylvania Health System, Philadelphia, PA*

Background: Current weight loss programs for breast cancer survivors utilize a hybrid of in-person visits or individualized telephone-based sessions modeled after the Diabetes Prevention Program. Telehealth may be an effective and efficient means of communicating with patients who otherwise cannot participate in in-person visits. To test this concept, we conducted a pilot single-arm study (NCT04855552) to examine the feasibility and acceptability of a weight loss group program via telehealth for breast cancer survivors. **Methods:** Patients > = 18 years with ECOG performance 0 or 1, a BMI of ^{3} 25 kg/m^{2}, and completion of adjuvant radio- and/or chemo-therapy > 6 months were eligible. Patients attended weekly zoom teleconference counseling grouped sessions either at noon or 5 pm led by a licensed clinical psychologist for 20 weeks followed by sessions in weeks 22 and 24. Patients were encouraged to use MyFitnessPal.com, an online tool, to monitor calorie intake and physical activity and digital scales to monitor weight to share with study staff to enhance accountability and provide opportunity for feedback. Feasibility was defined as a ratio of enrolled/eligible patients ≥50%. Acceptability was assessed from surveys pre- and post-treatment, and qualitatively from exit interviews. Secondary endpoints included changes in Quality of Life-Breast Cancer Patient (QOF-BC), Patient Health Questionnaire (PHQ-9), and percent weight loss from baseline to 24 weeks. **Results:** Clinical characteristics of patients are summarized in Table. The ratio of enrolled (n = 12)/eligible (n = 23) participants was 52% thus confirming study feasibility. One patient dropped out after 2 sessions. Qualitative results from exit interviews showed that 7/9 patients rated the telehealth format as "extremely acceptable". Surveys also indicated that the format and delivery of the program remained acceptable across most domains with no significant changes, except an increase in "approval" from 4.1 to 4.7 (p= 0.05). Patients' mood improved on the PHQ-9 from 4.2 to 1.2 (p = 0.03), and QOL-Physical Wellbeing improved from 56.9 to 66.3 (p = 0.004). Overall, 199 of 236 participant-sessions (84%) were attended. Percent weight loss was 6.5% +/- 2.5%. **Conclusion:** This proof-of-concept weight loss program was feasible and acceptable for our patients yielding improvements in QOL, mood, and a clinically significant weight loss over 6-months. This group-based video approach represents an intervention strategy that could be widely-disseminated and may provide stronger accountability/support than a one-on-one approach in some patients. Future work is aimed at refining strategies to increase patient enrollment/retention. Clinical trial information: NCT04855552. Research Sponsor: intramural institutional funds.

Participants (n = 12)	N or Average (SD)
Age	60 (14)
Race	
White	11
Black	1
Home distance from hospital (miles)	39 (42)
Pre-trial weight (lbs)	192 (40)
Post-trial weight (lbs)	170 (23)

2000 **Oral Abstract Session**

Phase II randomized study comparing proton craniospinal irradiation with photon involved-field radiotherapy for patients with solid tumor leptomeningeal metastasis. *First Author: Jonathan T. Yang, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Leptomeningeal metastasis (LM) is associated with limited survival and treatments. Photon involved-field radiotherapy (IFRT) is the standard of care radiotherapy (RT) but benefits are limited. We hypothesized that proton craniospinal irradiation (pCSI) encompassing the central nervous system (CNS) compartment would result in superior CNS disease control compared to IFRT. **Methods:** We conducted a randomized phase 2 study comparing pCSI vs. IFRT in patients with non-small cell lung cancer (NSCLC) or breast cancer LM. Eligibility criteria included radiographic and/or cytologic LM and Karnofsky performance status (KPS) ≥ 60. Patients were stratified by histology (breast vs. NSCLC) and systemic disease (active vs. stable) and were randomized in a 2:1 ratio of pCSI:IFRT. Patients with all other solid tumor histologies were enrolled to an exploratory pCSI arm. RT was 3Gy x 10 fractions for all patients. The primary endpoint is CNS progression-free survival (CNS PFS), defined as time from randomization to CNS progression (POD); secondary endpoints include overall survival (OS) and treatment-related adverse events (TAEs). A target of 81 patients to compare pCSI and IFRT was designed with a one-sided alpha of 0.025 and a power of 0.8 based on stratified log-rank test. Analysis is based on intent-to-treat. **Results:** From 4/2020-10/2021, 42 and 21 patients were randomized to pCSI and IFRT, respectively. Baseline factors were not different: median age was 56 vs. 61 years (p = 0.5); both cohorts included 57% NSCLC and 52% with active systemic disease. At median follow up of 7.1 months, 25 patients had CNS POD (pCSI = 9 [21%], IFRT = 16 [76%]) and 28 died (pCSI = 15 [36%], IFRT = 13 [62%]). At planned interim analysis, significant benefit in CNS PFS was observed with pCSI (median = 7.5 months, 95% CI: 6.6-NA) vs. IFRT (median = 2.0, 95% CI: 1.0-5.1, p < 0.001). As a result, the Data and Safety Monitoring Committee recommended early discontinuation of the trial. In addition, OS benefit with pCSI (median = 8.2 months, 95% CI: 7.4-NA) vs. IFRT (median = 4.9 months, 95% CI: 3.1-NA, p = 0.04) was observed. In a multivariable analysis including age, KPS and stratification factors, CNS PFS and OS benefit for pCSI remained significant. Grade 3 non-heme TAEs occurred in 3 patients with pCSI and 5 with IFRT. For the exploratory pCSI cohort, 35 patients enrolled, the median age was 61, 20 (57%) had active systemic disease and ovarian (7 [20%]) was the most common histology. At median follow up of 9.6 months, 7 (20%) had CNS POD and 20 (57%) died. Median CNS PFS was 5.4 months (95% CI: 4.8-9.1), OS was 6.6 months (95% CI: 5.4-12.1) and 4 patients had Grade 3 TAEs. **Conclusions:** In this trial, the first randomized study of RT for LM, we demonstrated improved CNS PFS of pCSI compared to IFRT, meeting the primary endpoint. pCSI also had a significant OS benefit. Grade 3 toxicities were comparable. Clinical trial information: NCT04343573. Research Sponsor: None.

2001 **Oral Abstract Session**

Randomized phase II/III trial of veliparib or placebo in combination with adjuvant temozolomide in newly diagnosed glioblastoma (GBM) patients with MGMT promoter hypermethylation (Alliance A071102). *First Author: Jann Nagina Sarkaria, Mayo Clinic, Rochester, MN*

Background: PolyADP-ribose polymerase (PARP) is an important modulator of DNA repair following temozolomide (TMZ) therapy. Pre-clinical testing demonstrated significant survival benefit for the combination of TMZ and PARP inhibitor veliparib in a subset of GBM pt-derived xenografts with MGMT promoter hypermethylation. **Methods:** After central pathology review and MGMT testing, patients (pts) with newly diagnosed, MGMT promoter hypermethylated GBM who had completed concurrent radiation and TMZ were randomized to adjuvant therapy with TMZ (Days 1-5 q28 days) combined with either placebo or veliparib (Days 1-7 q28 days). Veliparib/placebo+TMZ treatment was continued for up to 6 cycles. Pts accrued on the phase II and III portions of the trial were included in the primary endpoint analysis of overall survival (OS), with 90% power to detect a hazard ratio of 0.71 using a one-sided log-rank test with type I error rate of 0.05. The planned phase III sample size was 400 pts with data maturity after 302 deaths. **Results:** The phase II and III portions of the trial were open to accrual from 12/15/2014 to 2/6/2017 and 11/8/2017 to 10/15/2018, respectively; 447 pts were accrued to the trial and used in this intention to treat analysis. The two treatment groups were well balanced for prognostic factors, 421 pts initiated treatment, median follow-up was 57.8 months (mos), 380 pts had disease progression and 335 pts have died. There was no difference in OS (p = 0.15; HR 0.89 (0.71-1.11), median OS 28.1 vs. 24.8 mo. for TMZ+veliparib vs. TMZ+placebo, respectively) and no difference in secondary endpoint progression free survival (PFS, p = 0.31; HR 1.05 (0.86-1.30), median 13.2 vs. 12.1 mo, respectively). There was a notable trend for extended OS with TMZ+veliparib treatment at intermediate time-points between 24 and 42 mos (3-year OS 36.6% vs. 28.9% with TMZ+placebo, p = 0.09). In an unplanned exploratory analysis, treatment with TMZ at the time of first recurrence was associated with extended post-recurrence OS (p = 0.03) for pts treated on the experimental arm; median post-recurrence OS with TMZ salvage was 17.0 mo in the TMZ+veliparib arm and 12.6 mo in the TMZ+placebo arm, as compared to 9.6 mo in either arm if TMZ salvage was not used. These data are consistent with a possible effect of veliparib limiting the emergence of TMZ resistance in a subset of GBM pts. **Conclusions:** Veliparib combined with adjuvant TMZ therapy was not associated with significant extension in OS or PFS in newly diagnosed, MGMT hypermethylated GBM pts. However, a subset of pts treated with TMZ+veliparib may have an extended survival following re-treatment with TMZ at first recurrence. Clinical trial information: NCT02152982. Research Sponsor: U.S. National Institutes of Health, Alliance Industry Partners.

LBA2002 **Oral Abstract Session**

Primary analysis of a phase II trial of dabrafenib plus trametinib (dab + tram) in *BRAF* V600–mutant pediatric low-grade glioma (pLGG). *First Author: Eric Bouffet, The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

2003 **Oral Abstract Session**

Prognostic validation and refinement of a classification system for extent of resection in glioblastoma: A report of the RANO *resect* group. *First Author: Philipp Karschnia, Department of Neurosurgery, Ludwig-Maximilians-University, Munich, Germany*

Background: Terminology to describe extent of resection in glioblastoma is inconsistent across clinical trials. A surgical classification system for glioblastoma was previously proposed based upon the absolute residual contrast-enhancing (CE) tumor (in cm^3) and the relative reduction of CE tumor (in percentage) on postoperative MRI. Class 0 was defined as 'supramaximal CE resection' (also including removal of non-CE tumor), class 1 as 'maximal CE resection', class 2 as 'submaximal CE resection', and class 3 as 'biopsy'. We aimed to (I) explore the prognostic utility of the proposed classification system and (II) define how much non-CE tumor needs to be removed to translate into a survival benefit. **Methods**: An international Response Assessment in Neuro-Oncology (RANO) group was formed, entitled RANO *resect*. The members of the RANO *resect* group retrospectively searched the databases from seven neuro-oncological centers in the USA and Europe for patients with newly diagnosed glioblastoma. Clinical characteristics, volumetric information from pre- and postoperative MRI, and outcome were collected. Kaplan-Meier survival analysis and log-rank test were applied to calculate survival, and Cox's proportional hazard regression model to adjust for multiple variables. Significance level was set at $p \leq 0.05$. **Results**: We encountered 1021 patients with newly diagnosed glioblastoma, including 1008 IDHwt patients. 744 IDHwt patients were treated with radiochemotherapy per EORTC 26981/22981 following surgery. Among such homogenously treated patients, higher extent of resection was favorably associated with outcome: patients with 'maximal CE resection' (class 1) had superior outcome compared to patients with 'submaximal CE resection' (class 2) or 'biopsy' (class 3) (median OS: 20 versus 16 versus 10 months; $p = 0.001$). Similar findings were made when assessing progression (median PFS: 9 versus 8 versus 5 months; $p = 0.001$). Extensive resection of non-CE tumor (≥60% of non-CE tumor removed and ≤5 cm^3 residual non-CE tumor) provided an additional survival benefit in patients with complete CE resection (class 1), thus defining class 0 ('supramaximal CE resection') (median OS: 29 versus 20 months; $p = 0.003$). Smaller pre-operative tumor volumes were associated with larger extent of resection. The favorable prognostic effect of CE resection was conserved in a multivariate analysis when stratifying for molecular and clinical markers including pre-operative tumor volume and MGMT promotor status ($p = 0.001$). **Conclusions**: The proposed classification system for extent of surgery in glioblastoma is highly prognostic and may serve for stratification and design of clinical trials. Removal of non-CE tumor beyond the CE tumor borders translates into additional survival benefit in glioblastomas, providing a rationale to explicitly denominate such a 'supramaximal CE resection.' Research Sponsor: None.

2004 **Oral Abstract Session**

Intramuscular (IM) INO-5401 + INO-9012 with electroporation (EP) in combination with cemiplimab (REGN2810) in newly diagnosed glioblastoma. *First Author: David A. Reardon, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA*

Background: Novel T cell-enabling therapies plus checkpoint inhibition may improve OS in GBM. INO-5401 (synthetic DNA plasmid encoding hTERT, WT-1, PSMA) plus INO-9012 (synthetic DNA plasmid encoding IL-12), with cemiplimab (PD-1 inhibitor), was given to patients with newly diagnosed GBM with MRD to evaluate tolerability, efficacy, and immunogenicity. Median OS and immunogenicity at 18 months (OS18) are reported. **Methods**: This is a phase I/II, single arm, two cohort (A: unmethylated MGMT and B: methylated MGMT) study. Primary endpoint is safety; efficacy and immunogenicity are secondary. Nine mg INO-5401 plus 1 mg INO-9012 (4 doses Q3W, then Q9W) was given IM with EP in combination with cemiplimab (350 mg IV Q3W). Hypofractionated RT (40 Gy over 3 weeks) with TMZ was given to all patients, followed by maintenance (Cohort B only), which was a novel therapeutic approach. Immunogenicity was assessed by quantifying INO-5401-specific peripheral cellular immune responses via IFN-g ELISpot and flow cytometry. Intra-tumoral gene expression was analyzed by RNA-Seq of FFPE GBM tissue. Differences in gene expression were analyzed using the Wilcoxon rank sum test. **Results**: Fifty-two subjects were enrolled: 32 in Cohort A; 20 in Cohort B (35% women; median age 60 years [range 19-78 years]). The adverse event profile was consistent with known single-agent (INO-5401, INO-9012, EP or cemiplimab) events; most events were ≤Grade 2 and no related events were Grade ≥4. Median OS durations in Cohorts A and B were 17.9 months (95% CI 14.5-19.8) and 32.5 months (95% CI 18.4-not reached), respectively. Flow cytometry revealed activated, antigen specific CD4+CD69+PD1+ and CD8+CD69+PD1+ T cells, the latter with lytic potential as defined by presence of perforin and granzyme A. Both subsets exhibited HR < 1.0 and $p < 0.05$ when accounting for a 0.1% T cell frequency change, translating to a 23% and 28% reduced risk of death, respectively. Gene expression levels in pre-treatment tissues were similar between alive and deceased groups for INO-5401 antigens and immune cell markers; however, the alive group displayed significantly reduced expression of genes associated with anti-apoptosis, pro-proliferation, and immune response suppression. Post-treatment tumor tissue displayed altered gene expression for immune-related markers versus pre-treatment tissue, including markers of T cell infiltration, activation, and lytic potential. **Conclusions**: INO-5401 + INO-9012 has an acceptable risk/benefit profile and elicits robust immune responses that correlate with enhanced survival when administered with cemiplimab and RT/TMZ to newly diagnosed GBM patients. Pre-treatment gene expression signatures in MGMT-unmethylated patients were statistically associated with OS18. Overall, INO-5401 elicits antigen-specific T cells that can infiltrate GBM tumors. Clinical trial information: NCT03491683. Research Sponsor: Inovio.

2005 **Oral Abstract Session**

Reproducibility of outcomes in sequential trials using CMV-targeted dendritic cell vaccination for glioblastoma. *First Author: John H. Sampson, Duke University Medical Center, Durham, NC*

Background: Vaccination with dendritic cells (DCs) fares poorly in primary and recurrent glioblastoma (GBM). Moreover, GBM vaccine trials are often underpowered due to limited sample size. **Methods:** To address these limitations, we conducted three sequential clinical trials utilizing Cytomegalovirus (CMV)-specific DC vaccines in patients with newly diagnosed GBM eligible to receive standard of care resection and adjuvant radiation therapy and temozolomide chemotherapy. Autologous DCs were generated and electroporated with mRNA encoding for the CMV protein pp65. Serial vaccination was given throughout adjuvant temozolomide cycles, and ^{111}Indium radiolabeling was implemented to assess migration efficiency of DC vaccines. Patients were followed for median overall survival (mOS) and OS. **Results:** Our initial study was the phase II ATTAC study (NCT00639639; total n = 12) with 6 patients randomized to vaccine site preconditioning with tetanus-diphtheria (Td) toxoid. This led to an expanded cohort trial (ATTAC-GM; NCT00639639) of 11 patients receiving CMV DC vaccines containing granulocyte-macrophage colony-stimulating factor (GM-CSF). Follow-up data from ATTAC and ATTAC-GM revealed 5-year OS rates of 33.3% (mOS 38.3 months; CI_{95} 17.5-undefined) and 36.4% (mOS 37.7 months; CI_{95} 18.2-109.1), respectively. ATTAC additionally revealed a significant increase in DC migration to draining lymph nodes following Td preconditioning (*P = 0.049*). Increased DC migration was associated with OS (Cox proportional hazards model, HR = 0.820, *P = 0.023*). Td-mediated increased migration has been recapitulated in our larger confirmatory trial ELEVATE (NCT02366728) of 43 patients randomized to preconditioning (Wilcoxon rank sum, Td n = 24, unpulsed DC n = 19; 24h, *P = 0.031* and 48h, *P = 0.0195*). In ELEVATE, median follow-up of 42.2 months revealed significantly longer OS in patients randomized to Td (*P = 0.026*). The 3-year OS for Td-treated patients in ELEVATE was 34% (CI_{95} 19-63%) compared to 6% given unpulsed DCs (CI_{95} 1-42%). **Conclusions:** We report reproducibility of our findings across three sequential clinical trials using CMV pp65 DCs. Despite their small numbers, these successive trials demonstrate consistent survival outcomes, thus supporting the efficacy of CMV DC vaccine therapy in GBM. Clinical trial information: NCT00639639, NCT02366728. Research Sponsor: U.S. National Institutes of Health.

2006 **Oral Abstract Session**

Baseline tumor genomic and gut microbiota association with clinical outcomes in newly diagnosed glioblastoma (GBM) treated with atezolizumab in combination with temozolomide (TMZ) and radiation. *First Author: Shiao-Pei S. Weathers, The University of Texas MD Anderson Cancer Center, Department of Neuro-Oncology, Houston, TX*

Background: Checkpoint inhibitor (CPI) therapy has demonstrated overall limited efficacy in the treatment of GBM. Sixty newly diagnosed GBM patients unselected for MGMT status underwent treatment with concurrent atezolizumab with radiation therapy and TMZ followed by adjuvant atezolizumab and TMZ (NCT03174197). Clinical data has been reported previously. **Methods:** Genomic (WES with somatic mutation and SCNA determination N = total 42 samples, 33 baseline, 9 TP-2), transcriptomic (RNA seq N = total 72 samples, 54 baseline, 18 TP-2), and metagenomic sequencing of fecal samples (N = total 45 samples, 26 pre samples, 13 post RT samples, six 6m samples) analyses were conducted on pre-treatment samples. Findings were correlated with clinical outcome including OS and PFS. Twenty of the 60 patients underwent re-resection for suspected recurrent disease of which nine patients had WES and RNA seq performed successfully on paired pre and post treatment samples. **Results:** Somatic mutation, copy number and ploidy profiles were consistent with known aberrations in GBM. An unsupervised molecular network-based stratification of pre-treatment tumor mutations resulted in patients being grouped in 3 clusters with survival difference. Patients with GBM harboring an *EGFR* aberrancy were associated with a relatively worse mOS following treatment compared to patients with tumors enriched with *PTEN* alterations, while patients with *IDH1* mutations had the longest mOS. Gene set enrichment analysis of gene expression in tumors from patients (< mOS vs ≥mOS) identified genes associated with lymphocyte activation and immune response in patients with longer survival ($p < 0.01$) Unsupervised hierarchical clustering of bacterial taxa demonstrated two distinct clusters with significant difference by OS. Survival analysis and Analysis of Compositions of Microbiomes with Bias Correction (ANCOM-BC) revealed distinct taxa associated with OS (*Ruminococcus* spp.) and response to treatment (*Eubacterium* spp.), respectively. **Conclusions:** In this small CPI-treated GBM cohort, WES, SCNA and RNA seq identified pre-treatment tumor features that separated patients by survival. The fecal microbiome observations in our GBM cohort warrants further investigation. Clinical trial information: NCT03174197. Research Sponsor: Genentech.

2007 **Oral Abstract Session**

A targeted gene expression biomarker and association with meningioma outcomes and radiotherapy. *First Author: William Cheng Chen, UCSF Department of Radiation Oncology, San Francisco, CA*

Background: Improvements in risk stratification of meningioma are needed to guide post-operative management and application of adjuvant therapy. Although profiling of DNA methylation, copy number variants (CNVs), RNA sequencing, and exome sequencing have better elucidated meningioma biology, these approaches have not revealed clinically tractable biomarkers for radiotherapy responses. In this study, we develop and validate a targeted gene expression biomarker to predict meningioma outcomes and benefit from radiotherapy. **Methods:** Targeted gene expression profiling was performed on a development set of 173 meningiomas (median follow-up 8.1 years) and a validation set of 331 consecutive meningiomas (median follow-up 6.1 years) treated at independent institutions (70% WHO grade 1, 24% WHO grade 2, 6% WHO grade 3). All patients underwent surgery (n = 504) with or without postoperative radiotherapy (n = 73 with radiation). Regularized Cox regression within the development set resulted in a continuous gene expression risk score for local freedom from recurrence (LFFR). The model (34 genes and 7 housekeeping genes) and thresholds for low, intermediate, and high-risk scores were locked and applied to the validation set. **Results:** The gene expression risk score outperformed WHO grade (validation 5-year LFFR delta-AUC 0.15, 95% CI 0.076-0.229, p = 0.001) and DNA methylation grouping (delta-AUC 0.075, 95% CI 0.006-0.130, p = 0.01) for LFFR, disease-specific survival, and OS, achieving a negative predictive value for recurrence at 5-years of 93.2%. The biomarker reclassified 35.8% of WHO grade 1 tumors as intermediate or high risk (5-year LFFR/OS 62%/79%), and 18.3% of WHO grade 2-3 tumors as low risk (5-year LFFR/OS 78%/100%). The biomarker was independently prognostic after accounting for WHO grade, extent of resection, primary versus recurrent presentation, CNV status, DNA methylation group, and Ki67 labeling index, and was predictive for LFFR after postoperative radiotherapy, with a hazard ratio of 0.41 for intermediate to high risk propensity-matched meningiomas (95% CI 0.2-0.9, p = 0.0002) versus 0.79 for low risk meningiomas (95% CI 0.1-8.8, p = 0.5182). **Conclusions:** Targeted gene expression profiling of 504 meningiomas resulted in a biomarker which improved discrimination of meningioma local recurrence, disease-specific survival, and overall survival, and also predicted benefit from radiotherapy. Research Sponsor: UCSF.

2008 **Oral Abstract Session**

Genomic analysis and clinical correlations of non-small cell lung cancer (NSCLC) brain metastasis (BM). *First Author: Anna Skakodub, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Approximately 30% of patients with NSCLC present with BM, and up to 50% of patients ultimately develop BM. While modern NSCLC-directed agents yield excellent systemic response, most patients require focal treatment. Prior reports of BM genomics have been limited by low numbers, missing clinical data, and lack of matched specimens. Here, we report the largest cohort to date of molecularly profiled NSCLC BM samples with clinical correlates. **Methods:** Clinical data and outcomes for 244 patients with NSCLC and resected BM were identified, and BM samples were assessed with one of four versions (341, 410, 468, 505) of MSK-IMPACT, a custom FDA-approved next generation sequencing-based tumor sequencing assay. 51 (20.9%) patients had matched primary site tissue, and 44 (18%) patients had matched tissue from another metastatic site or CSF. Genomic alterations were filtered for driver variants using OncoKB. **Results:** Median age was 66 years (range 31-91), and median follow-up was 2.3 years (IQR 1.3-4.3). Adenocarcinoma was the most common histology (183, 78%). Half presented with a single BM, and 121 (51%) patients were treatment naive. Most (197, 83%) received adjuvant stereotactic radiosurgery (SRS) to the resection site and 28% received SRS to additional BM. After resection, 130 (55.1%) had CNS progression, often regional (54, 42%). SRS to new BMs (32%) was the most common salvage treatment. Median overall survival from BM diagnosis was 2.5 years (95%CI 2.1-3.2). Median CNS-progression-free survival was 1.2 years (95%CI 0.9-1.4). The most frequently altered genes in BM samples were *TP53* (72%), *CDKN2A* (34%), *KRAS* (31%), *KEAP1* (26%), and *EGFR* (21%). *CDKN2A* was more frequently altered in BM samples when compared to NSCLC primary samples (34% vs 14%, p = 0.003, q = 0.034). With regard to overrepresented gene sets, cell cycle pathway alterations were enriched in BM (56% vs 31%, p = 0.002, q = 0.022). BM samples had a significantly higher fraction of genome altered relative to the primary samples ($p < 0.0001$, $q < 0.0001$). After grouping patients based on type of CNS progression, we found that *EGFR* alterations were enriched in patients with leptomeningeal failures when compared to both patients without progression (42% vs 18%, p = 0.03, q = 0.93) and to patients with either local or regional progression (42% vs 19%, p = 0.03, q = 0.9). **Conclusions:** In the largest-ever assembled cohort of genomically-profiled NSCLC BM, we found significant enrichment for *CDKN2A* and cell cycle pathway alterations in BM compared to extracranial disease, as well as a higher fraction of genome altered, in BMs compared to matched primary tumor controls. We also observed *EGFR* alteration enrichment in patients who develop LMD, suggesting specific biologic underpinnings driving patterns of CNS failure. Further investigation into the role of systemic therapy and time course will elucidate potential mechanisms for CNS failure in patients with NSCLC. Research Sponsor: None.

2009 **Poster Discussion Session**

Dabrafenib + trametinib (dab + tram) in relapsed/refractory (r/r) *BRAF* V600–mutant pediatric high-grade glioma (pHGG): Primary analysis of a phase II trial. *First Author: Darren R. Hargrave, Great Ormond Street Hospital for Children NHS Foundation Trust, Great Ormond Street, London, United Kingdom*

Background: HGGs comprise ≈10% of pediatric central nervous system tumors and are a leading cause of childhood cancer-related death. Overall response rates (ORRs) with current standards of care are low, particularly in the second line, and 2-y overall survival (OS) rates are ≤35%. *BRAF* V600 mutation is infrequent (≈5% of pHGGs) but associated with improved survival from time of initial diagnosis. In previous trials, dab monotherapy and dab + tram yielded encouraging outcomes in *BRAF* V600–mutant HGG in pediatric and adult patients (pts), respectively. We describe the results of a Phase II study (NCT02684058) of dab + tram in r/r *BRAF* V600–mutant pHGG. **Methods:** Pts aged 1 to <18 y with *BRAF* V600–mutant HGGs and Karnofsky/Lansky performance status ≥50% who had failed first-line therapy were enrolled in a single-arm cohort. Pts received dab twice daily (<12 y, 5.25 mg/kg/d; ≥12 y, 4.5 mg/kg/d) + tram once daily (<6 y, 0.032 mg/kg/d; ≥6 y, 0.025 mg/kg/d). The primary endpoint was ORR (independent review; HGG-RANO criteria); secondary endpoints included ORR (investigator review), duration of response (DOR), progression-free survival (PFS), OS, and safety. **Results:** A total of 41 pts with diverse WHO Grade III/IV gliomas were enrolled; median time since diagnosis was 17.4 mo (range, 2.7-174.3 mo), and most had prior surgery (97.6%), radiotherapy (90.2%), and/or systemic antineoplastic therapy (80.5%). At data cutoff (August 23, 2021; median follow-up, 25.1 mo), 21 pts (51.2%) remained on treatment; most discontinuations (16 of 20) were due to progressive disease. Median exposure was 72.7 wk (range, 1.3-172.1 wk). The primary endpoint was met, with an independently assessed ORR of 56.1% (95% CI, 39.7%-71.5%). Median DOR was 22.2 mo (95% CI, 7.6 mo-not estimable [NE]; 12-mo Kaplan-Meier [KM] DOR rate, 62.2%), and median PFS was 9.0 mo (95% CI, 5.3-24.0 mo; 12-mo KM PFS rate, 44.1%). There were 14 deaths (34.1%), with 12 due to HGG and 2 due to serious adverse events (AEs; encephalomyelitis and intracranial pressure increased [n = 1 each], not treatment related per investigators); median OS was 32.8 mo (95% CI, 19.2 mo-NE; 12-mo KM OS rate, 76.3%). The most common all-cause AEs were pyrexia (51.2%), headache (34.1%), dry skin (31.7%), vomiting (29.3%), and diarrhea (24.4%). Two pts (4.9%) had AEs leading to discontinuation (both rash), and 26 (63.4%) had AEs leading to dose modification. **Conclusions:** Treatment with dab + tram demonstrated an improvement in ORR, response durability, and survival compared with estimates based on historical observations with current treatment approaches in r/r *BRAF* V600–mutant pHGG. Safety was consistent with the established profile of dab + tram in other indications. Thus, dab + tram may represent a critical treatment advance for this pt population with high unmet need. Clinical trial information: NCT02684058. Research Sponsor: Novartis Pharmaceuticals Corporation.

2010 **Poster Discussion Session**

Long-term control and safety of larotrectinib in a cohort of adult and pediatric patients with tropomyosin receptor kinase (TRK) fusion primary central nervous system (CNS) tumors. *First Author: Sébastien Perreault, Department of Neurosciences, CHU Hopital Sainte-Justine, Montréal, QC, Canada*

Background: Neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions are known oncogenic drivers in a variety of tumor types. Larotrectinib is a highly selective, CNS-active TRK inhibitor that demonstrated an objective response rate (ORR) of 30% and a 24-week disease control rate (DCR) of 73% across 33 evaluable adult and pediatric patients with TRK fusion primary CNS tumors, as of July 2020 (Doz et al, *Neuro Oncol* 2021). We report updated data on an expanded dataset of patients. **Methods:** Patients with TRK fusion primary CNS tumors in two clinical trials (NCT02637687, NCT02576431) were included. Larotrectinib was administered at 100 mg twice daily (BID) in adults and 100 mg/m^2 (max 100 mg) BID in pediatric patients. Response was investigator-assessed. **Results:** As of July 2021, 38 adult and pediatric patients with TRK fusion primary CNS tumors were identified: high-grade glioma (HGG; n =23), low-grade glioma (LGG; n =9), and other (n =6; includes glioneuronal, neuroepithelial, diffuse leptomeningeal, neuroblastoma, recurrent small round blue cell, and not otherwise specified). Median age at enrollment was 10.8 years (range 1.3–79.0; 28 [74%] patients < 18 years old). The gene fusions involved *NTRK2* (n = 28), *NTRK1* (n = 6), and *NTRK3* (n = 4). Sixteen (42%) patients received one prior line of systemic therapy and 16 (42%) received ≥2 prior lines. The ORR for 37 evaluable patients was 30% (95% confidence interval [CI] 16–47): three complete responses, eight partial responses, 21 stable disease (16 patients ≥24 weeks), and five progressive disease. The 24-week DCR was 73% (95% CI 56–86) for all patients, 68% (95% CI 45–86) for patients with HGG, and 89% (95% CI 52–100) for patients with LGG. Twenty-five of 31 patients (81%) with measurable disease at baseline had tumor shrinkage. Median time to response was 1.9 months. Median duration of response (DoR) was not reached; median follow-up was 25.6 months. The 12-month DoR rate was 64%. Median progression-free survival (PFS) was 16.5 months (95% CI 6.7–not estimable); median follow-up was 27.4 months. Median overall survival (OS) was not reached; median follow-up was 26.7 months. The 24-month OS rate was 65%. Treatment duration ranged from 0.1+ to 38.7+ months. Twenty-two patients (58%) progressed on treatment and three continued treatment post-progression for ≥4 weeks. Treatment-related adverse events (TRAEs) were reported in 21 patients (55%); the majority of these patients (18/21 [86%]) reported Grade 1 or 2 TRAEs. No Grade 3 or higher treatment-related neurological adverse events were reported. There were no treatment discontinuations due to TRAEs. **Conclusions:** Larotrectinib achieved a high DCR, rapid and durable responses, and a manageable safety profile in patients with TRK fusion primary CNS tumors. These results support testing for *NTRK* gene fusions in patients with CNS tumors. Clinical trial information: NCT02637687, NCT02576431. Research Sponsor: Bayer HealthCare and Loxo Oncology.

2011 **Poster Discussion Session**

CA-4948 for the treatment of melanoma brain metastasis. *First Author: Bently Patrick Doonan, The Medical University of South Carolina, North Charleston, SC*

Background: Melanoma is a growing clinical health concern where the incidence has doubled over the last 30 years. A major driver of melanoma associated deaths is the development of brain metastases (MBM). It is estimated that 40-60% of patients with metastatic melanoma will develop MBM. Current treatment strategies have a great local control rate, but do not prevent recurrent disease, with a distant intracranial failure rate of 50% at 1 year. Novel treatments and an improved understanding of the MBM tumor microenvironment are needed. Toll-like receptor signaling is activated in cutaneous melanoma, triggering innate inflammatory activation downstream through the adapter proteins MyD88 and interleukin (IL)-1 receptor-associated kinase (IRAK-1 and -4). Increased expression of IRAK-4 stimulates transcription of multiple cellular kinases and transcription factors, and production of inflammatory chemokines and cytokines. This places IRAK-4 as a central driver of both intrinsic tumorigenicity and immune evasion in melanoma. In this study we examine IRAK-4 activation in MBM, as well as preclinical responsiveness to CA-4948, an oral first-in-class small molecule inhibitor of IRAK-4 that has demonstrated clinical activity and has an acceptable safety in cancer patients. **Methods:** Using multiparameter IHC and proteomics analysis IRAK-1, IRAK-4, and NF-κB pathway activation were examined in patient MBM tissues and compared to normal controls. Plasma, cerebrospinal fluid, and brain tissue were assessed via UPLC-MS/MS for CA-4948 drug concentration following single oral high dose in a murine model. Using an aggressive preclinical model of MBM, B16F10, downstream biomarker response to treatment including phospho-NF-κB, phospho-ERK1/2, and phospho-P38 was measured in control and CA-4948 treated animals using multi-parameter IHC. Survival response was also tested using the B16F10 model. **Results:** Our data confirm elevated IRAK-1, IRAK-4, and NF-κB signaling in patient MBM. We also demonstrate that CA-4948 is capable of achieving therapeutically relevant concentrations in the brain parenchyma, and shows single agent activity in an aggressive preclinical model of MBM. We further confirm decreased ERK1/2, MAPK and NF-κB activation in response to CA-4948 treatment. **Conclusions:** We present here for the first time that IRAK-4 is a strong candidate for targeted therapy in MBM. We further validate CNS penetrance of the oral IRAK-4 inhibitor CA-4948, where single agent markedly reduces the proliferative capacity of aggressive preclinical MBM, resulting in improved survival. These data warrant further investigation of CA-4948 for the treatment of melanoma brain metastases, with far reaching potential as an adjunct to standard of care. Research Sponsor: Curis, Inc., J. David Vandivier Memorial Melanoma Research Fund.

2012 **Poster Discussion Session**

Feasibility and conduct of INSIGhT, a platform trial of patients with glioblastoma using Bayesian adaptive randomization. *First Author: Eudocia Quant Lee, Dana-Farber Cancer Institute, Boston, MA*

Background: Individualized Screening Trial of Innovative Glioblastoma Therapy (INSIGhT) trial is a phase II platform trial using response adaptive randomization and deep genomic profiling to more efficiently test experimental agents in MGMT unmethylated glioblastoma and potentially accelerate identification of novel therapies for phase III testing. We report on the feasibility and conduct of this approach. **Methods:** Tumor genotyping was performed prior to treatment assignment on eligible participants with newly diagnosed MGMT-unmethylated glioblastoma to identify biomarker signatures. Initial randomization was 1:1:1:1 between control (temozolomide) and 3 experimental arms (abemaciclib, CC-115, and neratinib). Subsequent randomization was adapted based on Bayesian estimation of biomarker-naïve and biomarker-specific probabilities of treatment impact on progression-free survival (PFS). Ineffective or toxic arms were discontinued by protocol amendment. The primary endpoint was overall survival (OS). **Results:** INSIGhT randomized 71 patients to the control arm, 73 patients to the abemaciclib arm, 12 patients to the CC-115 arm, and 81 patients to the neratinib arm between 2/9/2017 and 5/14/2021. Following the initial equal randomization period, early data were repeatedly analyzed during the study to capture early signals of treatment effects across the enrolled population or in specific biomarker subgroups. The results of these interim analyses influenced the randomization probability for future enrolled patients. In total, 77% of the participants were randomized before assessing their biomarker profile and 23% were biomarker randomized. The CC-115 arm opened and closed three times during the safety lead-in. The randomization probability to the CC-115 arm decreased based on poor early PFS results and the arm eventually closed after 12 patients due to toxicity. The randomization probability to the abemacicilb arm increased based on promising early PFS results. After the completion of accrual into the abemaciclib arm, the trial switched to block randomization to finish enrolling into the remaining neratinib and control arms. A total of 28 interim analyses and 32 randomization tables were created throughout the course of the trial with 4 adjustments (3 due to CC-115 closures and 1 due to completion of the abemaciclib arm). Biomarker association trends for neratinib and abemaciclib were similar to those seen in preclinical modeling of the trial. **Conclusions:** Relative to a standard randomization design, the adaptive platform design facilitated more efficient and economical testing of experimental arms by sharing a control arm, decreasing the probability of enrollment to potentially ineffective arms, and increasing the probability of enrollment to potentially effective arms. Additional future arms are planned on INSIGhT. Clinical trial information: NCT02977780. Research Sponsor: Lilly, PUMA , Beacon, Dana-Farber institutional funds.

2013 **Poster Discussion Session**

Radiosurgery dose reduction for brain metastases on immunotherapy (RADREMI): Results of an a priori interim analysis of a multicenter phase I trial. *First Author: Shearwood McClelland, Indiana University School of Medicine, Indianapolis, IN*

Background: Symptomatic radiation necrosis rates in patients treated with immune checkpoint inhibitor (ICI) therapy and concomitant single-fraction stereotactic radiosurgery (SRS) are as high as 20% (PMID: 29327059). We present updated results from the Radiosurgery Dose Reduction for Brain Metastases on Immunotherapy (RADREMI) trial following completion of an a priori interim analysis, aimed to identify reduced-dose SRS that is safe and efficacious for this patient population. **Methods:** RADREMI (clinicaltrials.gov, NCT04047602) is a prospective multicenter single arm Phase I trial involving patients age > 18 receiving ICI with SRS for 1-10 brain metastases on MRI. Patients had biopsy-confirmed primary malignancy with disease-specific graded prognostic assessment estimated median survival of at least 6 months and no previous whole brain radiation therapy. Six-month symptomatic radiation necrosis (radiographic radiation necrosis + clinical symptoms requiring steroid administration and/or operative intervention) was the primary endpoint, based on an expected rate of 5% and a historical rate of 16%. Secondary endpoints included 6-month local control and radiographic radiation necrosis. Response Assessment in Neuro-Oncology criteria defined local control; findings were compared to historical 6-month local control of 87-91% with RTOG 90-05 SRS dosing. A pre-determined interim futility analysis (based on the null hypothesis of no fewer than 15 of the first 20 patients reaching the primary endpoint achieving 6-month local control for RADREMI dosing) was performed using the Fisher's exact test. **Results:** Between December 18, 2019 and September 10, 2021, 43 lesions were treated in 16 patients receiving ICI delivered within 30 days before SRS who were enrolled on trial and met the primary endpoint (median follow-up = 9.1 months). All patients received RADREMI SRS dosing (18 Gy for lesions 0-2 cm, 14 Gy for lesions 2.1-3 cm, and 12 Gy for lesions 3.1-4 cm). The most common ICI used was single-agent pembrolizumab (51% of lesions, 56% of patients), followed by single-agent nivolumab (28% of lesions, 13% of patients). The six-month rates of symptomatic and radiographic radiation necrosis were zero; the six-month local control rate was 98% per treated lesion (42/43), and 94% per treated patient (15/16), comparable to historical controls ($p > 0.05$) and sufficient to not reject the interim futility analysis null hypothesis. **Conclusions:** Interim analysis reveals that the safety and efficacy of RADREMI dosing for reducing SRS dose in brain metastasis patients receiving concomitant ICI persists with excellent local control and no morbidity in a multi-institutional collaborative trial. Further results following completion of trial enrollment will provide additional evidence regarding the safety and efficacy of RADREMI SRS dosing. Clinical trial information: NCT04047602. Research Sponsor: Indiana University Simon Comprehensive Cancer Center Clinical Trials Office Core Services Grant.

2014 **Poster Discussion Session**

Evaluation of tumor responses and overall survival in patients with recurrent glioblastoma (GBM) from a phase IIa trial of a CMV vaccine immunotherapeutic candidate (VBI-1901). *First Author: Patrick Y. Wen, Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Boston, MA*

Background: Cytomegalovirus (CMV) antigens have been reported in over 90% of GBMs. $CD4^+$ and $CD8^+$ T cells are most frequently directed against the gB and pp65 antigens, respectively, which are immunogenic targets in a CMV-based GBM immunotherapeutic. **Methods:** A total of 20 first-recurrent GBM patients were enrolled, with Karnofsky Performance Status of at least 70, across 2 arms of the Phase IIa extension phase to receive VBI-1901 (a gB/pp65 enveloped virus-like particle [eVLP]) adjuvanted with either GM-CSF (given intradermally) or $AS01_B$ (given intramuscularly) (NCT03382977). Patients were vaccinated with VBI-1901 every 4 weeks, with serologic immune-monitoring 2 weeks after each vaccination and surveillance brain MRI scans every 6 weeks. **Results:** 10 patients (6 women, 4 men) with a median age of 58 (33-67 yrs) were enrolled into the GM-CSF arm and 10 patients (3 women, 7 men) with a median age of 65 (40-67) enrolled into the $AS01_B$ arm. The 12-month OS rates for the GM-CSF and $AS01_B$ arms were 60% and 70%, respectively; the 18-month OS rate for the GM-CSF arm was 30%, and for the $AS01_B$ arm is expected to be 30%-40% (data has not yet matured). Two durable partial responses (locally determined by RANO) have been observed in the GM-CSF arm, with one patient progression-free and on protocol after 2 years with a tumor size reduction of 93% relative to start of treatment. Immunological analyses demonstrate that prolonged, monthly dosing with VBI-1901 does not lead to immunological tolerance. Dynamic boosting and loss in the peripheral blood of CMV-specific CD4 Tem cells after treatment with VBI-1901 formulated with GM-CSF may correlate with tumor responses. **Conclusions:** The U.S. FDA granted Fast Track Designation to VBI-1901 adjuvanted with GM-CSF in first-recurrent GBM patients, and an expansion of the ongoing trial with this formulation in this patient population, with the addition of randomization with a contemporaneous control arm, is anticipated to begin in H1 2022. Acknowledgement: GlaxoSmithKline Biologicals SA provided the $AS01_B$ adjuvant used in this study. Clinical trial information: NCT03382977. Research Sponsor: VBI Vaccines, Cambridge, MA, USA.

2015 **Poster Discussion Session**

Risk of intracranial hemorrhage with direct oral anticoagulants versus low molecular weight heparin in glioblastoma: A retrospective cohort study. *First Author: Lauren Reed-Guy, Hospital of the University of Pennsylvania, Philadelphia, PA*

Background: Glioblastoma (GBM) is associated with a high rate of venous thromboembolism (VTE), but there is little data to guide anticoagulation in GBM patients, in whom the risks of VTE must be balanced against the risk of intracranial hemorrhage (ICH). **Methods:** We performed a single-institution retrospective cohort study of patients with GBM diagnosed with VTE from 2014-2021 who were treated with low molecular weight heparin (LMWH) or a direct oral anticoagulant (DOAC). The cumulative incidence of ICH was compared between the LMWH and DOAC groups. The primary outcome was clinically relevant ICH within the first 30 days of anticoagulation, defined as any ICH that was fatal, symptomatic, required surgical intervention, and/or led to cessation of anticoagulation. Key secondary outcomes included clinically relevant ICH within 6 months, fatal ICH within 30 days and 6 months, any bleeding within 30 days and 6 months, and recurrent VTE within 6 months. Fisher's exact test was used for comparison of primary and secondary endpoints between the two groups. Cumulative incidence curves were generated using the Kaplan-Meier method, and the cumulative incidence of clinically relevant ICH at both the 30-day timepoint and 6-month timepoint was compared between the DOAC and LMWH groups using the Gray test to account for death as a competing risk. **Results:** A total of 121 patients were identified in the primary cohort for 30-day outcome analyses (DOAC, n = 33; LMWH, n = 88). For 6-month outcome analyses, the cohort included only patients who were maintained on their initial anticoagulant (DOAC or LMWH) and did not switch anticoagulants during the 6 months following diagnosis of VTE (DOAC, n = 32; LMWH, n = 75). The cumulative incidence of clinically relevant ICH at 30 days was 0% (0/33) in the DOAC group and 9% (8/88) in the LMWH group ($p = 0.11$). The cumulative incidence of clinically relevant ICH at 6 months was 0% (0/32) in the DOAC group and 24% (18/75) in the LMWH group ($p = 0.001$), with 4 fatal ICHs in the LMWH group. Other outcomes are displayed in the Table. **Conclusions:** Our study suggests that DOACs are associated with a lower incidence of clinically relevant ICH in patients with GBM-associated VTE compared to LMWH. These data support the use of DOACs as a safe alternative to LMWH in patients with GBM. Research Sponsor: None.

Primary and secondary outcomes.

	LMWH (n = 88 at 30 days; 75 at 6 months)	DOAC (n = 33 at 30 days; 32 at 6 months)	p-value
Primary outcome – no. (%)			
Clinically relevant ICH within 30 days	8 (9)	0 (0)	0.11
Secondary outcomes – no. (%)			
Fatal ICH within 30 days	2 (2)	0 (0)	1.0
Any bleeding within 30 days	17 (19)	1 (3)	0.024
Clinically relevant ICH within 6 months	18 (24)	0 (0)	0.001
Fatal ICH within 6 months	4 (5)	0 (0)	0.32
Any bleeding within 6 months	31 (41)	3 (9)	0.001
Rate of recurrent VTE in 6 months	3 (4)	0 (0)	0.55

2016 **Poster Discussion Session**

Repeated opening of the blood-brain barrier with the skull-implantable SonoCloud-9 (SC9) device: Phase 1 trial of nab-paclitaxel and SC9 in recurrent glioblastoma. *First Author: Adam M. Sonabend, Northwestern Medicine Malnati Brain Tumor Institute of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL*

Background: The blood-brain barrier (BBB) is a major impediment to pharmacological treatment of gliomas, a diffuse tumor infiltrating the peri-tumoral normal brain. Low-intensity pulsed ultrasound directed at the brain with concomitant administration of intravenous microbubbles (LIPU/MB), temporarily opens the BBB. This technique was previously shown with a first generation of the device in combination with carboplatin chemotherapy (Idbaih et al. 2019). Here we investigate the pharmacokinetics and safety of this approach in the context of repeated delivery of albumin-bound paclitaxel (ABX) to the peri-tumoral brain. To perform LIPU/MB-based BBB opening prior to ABX infusions, we used a novel 6 x 6 cm device with 9 ultrasound emitters (SC9) that is implanted in a skull window after tumor resection. **Methods:** A Phase 1 dose-escalation trial using Bayesian adaptive design was initiated at our institution (NCT04528680). Patients with recurrent operable glioblastoma, a WHO PS $\leq$ 2 and normal bone marrow and organ function were eligible. After tumor resection and implantation of SC9, repeated cycles of BBB opening by LIPU/MB immediately followed by ABX, was performed every 3 weeks. Intraoperative LIPU/MB and low dose ABX was given prior to tumor resection for investigation of pharmacokinetics. **Results:** Seventeen patients have been enrolled and six dose levels of ABX were used (40-260 mg/m^2). Severe, reversible taxane-associated encephalopathy was observed in one patient at the max. planned dose level (260 mg/m^2). The patient continued treatment at a lower dose in subsequent cycles. One patient developed grade 2 cumulative peripheral neuropathy. Other mild to moderate and reversible toxicities for ABX including myelosuppression, fatigue, alopecia were observed as expected. Intraoperative sonication and pharmacokinetic studies showed that ABX tissue concentrations in non-enhancing peri-tumoral brain were increased several-fold after LIPU/MB. On electron microscopy, sonicated tissue showed ultra-structural alterations in brain capillary endothelial cells. Molecular studies showed transcriptional dysregulation of membrane transporters, pathways related to trans-cytosis, cell permeability as well as cell-cell and cell-matrix adhesion. Updated results will be presented. **Conclusions:** The LIPU/MB using skull-implantable ultrasound enhances the penetration of large chemotherapeutic drugs such as ABX in large regions of the brain, a procedure that can be performed repeatedly and safely. LIPU-based BBB opening leads to ultrastructural and transcriptional alterations in brain endothelial cells. A Phase 2 clinical trial is planned to investigate efficacy of this approach. Funding: NIH/NCI 1R01CA245969-01A1, Carthera (SC9 devices), Celgene/BMS, Malnati Brain Tumor Institute, Moceri Family Foundation. Clinical trial information: NCT04528680. Research Sponsor: NIH, Philanthropy.

2017 **Poster Discussion Session**

A controlled comparison of cerebral volume loss after brain irradiation with proton versus photon radiotherapy. *First Author: Melissa Gardner, Massachusetts General Hospital, Boston, MA*

Background: Previous work has demonstrated cerebral volume loss after glioma treatment with concurrent photon radiotherapy (PHT) and chemotherapy. Proton radiotherapy (PRT) minimizes exposure of normal brain tissue compared with PHT. The objective of this study was to compare neurotoxic effects of PRT vs PHT in a retrospective case-matched control series of WHO grade 2 and 3 gliomas. **Methods:** PRT subjects were selected from ongoing longitudinal single-arm outcome studies being conducted at our institution (NCT01358058, NCT03286335). PHT subjects were identified via medical record search and were individually matched to PRT subjects using an eleven-tiered criterion (i.e., age, sex, tumor type, tumor location, laterality, IDH mutation status, 1p19q deletion status, concurrent chemotherapy, adjuvant chemotherapy, total Gy dose, and number of fractions). When individual matching was not possible on all 11 variables, efforts were made to identify the closest possible match. Only those subjects with at least two years of progression free survival and available T1 and T2/FLAIR MRI at baseline, one year, and two years following RT were included. The resulting sample included 17 PRT and 17 PHT patients with grade 2 and 3 gliomas (19 male; mean age = 40.10y; SD = 11.27). Non-parametric analyses were used to compare groups on demographic and tumor/treatment-related variables. Diffuse cerebral volume loss was estimated by manually measuring lateral ventricular volume in the *tumor-free hemisphere*. **Results:** Mann-Whitney tests of independence showed no significant differences between groups on any of the demographic variables or clinical characteristics. One-way ANOVA demonstrated that ventricular volume increase after two years was significantly greater in patients treated with PHT than with PRT, ($F(1, 32.00) = 5.90$, $p < .021$, $\eta^2 = .156$). Change in ventricular volume in the PHT group was 24.85% (SD = 14.45%) and in the PRT group was 12.03% (SD = 16.3%). **Conclusions:** The findings of this study suggest that 2 years post treatment for glioma, PRT is associated with less brain volume loss and ventricular expansion than PHT. The findings support the hypothesis that PRT can reduce neurotoxicity within the tumor-free hemisphere. This study is limited by the retrospective design and lack of randomization to treatment arms, though cohorts were well-matched following a rigorous set of criteria. The effects of PRT beyond 2 years after treatment remain unknown. Preservation of brain structure may be critically important for maintenance of brain function in this population of patients who have prolonged survival. Longitudinal cognitive assessment in brain tumor patients undergoing PHT vs PRT is needed and is currently being collected in NRG BN-005 (NCT03180502), which may provide important data regarding functional impact of the brain changes we have demonstrated. Research Sponsor: Philanthropy.

2018 **Poster Discussion Session**

Real-world data to enable large-scale assessment of WHO CNS5 glioma classification. *First Author: Joshuah Kapilivsky, Tempus Labs, Inc., Chicago, IL*

Background: In 2021, the WHO revised its classification of central nervous system tumors (WHO CNS5) around IDH status and inclusion of key somatic alterations in addition to histopathological traits. While providing a more specific classification system for patients, the guidelines introduce new logistical challenges for pathologists, relying on multi-modal data for accurate classification. In this study, we use a combined clinical/molecular real world dataset to reclassify a cohort of adult diffuse gliomas and evaluate prognostic impact using real-world overall survival (rwOS). **Methods:** We retrospectively analyzed a de-identified dataset of 2,703 adult diffuse glioma samples profiled with the Tempus xT assay (DNA-seq of 595-648 genes at 500x coverage, whole-exome capture RNA-seq). Original diagnoses were identified from sample pathology reports. We assessed mutation status for genes relevant to WHO CNS5 classification (*IDH1/2*, *ATRX*, and *TERT*) and copy number alterations for genes *CDKN2A/B* and *EGFR*, as well as arms 1p, 19q and chromosomes 7 and 10. Samples were excluded if the original diagnosis or molecular findings indicated a diffuse midline or pediatric glioma. Necrosis and microvascular proliferation were inferred from gene expression profiles using machine learning. rwOS was defined as time from original diagnosis until death. To account for left truncation, samples were only considered at risk of death after study entry (*e.g.,* date of sequencing if sequenced as part of clinical care). **Results:** Using relevant clinicopathological traits and genomic alterations, we assigned WHO CNS5 labels to all samples—512 *astrocytoma,* IDH-*mutant*; 186 *oligodendroglioma,* IDH-*mutant, and 1p/19q co-deleted*; and 2,005 *glioblastoma,* IDH-*wildtype* (IDH-*wt*). We further stratified *astrocytoma,* IDH-*mutant* samples by grade, resulting in 308 classified as grade 4. Of the samples with an original diagnosis of astrocytoma, oligodendroglioma, or glioblastoma, 13.9% changed under the WHO CNS5 guidelines, including 166 glioblastomas re-classified as grade 4 *astrocytoma,* IDH-*mutant*, and 125 astrocytomas re-classified as *glioblastoma,* IDH-*wt*. WHO CNS5 reclassification resulted in more accurate prognostic stratification (rwOS) than the original diagnosis (likelihood ratio test; P < 8e-32). For example, the observed hazard ratio (HR) of an original astrocytoma diagnosis (versus glioblastoma) (Cox PH Model; HR = 0.42[CI:0.32,0.56]) was less extreme than the observed HR of an *astrocytoma,* IDH-*mutant* diagnosis (versus *glioblastoma,* IDH-*wt)* under WHO CNS5 (Cox PH Model; HR =0.08[CI:0.04,0.19] grades 2-3; HR = 0.18[CI:0.12,0.26] grade 4). **Conclusions:** This work highlights the utility of comprehensive molecular profiling in classifying patients with adult diffuse gliomas according to the newest WHO CNS5 guidelines, and confirms the improved prognostic stratification within a retrospective real-world dataset. Research Sponsor: Tempus Labs.

2019 **Poster Discussion Session**

Biological and prognostic relevance of epigenetic regulatory genes in high-grade gliomas (HGGs). *First Author: Sonikpreet Aulakh, West Virginia University, Morgantown, WV*

Background: Gliomagenesis is regulated by dynamic epigenetic modifications of DNA methylation, deregulation of histones and alteration of the human Switch/Sucrose Non-Fermentable (SWI/SNF) chromatin remodeling complexes. These epigenetic genes are responsible for treatment resistance by inducing stemness of glioma cells and immune cells with in the tumor microenvironement (TME). We evaluated the key chromatin remodeling (CR) genes and their interactions with other regulatory genes that are of prognostic importance. **Methods:** 1856 HGGs underwent molecular profiling at Caris Life Sciences (Phoenix, AZ). Analyses included next-generation sequencing of DNA (592 Genes, NextSeq or WES, NovaSeq) and RNA (WTS, NovaSeq). Cell infiltration in the TME was estimated by quanTIseq. X^2/Fisher's-exact/Mann-Whitney U tests were used for comparison, and significance was determined as p-value adjusted for multiple comparison by the Benjamini-Hochberg method ($q < 0.05$). Overall survival (OS) was calculated from the start of temozolomide (TMZ) to last contact using insurance claims data. **Results:** In a cohort of 1856 HGGs, 181 (9.8%) displayed >=1 mutation of 19 CR genes considered, including mutations (mt) of histone methyltransferases (HM) comprising *SETD2* (62, 3.4%), *KMT2D* (18, 1.0%), *KMT2C* (11, 0.6%); SWI/SNF complexes (SSNF) including *ARID1A* (32, 1.74%), *ARID2* (15, 0.82%), *SMARCA4* (14, 0.76%) and *ARID1B* (12, 0.66%); and others including (*DNMT3A*, 0.94%, *ASLXL1*: 13, 0.98%). When compared to CR-WT, CR-mt HGGs showed higher prevalence of Tumor Mutational Burden-High (TMB-H) (23% vs. 1.3%), MSI-H/dMMR (13% vs. 0.2%), gLOH (9.5% vs 4.3%), and mts in *IDH1/2* (29% vs. 14%), *TP53* (55% vs. 36%), *MSH6* (8.8% vs. 0.6%), and *PIK3CA* (18.8% vs. 8.3%) (all $q<0.05$). Investigation of CR-mt subgroups showed that SSNF mt had the highest *MGMT*-promoter methylation (68%) and *IDH1/2* mt (46%), while HM and others showed similar prevalence. In *IDH*-WT and MSS HGGs, the CR association with TMB-H, *MSH6*, *TP53* and *PIK3CA* persisted ($q<0.05$). When studying the immune profile, CR-mt HGGs showed significantly lower expression of immune-related genes including PD-L1 (Fold change: 0.76), PD-L2 (0.72), IDO1 (0.65), TIM3 (0.76) and CD86 (0.77) and colder TME as manifested by lower infiltrations of M2 (0.87) and higher Treg (1.27, all $q<0.05$); such effects were not observed in the subgroup of *IDH* WT/MSS tumors. Among TMZ-treated HGG tumors, CR mt was associated with improved OS (33 months vs 22m, HR: 0.713, 95% CI: 0.581-0.876, p = .001). In the *IDH* WT/MSS subgroup this effect was also observed (31.6m vs 19.2m, HR: 0.764, 95% CI: 0.59-0.99, p = 0.041). **Conclusions:** Nearly 10% of HGGs carry mts in CR genes. CR-mt HGGs possess significantly more favorable genetic alterations and colder TME compared to the CR-WT HGGs and showed better OS when treated with TMZ. Multivariate modeling and analysis of associations with specific targeted therapies is underway. Research Sponsor: None.

2020 **Poster Discussion Session**

Evaluation of the response assessment criteria in newly diagnosed and recurrent glioblastoma. *First Author: Gilbert Youssef, Dana-Farber Cancer Institute, Boston, MA*

Background: The Response Assessment in Neuro-Oncology (RANO) and modified RANO (mRANO) criteria are the two most widely used criteria to evaluate treatment response in glioblastoma (GBM) clinical trials. Unlike RANO, mRANO omits the evaluation of FLAIR sequence and requires a repeat scan to confirm responses. It also uses the post-radiation (RT) MRI as a baseline MRI in the newly diagnosed setting instead of the pre-RT MRI used in RANO. We sought to compare the 2 response assessment criteria and evaluate the differences between them in a large patient population. We also sought to compare them to immunotherapy RANO (iRANO) in patients who received immunotherapy. **Methods:** We conducted a retrospective review of consecutive patients with newly diagnosed (nGBM) and recurrent (rGBM) IDH wild-type GBM treated at Dana-Farber Cancer Institute from 2014 to 2020. Bidimensional measurements of enhancing disease and evaluation of FLAIR sequences were performed by two independent readers on patients' brain MRIs obtained before change of treatment, and discrepancies were evaluated by a third reader. Dates of disease progression (PD) were identified using RANO, mRANO, iRANO, and other response assessment criteria variations. Spearman's correlations between PFS and OS were calculated using an iterative multiple imputation method to account for any right-censoring. **Results:** 526 and 580 patients were included in the newly diagnosed and recurrent cohorts, respectively. Spearman's correlations were not significantly different between RANO and mRANO in the nGBM (0.69 [95% CI 0.62 to 0.75] vs. 0.67 [0.60, 0.73]) and rGBM (0.45 [0.37, 0.52] vs. 0.50 [0.42, 0.57]) cohorts. Evaluation of FLAIR sequences did not improve the correlation between PFS and OS in patients who received antiangiogenic therapy. Addition of confirmation scans was associated with stronger Spearman's correlations only when PD was identified within 12 weeks of completion of RT in the nGBM cohort, but did not affect the Spearman's correlations in the rGBM cohort. The use of the post-RT MRI as a baseline was associated with a higher Spearman's correlation in nGBM than the use of pre-RT MRI (0.67 [0.60, 0.73] vs. 0.53 [0.42, 0.62]). Among 98 patients with nGBM and 175 patients with rGBM who received immunotherapy, the Spearman's correlations (nGBM and rGBM) with iRANO (0.63 [0.44, 0.76] and 0.34 [0.17, 0.49]) were similar to RANO (0.73 [0.60, 0.82] and 0.42 [0.28, 0.54]) and mRANO (0.65 [0.48, 0.77] and 0.43 [0.28, 0.56]). **Conclusions:** RANO and mRANO demonstrated similar correlation between PFS and OS. The evaluation of FLAIR can be omitted, while confirmation scans appear to be only beneficial in the nGBM settings during the first 12 weeks of completion of RT. There was a nonsignificant trend in favor of the use of post-RT MRI as the baseline scan in the nGBM setting. The application of iRANO criteria did not add significant benefit in patients who received immunotherapy. Research Sponsor: None.

2021 **Poster Session**

CSF proteomics for differentiation of brain malignancies. *First Author: Nicholas Mikolasjewicz, University of Toronto, Toronto, ON, Canada*

Background: Accurate diagnosis and prognostication of intra-axial brain tumors hinges on invasive brain sampling, which carries risk of morbidity. Minimally invasive sampling of proximal fluids, also known as liquid biopsy, can mitigate this risk. Although the cerebrospinal fluid (CSF) is the ideal liquid biopsy source, the traditionally high volumes required for impactful analyses have deterred progress. The objective of this study was to identify diagnostic and prognostic CSF proteomic signatures in glioblastoma (GBM), brain metastases (BM), and central nervous system lymphoma (CNSL). **Methods**: CSF samples were retrospectively retrieved from the Penn State Neuroscience Biorepository and profiled using shotgun proteomics with ultra-low sample volumes. Proteomic signatures were identified using machine learning classifiers and survival analyses. **Results**: Using 30μL CSF volumes, we recovered 800 unique peptides across 73 samples [20 normal pressure hydrocephalus (NPH, non-tumor control), 22 GBM, 17 BM, and 14 CNSL]. Externally-validated proteomic-based classifiers identified malignancy with AUROC of 0.94 and distinguished individual tumor entities from others with AUROC ≥0.96. More clinically relevant triplex classifiers, comprised of just 3 peptides, distinguished individual tumor entities with AUROC ≥0.90. Novel biomarkers were identified among the top classifiers, including TFF3 and CACNA2D2, and characterized using single-cell RNA sequencing data. Survival analyses validated previously implicated prognostic signatures, including blood brain barrier disruption. **Conclusions**: Reliable classification of intra-axial malignancies using ultra-low CSF volumes is feasible, which has ramifications for longitudinal tumor surveillance. Novel biomarkers identified here necessitate future validation. Based on emerging evidence, upfront implantation of CSF reservoirs in brain tumor patients warrants consideration. Research Sponsor: None.

2022 **Poster Session**

Brain metastases in the setting of stable extracranial disease: A systematic review and meta-analysis. *First Author: Alyssa Y. Li, University of Toronto, Toronto, ON, Canada*

Background: Intracranial metastatic disease (IMD) is a life-altering complication for many patients with cancer. Improvements in systemic therapies have transformed the epidemiology of IMD, with some patients presenting with IMD in the context of stable extracranial disease (IMD-SECD). Among patients with metastases in other sites with similarly stable systemic disease, surgical resection and targeted therapy can result in long-term disease control and extended overall survival (OS), yet little is known about the clinical outcomes for patients with IMD-SECD. **Methods:** We searched MEDLINE, EMBASE, CENTRAL, and grey literature sources up to June 21, 2021 for studies reporting brain metastasis (BrM) with controlled extracranial disease (ECD) as well as IMD-SECD secondary to any primary cancer (criteria: presence of BrM and ≤2 extracranial metastatic sites, with no prior second-line chemotherapy and second-line brain-directed therapy). In studies comparing IMD-SECD and IMD patients, hazard ratios (HR) for OS and intracranial progression-free survival (iPFS) were pooled using random-effects meta-analysis, while medians for OS were estimated from single-arm IMD-SECD studies based on distribution-free summary survival curves. **Results:** Of 1067 records identified, 68 studies involving 5325 patients with IMD-SECD were included. Patients with IMD-SECD had prolonged OS (HR 1.93; 95% CI, 1.44-2.59; n = 10 studies; n = 877 patients) and iPFS (HR 1.59; 95% CI 1.31-1.92; n = 4 studies; n = 673 patients) compared with IMD patients. Subgroup analysis of patients with BrM and controlled versus uncontrolled ECD found prolonged OS with controlled ECD (HR 2.46; 95% CI, 1.36-4.44; n = 4 studies; n = 135 patients). Pooled median OS for all IMD-SECD patients was 20.85 months (mo) (95% CI, 16.35-25.98; n = 27 studies; n = 2159 patients). Stratification by primary cancer type showed median OS 20.18 mo (95% CI, 10.43-38.20; n = 2 studies; n = 109 patients) and 27.46 mo (95% CI, 18.27-49.66; n = 13 studies; n = 497 patients) for patients with IMD-SECD secondary to breast cancer and non-small cell lung cancer, respectively. **Conclusions:** Patients with IMD-SECD demonstrate prolonged OS and iPFS compared with patients with IMD, who may have more extensive systemic disease. Our results suggest that patients with IMD-SECD may represent a distinct subpopulation of patients with IMD with a uniquely favourable prognosis. It is possible that aggressive and timely treatment may significantly prolong survival for these patients. Future prospective trials should aim to investigate the efficacy of current treatment regimens in patients with IMD-SECD to further clarify optimal treatment pathways in this unique population of patients. Research Sponsor: None.

2023 **Poster Session**

Dynamic monitoring of cerebrospinal fluid circulating tumor DNA to identify unique genetic profiles of brain metastatic tumors and to better predict intracranial tumor response in patients with non–small cell lung cancer with brain metastases: A prospective cohort study. *First Author: Meichen Li, Department of Medical Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, China*

Background: Cerebrospinal fluid (CSF) can be used as a type of liquid biopsy to detect brain tumors. We aimed to explore the genetic profiles of CSF-derived circulating tumor DNA (ctDNA) to predict intracranial tumor response and monitor mutational evolution during systemic treatment in non-small cell lung cancer (NSCLC) patients with brain metastases. **Methods:** We conducted aprospective study of 92 newly diagnosed NSCLC patients with brain metastases. Paired CSF and plasma samples were collected at baseline, 8 weeks after treatment initiation, and at disease progression. Primary extracranial tumor samples were available for 58 patients and all samples underwent targeted next generation sequencing of 425 cancer-related genes. **Results:** At baseline, the positive detection rates of ctDNA in CSF, plasma, and extracranial tumors were 63.7% (58/91), 91.1% (82/90), and 100% (58/58), respectively. A high level of heterogeneity was observed between paired CSF and plasma samples, while concordance in driver mutations was also observed. A higher number of unique copy number variations (CNVs) were detected in CSF ctDNA than in plasma. CtDNA-positivity in baseline CSF samples was associated with poor outcomes (HR = 2.565, P = 0.003). Moreover, patients with increased concentrations of ctDNA in CSF after 8 weeks of treatment had significantly shorter intracranial progression-free survivals (PFS) than patients with decreased concentrations of CSF ctDNA (6.13 months vs 13.27 months, HR = 3.92, P = 0.007). Increased concentrations of plasma ctDNA were associated with shorter extracranial PFS (6.13 months vs 11.57 months, HR = 2.626, P = 0.032). From clonal evolution analyses, the accumulation of subclonal mutations in CSF ctDNA was observed after 8 weeks of systemic treatment. The clonal mutations remained more than 80% in CSF after 8-weeks of treatment also predicted a shorter intracranial PFS (HR = 3.785, P = 0.039). **Conclusions:** CSF ctDNA revealed unique genetic profiles of brain metastases, and dynamic changes in CSF ctDNA could better predict intracranial tumor response and track clonal evolution during treatment in NSCLC patients with brain metastases. Research Sponsor: None.

2024 **Poster Session**

Comparison of TAS0953/HM06 and selpercatinib in *RET* fusion-driven preclinical disease models of intracranial metastases. *First Author: Igor Odintsov, Brigham and Women's Hospital, Boston, MA*

Background: Patients with *RET* fusion-positive NSCLC have an estimated 25% incidence of CNS metastasis at diagnosis, and up to 40% during disease progression. Effective anti-RET therapy that penetrates the blood-brain barrier is essential to extending survival. TAS0953/HM06 is a structurally distinct RET-specific inhibitor that exhibits a distinct binding mode to RET and is effective against RET solvent front (G810) and gatekeeper (V804) mutations. TAS0953/HM06 also inhibits growth of xenograft tumors established from *RET* fusion-driven tumors of multiple histologies. TAS0953/HM06, therefore, represents a potentially effective strategy to overcome the emergence of acquired resistance to first generation RET-selective inhibitors. Here, we compared the brain penetration and efficacy of TAS0953/HM06 to selpercatinib (FDA-approved RET inhibitor) in models of intracranial *RET* fusion-positive cancers, specifically NSCLC and sarcoma. **Methods:** We compared the brain: plasma ratio of unbound TAS0953/HM06 and selpercatinib in mice to determine the unbound partition coefficient, Kp_{uu}, brain. We injected ECLC5 (NSCLC cell line, *TRIM33-RET*) and HMSC-RET (immortalized human mesenchymal stem cells in which *SPECCL1-RET* was introduced by CRISPR-Cas9 genomic engineering, sarcoma model) cells expressing luciferase into the cerebellum of mice. Tumor-bearing mice were treated with TAS0953/HM06 (50 mg/kg BID), selpercatinib (10 mg/kg BID) or vandetanib (multi-kinase RET inhibitor, 50 mg/kg QD), and assessed weekly for tumor growth via bioluminescence imaging. **Results:** Kp_{uu}, brain, of TAS0953/HM06 and selpercatinib were 1.3 and 0.20, respectively. Substances with brain $Kp_{uu} > 0.3$ in mice are regarded as brain-penetrable. TAS0953/HM06 was superior to selpercatinib at inhibiting growth of ECLC5 ($p < 0.0001$) and HMSC-RET ($p = 0.0005$) brain xenograft tumors, and increasing survival of tumor-bearing animals (ECLC5: TAS0953/HM06 139±0.5 days, selpercatinib 95+2.3 days, $p = 0.002$; HMSC-RET: TAS0953/HM06 41± 2.2 days, selpercatinib 20±3 days, $p = 0.0001$). Vandetanib, which is highly brain-penetrant, did not cause a significant decrease in growth of either brain tumor xenograft models. At the doses used, the 3 RET inhibitors induced similar regression in several peripheral subcutaneous xenograft tumor models. **Conclusions:** Our data in animal models suggest that TAS0953/HM06 penetrates the CNS more effectively than selpercatinib, and is superior at decreasing CNS disease and extending survival. TAS0953/HM06 represents a promising new therapeutic option for patients with RET fusions with acquired resistance mutations, including those with brain metastasis and those resistant to first-generation selective RET inhibitors. TAS0953/HM06 is currently undergoing a biomarker-driven phase 1/ 2 clinical trial for patients with solid tumors driven by *RET* alterations (NCT04683250). Research Sponsor: Helsin Heathcare, U.S. National Institutes of Health.

2025 **Poster Session**

HER2 expression and extensive molecular characterization of resected brain metastases from colorectal cancer: The HEROES study. *First Author: Alessandra Prete, Medical Oncology 1, Veneto Institute of Oncology IOV–IRCCS, Padua, Italy*

Background: Brain metastases (BM) from primary colorectal cancer (prCRC) are rare (1-3%); few is known about CRC BM predictive factors, prognosticators and molecular pathways. High rate of *HER2* amplification (*HER2*+) in CRC with BM was previously described, being *HER2*+ overall rare in CRC (<5%); however, *HER2*+ impact on prognosis of CRC with BM is uncertain. Enrichment in high microsatellite instability (MSI-H) and *BRAF*V600E mutations (mut) was also documented in BM tissue compared to matched prCRC. We designed this study to describe molecular landscape and clinical characteristics of CRC with BM, with special focus on *HER2*. **Methods:** HEROES was a retrospective-prospective, observational study in which patients (pts) with resected BM from CRC and treated at our institution from 1 January 2010 until 31 December 2021 were enrolled to perform extensive molecular analysis of matched prCRC and BM tissue. Molecular characterization and TMB were obtained with Next Generation Sequencing (NGS, FoundationOne CDx). *RAS/BRAF* and MSI were respectively assessed with MassArray (Myriapod Colon Status kit) and immunohistochemistry (IHC) to validate NGS results. *HER2* status was assessed with IHC/in situ hybridization (ISH). Tumor-infiltrating lymphocytes (TILs) were counted on hematoxylin-eosin-stained tissue. TMB was defined high if ≥ 5.02 mut/mB; TILs if ≥ 1.6 (cutoff set with ROC curve using R software v 4.1.2). Primary objective was to describe molecular landscape of paired BM and prCRC, with special focus on HER2. Secondary objectives were to search for new prognosticators of PFS after BM resection (BM-PFS), intracranial-only PFS (BM-iPFS) after BM resection, and OS in pts with resected BM from CRC. **Results:** Out of 100 pts with BM from CRC, 22 underwent BM resection and were included in the analysis. 18 out of 22 pts were aged ≥ 70 (82%); 19 (86%) had left colon or rectal origin. 17 (70%) had concomitant lung metastases. *HER2*+ was found on 4 (18%) BM, 3 (14%) of which had also *HER2*+ in matched prCRC; 3 (14%) BM carried *BRAF*V600Emut; 2 (9%) BM had MSI-H. Acquired *HER2*+ and *BRAF*V600Emut on BM were reported in two different pts. *KRAS*mut were consistent between BM and prCRC. Factors positively influencing BM-iPFS were low TMB (HR 0.36; 95%CI 0.12-1.10; p = 0.0275) and absence of *HER2* (*HER2*neg) on BM (HR 0.20; 95%CI 0.03-1,52; p = 0.0013). *HER2*neg BM were also related to longer BM-PFS (HR 0.35; 95%CI 0.07-1.76; *p*=0.0402), as well as *KRAS*mut BM (HR 0.35; 95%CI 0.11-1.06; *p*=0.0096). Longer OS was found in pts with ECOG PS 0-1 (p<0.0001), with ≤ 1 metastatic site (HR 0.30; 95%CI 0.09-0.94; p = 0.0076) or with high TILs in prCRC (HR 0.32; 95%CI 0.10-1.03; p = 0.0368). **Conclusions:** Even with the limitation of small sample size, this study supports *HER2*+ enrichment in both prCRC and BM from CRC. *HER2*neg, low TMB or *KRAS*mut BM conferred better prognosis. ECOG PS 0-1, ≤ 1 metastatic site and TILs-enriched prCRC were related to better OS. Research Sponsor: None.

2026 **Poster Session**

Prospective validation of a new imaging scorecard to assess leptomeningeal metastasis: A joint EORTC BTG and RANO effort. *First Author: Emilie Le Rhun, Lille University Hospital, Lille, France*

Background: Validation of the 2016 RANO MRI scorecard for leptomeningeal metastasis failed for multiple reasons. Accordingly, this joint EORTC Brain Tumor Group and RANO effort sought to prospectively validate a revised MRI scorecard for response assessment in leptomeningeal metastasis. **Methods:** Coded paired cerebrospinal MRI of 20 patients with leptomeningeal metastases from solid cancers at baseline and follow-up after treatment and instructions for assessment were provided via the EORTC imaging platform. The Kappa coefficient was used to evaluate the inter-observer pairwise agreement. **Results:** Thirty-five raters participated, including 9 neuroradiologists, 17 neurologists, 4 radiation oncologists, 3 neurosurgeons and 2 medical oncologists. Among single leptomeningeal metastases-related imaging findings at baseline, the best median concordance was noted for hydrocephalus (Kappa = 0.63), and the worst median concordance for spinal linear enhancing disease (Kappa = 0.46). The median concordance of raters for the overall response assessment was moderate (Kappa = 0.44). Notably, the interobserver agreement for the presence of parenchymal brain metastases at baseline was fair (Kappa = 0.29) and virtually absent for their response to treatment. 394 of 700 ratings (20 patients x 35 raters, 56%) were fully completed. In 308 of 394 fully completed ratings (78%), the overall response assessment perfectly matched the summary interpretation of the single ratings as proposed in the scorecard instructions. **Conclusions:** This study confirms the principle utility of the new scorecard, but also indicates the need for training of MRI assessment with a dedicated reviewer panel in clinical trials. Electronic case report forms with "blocking options" may be required to enforce completeness and quality of scoring. Research Sponsor: EORTC Brain Tumor Group.

2027 **Poster Session**

Changing recognition of breast cancer–related leptomeningeal disease and response to therapy: A retrospective single institution review. *First Author: Gerald Carter Wallace, Moffitt Cancer Center, Tampa, FL*

Background: Breast cancer related leptomeningeal disease (BC-LMD) is a dire diagnosis for 5-8% of breast cancer patients with overall survival (OS) measured in weeks without treatment. As new treatments prolong survival with breast cancer, the risk of developing BC-LMD may be increasing. We hypothesized that the rate of BC-LMD diagnosis increased significantly with time. We also predicted that OS with BC-LMD had changed with time and in relationship to molecular subtype and treatment following BC-LMD diagnosis. **Methods:** With approval of the local Scientific Research Committee and IRB, we conducted a retrospective analysis of medical records for patients treated or diagnosed with breast cancer at MCC from 2011-2020. Patient demographics, tumor characteristics, treatments, and outcomes were collected. Kaplan Meier survival curves were used to determine median overall survival (OS), progression of disease, and differences by molecular subtype. Univariate and multivariate analyses were used to determine characteristics of primary tumors and treatments which affected OS. **Results:** Of the 133 cases identified, significantly more were diagnosed between 2016-2020 than 2011-2015 ($p < 0.01$). Significant increases were seen in HER2+ and TNBC patients ($p < 0.05$) but not for ER/PR positive (HR+) disease ($p = 0.058$). HER2+ LMD associated with longest overall survival (OS; 7mths) followed by HR+ disease (3mths) and TNBC with the shortest OS (2mths). Systemic metastases preceded BC-LMD diagnosis in 72% of cases and CNS metastases in 85% of cases. HER2+ disease also conferred increased survival after CNS metastases were diagnosed until progression to LMD (8mth vs 2mth for HR+ and 1mth for TNBC LMD; $p < 0.05$). Positive impact on survival by HER2 targeted therapies may account for improved OS in this population. Other factors which increased OS generally were: WBRT, continuation of systemic therapy, delivery of intrathecal chemotherapy, and participation in clinical trials. Having TNBC and decision to defer treatment were associated with reduced OS. **Conclusions:** This study highlights the importance of identifying patients with BC-LMD early and with the intention to treat. Prospective clinical trials and population-based studies are needed to advance treatment of BC-LMD. Research Sponsor: None.

2028 **Poster Session**

Multi-institutional randomized phase 3 trial comparing cancer stem cell-targeted versus physician-choice treatments in patients with recurrent high-grade gliomas (NCT03632135). *First Author: Tulika Ranjan, Department of Neuro-Oncology, Cancer Center Southern Florida, & Tampa General Hospital, Tampa, FL*

Background: Clinical outcomes in patients with recurrent high-grade glioma (HGG) remain poor. Cancer stem cells (CSCs) have been implicated in metastasis, treatment resistance and recurrence of HHGs. We have shown in several clinical studies that anti-CSC-directed therapy selected by ChemoID assay provides benefits in many cancer types; however, this is the first report of a randomized clinical trial evaluating whether CSC-targeted cytotoxic agents selected by ChemoID assay-guided therapy improves survival in patients with recurrent HGG. **Methods:** In this parallel-group, randomized, phase-3 clinical trial, patients at 13 clinical sites in the USA with grade-III/IV recurrent glioma (2016 WHO guidelines) were randomized 1:1 to either ChemoID assay-guided therapy or physician-choice therapy, and then treated and followed until unacceptable toxic effects, hospice, or death. The primary endpoint was overall survival (OS). **Results:** Combined median follow-up was 9 months. Median OS (mOS) was 12.5 months (95% CI, 10.2-14.7) in the ChemoID assay-guided group vs 9 months (95% CI, 4.2-13.8) in the physician-choice group (log-rank $P = .010$). Risk of death was significantly lower in the ChemoID assay group (HR = 0.44; 95% CI, 0.24-0.81; $P = .008$). Median progression free survival (PFS) was 10.1 vs 3.5 months (95% CI, 4.8-15.4 vs 1.9-5.1) (HR, 0.25; 95% CI, 0.14-0.44; $P < .001$). **Conclusions:** Primary endpoint was met in this randomized clinical trial. The mOS was 3.5 months longer in the ChemoID assay-guided group vs the physician-choice group. Clinical trial information: NCT03632135. Research Sponsor: Cordgenics, LLC.

2029 **Poster Session**

Mebendazole in recurrent glioblastoma: Results of a phase 2 randomized study. *First Author: Nandini Menon, Tata Memorial Centre, Mumbai, India*

Background: Recurrent glioblastoma (GBM) has dismal outcomes and limited treatment options. Mebendazole (MBZ) is an anti-helminthic drug with in-vivo and in-vitro activity against glioma cell lines and has been demonstrated to be well tolerated in combination with lomustine (CCNU) and temozolomide (TMZ). In this phase 2 study, we sought to determine whether the addition of MBZ to CCNU or TMZ would improve overall survival (OS) in recurrent GBM. **Methods:** Adult patients with ECOG PS 0-3, with recurrent glioblastoma who were not eligible for re-radiation, were randomized 1:1 between CCNU-MBZ (n = 44) and TMZ-MBZ (n = 44). The primary endpoint was OS at 9 months, selected to reflect the BELOB trial. A 9-month OS of 55% or more in any arm was hypothesized to warrant further evaluation and a value below 35% was too low to warrant further investigation. **Results:** At 17.4 months, 68 events for OS analysis had occurred. The 9-month overall survival was 36.6% (95%CI 22.3-51) and 45% (95%CI 29.6-59.2) in the TMZ-MBZ and CCNU-MBZ arms respectively. ECOG PS was the only independent prognostic factor impacting OS (HR-0.478 95%CI 0.268-0.851; P = 0.012). Twenty-three patients (28.6%) enrolled had an ECOG PS 2-3 with inferior outcomes (median OS-5.67, HR-2.092 95%CI 1.175-3.731). Analysis restricted to ECOG PS 0-1 (n = 65) patients revealed a 9-month OS of 39.6% (95% CI 22.4-56.3) and 57.9% (95% CI 38.7-73) in TMZ-MBZ and CCNU-MBZ arms respectively. Grade 3-5 adverse events were seen in 8 (18.6%; n = 43) and 4 (9.5%; n = 42) patients in the TMZ-MBZ and CCNU-MBZ arms respectively. **Conclusions:** The addition of MBZ to TMZ or CCNU failed to achieve the pre-set benchmark of 55% 9-month OS. This was probably due to 28.6% of patients with poor PS of 2-3. In patients with ECOG PS 0-1, CCNU-MBZ had a 9 month OS of 57.9% and needs to be evaluated further. Clinical trial information: CTRI/2018/01/011542. Research Sponsor: Brain Tumor Foundation (BTF) of India, the Indian Cooperative Oncology Network (ICON) and the India Cancer Research Consortium (ICRC) under ICMR (Indian Council of Medical Research).

2030 **Poster Session**

Phase 2 trial of bavituximab with chemoradiation and adjuvant temozolomide in newly diagnosed glioblastoma. *First Author: Ina Ly, Massachusetts General Hospital, Boston, MA*

Background: Glioblastoma (GBM) and tumor endothelial cells express phosphatidylserine (PS), a highly immunosuppressive membrane phospholipid. PS receptors engage with immune cells, leading to expansion of myeloid-derived suppressor cells (MDSCs) which promote an immunosuppressive and pro-angiogenic tumor microenvironment. Bavituximab (BAV) – a chimeric monoclonal antibody – binds to β2-glycoprotein 1 (β2-GP1) to form a complex of β2-GP1 with PS, resulting in immune activation against tumor cells and anti-angiogenic effects. Pre-clinical data in GBM models suggest synergistic effects of PS blockade, radiation (RT), and temozolomide (TMZ). Here, we present results from a phase II trial (NCT03139916) of BAV, RT and TMZ in GBM patients. **Methods:** 33 adults with newly diagnosed IDH-wild-type GBM were enrolled and received 6 weeks of RT+TMZ, followed by 6 cycles of TMZ. BAV (3 mg/kg) was given weekly, starting at week 1 of RT+TMZ, for 18 weeks with the option to continue if tolerated. The primary endpoint was the proportion of patients alive at 12 months (OS-12). The null hypothesis would be rejected if OS-12 was ≥ 72%. As an exploratory endpoint, the immune profile in tumor tissue and peripheral blood mononuclear cells (PBMCs) was assessed using nanoString and multispectral immunofluorescence, with the goal to assess on-target effects of BAV in longer vs. shorter surviving patients (split based on median survival). Relative cerebral blood flow (rCBF) from dynamic susceptibility contrast MRI was also obtained. **Results:** 24 patients were alive at 12 months and OS-12 was 73% (95% CI 59-90%) so the study met its primary endpoint. Median OS was 15.4 months. As best response, 79% of patients had stable disease, 12% had a partial response and 9% had progressive disease. Eight grade 3 or 4 adverse events were seen (no grade 5 AEs). Ten pre-treatment and 7 post-treatment tissue samples were available. Analysis of RNA from pre-treatment tumor specimens showed a significantly positive shift in myeloid-related gene expression in patients with longer survival, with enrichment of 116 and 120 transcripts as well as downregulation of 2 and 1 gene for PFS and OS, respectively. There was no differential expression in PBMCs. Including all tissue samples, there was a marked reduction of MDSCs after BAV compared to time of diagnosis (p = 0.011). Decreased rCBF post-RT/pre-cycle 1 TMZ was associated with improved OS (HR 4.63, p = 0.029). **Conclusions:** OS-12 was 73%, meeting the primary endpoint and suggesting potential activity of BAV in newly diagnosed GBM. BAV leads to on-target depletion of intratumoral immunosuppressive MDSCs and anti-angiogenic effects. As expected, based on the mechanism of action of BAV, there was no difference in PBMC gene expression profile in patients with long and short survival. Combining BAV with immune checkpoint inhibitors in the future may augment tumor immune response. Clinical trial information: NCT03139916. Research Sponsor: NCCN.

2031 **Poster Session**

Clinical application of a functional 3D ex vivo test to predict therapeutic response in patients with HGG: A progression-free survival analysis. *First Author: Lindsay J Lipinski, Roswell Park Comprehensive Cancer Center, Buffalo, NY*

Background: High grade gliomas (HGG) including glioblastoma (GBM) are among the most aggressive brain cancers, with patients exhibiting highly variable treatment responses in both newly diagnosed (ND) and recurrent disease. Temozolomide (TMZ) + radiation therapy is the guideline directed standard of care (SOC) in the ND setting; it has remained relatively unchanged for > 15 years, despite variable patient responses. Current available biomarkers do not inform personalized therapy. Functional drug response testing using patient specific tumor cells may have the potential to inform effective therapy selection, thus advancing functional precision oncology. Progression free survival (PFS) is a meaningful surrogate to overall survival (OS) in GBM and therefore, represents a measure of clinical benefit. **Methods:** The 3D-PREDICT clinical study (NCT03561207) allows enrollment of HGG patients with ECOG ≤ 3, perhaps representing a more accurate real-world population compared to most clinical studies in the same patient cohort. Tumor tissue was prospectively collected during SOC biopsy/resection and analyzed in an *ex vivo* cell culture test using a panel of agents prescribed as HGG therapeutics. **Results:** Data pertain to 56 3D-PREDICT patients who had > 6 months of follow up as of December 31, 2021 or experienced progression/death < 6 months post tissue collection. There were 42 3D-PREDICT patients who had *IDH* wild type ND GBM and received SOC. PFS analysis of these patients showed 3D *ex vivo* testing was able to prospectively predict TMZ clinical responders vs. non-responders (Kaplan-Meier, p = 0.039; HR 0.516, 95% CI 0.234,1.137). Test predicted TMZ responders had a relative PFS advantage of 3.7 months. Of the 42 patients, 38 had known *MGMT* methylation status with 23 patients (60%) being unmethylated. Test predicted responders (9) included unmethylated patients; test predicted non-responders (33) included methylated patients. The data suggest *ex vivo* testing of patient specific tumor tissue may identify ND HGG patients *a priori* who respond to TMZ, irrespective of *MGMT* methylation status. Beyond TMZ response prediction, the test assesses tissue response to 11 additional known HGG therapies and therefore may provide a tool to inform potential alternative treatments to TMZ for ND patients. Also evaluated were 14 3D-PREDICT recurrent HGG patients who received test directed salvage therapy; mean PFS after tissue collection from re-resection was 9.0 months (range 2.3 – 24.7 mo) for 9 patients at first recurrence, and 5.7 months (range 1.8 – 11.4 mo) for 5 patients with 2 to 6 recurrences. These examples demonstrate initial test utilization informing salvage therapy selection, correlated with PFS improvements in recurrent HGG. **Conclusions:** This functional 3D *ex vivo* cell culture platform provided survival benefit in analyzed ND and recurrent cohorts. Clinical trial information: NCT03561207. Research Sponsor: None.

2032 **Poster Session**

Investigating the impact of NGS data availability on clinical decision-making in brain cancer. *First Author: Adam Eckburg, Northwestern University Feinberg School of Medicine, Chicago, IL*

Background: Next-generation sequencing (NGS) of cancer specimens is a valuable diagnostic tool that can provide detailed information regarding specific somatic genetic alterations within a tumor with potential for targeted treatment. Despite the increasing availability of NGS, preliminary data by John et al. from ASCO 2021 suggested that clinical decision making is not frequently impacted by NGS results in the setting of glioblastoma. Herein, we report how NGS data impacts other primary tumor types, including astrocytoma, oligodendroglioma, and various rare subtypes. **Methods:** A retrospective chart review was performed to assess the proportion of brain cancer patients receiving targeted treatment instead of standard therapeutics after NGS sequencing. Pertinent medical information was ascertained from Epic and the Electronic Data Warehouse. Targeted treatments were defined as those recommended by the Tempus report for NGS-identified potentially actionable mutations. Patients were stratified into one of three categories: astrocytoma, oligodendroglioma, or other rare subtypes (including meningioma, ependymoma, ganglioma, pleomorphic xanthoastrocytoma, atypical teratoid rhabdoid tumors, glioneuronal tumors, and CNS lymphomas). **Results:** Of 44 Astrocytoma patients with potentially actionable mutations, four (9.1%) were treated with targeted therapy in the form of Enasidenib, ONC201, Nivolumab, and Depatuxizumab, while 40 received NGS agnostic treatment. In 37 Oligodendroglioma patients, three (8.1%) were treated with either targeted Vorasidenib or Ivosidenib, while 34 were started on NGS agnostic therapies. Lastly, four (10.0%) of 40 patients with other rare primary tumor types received either Ibrutinib, Dabrafenib+Trametinib, Vigabatrin, or Vemurafenib as targeted therapy. Avastin and/or standard Temozolomide chemotherapy were the most common NGS agnostic therapies employed by clinicians across all three subclasses. **Conclusions:** Although a substantial number of potentially actionable mutations were detected by NGS, the presence of this data paired with Tempus targeted recommendations rarely impacted clinician decision-making, ranging from 8.1-10.0% of the time. Despite the availability of resources to prescribe targeted treatment, providers consistently chose NGS agnostic therapies instead. Utilization of targeted treatment may become more frequent over time, as more novel agents come to market and their efficacy is further elucidated. Research Sponsor: None.

2033 **Poster Session**

A phase I clinical trial on intracranial administration of autologous myeloid dendritic cells (myDC) in combination with ipilimumab and nivolumab in patients with recurrent glioblastoma (rGB). *First Author: Julia Katharina Schwarze, Department of Medical Oncology, Vrije Universiteit Brussel (VUB)/ Universitair Ziekenhuis Brussel (UZ Brussel), Brussels, Belgium*

Background: Intracerebral administration of ipilimumab (IPI) and nivolumab (NIVO) following resection of rGB was demonstrated to be safe and resulted in encouraging survival (Duerinck, Schwarze et al. JITC 2021; Neyns et al. ESMO 2021). CD1c(BDCA-1)$^+$ and CD141(BDCA-3)$^+$ myDC play a pivotal role in initiating an adaptive anti-tumor immune response by re-licensing cytotoxic T lymphocytes within the tumor microenvironment. **Methods:** Eligible patients (pts)(diagnosed with rGB following radiation and temozolomide treatment; not in need of steroids) underwent a leukapheresis followed by immunomagnetic bead isolation and cryopreservation of CD1c (BDCA-1)$^+$ / CD141(BDCA-3)$^+$ myDC. At the time of surgery, an escalating number of myDC (1, 10, and 20x10^6 myDC) were injected into the brain tissue lining the resection cavity following maximal safe resection of the rGB (ICer) or injected intratumorally (ITum) following stereotactic biopsy (STx). IPI (5 mg) plus NIVO (10 mg) were co-injected with myDC. NIVO was administered intracavitary (ICav, 10mg) using an Ommaya port and intravenously (IV, 10mg) Q2w (max 12x). **Results:** Fourteen pts (9 male; median 48y [range 20-78]) were recruited (resection n = 11; STx n = 2) and underwent a successful leukapheresis and isolation of myDC; peroperative administration of myDC was preceded by resection in 10 pts (1 pt did not undergo surgery due to clinical deterioration/cerebral edema), and by STx in 2 pts. Respectively 6 (incl both pts who underwent a STx), 3, and 4 pts were treated at the 3 dose levels. All pts received ITum/ICer/IV-administrations of IPI and NIVO as planned. Median number of postoperative ICav/IV NIVO-administrations was 7 (range 2-11). Most frequent adverse events (AE) were headache (n = 11), fatigue (n = 9), transient dysphasia (n = 6), and nausea (n = 5). Bacterial colonization of the Ommaya occurred in 3 pts necessitating removal. Immune-related AE were infrequent and mild. No G5 AE occurred. No dose-limiting toxicities were seen with increasing numbers of myDC. After a median follow-up of 54w, 3 pts remain progression-free (after 42+, 51+, 54+ weeks of FU), 6 (46%) pts have died; median PFS is 13w (95% CI 0-26), median OS has not been reached; 6-months PFS- and OS-rate are respectively 30% and 84%, 12-months PFS- and OS-rate are respectively 23% and 51%. OS compares favorably to an historical cohort of Belgian rGB patients (n = 469; Log-Rank p = 0.018). Gene expression profiling of resected tissue, analysis of cellular counts, cytokines, NIVO/IPI-concentrations in on-treatment cerebrospinal fluid samples is ongoing. **Conclusions:** Intracranial administration of autologous myDC plus IPI and NIVO in combination with IV NIVO was found to be feasible, sufficiently safe and associated with encouraging survival justifying further investigation in pts with resectable rGB. Clinical trial information: NCT03233152. Research Sponsor: Kom op tegen Kanker.

2034 **Poster Session**

EO2401, a novel microbiome-derived therapeutic vaccine for patients with recurrent glioblastoma: ROSALIE study. *First Author: Wolfgang Wick, Universitätsklinikum Heidelberg and German Cancer Research Center, Heidelberg, Germany*

Background: EO2401 (EO) was designed to activate existing commensal memory T-cells cross-reacting with tumor associated antigens (TAAs). EO includes microbial-derived, synthetically produced peptides corresponding to HLA-A2 restricted epitopes with molecular mimicry to three TAAs upregulated in glioblastoma (GB), IL13Rα*2*, BIRC5 and FOXM1, with the CD4 helper peptide UCP2 and the adjuvant Montanide. Pre-clinically EO generates strong immune responses and cross-reactive CD8 cells recognizing the TAAs. **Methods:** This ongoing Ph 1/2 trial (NCT04116658) investigates EO (SC q2 wks X 4 then q4 wks), EO with nivolumab (3 mg/kg q2 wks; EN), and EN with bevacizumab (10 mg/kg q2 wks; ENB) among four Cohorts (Cs) of pts with GB at first progression after radiotherapy/temozolomide. After the Ph 1 of EO followed by EN (C1), C2 investigated EN without (C2a) or with (C2b) surgery while C3 investigated ENB (population as C2a). **Results:** Among 40 treated pts (C1 n = 3, C2a n = 23, C2b n = 3, C3 n = 11), median age was 60, 53% male, 40% had KPS 90-100% and 35% had O6-methylguanine DNA-methyltransferase promotor hypermethylated tumors. All evaluable pts demonstrated strong CD8 T-cell ELISPOT responses against the 3 vaccine peptides, with tetramer staining of specific CD8 detected in 24/25 investigated pts after in vitro stimulation and in 19/20 pts directly ex vivo. Cross-reactivity against targeted TAAs was confirmed in 20/21 pts. Majority of response were detected by week 4 after 1st dose and as early as 2 weeks for some pts. EO, EN, and ENB were well tolerated (max exposure EN 68 wks, ENB 30 wks) with EO associated toxicity limited to local administration site reactions (48%; grade 1-2). The frequency and severity of nivolumab- or bevacizumab-associated AEs was consistent with historical monocompound experience. With a median follow-up of 9.3 months (range, 2.8-15.6), median progression-free survival (PFS), survival at 6 months (OS-6) and at 12 months for EN (C1+C2a+C2b) were 1.8 months (3 ongoing at 5.9, 7.1, and 14.7 months), 85%, and 50.1% (19/29 alive), respectively. With a median follow-up of 3.7 months (range, 2.2-7.2), pts on ENB (C3) have median PFS and OS-6 of 5.5 months (7 ongoing), and 80% (10/11 alive), respectively. ORR for EN and ENB were 10% and 36%, respectively (5 of 7 ongoing). In C2a, 12/23 pts stopped treatment due to neurological symptoms and PD on first MRI (median 5 wks, range 2-8). In C3 (ENB), only 1/11 pts stopped early due to PD. **Conclusions:** EO2401 generated strong systemic immune responses and was well tolerated in combination with nivolumab +/- bevacizumab. The addition of bevacizumab to EN improved PFS while survival across treatment cohorts is pending ongoing follow-up. To prolong EN exposure that is likely required for therapeutic activity in recurrent GB, the trial has been expanded with additional pts to evaluate low-dose bevacizumab (5 mg/kg q2 wks up to x 6) for early progressive neurological symptoms. Clinical trial information: NCT04116658. Research Sponsor: Enterome.

2035 **Poster Session**

Multicenter phase 2 trial of the PARP inhibitor (PARPi) olaparib in recurrent IDH1 and IDH2-mutant contrast-enhancing glioma. *First Author: Kristina Fanucci, Yale Cancer Center, New Haven, CT*

Background: Isocitrate dehydrogenase (*IDH*) *1* and *IDH2* mutations (*IDH1/2*mt) are the most common mutations in gliomas, occurring in over 70% of low grade and 20% of higher grade gliomas. *IDH1/2*mts are associated with improved prognosis, although tumors typically recur and progress to a higher grade despite first lines of treatment. Recent preclinical studies have suggested *IDH*mt and accumulation of 2-HG confer a "BRCAness" phenotype, a vulnerability that can be targeted through PARPi. To test this hypothesis, we conducted a multicenter study of olaparib monotherapy in patients (pts) with *IDH1/2*mt gliomas that had progressed despite standard therapy. **Methods:** Eligible pts had contrast enhancing and biopsy confirmed *IDH1/2*mt glioma that progressed despite standard therapy. Pts with prior treatment with PARPi or *IDH*mt inhibitors were excluded. The primary endpoint was overall response rate (ORR). Secondary objectives were progression free survival (PFS), overall survival (OS) and duration of response (DR). Olaparib 300 mg orally twice daily was given. A standard Simon 2 stage design was used. Stage 1 included 15 pts. If 2/15 pts responded stage 2 would expand by 30 pts. Responses were assessed with RANO criteria and reviewed centrally. **Results:** 15 evaluable pts were enrolled. Most recent histology as per 2021 WHO classification was 12 astrocytoma (4 grade 2, 3 grade 3, 5 grade 4) and 3 oligodendroglioma (2 grade 2, 1 grade 3). A total of 13 pts' tumors had *IDH1* R132H mutations; 2 pts had *IDH2*mt (R172G, R172K). All pts had >1 and 10 pts had >2 prior lines of systemic therapy (median 2, range 1-4). Most toxicities were grade 1 or 2. Nausea (67%) and fatigue (47%) were most frequent. Grade 3 lymphopenia, thrombocytopenia, and hypertension were seen in 1 patient each. Best response was stable disease (SD) in 9 pts and 6 pts had disease progression (PD). The median PFS was 3.6 months, 6-month PFS rate 26.7%, median OS 13.2 months. For pts with SD, median PFS was 5.5 months; 4 pts had SD for > 6 months. 2/6 pts with PD had confirmed WHO grade 4 by histology; 4 had *CDKN2A* deletion. *CDKN2A* deletion was unknown for 2 pts. **Conclusions:** Olaparib was well tolerated in this pt population. The study did not meet the pre-specified response-based threshold for moving to step 2, but prolonged SD was observed in pts with grades 2 and 3 histologies, suggesting olaparib monotherapy could be of clinical benefit in select pts. Grade 4 tumors per the 2021 WHO classification defined by histology or *CDKN2A* mutation derived minimal to no benefit from this drug highlighting the usefulness of this new classification for future patient stratification and trial design and suggesting investigation of this treatment earlier in the disease course might be of interest. Further studies are needed to identify other molecular or clinical predictive markers of benefit from PARPi as well as novel drug combinations for improved efficacy in this population. Clinical trial information: NCT03212274. Research Sponsor: CTEP (1UM1CA186689), the Catherine Ivy Foundation and the Rising Tide Foundation.

2036 **Poster Session**

A phase II, multicenter, single-arm trial of eribulin in patients with bevacizumab-resistant recurrent glioblastoma. *First Author: Masamichi Takahashi, Department of Neurosurgery and Neuro-Oncology, National Cancer Center Hospital, Tokyo, Japan*

Background: Glioblastoma (GBM) is one of the worst prognostic cancers and there is no effective treatment after failure of bevacizumab. Eribulin is a microtubule inhibitor used for the treatment of patients with metastatic breast cancer and liposarcoma. We previously reported that eribulin strongly inhibits the RNA-dependent RNA polymerase (RdRP) activity of TERT protein in cancer cells, and has a strong anti-tumor effect against GBM cells with TERT promoter mutation. In this study we aim to investigate the efficacy and safety of eribulin in patients with bevacizumab-resistant recurrent GBM. **Methods:** This is an open-label, multicenter, single-arm phase II trial. Eligible patients aged 20-75 years with bevacizumab-resistant recurrent GBM were enrolled from 2018-2020. Patients received eribulin 1.4 mg/m^2 on days 1 and 8 of 21-day cycle until disease progression or intolerable toxicity was observed. The primary endpoint was one-year overall survival rate (1yOS%). The 35 patients are needed to achieve an 80% power at a one-sided alpha of 10%, under threshold 1yOS% of 10% and expected 1yOS% of 25%. **Results:** Thirty-seven patients aged 26-73 (median: 54) years were treated. Twenty-six of 37 (70.3%) patients were diagnosed as IDH-wildtype GBM, 4 (10.8%) were with IDH-mutant GBM and 7 (18.9%) were GBM, NOS. Thirty-four (91.9%) patients had a Karnofsky performance status of 70 or 80 at the registration. Thirty-one (83.8%) patients received additional treatments, including 28 (75.7%) bevacizumab, 11 (29.7%) re-irradiation and 3 (8.1%) resection after failure of eribulin. Among 37 subjects, 32 surgical specimens were analyzed for TERT promoter mutation and 15 for RdRP activity. 1yOS% was 29.7% [80% CI: 20.5 to 39.5 ($p < 0.0001$), 95% CI: 16.1 to 44.6]. Median OS was 9.0 months [95% CI: 6.2 to 11.0] and median progression-free survival was 1.5 months [95% CI: 1.4 to 1.7]. Neither TERT nor RdRP statuses was associated with prolonged OS. Among all the target lesions evaluated, two lesions decreased more than 50% in size and the patients survived more than one year, however no obvious PR was confirmed at the final evaluation. The disease control rate was 25.7% [95% CI: 12.5 to 43.3]. Common ≥ grade 2 AEs were neutropenia (70.3%), leukopenia (56.8%), lymphopenia (27.0%), elevation of γ-GTP (13.5%), elevation of ALT (10.8%), elevation of AST (8.1%), alopecia (8.1%). Treatment-related grade 3 or 4 AEs occurred in 59.5% of subjects. There were no AEs leading to death. **Conclusions:** Eribulin was safely applied for the patients with recurrent GBM. This phase II study met its primary endpoint of 1yOS%, although no obvious response was observed. Further investigation to reveal the biomarkers related to longer survival is underway. Clinical trial information: UMIN000030359. Research Sponsor: Japan Agency for Medical Research and Development (AMED).

2037 **Poster Session**

Final data from the phase 2a single-arm trial of SurVaxM for newly diagnosed glioblastoma. *First Author: Michael J Ciesielski, Roswell Park Comprehensive Cancer Center, Buffalo, NY*

Background: Newly diagnosed glioblastoma (nGBM) routinely treated with surgery, radiation, and temozolomide (TMZ), still result in early progression and near-universal lethality within 5 years. Tumor associated "survivin" is expressed in >95% of nGBM and targetable by SurVaxM immunotherapy. Results from the recently completed multi-center phase 2a trial of SurVaxM in nGBM are presented. **Methods:** nGBM patients (pts) were enrolled at 5 trial sites. Eligibility criteria included: age ≥ 18, Karnofsky performance status ≥70, IHC confirmation of survivin expression, expression of HLA-A*02, A*03, A*11 or A*24 MHC-I alleles and residual contrast enhancement of ≤1 cm^3 by MRI within 72h post-resection. Pts received standard TMZ chemoradiation followed by initiation of 4 priming doses of SurVaxM (500 mcg in emulsion with Montanide ISA 51, every 2 weeks) with 100 mcg sargramostim. Maintenance doses of SurVaxM-Montanide plus sargramostim were thereafter administered every 12 weeks. Adjuvant TMZ was administered for at least 6 cycles, after at least the first dose of SurVaxM and beginning no sooner than 28 days after completion of chemoradiation. Pts were monitored by MRI every 8 weeks, and progression was assessed using modified RANO criteria. The primary endpoint was 70% progression free survival (PFS) at 6 mos. Primary analyses of median PFS (mPFS) and median overall survival (OS) were measured from first immunization. Safety, tolerability, and immune responsiveness were also determined. **Results:** 63 pts with nGBM were enrolled, comprised of 38 males and 25 females with a median age of 60 years. The cohort was consistent with the 4 commonly observed primary molecular GBM subtypes (classical, mesenchymal, neural and proneural). SurVaxM was well tolerated, with no serious adverse events. A strong positive correlation, accounting for censoring, was observed between PFS and OS of all pts (r = 0.79; 95% CI (0.66,0.87)). SurVaxM was immunogenic and produced survivin-specific CD8+ T-cells and antibody (IgG) titers in both methylated and unmethylated MGMT pts and both groups showed clinical benefit. **Conclusions:** SurVaxM appeared to be safe and well-tolerated in pts with nGBM. SurVaxM was effective at stimulating survivin-specific immune responses and the primary endpoint was met. SurVaxM represents a promising therapy for nGBM, including for those pts with unmethylated MGMT genes. For pts treated with SurVaxM, PFS may be an acceptable surrogate for OS. Clinical trial information: NCT02455557. Research Sponsor: MimiVax, Other Foundation.

	mPFS	PFS12 (%)	95% CI	PFS24 (%)	95% CI	PFS36 (%)	95% CI
All Pts *n = 63*	11.4	47.6	34.9,59.3	26.6	16.4,37.9	22.6	12.9,33.9
unMGMT *n = 29*	7.0	27.6	13.1,44.3	17.2	6.3,32.7	8.6	0.9,27.9
meMGMT *n = 33*	17.9	63.6	44.9,77.5	35.6	19.7,51.7	32.3	17.2,48.5
	mOS	**OS12 (%)**	**95% CI**	**OS24 (%)**	**95% CI**	**OS36 (%)**	**95% CI**
All Pts *n = 63*	25.9	87.2	76.1,93.4	51.0	38.3,63.0	41.4	27.8,54.5
unMGMT *n = 29*	16.5	79.2	59.4,90.1	36.0	19.0,53.3	25.2	9.9,43.9
meMGMT *n = 33*	41.4	93.9	77.9,98.4	66.1	47.1,79.6	56.3	35.8,72.6

2038 **Poster Session**

Multiparametric analysis in GBM plasma extracellular vesicles (Evs) and surface marker expression profile. *First Author: Abudumijiti (Zack) Aibaidula, Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic Graduate School of Biomedical Sciences, Mayo Clinic, Rochester, MN*

Background: Glioblastoma (GBM) is the most common malignant brain tumor with poor clinical prognosis. Management of GBM is hampered by the lack of an accurate test that can be used for differential diagnosis of tumor progression from inflammatory pseudoprogression. Plasma extracellular vesicles (EVs) has been shown to be a promising source for biomarker identification. In this project, we aimed to identify GBM plasma EV markers that could serve as the basis of a liquid biopsy. **Methods:** Sample preparation, assay controls and instrument calibration were performed following MIFlowCyt-EV guideline. Plasma samples were subjected to 2-step centrifugations to remove cell debris and platelets. 10ul of plasma sample was diluted with 90ul filtered PBS, then stained for EV surface markers including CD9, CD31, CD45, CD41a and CD11b, as well as actin phalloidin. Stained plasma samples were purified using IZON qEV1/70nm column, then EV fractions were analyzed using full spectrum Cytek Aurora flow cytometer. Clustering analysis was performed on EV events (CD9 +/ actin phalloidin -) using t-SNE and FlowSOM extensions from FlowJo plugins. **Results:** Compared to normal donors, GBM plasma EVs were bigger in size (higher SSC value) and expressed higher levels of CD9, CD31, CD45 and CD11b while ND plasma EVs had higher CD41a expression. t-SNE and FlowSOM analysis demonstrated that GBM plasma EVs had a unique surface marker expression profile compared to ND EVs. It also showed 10 EV sub-populations that differed in size as well as various surface marker expression levels. Four of these subpopulations were enriched in GBM EVs, while three of these were enriched in ND EVs. **Conclusions:** This multiparametric analysis revealed that GBM plasma EVs had a unique surface marker expression profile compared to ND plasma EVs. Further separation and molecular profiling analysis based on each sub population could reveal EV biomarkers that are unique to each sample population. Research Sponsor: Brains Together For a Cure, Other Foundation.

2039 **Poster Session**

Convection-delivered adenoviral gene therapy reprograms the immunosuppressive glioblastoma microenvironment. *First Author: Jacob S Young, Department of Neurosurgery & Division of Neuro-Oncology, University of San Francisco, San Francisco, CA*

Background: Immune checkpoint inhibition has not improved outcomes for glioblastoma patients, and single- cell approaches reveal the glioblastoma microenvironment is largely comprised of immunosuppressive cells. We hypothesized intratumor convection enhanced delivery (CED) of adenoviral gene therapy could recruit and activate anti-tumor immune cells in the glioblastoma microenvironment. **Methods:** Syngeneic GL261 (3x105 cells/mouse) or SB28 glioblastoma (3 x 10^4) cells were implanted into the frontal lobe of immunocompetent C57BL/6J mice (18 mice/arm). Intracranial bioluminescence (BLI) and body weight (BW) measurements were used to assess glioblastoma growth and treatment toxicity, respectively. After tumor engraftment, glioblastomas were treated with conformal ionizing radiation mimicking stereotactic radiosurgery (SRS) in human patients as a positive control for tumor inhibition (18Gy/1Fx). Attenuated adeno-associated virus 9 (AAV9) vectors encoding *Gfp* as a negative control, or encoding experimental cytokines driving recruitment and activation of anti-tumor immune cells in other intracranial tumors (*Ccl4*, *Il1b*, or *Apoa1*) were delivered using CED (2x1011 vg/mouse). Glioblastomas were collected for histologic, single-cell, and molecular analyses 5 days after treatment (6 mice/arm) and at endpoints after monitoring for survival (12 mice/arm). CED targeting was validated using AAV9-GFP and confocal microscopy. Treatment responses were assessed using H&E, IHC, multiplexed cytokine assays, and single cell mass cytometry (CyTOF) to define immune cell types in the glioblastoma microenvironment. **Results:** Histologic analyses revealed AAV9-CCL4, AAV9-IL1B, or SRS induced glioblastoma macrophage infiltration, and AAV9-IL1B, AAV9-APOA1, or SRS induced glioblastoma T cell infiltration. AAV9-APOA1 (18.5 days versus 15 days, $p < 0.001$) or AAV9-IL1B (16.5 days versus 15 days, $p = 0.001$) CED treatments prolonged median survival from SB28 allografts. Glioblastoma cytokine analysis revealed inhibition of pro-tumor cytokines (IL6, LIF) after experimental CED treatments. Systemic cytokines were minimally changed by CED treatments. CyTOF showed decreased immunosuppressive macrophage infiltration and increased CD8+ T cell or microglia infiltration of the glioblastoma microenvironment after experimental CED treatments. There was no evidence of systemic or central toxicity in any treatment condition. **Conclusions:** Convection-enhanced delivered of adenoviral gene therapy reprograms the glioblastoma immune microenvironment and improves survival in an immunologically "cold" syngeneic glioblastoma model. Research Sponsor: Neurosurgery Research and Education Foundation.

2040 **Poster Session**

Harnessing genetically engineered hematopoietic progenitor cells to redirect the tumor immune microenvironment against glioblastoma (TEM-GBM Study). *First Author: Marica Eoli, Neuro-Oncology Unit-Istituto Neurologico Carlo Besta-Milano, Milan, Italy*

Background: Immunotherapies represent powerful tools that are transforming the treatment of many cancers. However, immune dysfunction in cancer is multifactorial requiring multiple points of action, especially in immunologically-cold tumors. **Methods:** We have developed a genetically modified, autologous hematopoietic stem cell-based platform designed to deliver Interferon-alpha (IFNa) specifically into the tumor microenvironment through Tie-2 expressing monocytes (Temferon), in order to activate the immune system in an agnostic way against the tumor and re-establish immunosurveillance. **Results:** As of Jan 2022, 3 escalating doses of Temferon (from 0.5 to $2.0x10^6$/kg) were tested across 15 patients assigned to 5 cohorts affected by newly diagnosed, unmethylated MGMT glioblastoma (GBM). The follow-up range from surgery is 5 – 27 mo (3 – 24 mo after Temferon). In all patients, we observed rapid engraftment of gene modified progenitors and fast recovery from sub-myeloablative conditioning (median engraftment across all the cohorts: Neu D+13, PLT D+14). Temferon-derived differentiated cells, as determined by the presence of vector genomes in the DNA, were found at increasing proportions in blood and bone marrow, reaching up to 30% at 1 mo for the highest dose cohorts tested and persisting up to 18 mo, albeit at lower levels. Despite the significant proportion of engineered cells, only very low median concentrations of IFNα were detected in the plasma (D+30, 5.9; D+90, 8.8pg/mL) and in the CSF (D+30, 1.5; D+90, 2.4pg/mL), indicating tight regulation of vector expression. SAEs were mostly attributed to conditioning chemotherapy (e.g. infections) or disease progression (e.g. seizures). 1 SUSAR (persistent GGT elevation) has occurred. Median OS is 14 mo from surgery (10 mo post Temferon). A patient from cohort 3, had at D+120 disease progression with two distant enhancing lesions, and increased tumor necrosis. One year following Temferon, with no 2nd line therapy added, there was approximately 40% reduction in enhancing tumor volume compared to D+180. Four pts from the low dose cohorts underwent 2nd surgery. Vector genomes were detectable in tumor biopsies. Single cell RNA seq performed on CD45+ cells purified from the GBM TME highlighted the presence of an Interferon gene signature in all patients, resulting in macrophage repolarization in some of them. **Conclusions:** Our interim results show that Temferon is well tolerated, with no dose limiting toxicities identified to date. The results provide initial evidence of Temferon's potential to modulate the TME of GBM patients. Clinical trial information: NCT03866109. Research Sponsor: Genenta Science.

2041 **Poster Session**

Population-based retrospective analysis of response assessment criteria in patients with glioblastoma. *First Author: Parandoush Abbasian, Medical Physics, Physics and Astronomy, University of Manitoba, Winnipeg, MB, Canada*

Background: Patients with glioblastoma are often treated with radiation and chemotherapy following surgery. Disease recurrence often occurs early in the disease course and during initial therapy, yet assessment of treatment response with MRI is highly variable in some situations. We sought to describe the clinical and imaging assessment and outcomes of an unselected cohort of patients with glioblastoma following the publication of the Response Assessment in Neuro-Oncology criteria. **Methods:** Patients diagnosed with glioblastoma in Manitoba, Canada, from 2012-2018 were identified from the Manitoba Cancer Registry. Chart review was performed to identify treatments given and decisions made by the treating team, and imaging analysis was performed to assess based on RANO and mRANO criteria. Determination of progression versus pseudoprogression according to these criteria was performed using clinical decision-making and review of follow-up imaging for confirmation. At time of the response assessment visit, patients were assessed by a primary oncologist (Radiation or Medical) and were also discussed at multidisciplinary Case Conference (comprised of Medical and Radiation Oncology, Neurosurgery, Neuropathology, and Neuroradiology). Treatment decisions were made with patient and primary oncologist, guided by input from the Case Conference. Tumour measurements were performed both in 2D using Product of Perpendicular Diameter analysis (PPD) and 3D volumetric measurements with/without necrotic region. Overall Survival (OS) and Progression Free Survival (PFS) were estimated to evaluate the effectiveness of response assessments and Kaplan-Meier method was used to compare the time to progression resulted from RANO, mRANO, and clinical impression. **Results:** A total of 285 patients were identified with a pathological diagnosis of glioblastoma. Of those, 199 (35% male, 65% female) were treated with concurrent temozolomide and radiation (75% 60Gy and 25% < 60Gy), and more than 90% went on to receive adjuvant temozolomide. Median Overall Survival of the 199 was 13.2 months. Of those treated with concurrent therapy, 122 (61%) had MRI studies with equivocal results within the first 6 months, with confirmatory MRI showing true progression in 73 (59.8%), pseudoprogression in 45 (36.9%), and 4 patients with undetermined outcome. Formal RANO and mRANO comparison is ongoing. **Conclusions:** Response assessment for patients with glioblastoma remains a frequent challenge despite the use of MRI and established response criteria, with more than half of patients having equivocal imaging changes and a high frequency of pseudoprogression. Research Sponsor: CancerCare Manitoba Foundation.

2042 **Poster Session**

A phase 2 study of trametinib for patients with pediatric glioma or plexiform neurofibroma with refractory tumor and activation of the MAPK/ERK pathway. *First Author: Sébastien Perreault, Department of Neurosciences, CHU Hopital Sainte-Justine, Montréal, QC, Canada*

Background: Pediatric low-grade gliomas (PLGG) are the most frequent brain tumors in children and the majority of PLGG have activation of the MAPK/ERK pathway. Plexiform neurofibromas (PN) are found in up to 50% of patients with neurofibromatosis type 1 (NF1). Trametinib has been used widely to treat PLGG and PN, but no clinical trial has reported its efficacy. **Methods:** This multicenter phase II trial includes patients aged ≥ 1 month to ≤ 25 years with progressing/refractory PLGG groups or PN. The primary objective was to evaluate the overall response rate after daily oral trametinib administration for eighteen 28-day cycles. **Results:** As of January 31st, 2022, 60 patients with PLGG and 45 patients with PN have been enrolled. Median age is 9.5 years (range 1.8-25.4) for PLGG and 11 years (range 0.7-19.8) for PN. Median follow-up is 18 months (range 0.1-38.1). Fifty-three patients with PLGG were evaluable. The overall response includes: 1 complete response (CR) (1.9%), 7 partial response PR (13.2%), 17 minor response MR (32.1%), 23 stable disease (SD) (43.4%) and 5 progressive disease (PD) (9.4%). Twenty-eight patients with a total of 32 PN were available for volumetric analysis. Volumetric assessment demonstrated an overall response rate of 60.7% compared to 24.1% when using RECIST 1.1 and 62.5% of PN showed a decrease of more than 20% in volume. Median volume change was a decrease of 30% (range -93.5 to 14.3). A total of 59 (69.4%) patients discontinued treatment as planned after 18 cycles and 9 (10.6%) patients had to stop trametinib due to adverse events. **Conclusions:** Response rates observed in our study suggest that trametinib is a potentially effective targeted therapy for patients with recurrent/refractory PLGG and PN. Treatment was overall well tolerated. This trial will continue to gather data on duration of response and long-term outcome for PLGG and PN treated with trametinib. Clinical trial information: NCT03363217. Research Sponsor: CIHR, Fondation des Gouverneurs de l'Espoir. Fondation des toiles.

2043 **Poster Session**

A single-institution, retrospective examination of new contrast enhancement, progression, and pseudoprogression in *IDH* mutant glioma. *First Author: Ethan A. Wetzel, UCLA, Los Angeles, CA*

Background: *IDH* mutant glioma patients are followed by MRI, where new contrast enhancement (CEnew) is a hallmark of tumor progression. Interpretation of CEnew is confounded by pseudoprogression (PsP), the appearance of CEnew that spontaneously resolves on subsequent scans. PsP has been characterized in *IDH* wildtype patients, but is poorly understood in the *IDH* mutant category. This study represents an examination of the characteristics and impacts on patient survival of CEnew in *IDH* mutant gliomas. **Methods:** Of the 724 confirmed *IDH* mutant glioma patients treated at UCLA between 1998 and 2022, 587 were included (median follow-up = 5.23 years). Patients were excluded based on these criteria: <4 MRI scans, unknown *IDH* status, and unknown WHO 2016 diagnosis. CEnew was first identified by direct review of images and confirmed by the radiology report. Any new enhancement appearing on the first post surgical MRI was not considered CEnew. CEnew was interpreted as progression after surgical resection indicating tumor or the re-initiation of chemotherapy or radiation and was considered PsP after the resolution of enhancement without new treatment initiation. Some PsP patients could have received bevacizumab. Kaplan-Meier survival analyses were used to examine overall survival differences between groups. **Results:** 327 of 587 patients developed CEnew. The incidence of CEnew was higher in Grade 4 Astrocytoma (G4 Astro) versus all other pathologies and lowest in LO ($p < 0.05$). The Enhancement Free Survival (EFS) was shortest for G4 Astro patients ($p = .002$); LO patients had the longest median EFS of 2602 days ($p = 0.002$). The development of CEnew and presence of preoperative enhancement were both found to be negative survival prognosticators in all pathologies ($p < 0.05$). From our analysis, 92 patients developed PsP and 177 developed progression. The median duration of a PsP spot was 244 days. PsP spots appeared earlier than progression spots (median 538 vs 1113 days, $p = .001$). The incidence of PsP was highest in the G4 Astro group and lowest in LO patients. Survival analysis of patients with progression versus those with PsP and progression shows PsP is associated with longer OS in the entire cohort and the LO, AO, AA, and G4 Astro groups ($p < 0.05$). 100% of PsP patients received radiation therapy (RT). The median time from the end of RT to PsP was 209 days. **Conclusions:** While CEnew in *IDH* mutant gliomas is associated with reduced OS, poorer outcome is driven by progressors. PsP represents 28% of CEnew instances, typically occurs within 1 year of RT and have superior outcome to progressors and equivalent to of patients that do not display CEnew. Research Sponsor: None.

	All	CEnew (%)	PsP (%)	Progression (%)	No CEnew (%)
LO	147	44 (30)	16 (12)	26 (18)	91 (62)
AO	72	36 (50)	11 (17)	24 (33)	31 (43)
LA	139	62 (45)	22 (13)	44 (32)	62 (45)
AA	132	63 (48)	21 (19)	38 (29)	56 (42)
G4 Astro	92	74 (81)	22 (32)	45 (49)	17 (19)
Median OS (years)	5.23	5.14	6.26	4.83	6.08

2044 **Poster Session**

Phase I study of drug-resistant immunotherapy (DRI) with gene-modified autologous $\gamma\delta$ T cells in patients with newly diagnosed glioblastoma multiforme (GBM) receiving maintenance temozolomide (TMZ). *First Author: Louis B. Nabors, University of Alabama, Birmingham, AL*

Background: $\gamma\delta$ T cells, MHC unrestricted immune cells, target NKG2D ligands differentially expressed on tumor cells. DeltEx drug resistant immunotherapy (DRI), a novel ex vivo expanded, activated $\gamma\delta$ T cell expresses MGMT, conveying TMZ resistance. NCT04165941, a phase 1 trial assessing the safety of single and multiple infusions of autologous DeltEx DRI cells presents updated safety and efficacy data. **Methods:** Adult newly diagnosed GBM patients with adequate organ function and KPS≥70% are enrolled. Cells engineered from apheresis after tumor resection were infused through a Rickham catheter placed during surgery. Cohort (C) 1, 2 and 3 receive 1, 3 and 6 doses of cells respectively on day (D) 1 of each 28-day maintenance cycle. Patients receive 1 x 10^7 $\gamma\delta$ T cells intratumorally on D1 with 150 mg/m^2 of TMZ intravenously with the Stupp regimen. Primary endpoint is safety; secondary endpoints include progression free and overall survival. Immunologic and genomic correlative analyses are being conducted. Dose limiting toxicities (DLTs) are defined as treatment related ≥ grade 3 cardiopulmonary or hepatic toxicity, grade 4 toxicity exceeding 72 hours or neurologic deterioration that exceeds 2 weeks. **Results:** 12 patients (58% male; median age 66.5 (range: 21-76); 66.7% IDH-WT, 66.7% MGMT unmethylated) were enrolled with 6 dosed (3 in C1, 3 in C2). No patients had DLTs, cytokine release syndrome (CRS), or neurotoxicity. The most common adverse events (AEs) were Grade 1/2 events including fever, leukopenia, nausea, and vomiting attributable to TMZ or radiotherapy. One subject had Grade 3 treatment related AEs of UTI, dehydration, and thrombocytopenia. Three evaluable C1 patients have PFS of 8.3, 11.9, 7.4 months and OS of 15.6, 17.7 and 9.6 months respectively. In C2, three patients have been dosed, with one patient with stable disease at 8.2 months after receiving all three doses and no DLTs. Patient recruitment continues with anticipated completion in 2022. **Conclusions:** Data demonstrates that single, repeat doses of DRI T cells have manageable toxicity with encouraging trend in PFS. Research Sponsor: In8Bio, Inc.

2045 **Poster Session**

Digital monitoring and assessments in patients with glioblastoma. *First Author: Yasaman Damestani, Karyopharm Therapeutics Inc., Newton, MA*

Background: Glioblastoma (GBM) is an aggressive primary tumor with poor prognosis and survival. Patients (pts) experience debilitating symptoms that have a negative effect on quality of life (QoL). A multidisciplinary approach is necessary to facilitate the reduction of morbidity, preserve QoL, and maximize benefits of treatment. Selinexor (SEL) is a first-in class, oral, selective inhibitor of nuclear export that blocks exportin 1 approved for use in multiple myeloma and diffuse large B-cell lymphoma and has shown activity in GBM. Digital measurements in the KING study through wearable sensors and other devices capture actionable daily data at home for improved care, symptom management, and QoL, are reported here. **Methods:** XPORT-GBM-029 (NCT04421378) is an ongoing phase 1 dose finding study followed by an open-label randomized phase 2, 5-arm trial to evaluate SEL in combination with standard therapies for newly diagnosed and recurrent GBM (n = 350): radiation+-SEL /radiation and temozolomide; radiation and temozolomide±SEL; lomustine±-SEL; bevacizumab±SEL; tumor treating field±SEL. The study is conducted at 18 sites in the US and Canada. GBM progression is assessed by standard clinical and imaging as well as QoL measurements by novel digital tools. Four parameters to determine the impact on QoL (cognitive function, lateralization, fatigue, sleep) are measured remotely by smartwatch and smartphone to continuously measure activity and sleep, and to complete a cognitive battery at baseline and before each MRI. **Results:** To date, pts wearing the smartwatch had higher compliance during the day for activity and gait measures compared to night for sleep measures. Younger pts had better compliance. Over the course of SEL treatment, changes were observed in balance (characterized by double support % and walking asymmetry) and activity level (characterized by step count and walking distance). Of the pts who participated in the cognitive battery (CANTAB) tests, 2 pts had a minor change in cognition measures including psychomotor and processing speed, episodic and spatial working memory, and executive function after 2 SEL treatment cycles. Overall, the CANTAB measures are stable, which align with the mRANO (MRI) results. The correlation between the CANTAB cognition measures and MRI data will be evaluated once more clinical data become available. Ongoing analyses will apply machine learning and statistical tools to determine potential correlations between digital and clinical data, such as physical examinations, AEs, Karnofsky scores, mRANO, NANO, KPS, and PRO QoL questionnaires. **Conclusions:** This is the first demonstration of digital measurement feasibility in a longitudinal study of pts with GBM. Digital measurements for pts with GBM could provide information on the impact of SEL-based treatment and functional outcomes in clinical trials and increase communication between clinicians and pts, thereby improving QoL and care management. Clinical trial information: NCT04421378. Research Sponsor: Karyopharm Therapeutics.

2046 **Poster Session**

Impact of *EGFR*$^{A289T/V}$ mutation on relapse pattern in glioblastoma. *First Author: Fontanilles Maxime, Cancer Centre Henri Becquerel, Rouen, France*

Background: The prediction of the relapse pattern is an important issue in glioblastoma for personalized approach. Molecular factors, such as *MGMT* promoter methylation, influence relapse in- or out-field of the initial radiotherapy volume. Recently, a recurrent mutation located at position 289 of the extracellular domain of the *epidermal growth factor receptor* (*EGFR*^{A289mut}) has been associated with a more infiltrative phenotype in glioblastoma. The primary objective of the present study was to explore the impact of *EGFR*^{A289mut} on the pattern of relapse after a chemo-radiotherapy based treatment of patients suffering from glioblastoma. **Methods:** An ancillary study from a monocentric prospective cohort of patients suffering from glioblastoma was conducted. All patients received radiotherapy and concomitant temozolomide. The population was divided into two groups according to *EGFR*^{A289} status (mutated versus wild-type). Primary endpoint was the overlap score (varying from 0 to 1) between initial irradiated tumor volume (Vinit) and relapse volume (Vr). Vinit was the initial 95% isodose of the radiotherapy and Vr was delineated using the enhanced MRI T1-weighted part of the relapse tumor. Secondary endpoints explored the impact of other *EGFR* extracellular mutations, *EGFR* amplification and *EGFRvIII* on the relapse pattern, as well as the impact of *EGFR*^{A289mut} on survival. *EGFR* alterations were identified using next-generation sequencing or droplet-digital PCR based methods on formalin-fixed paraffin-embedded samples collected at initial diagnosis. **Results:** One hundred patients were included: 11% of the population had *EGFR*^{A289mut} glioblastoma (n = 11/100). *EGFR*^{A289mut} glioblastomas had a relapse pattern more marginal compared to *EGFR*^{A289wt} glioblastomas: a mean overlap score Vinit/Vr of 0.78 was observed in the EGFR^{A289mut} group versus 0.94 in the *EGFR*^{A289wt} group (p = 0.021). The proportion of *EGFR*^{A289mut} glioblastomas in the outfield relapse (overlap score < 0.8) has a trend to be higher than in the infield relapse (overlap score > 0.8): 25% (n = 2/8) versus 9.8% (n = 9/92) for the EGFR^{A289wt} population, p = 0.21. Neither *EGFR* amplification nor *EGFRvIII* did influence overlap score Vinit/Vr. In our population, *EGFR*^{A289mut} did not influence survival. **Conclusions:** *EGFR*^{A289mut} influences the relapse pattern in a population of patients suffering from glioblastoma. The role of *EGFR*^{A289mut} as a decision-making biomarker for personalized radiotherapy should now be investigated in dedicated clinical trial. Clinical trial information: NCT02617745. Research Sponsor: Ligue Contre le Cancer Normandie.

2047 **Poster Session**

Paxalisib in patients with newly diagnosed glioblastoma with unmethylated MGMT promoter status: Final phase 2 study results. *First Author: Patrick Y. Wen, Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Boston, MA*

Background: Paxalisib, a potent oral selective brain-penetrant small molecule PI3K/mTOR inhibitor, has shown activity in nonclinical brain cancer models and promising phase 1 data in progressive / recurrent high-grade gliomas (NCT01547546). This multicenter phase 2 progressive design trial (NCT03522298) aimed to establish the maximum tolerated dose (MTD) for once-daily (QD) dosing, and to evaluate safety, tolerability, pharmacokinetics (PK), and clinical activity of paxalisib in patients with newly diagnosed glioblastoma and unmethylated MGMT promotor status. **Methods:** Eligible patients were males or females, aged ≥18 years, who had undergone surgical resection and chemoradiotherapy (Stupp Regimen), and were considered to be progression free before starting adjuvant paxalisib. Stage 1 used a standard 3+3 dose-escalation design to determine the MTD in this population. Stage 2 was a two-arm, open-label, expansion cohort with patients randomized 1:1 to receive paxalisib at the MTD under fed or fasted conditions. In both stages, treatment comprised daily paxalisib administered in 28-day cycles, continuously until disease progression or unacceptable toxicity. Efficacy analyses are based on investigator review and from date of diagnosis. **Results:** Patients (n = 30; 70.0% males, 83.3% white, mean age 58.5 years) had a mean time since diagnosis of 3.75 months. The majority (n = 29) received between 1 and 6 treatment cycles and one received 29 cycles. In Stage 1 (n = 9), an MTD of 60mg was established on the dose-limiting toxicities of hyperglycemia (n = 1) and stomatitis (n = 1) at 75mg. Paxalisib at 60mg was well-tolerated and adverse events were consistent with other PI3K inhibitor medicines. At the MTD (60mg), the PK profile was linear and dose-proportional with no differences in T_{max} and elimination half-life under fed and fasted conditions. For the overall ITT population, the median progression free survival was 8.4 months (RANO) and 8.6 months (mRANO) and the median overall survival was 15.7 months. In a mITT (n = 22 patients treated with 60mg daily and ≥1 post-baseline assessment), the median PFS was 9.6 months (mRANO). **Conclusions:** The primary study endpoints were met; PK and safety were consistent with prior clinical experience. The MTD showed encouraging clinical activity, prolonging PFS and improving OS. Further efficacy confirmation of paxalisib 60 mg QD in newly diagnosed glioblastoma in a pivotal trial is ongoing (GBM AGILE, NCT03970447). Clinical trial information: NCT03522298. Research Sponsor: Kazia Therapeutics Ltd.

2048 **Poster Session**

Revolumab: A phase II trial of nivolumab in recurrent IDH-mutant high-grade gliomas. *First Author: Caroline Dehais, AP-HP, Sorbonne Université, Hôpital Pitié-Salpêtrière, Service de Neurologie 2 - Mazarin, Paris, France*

Background: Novel effective treatments are urgently needed for IDH-mutant high-grade gliomas (HGGs) recurring after radiotherapy and chemotherapy. While single-agent immune checkpoint blockade (ICB) showed limited efficacy in IDH-wildtype glioblastoma, results in IDH-mutated HGGs are not yet available. In this multicenter, single-arm, phase II trial (REVOLUMAB, NCT03925246), we assessed the efficacy of the anti-PD1 Nivolumab in recurrent IDH-mutant HGGs. **Methods:** Main eligibility criteria: adult patients with IDH-mutant HGG recurring after radiotherapy and ≥ one line of alkylating chemotherapy, KPS > 50%, less than 10mg/day prednisone equivalent. The primary endpoint was the 24-weeks progression-free survival (PFS) rate according to the RANO criteria by investigator assessment. Patients received intravenous Nivolumab 240 mg every 2 weeks for 8 cycles, followed by 480 mg every 4 weeks for a maximum duration of one year. 39 patients were planned to be enrolled based on a one-stage A'Hern's design (p0 = 30%, p1 = 50%, type I error rate = 5%, power = 80%). **Results:** Between July 2019 and June 2020, 39 patients with recurrent IDH-mutant HGG (n = 21 WHO grade 3, 13 grade 4, and 5 grade 2 tumors with MRI evidence of anaplastic transformation; n = 10 1p/19q- codeleted, 17 non-codeleted tumors) were enrolled. The median follow-up duration was 17.6 months (11.6-24). The median time since diagnosis was 4.05 years (0.39-16.72), the median time since radiotherapy was 4.47 years (0.55-12.66), the median number of previous chemotherapy lines was 2 (1-4). Eight patients completed Nivolumab treatment as planned, thirty patients stopped treatment due to tumor progression and one patient due to adverse event (AE) unrelated to study drug. At 24 weeks, 11/39 patients were alive without disease progression (28.2% CI95% [15%; 44.9%]). According to RANO, one patient (2.6%) achieved complete response (CR), 3 patients (7.7%) partial response (PR), 13 patients (33.3%) stable disease, and 22 (56.4%) had progression as their best response. Median PFS and OS were 1.84 (CI95% [1.81 ; 5.89]) and 14.7 months (CI95% [9.18; NR]), respectively. There was no difference in PFS between 1p/19q-codeleted and non-codeleted tumors. No patient definitively stopped Nivolumab due to side effects; the safety profile was consistent with prior studies of Nivolumab in gliomas and other cancers. **Conclusions:** To our knowledge, this is the first reported trial of ICB in IDH-mutant gliomas. Nivolumab failed to achieve its primary endpoint. However, Nivolumab was well tolerated and long-lasting responses were observed in a subset of this population, which support further evaluation in combination with other agents such as anti-VEGF or IDH inhibitors. This trial was funded by French Ministry of Health.The sponsor was Assistance Publique – Hôpitaux de Paris. Study drug was supplied by Bristol Myers Squibb (CA209-818). Clinical trial information: NCT03925246. Research Sponsor: PHRC-K 2016.

2049 **Poster Session**

Prognostic value of hPG_{80} (circulating progastrin) in IDH-wild type glioblastoma treated with radio-chemotherapy. *First Author: Ludovic Doucet, Institut de Cancerologie de l'Ouest, Medical Oncology, Saint-Herblain, France*

Background: hPG_{80} (circulating progastrin) is a protein secreted by many cancer types, playing a role in tumorigenesis by regulating cancer stem cells, angiogenesis, proliferation/differentiation and decreasing apoptosis. hPG_{80} is detectable in plasma of cancer patients and previous studies have shown its prognostic role in various cancers. Given the lack of circulating biomarker in glioblastoma, we evaluated the prognostic value of plasma hPG_{80} in patients with *IDH* wild type glioblastoma **Methods:** This multicentric retrospective study included *IDHwt* glioblastoma patients treated with standard radio-chemotherapy. The ELISA DxPG80.lab kit (Biodena Care, Lausanne, Switzerland) was used to measure hPG80 levels after surgery with a detection threshold of 1 pM in all plasma EDTA samples according to the manufacturer's instruction. The prognostic impact of hPG_{80} was evaluated on patient's progression-free survival (PFS) and overall survival (OS). **Results:** We included 70 patients (38 males /32 women) with a median age of 64 years (Range 19 - 84). Karnofsky index was > 70% in 52 (91%) of 57 evaluable patients. Tumor biopsy (B), partial resection (PR), complete resection (CR) were performed in 22, 25 and 23 patients respectively. MGMT promotor was methylated in 22 (40%) of the 55 evaluable patients. After surgery, hPG_{80} was detected in 48 (69%) patients (hPG80+) with a median concentration of 9.52 pM (IQR 5.21 - 21.20). Complete surgery was associated with undetectable levels of hPG80 (52% (CR) vs 28% (PR) vs 14% (B), p = 0.006) and lower concentration if hPG80+ (CR: 5.8 pM [IQR 1.92 - 11.38] vs PR: 12.84 pM [IQR 8.09 - 37.09]; p = 0.04 vs B: 9.86 pM [IQR 4.66 - 21.63]; p = 0.16). With a median follow-up of 39 months (22.4-NR), 86% of patients had progressed and 70% had died. In univariate analysis, hPG_{80} positivity was associated with PFS (5.6m vs 8.5m, p = 0.053) and OS (14.5 vs 22m, p = 0.04) in hPG_{80}+ vs hPG_{80}- patients respectively. hPG_{80}+ patients with complete surgery had worse median OS than hPG_{80}- patients (14.5 vs 22.0 m; p = 0.051 respectively. Cox proportional hazards model did not fit for covariate analysis. **Conclusions:** Our findings show that hPG_{80} could serve as a new circulating prognostic biomarker in IDHwt glioblastoma patients treated with radio-chemotherapy. Further explorations are ongoing in larger cohorts including longitudinal evaluation during the course of the disease. Research Sponsor: None.

2050 **Poster Session**

Radiotherapy and olaptesed pegol (NOX-A12) in partially resected or biopsy-only MGMT-unmethylated glioblastoma: Interim data from the German multicenter phase 1/2 GLORIA trial. *First Author: Frank Anton Giordano, Department of Radiation Oncology, University Hospital Bonn, Bonn, Germany*

Background: Pre-clinical studies consistently demonstrate that inhibition of the CXCL12/CXCR4/CXCR7 axis abrogates recruitment of pro-vasculogenic bone marrow-derived cells after radiotherapy (RT) of glioblastoma (GBM) and promotes T cell exclusion from the tumor microenvironment (TME). The German multicenter phase 1/2 trial GLORIA (NCT04121455) assesses safety of RT plus escalating dose levels (DL) of the CXCL12-neutralizing RNA-Spiegelmer Olaptesed pegol (OLA; NOX-A12) in patients with chemotherapy-resistant GBM. **Methods:** Until now, GLORIA enrolled 10 patients newly diagnosed with incompletely resected (n = 8) or biopsied (n = 2) GBM with ECOG≤2, age ≥18 and without MGMT promoter hypermethylation. All patients receive standard RT (60 Gy in 30 fractions or 40.05 Gy in 15 fractions) and continuous (24/7) i.v. infusions of either 200 mg (DL1; n = 3), 400 mg (DL2; n = 3) or 600 mg (DL3; n = 4) per week of OLA for 26 weeks. The primary endpoint (EP) is safety as per incidence of treatment-related adverse events (AE). Secondary EPs include radiographic response as per mRANO criteria, dynamic susceptibility contrast perfusion (DSC) and the fraction of highly-perfused tumor (FTB^{high}) as well as the apparent diffusion coefficient (ADC). Target lesions (TL) and non-target lesions (NTL, i.e. in-field satellite lesions) are analyzed separately. Tumor tissue is assessed by high-plex immunofluorescence imaging (co-detection by indexing; CODEX). Matched reference cohorts serve as controls for MRI (n = 14) and CODEX (n = 8) data. **Results:** Combination of RT and OLA was well-tolerated and safe. Of all G ≥ 2 AEs (n = 77), 3 (4%) were deemed to be solely OLA-related, including 1 grade 3 AE at DL3. There were no dose limiting toxicities and no treatment-related deaths. In total, eight of the nine patients (89%) with TLs at baseline showed a TL response during OLA therapy, with four (40%) reaching partial remission (PR) as per radiologic mRANO criteria (n = 2 at DL1 and n = 2 at DL3). All three patients treated at DL1 and all four of DL3 reached PR of one or more NTLs. In three cases (n = 2 at DL1; n = 1 at DL3), at least one NTL completely disappeared. Under OLA, radiographic responses of NTL were best at the highest DL (DL1 +49.5/DL2 +488.3/DL3 -59%), as was the increase in diffusion (mean ADC increase +46.4/+28.2/+56.7%) and the decrease in FTB^{high} (mean -33.5/-32.8/-47.7%). Matched pre-/post-surgery CODEX of a confirmed pseudoprogression revealed intralesional clusters of proliferating cytotoxic T cells. Analysis of tissue from a non-responding patient showed T-cell encapsulation by M2-polarized macrophages in an immune-cell enriched TME. Additional follow-up is ongoing. **Conclusions:** Interim data from the ongoing GLORIA trial demonstrates safety of RT plus OLA and suggests promising clinical efficacy of a new class of drugs targeting CXCL12 in GBM. Clinical trial information: NCT04121455. Research Sponsor: Noxxon Pharma AG.

2051 **Poster Session**

Comparison of survival outcomes of patients with newly diagnosed glioblastoma treated with standard chemoradiation in and outside of clinical trials. *First Author: Rifaquat Rahman, Dana-Farber/Brigham and Women's Cancer Center, Boston, MA*

Background: Randomized clinical trials use stringent eligibility criteria to select patients which can raise concerns about generalizability of study results. Recent interest in external controls and new trial designs has increasingly focused on the possible use of real-world data sources. We examined potential differences of survival outcomes in clinical trial and real-world datasets in newly diagnosed glioblastoma. **Methods:** Patient-level data from 4 independent datasets were analyzed. Non-trial data were derived from an institutional dataset of 453 patients with newly diagnosed glioblastoma treated outside of a clinical trial with standard radiation therapy with concurrent and adjuvant temozolomide at a large academic center. Trial patients included patients on the control arm of several multi-institutional trials (NCT00689221, n = 273; NCT00813943, n = 89; NCT00943826; n = 459) and patients treated on trial at our institution (n = 210). Non-trial patients were compared with each of the 4 clinical trial datasets in pairwise comparisons with Cox regression with adjustments for age, sex, extent of resection, KPS and MGMT status. **Results:** Patient-level data from 1,484 patients were analyzed. Non-trial patients were older compared to patients in the multi-institutional trials (mean 58.6 vs. 56.1 years (NCT00943826), 53.9 years (NCT00813943), 55.7 years (NCT00689221); p < = 0.001). The non-trial cohort had fewer women (43.5% vs. 35.9%, p = 0.02), greater proportion of lower KPS patients (47% KPS <90 vs. 31% KPS <90, p < 0.001) and greater proportion of MGMT methylated patients (49% vs. 33%, p < 0.001) compared to NCT00943826 patients. There were no other significant differences between patient characteristics of non-trial patients and the 4 trial datasets. Trial participation was not associated with improved survival in multivariable analysis after adjustments for clinical covariates (non-trial patients vs. each trial dataset; Table, P > 0.05). **Conclusions:** Glioblastoma patients treated on multi-institutional clinical trials that were included in our analysis did not have statistically significant differences in survival compared to patients treated outside of a clinical trial at a large academic center after adjustment for relevant variables. Our findings support the possible use of real-world data in the development of external control arms for future trials in newly diagnosed glioblastoma. Research Sponsor: Joint Center for Radiation Therapy Foundation Grant.

Hazard ratio of trial participation.

Dataset	Univariable analysis		Multivariable analysis	
	HR (95%CI)*	P-value	HR (95%CI)*	P-value
Non-trial (reference)	1		1	
NCT00689221	1.39 (1.04-1.85)	0.026	1.32 (0.98-1.18)	0.07
NCT00813943	1.12 (0.87-1.43)	0.375	1.27 (0.98-1.66)	0.07
NCT00943826	1.40 (1.20-1.63)	<0.001	1.16 (0.97-1.40)	0.11
Institutional Trial Patients Dataset	1.04 (0.96-1.84)	0.704	0.90 (0.71-1.13)	0.35

*Compared to non-trial patients.

2052 **Poster Session**

Clinical characteristics and outcome of a large cohort of patients with primary central nervous system (CNS) tumors and tropomyosin receptor kinase (TRK) fusion. *First Author: Audrey-Anne Lamoureux, CHU Sainte-Justine, Montréal, QC, Canada*

Background: TRK fusions are detected in less than 3% of central nervous system (CNS) tumors. Given their rarity, there are limited data on the clinical course of affected patients. **Methods:** We contacted 166 oncology centers worldwide to retrieve data on patients with TRK fusion-driven CNS tumors. Data extracted included demographics, histopathology, *TRK* gene fusion, treatment modalities and outcomes. **Results:** Ninety-two patients with TRK fusion-driven primary CNS tumors were identified including 76 pediatric patients (82.6%), 15 adults (16.3%) and 1 not specified (1.1%). Median age at diagnosis was 4.4 years (range 0.0–78.3) and 58.7 % were male. *NTRK2* gene fusions were found in 45 patients (48.9%), *NTRK1* and *NTRK3* aberrations were detected in 27 (29.3%) and 20 (21.7%), respectively. Tumor types included 56 high-grade gliomas (HGG; 60.9%), 20 low-grade gliomas (LGG; 21.7%), 4 embryonal tumors (4.3%) and 12 others (13.0%). Median follow-up was 40.5 months (range 3–226). During the course of their disease, 75 (81.5%) patients underwent surgery with a treatment intent, 67 (72.8%) patients received chemotherapy, 50 (54.3%) patients received radiation therapy, while 47 (51.1%) patients received NTRK inhibitors (6 as first line treatment). There were significant differences in the median progression-free (PFS) and overall survival (OS) between pediatric patients compared to adults. The pediatric median PFS was 32 months (95% CI: 15.5–48.5) compared to 8 months for the adult (95% CI: 4.5–11.5, p = 0.015). The pediatric median OS was 182 months (95% CI: 25.1–338.9) compared to 24 months (95% CI: 18.3–29.7 p < 0.001) for adult patients. There was no difference in the PFS of LGG compared to HGG. However, the OS was significantly worse for the HGG when compared to LGG (p = 0.039). The median OS for LGG was not reached and the median OS for HGG was 70 months (95% CI 7.5–132.5). Nineteen patients with HGG (38.0 % 19/50 evaluable patients) died compared to only one patient with LGG (5.6% 1/18 evaluable patients, p = 0.014). **Conclusions:** We report the largest cohort of patients with TRK fusion-driven primary CNS tumors. These results will help us to better understand clinical evolution and compare outcomes with ongoing clinical trials. Research Sponsor: None.

2053 **Poster Session**

Predictions of overall survival (OS) and progression-free survival (PFS) for specific therapeutic interventions in newly diagnosed glioblastoma multiforme (GBM) using Cellworks Singula: myCare-024-04. *First Author: Manmeet Singh Ahluwalia, Baptist Health South Florida, Coral Gables, FL*

Background: Comprehensive molecular profiling reveals significant differences in treatment response among GBM patients. A mechanistic multi-omics biology model allows biosimulation of molecular effects of cell signaling, drugs and radiation on patient-specific *in silico* diseased cells. The Cellworks Singula Therapy Response Index (TRI) identifies the magnitude of disease control and survival for specific anti-tumor strategies. TRI ranks the anticipated outcome of each therapy with a continuous TRI Score, 0 to 100, for each patient's unique genomic network. **Methods:** TRI's ability to predict OS and PFS was prospectively evaluated in a retrospective cohort of 270 IDH wildtype GBM patients from The Cancer Genome Atlas (TCGA) with known clinical outcomes treated with physician prescribed therapies (PPT). The median age was 57.5 years for 162 males and 108 females. There were 73 MGMT methylated with median OS deceased of 17.1 months and living of 9.5 months and median PFS of 6.5 months. There were 197 MGMT unmethylated with median OS deceased of 14.0 months and living of 13.6 months and median PFS of 6.0 months. Stratified random sampling was used to split the data into independent training (N = 153) and validation (N = 117) subjects. Multivariate Cox Proportional Hazard and Proportional Odds models were used to model OS and PFS as a function of the pre-defined Singula TRI and clinical thresholds. Cox Proportional Hazards (PH) regression and likelihood ratio (LR) tests were used on the independent validation subjects to assess the hypothesis that Singula is predictive of OS and PFS above and beyond standard clinical factors. **Results:** In the validation set, Singula TRI was significantly predictive of OS and PFS in univariate analyses and remained significantly predictive in multivariate analyses which included age, sex, MGMT methylation status and drug class. Singula TRI facilitates selection of optimal personalized therapies by providing patient-specific estimates of OS and PFS for 18 NCCN guideline GBM therapies. **Conclusions:** Cellworks Singula was strongly predictive of OS and PFS and provided predictive value beyond physician prescribed therapy, patient age, sex and MGMT methylation status. This information may be used to estimate increases in OS and PFS when comparing Singula TRI recommended therapies versus standard care. These positive results suggest the utility of biosimulation-informed therapy selection to improve survival of GBM and merits validation in prospective clinical studies. Research Sponsor: None.

	Multivariate			Univariate		
Outcome	Likelihood Ratio χ_1^2	*p*-value	HR	Likelihood Ratio χ_1^2	*p*-value	HR
OS[1]	5.0195	0.0251	0.739 (0.559, 0.951)	5.1105	0.0238	0.758 (0.619, 0.975)
PFS[1]	6.9058	0.0086	0.739 (0.603, 0.928)	6.7127	0.0081	0.758 (0.635, 0.928)

[1]Adjusted for age sex drug class MGMT methylation & PPT.

2054 **Poster Session**

Deep learning-based brain tumor segmentation on limited sequences of magnetic resonance imaging. *First Author: Jacky Huang, Stanford University-School of Medicine, Stanford, CA*

Background: Deep learning algorithms trained to segment brain tumors from magnetic resonance imaging (MRI) perform well in ideal conditions supplied by curated datasets. An example is the MICCAI BraTS 2018 dataset, which provides a set of four MRI sequences (T1, T1 post-gadolinium contrast-enhanced, T2, FLAIR) on 285 samples, along with ground truth segmentations annotated by experts. In real-world settings, however, it is not uncommon for patients to undergo MRI with a limited number of image sequence acquisitions. We examined the effect of restricting the imaging sequence set when training a deep learning model for brain tumor segmentation. Our goal was to identify a limited subset that still achieved acceptably high performance. **Methods:** In our experiments, we used the convolutional neural network-based U-Net architecture. Instead of the standard BraTS task, we focused on sub-segmenting specific areas of brain tumors: the active, enhancing tumor (AT) and the tumor core (TC; AT plus the cystic/necrotic core). We trained the architecture on 285 samples of the BraTS 2018 dataset using one or both of two sequences: T1 contrast-enhanced (T1CE) and FLAIR. Using each training model, we predicted segmentation masks given a volumetric MR image of a brain tumor on 66 samples in the held-out validation dataset. We submitted the predicted segmentations to the Center for Biomedical Image Computing and Analytics (CBICA) imaging portal for evaluation, which reports prediction accuracy by returning dice scores on each prediction. **Results:** As shown in the Table, the U-Net model using T1CE alone yielded high performances, with median dice scores of 0.84461 and 0.88267, when segmenting AT and TC, respectively. On the other hand, using FLAIR alone generated lower performances on the same tasks of segmenting the AT (0.25996) and the TC regions (0.51153). Combining T1CE and FLAIR provided no additional performance improvement compared with T1CE used as a standalone sequence. **Conclusions:** We achieved high performances in two brain tumor sub-segmentation tasks using a limited number of MRI sequences in training a deep-learning algorithm. T1CE alone produced high performances on both TC and AT segmentations. Given the ubiquity of the T1CE sequence, the ability to achieve high performance tumor segmentations in the face of limited image sequence availability is critical when applying our algorithm in real-world clinical or research settings. Research Sponsor: U.S. National Institutes of Health.

Median dice scores achieved on each segmentation task.

Segmentation type	Imaging Sequence Subset	Median Dice Score
AT	T1CE	0.84461
AT	FLAIR	0.25996
AT	T1CE + FLAIR	0.84208
TC	T1CE	0.88267
TC	FLAIR	0.51153
TC	T1CE + FLAIR	0.83766

2055 **Poster Session**

Prognostic significance of therapy-induced myelosuppression in newly diagnosed glioblastoma. *First Author: Michael Weller, Department of Neurology, University Hospital and University of Zurich, Zurich, Switzerland*

Background: Myelosuppression is the major toxicity encountered during temozolomide chemoradiotherapy for newly diagnosed glioblastoma. **Methods:** We assessed the association of myelosuppression (neutropenia, thrombocytopenia, anemia, lymphopenia) during temozolomide chemoradiotherapy alone or in combination with experimental agents with progression-free survival (PFS) or overall survival (OS) in 2073 patients with newly diagnosed glioblastoma enrolled into five clinical trials: CENTRIC, CORE, EORTC 26082, AVAglio, and EORTC 26981. A landmark analysis approached was used. For each primary association analysis, a significance level of 1.7% was used. **Results:** Lower neutrophil counts at baseline were associated with better PFS (p = 0.011) and OS (p < 0.001), independently of steroid intake. Females experienced uniformly more myelotoxicity than males. Lymphopenia during concomitant chemoradiotherapy was associated with OS (p = 0.009): low-grade (1-2) lymphopenia might be associated with superior OS (HR 0.78, 98.3% CI 0.58-1.06) whereas high-grade (3-4) lymphopenia might be associated with inferior OS (HR 1.08, 98.3% CI 0.75-1.54). There were no associations of altered hematological parameters during concomitant chemoradiotherapy with PFS. During maintenance chemoradiotherapy, no significant association was found between any parameter of myelosuppression and PFS or OS, although exploratory analysis at 5% significance level indicated that either mild-to-moderate (HR 0.76, 95% CI 0.62-0.93) or high-grade lymphopenia (HR 0.65, 95% CI 0.46-0.92) were associated with superior OS (p = 0.013), but not PFS. **Conclusions:** The association of higher neutrophil counts at baseline with inferior PFS and OS requires further prospective evaluation. The link of therapy-induced lymphopenia to better outcome may guide the design for immunotherapy trials in newly diagnosed glioblastoma. Research Sponsor: EORTC Brain Tumor Group.

2056 **Poster Session**

Capicua (CIC) mutations in gliomas in association with MAPK activation for exposing a potential therapeutic target. *First Author: Sourat Darabi, Hoag Family Cancer Institute, Newport Beach, CA*

Background: Capicua (CIC) Gene is a tumor suppressor, transcriptional repressor, and a member of the high mobility (HMG)-box protein family. *CIC* is a negative regulator of MAPK and RTK pathways; inactivating *CIC* mutations (mut) occur in approximately 40% of oligodendrogliomas (OLIG) and less frequently in other gliomas putatively activating downstream signaling. With a goal to identify potential novel treatment options for various gliomas, we explored key signaling pathways associated with *CIC* mut. **Methods:** Consecutive glioma tumors were analyzed using Next-Gen DNA sequencing (NextSeq, 592 genes or NovaSeq, whole-exome), RNA sequencing (NovaSeq, WTS) and IHC (Caris Life Sciences, Phoenix, AZ). Immune cell fraction was calculated by QuantiSeq; MAPK activation score (MPAS) was evaluated using RNAseq data. A comparison was made using Chi^2 or Fisher's-exact test with correction for multiple-comparison (q) using Benjamini-Hochberg. **Results**: A total of 196 (3.7%) tumors with *CIC* mut were seen in 5266 gliomas tumors analyzed, with the highest prevalence seen in OLIG (143 of 285, 50.2%). There was no difference between grade 3 (73 of 142, 51.4%) and grade 2 OLIG (70 of 143, 49%). *CIC* mut were infrequent in astrocytomas (16 of 829, 1.9%; grade 3, 12/510 or 2.4%; grade 2, 4/261 or 1.5%; grade 1, 0/58). *CIC* mut were present in glioblastomas (24/2753 or 0.6%), gliosarcomas (1/128 or 0.8%), and other mixed subtypes (12/185 or 6.5%). *CIC* mut were associated with higher prevalence of *IDH1/2* mut (92% in *CIC*-mut vs. 17% in wild type), *MGMT* promoter methylation (97% vs. 47%), *FUBP1* mut (32% vs. 1%) but lower *PTEN* mut (1% vs. 25%) and *TP53* mut (12% vs. 39%) (all $q < 0.05$). Significant mutual exclusivity for *CIC* mut and MAPK pathway drivers observed: *EGFR* amplification (1.5% vs. 27%), *EGFR* mut (0.5% vs. 12.6%), *NF1 mut (4% vs. 18%) (all q < 0.05). BRAF* mut rate was similar in *CIC*-mut or wild-type (1% vs. 3%, p = ns). Although associated with a higher tumor mutation burden (cutoff > = 10 mut/MB, 13% vs. 3%), a lower prevalence of PDL1 expression (1% vs. 16%) and lower M1 macrophage infiltration were seen (all $q < 0.05$). Similar effects were seen when stratifying by oligodendroglial and astrocytic histology. *CIC* mut were associated with increased MPAS score in OLIG (p = 0.01), particularly when compared to tumors lacking additional MAPK drivers (p = 0.001). This effect was not seen in astrocytic tumors, although *EGFR* alterations (including CNA, *EGFRvIII, EGFR* fusion and mut) were independently associated with increased MPAS scores ($p < 0.001$). **Conclusions**: *CIC* mut were frequent in oligodendrogliomas but occurred rarely in other glioma tumors and are associated with favorable prognostic markers. RNA expression analysis suggests *CIC* mut is associated with MAPK activation in OLIG, as are *EGFR* alterations in astrocytomas. Targeted inhibition of this pathway in selected gliomas may be a promising therapeutic avenue and should be explored further. Research Sponsor: None.

2057 **Poster Session**

Phase IB trial of pegylated arginine deiminase (ADI-PEG 20) plus radiotherapy and temozolomide in patients with newly diagnosed glioblastoma. *First Author: John S. Bomalaski, Polaris Pharmaceuticals Inc., San Diego, CA*

Background: ADI-PEG 20 exploits the different metabolic ability for synthesizing arginine (Arg) between normal and neoplastic cells to reduce tumor cell growth. Preclinical and clinical studies have shown that cancers which are either Arg auxotrophic, with silencing of argininosuccinate synthetase (*ASS1*), or Arg non-auxotrophic, respond to ADI-PEG 20 monotherapy or ADI-PEG 20 combined with various chemotherapies, respectively. ADI-PEG 20 has shown efficacy as monotherapy in ASS1 negative mouse glioblastoma (GBM) models and the combination of ADI-PEG 20 with temozolomide (TMZ) and with radiation (RT) in both ASS1 negative and ASS1 positive mouse GBM models. Based on these rationales, ADI-PEG 20 was added to standard RT + TMZ in patients with newly diagnosed GBM. This is the first clinical trial combining ADI-PEG 20 with RT. **Methods:** This phase IB, open-label, single-arm, standard 3+3 dose escalation with a recommended phase 2 dose (RP2D) expansion study (NCT04587830) was initiated in June 2020. Weekly ADI-PEG 20 is added to concurrent RT + TMZ and to 6 cycles of adjuvant TMZ (Stupp protocol). ADI-PEG 20 could be continued for up to 2 years. RANO criteria are used to determine response by evaluating MRI at 1, 3 and 6 months after RT, and every 3 months thereafter. Major eligibility criteria are age 20-75 years with newly diagnosed, histologically confirmed GBM with Karnofsky performance status ≥ 60. Endpoints include safety, pharmacodynamics, immunogenicity, progression free survival (PFS) and overall survival (OS). **Results:** Cohorts 1 (18 mg/m^2) and 2 (36 mg/m^2) were completed without dose limiting toxicity (DLT). Enrollment to cohort 3 (RP2D phase, 36 mg/m^2) is ongoing with 23/26 patients. The major adverse events (AEs) were fatigue (52%), constipation (39%) and neutrophil decrease (39%). Dermatologic or allergic reactions occurred in 12/23 (52%), and all were grade 1-2 except for anaphylactic shock in 1 and vasculitis/rash in 1. 22/23 are alive, with median PFS = 9.5 months. The first 6 study patients are all alive for at least 11 months, with the longest at 1.5 years. 10 are off treatment due to progressive disease in 6, severe AE in 2, consent withdrawal in 1, and medical decision in 1. Mean peripheral blood Arg levels were suppressed (< 10uM) for 4-6 weeks in most subjects, with a reciprocal elevation of citrulline levels. Anti-ADI-PEG 20 antibodies tended to increase as peripheral Arg levels increased. **Conclusions:** The addition of ADI-PEG 20 to RT + TMX was safe, and no DLT was observed. The RP2D of ADI-PEG 20 was determined to be 36mg/m^2. AEs were those typically seen with RT + TMZ, with perhaps an increase in rash reported with the addition of ADI-PEG 20. Anaphylaxis and vasculitis were seen (1 subject with each), and have been observed previously with ADI-PEG 20. The preliminary OS data are encouraging. A registration phase 2/3 trial of this triplet is being considered. Clinical trial information: NCT04587830. Research Sponsor: Polaris Pharmaceuticals, Inc.

2058 **Poster Session**

Preliminary results of a phase II study of retifanlimab (PD-1 inhibitor) plus or minus epacadostat (IDO1 inhibitor) in combination with bevacizumab and hypofractionated radiotherapy for recurrent glioblastoma: NCT03532295. *First Author: Jian Li Campian, Mayo Clinic in Rochester, Rochester, MN*

Background: Immunotherapies targeting the programmed cell death-1 (PD-1) pathway in recurrent glioblastoma (rGBM) have failed. We hypothesize that combining therapies targeting multiple immunosuppressive pathways with cytotoxic and antiangiogenic therapies will improve survival. Here, we evaluate the safety and efficacy of an anti-PD-1 monoclonal antibody (retifanlimab), hypofractionated radiotherapy (HFRT), and bevacizumab, with or without an oral IDO1 inhibitor (epacadostat), in patients with rGBM in a nonrandomized, noncomparative sequential two-arm Phase II study. **Methods:** This is an open-label Phase II study of 2 sequential cohorts (Table). Cohort A first examines retifanlimab + bevacizumab + HFRT in patients with *IDH1/2-WT* rGBM. After a toxicity monitoring period, Cohort B, which adds epacadostat, starts enrolling. Key inclusion criteria includes dexamethasone ≤ 4 mg/day at registration and candidacy for reirradiation. Previous bevacizumab use for radiation necrosis is permitted. The primary endpoint is OS probability at 9 months (OS-9). Secondary endpoints include PFS, OS, and toxicity. Exploratory endpoints include immunological phenotyping of blood and tissue. An increase of OS-9 from 38% (bevacizumab alone) to 60% is considered clinically relevant. **Results:** From 6/2020 to 12/2021, we have completed accrual for cohort A and the interim analysis results are presented here: 25 patients with rGBM enrolled, with 23 evaluable. Median age is 64.3 years (42.1-81.8), 30.4% female, 30.4% *MGMT* promotor methylated, median KPS 90 (range 70-100), baseline dexamethasone 0 mg (range 0-4) with 52.2% of patients on dexamethasone during the first 3 cycles, median baseline ALC 1,000 cells/μl (range 300-3,700). Patients received a median of 6 cycles to date (range 2-20). Median follow-up is 11.97 months per the reverse Kaplan-Meier method. Interim analysis shows a median PFS of 9.9 months (95%CI: 5.5 to not reached (NR)) and median OS of 12.2 months (95%CI 7.3-NR). Notably, Cohort A met the primary endpoint with an OS-9 of 71.4% (95%CI: 46.7% -86.1%). No dose limiting toxicities have been yet observed. Two treatment-related grade 3 toxicities have occurred (myositis, hypertension). Cohort B enrollment is ongoing, and correlative studies pending. **Conclusions:** Interim analysis suggests retifanlimab combined with HFRT and bevacizumab in patients with rGBM is well-tolerated and had encouraging OS and PFS at the time of data cutoff. Cohort B, which adds epacadostat, is currently enrolling. Clinical trial information: NCT03532295. Research Sponsor: Incyte.

Treatment regimen.

		Dose			
Treatment	**Total *n***	**Retifanlimab**	**Epacadostat**	**Bevacizumab**	**Radiation**
Cohort A	24	500 mg IV Q4W	-	10 mg/kg IV Q2W	3.5 Gy/day x 10
Cohort B	24	500 mg IV Q4W	600 mg PO BID	10 mg/kg IV Q2W	3.5 Gy/day x 10

2059 **Poster Session**

Indirect assessment of tumor-infiltrating lymphocyte activity in serum for predicting outcome in patients with glioblastoma treated with immunotherapy in the recurrent setting. *First Author: Christina Jensen, Biomarkers & Research, Nordic Bioscience, Herlev, Denmark*

Background: Glioblastoma (GBM) is an aggressive brain tumor and despite efforts in developing new effective therapies, patient survival remains low. There is increasing interest in using immune checkpoint inhibitors (ICIs) for GBM, however the immunosuppressive (cold tumor) characteristics of GBM limit the efficacy of ICIs. Consequently, there is a need to identify patients with active tumor-infiltrating lymphocytes (hot tumor). Several studies have shown that brain extracellular matrix such as type IV collagen has a dynamic composition with protease-induced alterations. In this study, we evaluated the clinical utility of a non-invasive biomarker of granzyme B degraded type IV collagen (C4G) reflecting tumor-infiltrating lymphocyte activity and of matrix metalloproteinase (MMP) degraded type IV collagen (C4M) in GBM patients treated with nivolumab (anti-PD-1) and bevacizumab (anti-VEGF) in the recurrent setting. **Methods:** C4G and C4M were measured in serum from 22 controls and 39 GBM patients previously treated with surgery, radiotherapy and chemotherapy in the primary setting. After GBM recurrence, 18 patients underwent salvage resection (arm A) however 21 patients had no possibility for resection (arm B). All patients were treated with nivolumab and bevacizumab (NCT03890952 phase II study). Baseline GBM samples were taken before the second-line treatment. The association between C4G levels and outcome was evaluated by Cox regression analysis for overall survival (OS) and odds ratio (OR) calculations for complete response (CR) rate after dichotomizing patients into low vs high levels of C4G (median cutpoint). **Results:** C4G (p = 0.004), but not C4M (p = 0.166), was significantly elevated in serum from GBM patients compared to controls. Moreover, patients with high C4G levels had a significantly increased likelihood of experiencing CR (OR=6.68, p<0.0001). Furthermore, patients with high C4G experienced improved OS compared to low C4G (HR=0.39), and this remained significant after adjusting for other significant risk factors (treatment arm and MGMT methylation) by multivariate analysis (HR=0.44) (table). **Conclusions:** A non-invasive biomarker reflecting tumor-infiltrating lymphocyte activity (C4G) has the potential to identify GBM patients responding to nivolumab and bevacizumab in the recurrent setting. In the future, this may provide a non-invasive biomarker tool for stratifying patients with GBM for ICI trials. Clinical trial information: NCT03890952. Research Sponsor: Danish Cancer Society.

Cox regression analysis.

Univariate analysis	**HR (95%CI)**	**P value**
Age	0.99 (0.97-1.02)	0.637
Gender	0.50 (0.23-1.09)	0.082
Treatment arm, B vs A	2.23 (1.07-4.67)	0.033
LDH	0.99 (0.99-1.01)	0.933
IDH mutation	0.69 (0.28-1.73)	0.429
MGMT methylation	0.31 (0.14-0.68)	0.004
C4G, high vs low	0.39 (0.18-0.82)	0.013
C4G high adjusted for MGMT and treatment arm by multivariate analysis	0.44 (0.19-0.99)	0.048

2060 **Poster Session**

Safety and efficacy of glasdegib in combination with temozolomide and radiotherapy in patients with newly diagnosed glioblastoma: Phase Ib/II GEINO 1602 trial. *First Author: María Ángeles Vaz, Medical Oncology Department, Hospital Universitario Ramón y Cajal, Madrid, Spain*

Background: Hedgehog signaling through Smoothened (SMO) protein in gliomas promotes cell cycle progression and leads to glioma stem cells (GSCs) maintenance, which constitutes one of the key hallmarks for glioblastoma (GB) resistance against anticancer therapies. Glasdegib, a SMO inhibitor, may disrupt GSCs and lead to enhanced efficacy of the Stupp scheme. **Methods:** Newly diagnosed GB pts received glasdegib with standard radiotherapy (RT)/ temozolomide (TMZ) followed by maintenance with glasdegib monotherapy. The primary objective was to determine the recommended phase 2 dose (RP2D) in a 3+3 dose escalation (DE) strategy in phase Ib and overall survival (OS) in phase II. Secondary objectives included progression-free (PFS) according to RANO criteria, safety, changes in performance status, and exploratory biomarker analysis. **Results:** Between 2018 and 2020, 79 GB pts were enrolled and 78 received at least one dose of glasdegib. In DE, 4 pts received Glasdegib at 100 mg/QD and 6 pts received 75 mg/QD. DLTs were reported in 3/4 pts in 100 mg dose level, and 1/6 pts in 75 mg dose level, declaring 75 mg/QD of glasdegib as RP2D. For phase II, 68 additional pts were treated at 75 mg/QD dose. The median age was 55 years (range: 28-78), 54% were male, 45% were MGMT unmethylated, and 1 pts had an IDH1/2 mutation. Glasdegib treatment lasted a median of 6 m (range: 0.5-21.9). Overall, 72 (97.3%) pts completed concomitant therapy, 65 (87.8%) started adjuvant therapy, 28 (37.8%) completed adjuvant therapy, and 23 (31.1%) continued glasdegib monotherapy. Treatment combination was discontinued due to treatment-related adverse events (TRAEs) in 9 (12.2%) pts. For those pts that received RT/TMZ combined with glasdegib at 75 mg/QD dose, 7 (9.5%) presented grade (G) ≥3 hematological TRAEs during concomitant treatment and 2 (3.1%) during the adjuvant treatment. There were no G≥3 TRAEs of any type during the maintenance phase. Neutrophil count decrease G≥3 was reported in 6 (8.1%) pts and platelet count decrease G≥3 in 7 (9.5%) pts. Cutaneous events G≥3 were reported in 3 (4.1%) pts. ECOG, Minimental and Barthel indexes, were maintained when comparing baseline with end of treatment (p = 0.181, 0.25 and 0.346 respectively). Stabilization was the most common response, reported in 60 (81.1%) pts. After a median follow up of 7.8 m (range 0.7-25.9), median PFS was 6.9 m (95% CI: 6.1-8.5). The 6-m PFS rate was 62.1% (95% CI: 50.9-75.8) and the 18 m OS rate was 63.3% (95% CI: 47.5-84.4). **Conclusions:** The addition of glasdegib to standard RT and TMZ was safe. Glasdegib monotherapy showed no G ≥3 TRAEs. Most patients had disease stabilization, with a promising preliminary PFS and OS for newly diagnosed GBM. Final survival results are awaited. Clinical trial information: NCT03466450. Research Sponsor: GEINO though industry partner Pfizer.

2061 **Poster Session**

Phase 1 trial of ruxolitinib, temozolomide, and radiation in high-grade gliomas. *First Author: Manmeet Singh Ahluwalia, Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center, Neurological Institute, Taussig Cancer Institute and Cleveland Clinic, Cleveland, OH*

Background: Ruxolitinib is a novel, selective inhibitor of JAK1 (Janus kinase 1) and JAK2 and JAK3. JAK signaling involves recruitment of signal transducers and activators of transcription (STATs) to cytokine receptors, activation, and subsequent localization of STATs to the nucleus leading to modulation of gene expression. Dysregulation of the JAK/STAT pathway has been associated with several types of cancer and increased proliferation and survival of malignant cells. Preclinical evidence supports inhibition of JAJK STAT pathway arrogated glioma growth. **Methods:** Ruxolitinib is a novel, selective inhibitor of JAK1 (Janus kinase 1) and JAK2 and JAK3. JAK signaling involves recruitment of signal transducers and activators of transcription (STATs) to cytokine receptors, activation, and subsequent localization of STATs to the nucleus leading to modulation of gene expression. Dysregulation of the JAK/STAT pathway has been associated with several types of cancer and increased proliferation and survival of malignant cells. Preclinical evidence supports inhibition of JAJK STAT pathway arrogated glioma growth. **Results:** 60 patients were treated on the study and there were no dose limiting toxicity seen on the protocol. Survival data was calculated for GBM. The OS for arm 1 was 18.17 (10.15, NA) and was not reached for arm 2. The 1 year OS was 0.62 for arm 1 and 0.93 for arm 2. Patients that received ruxolitinib + radiation x 60 Gy + daily temozolomide at 75 mg/m2 for 6 weeks over 6 weeks (Arm 2) had significantly better PFS and OS than those that received ruxolitinib + radiation x 60 Gy alone. **Conclusions:** Dose of 20 mg twice daily of ruxolitinib is safe with radiation and temozolomide. Preliminary survival data appears promising compared to the historical benchmarks and randomized phase 2 trial is planned. Clinical trial information: NCT03514069. Research Sponsor: Incyte.

		Total N	Number of Deaths	Median OS in Month (95%CI)	Rate at 1 Year (95%CI)	P-value
All patients		37	11	NA (18.17 , NA)	0.75 (0.61 , 0.91)	
Arm	Arm 1	22	10	18.17 (10.15 , NA)	0.62 (0.44 , 0.87)	0.015
	Arm 2	15	1	NA (NA , NA)	0.93 (0.82 , 1)	
Gender	F	16	4	NA (15.93 , NA)	0.8 (0.62 , 1)	0.554
	M	21	7	NA (18.17 , NA)	0.71 (0.54 , 0.94)	

2062 **Poster Session**

Predicting CNS penetration of precision medicine therapies in oncology: A comparison of the CNS TAP tool and the BOILED-Egg computational model. *First Author: Gianni Walker, University of Michigan College of Pharmacy, Ann Arbor, MI*

Background: The number of available targeted therapies has vastly expanded in recent years; however, only a selection of such therapies achieve adequate central nervous system (CNS) penetration. The CNS Targeted Agent Prediction (CNS TAP) Tool was developed to aid in the selection of precision medicine therapies based on preclinical data, clinical data, patient-specific genomic data, and importantly, optimal blood brain barrier penetration. Using a standardized murine pharmacokinetic (PK) model, we sought to determine the concordance of CNS penetration prediction by the CNS TAP Tool compared to the SwissADME BOILED-Egg computational model. **Methods:** Eleven drugs were chosen based on the most commonly altered and targeted pathways by our CNS tumor board. Mice were injected individually with the compounds of interest and sacrificed at four different time points to quantify drug concentration via LC-MS in brain tissue and blood samples for PK analyses (1,2,4,7 hours). The percent brain penetration ($AUC_{brain/plasma}$) was compared to published human phase I PK data and pathway IC-50 to determine if agents were adequately CNS penetrant. These results were compared against the CNS TAP Tool and BOILED-Egg prediction of CNS penetrance. **Results:** All 11 drugs chosen (Table) demonstrated adequate CNS penetration, suggesting likely CNS efficacy. The CNS TAP Tool correctly predicted 10/11 agents (91% concordance), the lone exception being panobinostat. In contrast, the BOILED-Egg model only successfully predicted 3/11 agents (27%). When restricting the analysis to drugs with >50% CNS penetration (ponatinib, panobinostat, and ONC-201), the BOILED-Egg model successfully predicted CNS penetration of all agents. **Conclusions:** The clinician-curated CNS TAP Tool more accurately predicted CNS penetration of precision medicine therapies than the BOILED-Egg computational model, which performed best for drugs that achieve extremely high CNS penetration. The resulting PK and CNS penetration data for all agents was utilized to update and refine the CNS TAP tool for future patient use. Research Sponsor: Hematology Oncology Pharmacy Association (HOPA) Research Fund Award.

Pathway	Drug	AUC Brain/ Plasma Mouse	C_{1hr} Brain/ Plasma Mouse	C_{max} Human, Plasma (ng/mL)	C_{max} Human, Brain (ng/mL)	IC50 (ng/mL)	Murine CNS PK Result	Boiled Egg Prediction	CNS TAP Prediction
Histone	Panobinostat	263%	222%	28.8	75.79	4.19	Yes	Yes	No
Dopamine receptors	Onc-201	620%	1058%	3600	22325.09	183.76	Yes	Yes	Yes
PDGFR	Dasatinib	50.7%	29%	133.6	38.74	29	Yes	No	Yes
PDGFR/FGFR	Ponatinib	218%	242%	82.74	180.48	0.057	Yes	Yes	Yes
PI3K/AKT/MTOR	Everolimus	8%	5%	60.6	4.68	1.53	Yes	No	Yes
MEK	Trametinib	9%	8%	22.2	2.04	0.43	Yes	No	Yes
	Selumetinib	3%	3%	1400	41.58	6.41	Yes	No	Yes
NTRK	Entrectinib	29%	33%	1289.47	372.9	0.56	Yes	No	Yes
	Larotrectinib	2%	10%	1010	23.51	2.27	Yes	No	Yes
BRAF	Dabrafenib	2%	6%	1478	26.68	0.31	Yes	No	Yes
	Vemurafenib	2%	2%	61400	1157.44	15.19	Yes	No	Yes

2063 **Poster Session**

3D-volumetric assessment of response to ivosidenib in IDH-mutant gliomas. *First Author: Sushant Puri, Johns Hopkins Hospital, Baltimore, MD*

Background: Isocitrate Dehydrogenase (IDH) mutant gliomas represent a distinct class of primary brain tumors. Mutant IDH is a driver mutation implicated in gliomagenesis and a potential therapeutic target. Ivosidenib, an inhibitor of mutant IDH1, is currently being evaluated to treat gliomas. In the present study we assess our single-institutional experience with the off-label use of ivosidenib to reduce tumor growth rate in patients with IDH mutant gliomas. **Methods:** We have longitudinally analyzed the imaging of patients with histology-proven radio- and chemotherapy-naïve IDH-mutant WHO Grade 2 and 3 astrocytomas (AS) and oligodendrogliomas (OG) treated with off-label ivosidenib between 2019 and 2022. First, each patients' FLAIR images were anonymized, bias-corrected, co-registered and semi-automatically segmented for volumetric analysis using 3D Slicer 4.11. MR acquisition dates were hidden, and the order of scans was randomized to prevent expectation bias. Volumetric trends and PFS were analyzed. Progressive disease was defined as a ≥40% increase in volume from baseline as per modified RANO criteria. **Results:** Eleven patients were included in the analysis (median age 46 years [range 26-62], 2F, 8AS/3OG, 7 Grade 2). Mean±SD follow-up time on ivosidenib was 16.1±15.5 months. Tumor volume reduction was noted in 82% of patients at least at one time point. Average volume change at best response was -11.4±12.8%. Mean time to best response was 12.1±9.3 months. PFS-6 and PFS-12 were 91% (n = 11), and 88% (n = 8), respectively. Mean PFS was 24.4 months (CI95% 18.8-29.9). Median PFS was not reached. Patients older than 45 years had significantly higher volume reduction compared to younger patients (18.9±6.3% vs. -2.4±13.2%;-p = 0.047, 2-tailed T-test). Ivosidenib was discontinued in in 2 patients for 2D radiographic changes, and in one for increased seizure frequency. **Conclusions:** The use of ivosidenib in treatment-naïve gliomas was associated with a high response rate; however, on average it required longer than a year to achieve best response. In this cohort, older patients had higher volume reduction. The drug was well tolerable. Further analysis of an expanded cohort is underway. Research Sponsor: None.

2064 **Poster Session**

The epileptic landscape of IDH mutant gliomas. *First Author: Michael Drumm, Northwestern University Feinberg School of Medicine, Chicago, IL*

Background: Tumor-associated epilepsy (TAE) is a frequent complication of diffusely infiltrative gliomas. TAE not only impairs quality-of-life, but it can even be life-threatening. Furthermore, glioma cells have been shown to proliferate and migrate faster when exposed to firing neurons. We previously showed that isocitrate dehydrogenase 1 mutant (IDHmut) gliomas were more likely to cause preoperative seizures than IDH wildtype (IDHwt) gliomas, and that the chemical product of IDHmut, D2HG, increased synchronized network bursts in cultured neurons (PMID: 28404805). But the mechanism whereby this occurs, whether IDHmut inhibitors can block this, and whether seizure risk also varies by IDHmut status postoperatively, are unknown. **Methods:** Methods are embedded in Results. **Results:** We discovered that exogenous 3 mM D2HG had a 150% greater effect on the firing rate of cultured mouse cortical neurons when nonneoplastic glia cells were present versus when they were absent (P=0.002). Although a recently published study suggested that D2HG causes seizures through mTOR activation (PMID: 34994387), we found that D2HG reduced neuronal mTOR activity in neuronal-glial cocultures by 54% (P=0.0004). Patch clamp analyses showed that, while D2HG does not directly activate glutamate receptors, it does act as a glutamate transport substrate, thus potentially interfering with the ability of glial cells to take up glutamate released into the synaptic cleft. Coculture with patient-derived IDHmut glioma cells increased the firing rate of human cortical neuron/astrocyte spheroids by up to 272%, and an IDHmut inhibitor currently being tested in clinical trials, AG881, reduced the excitatory effect of IDHmut glioma cells on spheroids by 79% (P=0.0008). Using a novel *in vivo* model of TAE, wherein EEG recordings were taken of immunocompetent mice engrafted with an isogenic pair of Sleeping Beauty transposase-engineered mouse glioma lines (NRAS/ATRX/TP53mut ± IDHmut), we found that IDHmut gliomas produced 7.6-fold more epileptiform spikes than IDHwt gliomas (P=0.004). RNA-Seq analysis of the peritumoral mouse brain tissue showed that this increase in spikes was associated with significantly increased expression of key genes known to be upregulated in epilepsy, including *SLC12A5*, *THSB1*, *VEGFA, FOSL2*, and *SYNPO*. Treatment with 5 mg/kg AG881 by daily oral gavage reduced those spikes in IDHmut-engrafted mice by 51% within three days (P=0.027), whereas vehicle control had no effect (P=0.33). Among 247 patients with grade 2–4 adult-type diffuse gliomas, multivariable time-to-event analysis showed that postoperative seizure risk increased with preoperative seizures, subtotal resection, and IDHmut astrocytoma. **Conclusions:** Together, these data show that (i) the D2HG product of IDHmut gliomas increases neuronal excitation in a glial-dependent manner; (ii) IDHmut also affects postoperative seizure risk; (iii) IDHmut inhibitors may improve TAE control. Research Sponsor: U.S. National Institutes of Health, Lou and Jean Malnati Brain Tumor Institute at Northwestern Medicine.

2065 **Poster Session**

Characterizing malignant transformation in patients with *IDH*-mutant glioma. *First Author: Vicki Liu, University of California-Los Angeles, Los Angles, CA*

Background: Gliomas, which constitute the majority of primary brain cancers in adults, are assigned to a particular grade based on histological and molecular criteria set forth by the World Health Organization (WHO). A subset of initially low grade glioma patients transition to a higher grade at recurrence through a process known as malignant transformation (MT). Despite its significant implications on clinical prognosis, MT remains a poorly understood phenomenon in regards to its incidence rates, effects on survival, and potential prognostic factors. Our study aims to elucidate MT in patients that possess a mutation in the *isocitrate dehydrogenase* (*IDH*) gene, one of the most common genetic alterations in gliomas. **Methods:** All known *IDH* mutant glioma patients, seen at UCLA between 1986 and 2022, who received at least 1 repeat resection for presumed recurrent disease were included. Based on surgical pathology reports, patients were categorized into MT and non-transforming progression groups, and further stratified by diagnosis in compliance with the 2016 WHO Classification of Tumors of the Central Nervous System. Relevant clinical information, including patient demographics, survival data, tumor microscopic descriptions, and magnetic resonance imaging, was accessed via electronic medical records. Kaplan Meier analyses were conducted to evaluate the predictive power of various clinical, pathological, and radiological markers. **Results:** Of 724 total *IDH* mutant patients screened, 253 received a second surgery and were thus incorporated in this study. Among the 196 patients with lower grade pathologies capable of MT, 129 (65.8%) progressed to a higher grade at recurrence while 71 (36.2%) did not. By diagnosis, the incidence rates of MT for initial grade 2 astrocytomas, grade 3 astrocytomas, and grade 2 oligodendrogliomas were determined to be 74.7%, 48.9%, and 66.1%, respectively. MT was associated with worse overall survival and post-recurrence survival compared to non-transformation in astrocytomas, a trend not seen in oligodendrogliomas. Across all relevant diagnoses, a subset of 36 MT patients did not receive treatment in the interval between initial and recurrent surgery, demonstrating the existence of spontaneously occurring MT. Furthermore, consolidating data from pathology and MRI reports revealed that a greater extent of abnormal molecular characteristics at initial diagnosis and earlier post-operative contrast enhancement may predict MT. **Conclusions:** These results highlight the distinct nature of gliomas that undergo MT, particularly in tumors of astrocytic differentiation. Considering its adverse impact on clinical outcome, understanding and anticipating this phenomenon is instrumental for the determination of optimal treatment among glioma patients. Research Sponsor: None.

2066 **Poster Session**

Risk factors for cranial irradiation-related late neurocognitive toxicity: A prospective cohort study. *First Author: Debarati Bhanja, Penn State College of Medicine, Hershey, PA*

Background: Neurocognitive dysfunction is a common complication of cranial irradiation, occurring in up to 50% of irradiated brain tumor patients. Symptoms often severely compromise quality of life long before patients succumb to their tumor; however, risk factors are poorly understood, and consequently, prognostication and prevention have not been possible. The objective of this study was to evaluate the prognostic value of vascular risk factors for the development of irradiation-related brain injury. **Methods:** This single-institution prospective cohort study included patients with malignant primary brain tumors who received cranial irradiation as part of their initial tumor-directed therapy. Three putative vascular risk factors – homocysteine, total cholesterol, apoprotein E genotype (ApOE) – were measured and dichotomized (above vs. below the laboratory normal). Univariate analyses compared each risk factor with four measures of neurocognitive dysfunction: mini-mental status exam (MMSE), MRI white matter changes at 6 months (MRI), physician (Phys) assessment, and patient (Pat) assessment. Decision analysis was used to construct a prediction algorithm. **Results:** 80 patients were included in this analysis. Elevated homocysteine was the most powerful and consistent predictor of neurocognitive toxicity, followed by elevated triglycerides and the ApOE genotype (Table). Logistic regression revealed a highly significant ($p<0.01$) association between homocysteine level and each of the four outcome variables. Decision tree analysis using homocysteine level (high vs. low) and ApoE genotype (yes vs. no) provided the most efficient predictive algorithm. **Conclusions:** Two putative vascular risk factors (homocysteine level > 14 and ApOE genotype) provide moderate ability to predict post-radiation neurocognitive dysfunction using a variety of simple but clinically meaningful definitions of dysfunction. This predictive algorithm should be validated in prospective trials. If these findings are corroborated, studies examining additional risk factors as well as studies looking at risk factor mitigation will be appropriate. Research Sponsor: None.

Association of vascular risk factors with four measures of neurocognitive dysfunction (Risk Ratio [95% CI]).

Risk Factor	MMSE	MRI	Phys Assessment	Pat Assessment
Homocysteine	2.72 [1.71-4] P = 0.0002	2.20 [1.32-3.68] P = 0.0068	2.13 [1.89-5.18] P<0.0001	2.04 [1.38-3.00] P = 0.0029
Triglycerides	1.86 [1.22-2.83] P = 0.0076	2.13 [1.35-3.35] P = 0.0021	1.93 [1.23-3.06] P = 0.0082	1.39 [0.97-2.00] P = 0.1
ApOE	1.96 [1.27-3.00] P = 0.0029	1.38 [0.86-2.21] P = 0.2	1.86 [1.17-3.00] P = 0.011	1.43 [1.00-2.05] P = 0.064

2067 **Poster Session**

Treatment patterns of patients with glioblastoma multiforme in the real-world setting in a developing country. *First Author: Juan José Sánchez Hernández, Hospital de Oncologia Centro Medico Nacional Siglo XXI, Mexico City, Mexico*

Background: Glioblastoma multiforme (GBM) is the most common and aggressive malignant primary brain tumor. Surgery followed of temozolomide administered concurrently with radiation therapy (RT) and followed by adjuvant temozolomide for six cycles significantly improved survival compared with radiation therapy alone in a randomized controlled trial published by Stupp and colleagues. Real world evidence in patients with GBM is scarce in Latin America. **Methods:** A retrospective study was conducted at the Hospital de Oncología, Centro Médico Nacional Siglo XXI, a referral center in Mexico City. We included histologically confirmed patients with GBM treated in a period from January 2015 to January 2019. Descriptive statistics and Kaplan-Meier method with log-rank were used for analysis. Cox regression was used for multivariate analysis. **Results:** A total of 184 patients were included, 96 were men (52,2%) and 88 were women (47.8%); median age was 56 years (range 18 - 87). ECOG performance status scale 0-1, and ≥ 2 represented 34.2% and 65.8% of the cohort, respectively. Maximal surgical resection was performed in 172 patients (93%). After surgery or biopsy, 12 patients (6.5%) did not receive any subsequent oncology treatment. Treatment with concomitant RT with TMZ was offered to 156 patients (84.4%) and RT alone to 16 patients (8.7%). The most common RT modality was conventional fractionation (60 Gy in 30 fractions) in 75% of cases. After concurrent therapy, 135 (86.5%) received adjuvant TMZ, of which 53.4% received ≤ 5 cycles and 46.6% received ≥ 6 cycles. The median overall survival of the entire cohort was 20.1 months (95% CI 13.3 - 26.9 months). Survival in patients with adjuvant TMZ was superior versus patients who did not receive complete multimodal treatment (26.3 months vs 10.5 months, $p < 0.001$). In the multivariate analysis, adjuvant chemotherapy was the only independent factor with statistical significance HR 0.18 (95% CI, 0.08 to 0.41 [$p < 0.001$]). **Conclusions:** In this retrospective study our data confirm that receiving adjuvant TMZ treatment is beneficial in prolonging overall survival compared to those who do not receive adjuvant therapy in patients with GBM. Research Sponsor: None.

2068 **Poster Session**

The interim result of a phase I/II study of nivolumab with or without ipilimumab in combination with multi-fraction stereotactic radiosurgery for recurrent, high-grade, radiation-relapsed meningioma. *First Author: Jiayi Huang, Washington University School of Medicine in St. Louis, St. Louis, MO*

Background: There is a lack of effective therapy for recurrent high-grade meningiomas who relapsed after prior radiation therapy (RT). ETCTN 10186 is a phase I/II study to evaluate the feasibility and preliminary clinical efficacy of combining reirradiation using fractionated radiosurgery with nivolumab plus or minus ipilimumab for recurrent high-grade meningiomas. The preliminary results from the phase I portion are reported here. **Methods:** Recurrent grade II-III meningioma patients were treated with radiosurgery plus nivolumab with or without ipilimumab. Key eligibility criteria include age ≥ 18 years; ECOG score ≤ 2; tumor diameter 1-5 cm; prior radiation dose ≤ 70 Gy; normal organ function; no active autoimmunity. During the phase I portion, eligible patients were treated according to treatment-escalation schema following the modified 3+3 design (Table 1). The maximum tolerated combination (MTC) will be the regimen at which ≤ 1/6 patients experience dose-limiting toxicity (DLT) within 8 weeks of the start of study therapy. During the phase II portion, a total of 24 evaluable patients will be enrolled at the MTC using Simon's MiniMax two-stage design. The primary endpoint of the phase I portion is to determine the MTC. Objective radiological responses (ORRs) are defined as per the Macdonald criteria. One cycle of immunotherapy is defined as 4 weeks of nivolumab with or without concurrent ipilimumab. **Results:** From 7/2019 to 3/2021, 13 patients were enrolled in the phase I, including 6 with regimen A and 7 with regimen B (Table). The median prior RT dose was 56 Gy (18-70) at a median interval of 2.8 years (1.3-13.3). There was no DLT in either cohort, so regimen B was deemed the MTC. The median cycles of immunotherapy completed were not significantly different between cohort A and B (11 vs. 6, p = 0.41, respectively). Three cohort A patients and 2 cohort B patients completed all planned doses of immunotherapy. Most patients stopped due to progression, and only one cohort B patient stopped due to treatment-related toxicity (grade 3 hypophysitis and encephalitis after 6 cycles of immunotherapy). After a median follow-up of 11.1 months, there have been 5 progressions and 4 deaths. The 6 month-PFS and 12 month-PFS rates are 62% and 54%, respectively. Two ORRs have been reported by institutional assessment, and central radiology review is ongoing and will be reported. **Conclusions:** Reirradiation using fractionated radiosurgery with nivolumab plus or minus ipilimumab are well tolerated for radiation-relapsed high-grade meningiomas. Phase II study of regimen B is currently enrolling. Clinical trial information: NCT03604978. Research Sponsor: U. S. National Institutes of Health.

Treatment regimens.

	Dose		
Treatment Level	**Nivolumab**	**Ipilimumab**	**Radiosurgery**
Regimen A (n = 6)	480 mg IV Q4W x 13 doses	–	8 Gy x 3 QOD
Regimen B (n = 7)	3 mg/kg IV Q2W x 12 doses; then 480 mg IV Q4W x 7 doses	1 mg/kg IV Q6W x 4 doses	8 Gy x 3 QOD

2069 **Poster Session**

Spatiotemporal multiomic landscape of human medulloblastoma at single cell resolution. *First Author: Hailong Liu, Beijing Tiantan Hospital Capital Medical University, Beijing, China*

Background: Medulloblastoma is the most common malignant childhood tumor type with distinct molecular subgroups. While advances in the comprehensive treatment have been made, the mortality in the high-risk group is still very high, driven by an incomplete understanding of cellular diversity. **Methods:** We use single-nucleus RNA expression, chromatin accessibility and spatial transcriptomic profiling to generate an integrative multi-omic map in 40 human medulloblastomas spanning all molecular subgroups and human postnatal cerebella, which is supplemented by the bulk whole genome and RNA sequences across 300 cases. **Results:** This approach provides spatially resolved insights into the medulloblastoma and cerebellum transcriptome and epigenome with identification of distinct cell-type in the tumor microenvironment. Medulloblastoma exhibited three tumor subpopulations including the quiescent, the differentiated, and a stem-like (proliferating) population unique to cancer, which localized to an immunosuppressive-vascular niche. We identified and validated mechanisms of stem-like to differentiated process among the malignant cells that drive tumor progression. Integration of single-cell and spatial data mapped ligand-receptor networks to specific cell types, revealing stem-like malignant cells as a hub for intercellular communication. Multiple features of potential immunosuppression and angiogenesis were observed, including Treg cells and endothelial cells co-localization in compartmentalized tumor stroma. **Conclusions:** Our study provides an integrative molecular landscape of human medulloblastoma and represents a reference to advance mechanistic and therapeutic studies of pediatric neuro-oncological disease. Research Sponsor: National Science Foundation of China.

2070 **Poster Session**

Impact of systemic therapy regimen on survival of PCNSL. *First Author: James Janopaul-Naylor, Department of Radiation Oncology at Winship Cancer Institute at Emory University, Atlanta, GA*

Background: Primary CNS Lymphoma (PCNSL) is a rare and often fatal disease. Treatment includes multi-agent systemic therapy with a backbone of high-dose methotrexate (HD-MTX). Despite multiple drug and radiotherapy combinations for induction and consolidation treatment there remains no clear standard of care. The purpose of this analysis is to evaluate how varying treatment approaches impacted clinical outcomes at our institution. **Methods:** Data retrospectively collected for 95 consecutive patients with PCNSL pathologically confirmed from 2002 to 2021. Primary endpoint was OS with secondary endpoints of PFS and LC. Progression based on RANO criteria. Kaplan-Meier analyses, Log-rank test and Cox proportional hazard models used for time to event endpoints. MVA by backward selection applying an alpha of 0.2 for associations with 1st line chemo agents, number of cycles of HD-MTX (>6 or 0-5), size of enhancing tumor at presentation, CSF cytology, type of surgery (biopsy, STR, or GTR), and use of WBRT. **Results:** Most patients had KPS >70 (64.2%), were HIV negative (89.5%), and had no history of solid organ transplant (95.8%). Diagnosis was made by biopsy (73.7%) or resection (GTR 13.7%, STR 12.6%). 54.3% had <14 cc contrast-enhancing tumor volume (median 12.6 cc, range 0.5 - 67.8 cc) and 48.6% had single enhancing lesion. Of the 62 patients treated first line with at least 1 cycle of HD-MTX, 61.3% were treated with HD-MTX + Rituximab (R) and 33.9% with HD-MTX + R + temozolomide (TMZ). With or after induction HD-MTX, 1-3 patients received one or a combination of cytarabine, thiotepa, procarbazine, vincristine, carmustine, or ASCT. Of the 60 patients with evaluable CSF, 30.0% had positive cytology. IT chemotherapy (ITc) was administered to 12 patients (5 with + cytology, 4 with - cytology, 3 with unknown cytology). WBRT for consolidation after chemotherapy used for 3 patients and as monotherapy for 9 patients. 2-year OS and PFS rate was 50.1% (95% CI 38.6%-60.5%) and 38.5% (95% CI 27.9%-49.0%). On MVA, > 6 cycles of MTX was associated with superior OS, PFS, and LC. For patients receiving any chemotherapy, addition of R was associated with inferior OS while ITc was associated with improved OS, PFS, and LC (Table). There was no OS association on MVA with TMZ, GTR, consolidation WBRT, or size or number of initial lesions (p>0.05). **Conclusions:** Completion of induction HD-MTX and use of ITc was associated with better outcomes in this population. Incorporation of R into 1st line therapy was associated with worse OS. Survival remained poor throughout the study period, underscoring importance of further innovation. Research Sponsor: U.S. National Institutes of Health.

		OS		**PFS**		**LC**	
Covariate	Level	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
# Doses MTX	>6	0.34 (0.15-0.78)	0.011	0.35 (0.17-0.75)	0.006	0.10 (0.01-0.65)	<0.001
	0-5	-	-	-	-	-	-
1st line R	Yes	4.05 (1.39-11.80)	0.010	1.94 (0.98-3.86)	0.059	2.42 (0.79-7.38)	0.120
	No	-	-	-	-	-	-
1st line ITc	Yes	0.32 (0.11-0.91)	0.033	0.39 (0.15-0.99)	0.048	0.03 (0.00-0.32)	0.004
	No	-	-	-	-	-	-

2071 **Poster Session**

Phase II single-arm, multi-center, physician-initiated clinical trial of convection-enhanced delivery of nimustine hydrochloride (ACNU) against diffuse intrinsic pontine gliomas. *First Author: Ryuta Saito, Department of Neurosurgery, Nagoya University Graduate School of Medicine, Nagoya, Japan*

Background: Diffuse intrinsic pontine glioma (DIPG) is one of the deadliest central nervous system tumors of childhood, with a 1 year survival of 40%. Intracerebral convection-enhanced delivery (CED) is an approach for administering chemotherapy to patients with brain tumors. We present the results of a multi-institute physician-initiated phase II clinical trial of CED of nimustine hydrochloride (ACNU) against DIPGs. **Methods:** We did a phase 2, single-arm, multi-center, prospective, physician-initiated clinical trial. Eligible patients were aged 3–21 years and had initially diagnosed DIPG. A Karnofsky performance score of at least 50 at study entry; and had completed standard external beam radiation therapy at least 4 weeks but no more than 5 weeks before enrollment. Accrual of 20 patients were planned. The 1 year survival rate from study entry was set as the primary endpoint, and prespecified threshold of the lower limit level of the 95% confidence interval was set as 30%. CED of 7 mL ACNU at the concentration of 0.75 mg/mL was given intratumorally through the 1-2 cannulas implemented surgically. Use of oral or intravenous temozolomide chemotherapy was allowed simultaneously with CED of ACNU. The analysis of the primary endpoint was done in the per-protocol population (patients who received the full dose of treatment), and all patients who was recruited in this trial were included in the safety analysis. This study is registered with Japan Registry of Clinical Trials (jRCT2021190003). **Results:** From April, 2018 to March, 2020, 21 children were enrolled in the trial, of whom 20 were evaluable for the primary endpoint. ACNU was not given for one patient because of the adverse event of intracerebral hemorrhage due to catheter insertion surgery. Other than this patient, all 20 patients got 1-2 catheters inserted and received CED of ACNU. For these patients, CED of 7 mL ACNU at the concentration of 0.75 mg/mL was given intratumorally through the 1-2 cannulas implemented surgically. Temozolomide chemotherapy was administered simultaneously in 15 patients. As a result, progression-free survival was 8.0 months and overall survival was 15 months. 1 year survival from recruitment was 55% and was 65% from initiation of standard radiation therapy. **Conclusions:** As the lower limit level of the 95% confidence interval of the 1 year survival rate from recruitment to the study, which was the primary end-point of the study, exceeded prespecified threshold of 30%, CED of ACNU in the brainstem of children with diffuse intrinsic pontine glioma who have previously received radiation therapy seems to be an effective therapeutic strategy. This therapeutic strategy warrants further development for children with DIPG. Clinical trial information: jRCT2021190003. Research Sponsor: Japan Agency for Medical Research and Development (AMED).

2072 **Poster Session**

Prostate-specific membrane antigen expression in meningioma. *First Author: Heinrich Elinzano, Rhode Island Hospital, Providence, RI*

Background: Meningioma is the most common CNS tumor, yet there is no effective therapy for relapsed/refractory meningioma after surgery and radiation therapy. Although most meningiomas follow a relatively benign course, some have a more aggressive course with rapid tumor growth, brain invasion, higher recurrence rates or extracranial metastasis. Prostate-specific membrane antigen (PSMA) is a transmembrane peptidase upregulated on endothelial cells of malignant solid tumors including glioblastoma and metastatic brain tumors, but not in normal vasculature. PSMA has been investigated as a therapeutic target and as a molecular imaging marker to monitor response to treatment and evaluate disease activity in PSMA-avid tumors. PSMA expression however has not been studied in meningioma. **Methods:** Archival tumor specimens (96 tumor samples: 58 WHO grade 1, 35 WHO grade 2, 3 WHO grade 3) from 69 patients were stained for H&E, PSMA and CD31 and slides were scanned (Leica Aperio AT2 whole slide image scanner). 37 of these samples were recurrent tumors and 13 had prior radiation therapy (intensity-modulated, Gamma knife, craniospinal). 21 of the 69 patients had paired samples of initial and recurrent tumors. QuPath was utilized as open access solution to machine learning generating raw data for PSMA, CD31, PSMA/CD31 ratio and PSMA/vasculature ratio. Paired t-test, unpaired t-test and ROC curves were used for statistical analysis. **Results:** PSMA expression was seen in all of the study samples. PSMA expression ($p = 0.0147$) was lower in grade 1 compared to grade 2 and 3 tumors, but not different among histologic subtypes. PSMA/vasculature ratio ($p = 0.0015$) was lower in grade 1 compared to grade 2 and 3 tumors. PSMA expression ($p = 0.002$) and PSMA/vasculature ratio ($p = 0.0015$) were higher in recurrent compared to non-recurrent tumors. PSMA expression ($p = 0.0442$) was higher in recurrent compared to initial tumors among paired samples. When comparing initial tumors of paired samples to non-recurrent tumors, ROC curves demonstrated CD31 expression (AUC:0.7278; $p = 0.0008$), PSMA/CD31 ratio (AUC:0.7843; $p = < 0.0001$) and PSMA/vasculature ratio (AUC:0.6256; $p = 0.0328$) to be predictors of tumor recurrence. Tumors with prior radiation therapy had higher PSMA/vascular ratio ($p = 0.0439$) compared to those without. **Conclusions:** PSMA is expressed in tumor vasculature of meningioma of any grade, increases at recurrence and persists with prior radiation therapy. Since it is present in meningioma of different grades and throughout the course of the disease, it could potentially be utilized as consistent diagnostic biomarker, relevant factor for risk of recurrence stratification and novel therapeutic target for these tumors. Research Sponsor: None.

TPS2073 **Poster Session**

Phase II multicentric Italian trial on repositioning of the antipsychotic drug chlorpromazine and its combination with temozolomide in patients with MGMT unmethylated glioblastoma: The RACTAC trial. *First Author: Giuseppe Lombardi, Department of Oncology, Oncology 1, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy*

Background: The poor prognosis of patients affected by glioblastoma (GBM) prompts the search for new and more effective therapies, particularly for GBMs with unmethylated MGMT. In this regard, drug repurposing, can represent a safe and inexpensive way to bring novel pharmacological approaches from bench to bedside. Chlorpromazine, a medication in use since six decades for the therapy of psychiatric disorders, shows in vitro features that make it eligible for repositioning in GBM therapy. In our experimentation on six GBM cell lines, chlorpromazine inhibited cell viability in an apoptosis-independent way, induced polyploidy, reduced cloning efficiency as well as neurosphere formation and downregulated the expression of stemness genes. Notably, we found that chlorpromazine synergized with temozolomide, in reducing cell viability and strongly cooperated in reducing cloning efficiency and inducing cell death in vitro for all the GBM cell lines assayed. **Methods:** With these assumptions, we started a multicentric single arm Phase II clinical trial on newly diagnosed GBM patients with unmethylated MGMT by adding chlorpromazine to temozolomide in the adjuvant phase of the standard first-line therapeutic protocol. The experimental procedure involves the combination of CPZ with standard treatment with TMZ in the adjuvant phase of the Stupp protocol after radiochemotherapy combination. CPZ is administered orally at a dose of 50 mg/day – GG 1-28 – of every cycle of the adjuvant treatment with TMZ. At present, 38 patients out of 41 patients planned have been enrolled. Clinical trial information: NCT04224441. Research Sponsor: None.

TPS2074 **Poster Session**

A phase Ia/Ib study of intrathecal deferoxamine in patients with leptomeningeal metastases. *First Author: Jessica Wilcox, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Leptomeningeal metastases (LM) represent an aggressive form of advanced cancer with few durable therapeutic options. One of the principal barriers in treating LM is the paucity of knowledge on cancer cell survival and proliferation within the nutrient-sparse cerebrospinal fluid (CSF). Single-cell RNA sequencing of patient-derived CSF has identified that cancer cells in the spinal fluid employ the single iron-binding transporter and receptor system, lipocalin-2/SLC22A17, to gather sparse iron to sustain their metabolic needs. This phenotype is recapitulated in preclinical mouse models of LM. Depletion of CSF iron via intracisternal administration of deferoxamine, a parenteral iron chelator, dramatically reduced LM growth and significantly prolonged survival in preclinical models. Exploiting LM iron dependency using intrathecal deferoxamine (IT-DFO) represents a novel therapeutic approach for patients with LM. **Methods:** This is a prospective, open-label, single center phase Ia dose escalation study of IT-DFO in patients with LM from any solid tumor malignancy to determine the maximum tolerated dose (MTD) and recommended phase II dose (RP2D), followed by a phase Ib dose expansion of IT-DFO at the RP2D in patients with LM from non-small-cell lung cancer (NSCLC). Eligibility criteria include newly diagnosed or recurrent LM identified by magnetic resonance imaging (MRI), positive CSF cytology, and/or elevated CSF circulating tumor cells (CTCs), age $\geq$ 18 years, Karnofsky Performance Status $\geq$ 60, and life expectancy $\geq$ 8 weeks. All patients will receive IT-DFO in 28-day cycles at a frequency of twice weekly (cycle 1), once weekly (cycle 2), and once every two weeks (cycle 3+). Patients will be monitored for LM progression by neurological examination, neuraxial MRI, and CSF cytology as per modified Response Assessment in Neuro-Oncology LM criteria. Phase Ia will involve a modified accelerated titration over 9 dosing cohorts (IT-DFO dose range 10mg to 495mg) with monitoring for dose-limiting toxicities until the MTD is reached. Phase Ib will further explore the safety of IT-DFO at the RP2D in 20 patients with NSCLC LM. Secondary objectives include the determination of pharmacokinetic and pharmacodynamic properties of IT-DFO and its metabolite, ferrioxamine, in the CSF and serum (phase Ia/Ib), and efficacy outcomes (phase Ib) including LM-objective response rate, LM-clinical benefit rate, LM-duration of response, LM-progression-free survival, and overall survival. Exploratory analyses will prospectively correlate CSF CTC enumeration with treatment response and characterize the impact of IT-DFO on cancer cell metabolism, resistance pathways, and the CSF immune microenvironment. Clinical trial information: NCT05184816. Research Sponsor: MSK Center for Experimental Therapeutics, Other Foundation.

TPS2075 **Poster Session**

A study of neo-adjuvant and adjuvant ofra-vec (VB-111) for treatment of surgically accessible recurrent GBM. *First Author: Patrick Y. Wen, Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Boston, MA*

Background: Ofranergene obadenovec (ofra-vec, VB-111) is an anti-cancer gene based immune activator and targeted vascular disruptor. The dual mechanism of action triggers a broad antiangiogenic effect and induces of a tumor directed immune response. A previous study demonstrated a survival benefit for patients with recurrent glioblastoma (rGBM) treated with ofra-vec monotherapy, that was continued after progression in combination with bevacizumab. Glioblastoma is an immunologically "cold" microenvironment which fosters immunosuppression and antagonizes anti-tumor immune responses. The role of T-cell infiltration in combating cancer has been increasingly recognized and associated with improved participant outcomes. Based on these observations, this study will assess the hypothesis that neoadjuvant use of ofra-vec will lead to a statistically significant increase in tumor infiltrating T lymphocyte (TIL) density within the tumor and enhanced systemic tumor-specific T cell responses. **Methods:** Study NCT04406272 is a multicenter, randomized, blinded, placebo-controlled, phase 2 surgical trial to evaluate early immunologic pharmacodynamic parameters for the viral cancer therapy ofra-vec in rGBM. 45 participants with rGBM indicated for resection will randomized to one of three treatment arms: Neoadjuvant Arm: intravenous ofra-vec prior to resection, and ofra-vec every 6 weeks after resection. Adjuvant Arm: placebo prior to resection, and ofra-vec every 6 weeks afterwards. The control arm will receive placebo prior to resection followed by standard of care. Upon evidence of contrast-enhancing progression, bevacizumab may be initiated as needed for supportive care; however, ofra-vec will continue until progression is supported at two consecutive time points. Tumor samples will be obtained and archived at the time of surgery, and blood samples will be obtained as pharmacodynamic markers throughout the study to allow DNA sequencing of T cells. The primary endpoint is to evaluate the influence of neoadjuvant ofra-vec on TIL density. Other endpoints include safety and tolerability, peripheral T cell response, 6mPFS and OS. Study is open for enrolment. Clinical trial information: NCT04406272. Research Sponsor: VBL therapeutics.

TPS2076 **Poster Session**

A phase 0/surgical window-of-opportunity study in progress, evaluating evolocumab in patients with high-grade glioma or glioblastoma. *First Author: Kirit Singh, Duke Brain Tumor Immunotherapy Program, Duke University Medical Center, Durham, NC*

Background: High-grade gliomas (HGGs) are immunologically 'cold' tumors. This phenomenon is partly due to reduced expression of major histocompatibility class (MHC) I on the surface of tumor cells, which prevents CD8+ cytotoxic T lymphocyte activity (CTLs). Blockade of proprotein convertase subtilisin/kexin type 9 (PCSK9) increases MHC class I expression, enhances CTL tumoral infiltration, and potentiates checkpoint inhibition *in vivo*. Evolocumab is an FDA-approved fully human IgG2 monoclonal antibody PCSK9 inhibitor which is clinically indicated for hyperlipidemia. This study seeks to determine whether evolocumab can cross the blood-brain barrier (BBB) and enhance MHC I expression on resected tumor cells, serving as a potential future adjunct for immunotherapy. **Methods:** This study will enroll ten patients over 18 years who have newly diagnosed or recurrent HGG. These patients will also need to be undergoing resection of their tumor as part of their planned treatment pathway. Following informed consent, patients will receive evolocumab (420mg, subcutaneously) 7-14 days before surgical debulking of the tumor. We will collect tissue which is not required for histological tumor analysis and compare it with a contemporaneous matched control cohort. This will consist of resected tumor specimens from patients not treated with evolocumab. Quantification of the drug will be performed using mass spectroscopy, flow cytometry, and single-cell sequencing. The primary objective of this study is to evaluate whether evolocumab can cross the BBB and be measured in resected tumor specimens taken from patients with HGG. Secondary objectives include an analysis of lipid metabolism and MHC-I expression on the tumor via flow cytometry and CITEseq. Wilcoxon rank-sum test or a two-sample t-test, will compare groups for these endpoints. Exploratory analyses will determine if evolocumab leads to changes in tumorigenic pathways and the immune profile of tumor infiltrating lymphocytes (TILs). Bioinformatic analyses will be performed using protein set enrichment, gene ontology (GO) annotations, and search tools from the retrieval of interactive genes/proteins (STRING). Progress: The study was activated on 10/04/2021 (NCT04937413) and at the time of submission has enrolled 5 participants (4 to control arm, 1 to intervention arm). Clinical trial information: NCT04937413. Research Sponsor: Duke's Brain Tumor Immunotherapy Program.

TPS2077 **Poster Session**

DSP-0390, an oral emopamil binding protein (EBP) inhibitor, in patients with recurrent high-grade glioma: A first-in-human, phase 1 study. *First Author: David A. Reardon, Center for Neuro-Oncology, Dana-Farber Cancer Institute, Boston, MA*

Background: The brain's cells are fully dependent on their own de novo biosynthesis of cholesterol as the blood-brain barrier prevents its uptake from the circulation. In normal glial cells, proper regulation of cholesterol synthesis depends on its cell density and is turned off when the cell density exceeds a certain level. On the other hand, gliomas maintain high levels of cholesterol synthesis to support abnormal growth under any condition. Upregulation of cholesterol synthesis genes is associated with decreased survival in patients with glioblastoma (GBM). Therefore, gliomas are potentially sensitive to cholesterol synthesis inhibition. DSP-0390, an investigational small molecule, is an inhibitor of EBP, an enzyme in one of the last and crucial steps of cholesterol biosynthesis. By inhibiting de novo cholesterol synthesis, cytotoxicity can be induced more selectively against hyperproliferative GBM cells. DSP-0390 has shown significant antitumor activity in orthotopic xenograft models of human GBM (data on file). **Methods:** DSP-0390 will be evaluated in a phase 1 study in patients with recurrent, high-grade glioma (NCT05023551). Key eligibility criteria: age ≥18 years; Karnofsky Performance Status score ≥70%; and adequate renal, hepatic, and hematologic function. Patients must not have multifocal disease, leptomeningeal metastasis or extracranial metastasis, abnormal electrocardiograms, or significant cardiovascular disease. In Dose Escalation, 21–30 patients with World Health Organization (WHO) grade III or IV malignant glioma who progressed after ≥1 prior therapy will be enrolled. Dose level enrollment will be guided by a Bayesian Logistic Regression Model until identification of the maximum tolerated dose or recommended dose for expansion. Dose Expansion for clinical activity will enroll approximately 20–40 patients with WHO grade IV GBM who progressed after primary therapy and have measurable disease. Patients will receive oral DSP-0390 once daily. Study endpoints include safety (treatment-emergent adverse events [AEs], serious AEs, and dose-limiting toxicities), efficacy (6-month progression-free survival [PFS], objective response, PFS, duration of response, and 12-month overall survival), pharmacokinetics (PK), and pharmacodynamic biomarkers. This study is currently recruiting in the United States and Japan. Clinical trial information: NCT05023551. Research Sponsor: Sumitomo Dainippon Pharma Oncology, Inc.

TPS2078 **Poster Session**

GBM AGILE: A global, phase 2/3 adaptive platform trial to evaluate multiple regimens in newly diagnosed and recurrent glioblastoma. *First Author: Timothy Francis Cloughesy, University of California, Los Angeles, CA*

Background: GBM AGILE (Glioblastoma Adaptive, Global, Innovative Learning Environment) is a biomarker based, multi-arm, international, seamless Phase 2/3 Response Adaptive Randomization platform trial designed to rapidly identify experimental therapies that improve overall survival and confirm efficacious experimental therapies and associated biomarker signatures to support new drug approvals and registration. GBM AGILE is a collaboration between academic investigators, patient organizations and industry to support new drug applications for newly diagnosed and recurrent GBM. With its adaptable structure, GBM AGILE has continued trial activation, inclusion of new investigational therapies, and enrollment globally through the challenges of a global pandemic. **Methods:** The primary objective of GBM AGILE is to identify therapies that effectively improve the overall survival in patients with ND or recurrent GBM. Bayesian response adaptive randomization is used within subtypes of the disease to assign participants to investigational arms based on their performance. Operating under a Master Protocol, GBM AGILE allows multiple drugs from different pharmaceutical/biotech companies to be evaluated simultaneously and/or over time against a common control. New experimental therapies are added as new information about promising new drugs is identified while other therapies are removed as they complete their evaluation. The master protocol/ trial infrastructure includes efficiencies through an adaptive trial design, shared control arm and operational processes such as risk-based monitoring and enhanced remote activities. GBM AGILE has screened over 1000 patients and enrollment rates are 3 to 4 times greater than traditional GBM trials, with active sites averaging 0.75 to 1 patients/sites/month. While enrollment had an initial dip during the early stages of the pandemic (April-May, 2020), with flexible processes including remote based monitoring, minimizing in person visits, and remote provision of IMP, the enrollment rebounded by June, 2020. Through the use of improved and efficient processes allowed within a master protocol/adaptive platform trial infrastructure, GBM AGILE has been seamlessly operating a global trial during a global pandemic. Clinical trial information: NCT03970447. Research Sponsor: Bayer, Kazia Therapeutics Limited, Kintara Therapeutics, Inc., Asian Fund for Cancer Research, National Brain Tumor Society, National Foundation for Cancer Research.

TPS2079 **Poster Session**

A randomized phase II study of anlotinib combined with STUPP versus STUPP alone in patients with newly diagnosed glioblastoma (GBM). *First Author: Yuanyuan Chen, Sun Yat-Sen University Cancer Center, Guangzhou, China*

Background: Postoperative with radiotherapy, and concomitant and up to 6 cycles of maintenance temozolomide (TMZ) chemotherapy (STUPP regimen) is now the standard treatment for newly diagnosed GBM, while the effectiveness is limited. Anlotinib is a novel, multi-kinase inhibitor against both tumor angiogenesis and tumor cell proliferation with encouraging findings in preclinical GBM models. Our previous single-arm study (NCT04119674) showed that the addition of anlotinb to STUPP exhibited promising progression-free survival (PFS) in patients with GBM. Therefore, a phase II trial was designed to assessed the efficacy and safety of anlotinib with the STUPP regimen. **Methods:** This is a multicenter, randomized, controlled, phase II superiority trial. Approximately 150 patients will be randomly assigned 1:1 to receive TMZ-based radiochemotherapy with anlotinib or TMZ-based radiochemotherapy with placebo. All patients will receive radiotherapy (fractionated focal irradiation in daily fractions of 1.8–2.0 Gy given 5 days per week for 6 weeks, for a total of 54–60 Gy) concurrently with TMZ (75 mg/m2 QD) and anlotinib (10 mg QD, d1–14/3wks) or placebo. Anlotinib or placebo is administrated during the 28-day treatment break. Adjuvant therapy start four weeks after radiotherapy completion, including six cycles of TMZ (150–200mg/m2, d1–5/4wks) and eight cycles of anlotinib (10 mg QD, d1–14/3wks) or placebo. Patients who complete adjuvant therapy are administrated anlotinib or placebo continuously until the disease progressed or unacceptable toxic effects developed. Eligibility criteria include histologically confirmed newly diagnosed GBM and a World Health Organization (WHO) performance status ≤ 2. Additional inclusion criteria include patients between 18 and 75 years old with adequate wound healing of craniotomy or biopsy; adequate hematologic, hepatic, and renal function; acceptable blood coagulation levels; and the stable or decreasing usage of glucocorticoid doses within 5 days before randomization. Exclusion criteria include potentially fatal intracranial hemorrhage on magnetic resonance imaging (MRI); tumors located only in the brainstem; prior chemotherapy or radiotherapy administered for GBM; and IDH1/2 mutation. The primary objective of this study is to compare PFS accessed by Independent Review Committee in patients receiving anlotinib in addition to standard treatment with patients receiving standard treatment only. Secondary endpoints include overall survival (OS), PFS accessed by investigators, overall response rate (ORR), severity and frequency of AEs (CTCAE V5.0), and quality of life (QOL). The disease control rate (DCR) and duration of response (DOR) will also be explored. Clinical trial information: NCT04959500. Research Sponsor: Chia Tai Tianqing Pharmaceutical Group Co., Ltd. Research Sponsor: None.

TPS2080 **Poster Session**

A phase I/IIa, open-label, multicenter, non-randomized clinical trial to assess the safety and efficacy of CYNK-001 in combination with recombinant human interleukin 2 in adults with recurrent resection eligible IDH1 wild-type glioblastoma (GBM). *First Author: Daniela Annenelie Bota, University of California Irvine, Irvine, CA*

Background: CYNK-001 is a CD56+CD3- enriched, off-the-shelf, allogeneic natural killer (NK) cell product expanded from placental CD34 cells. CYNK-001 exhibits *in vitro* cytotoxicity against patient-derived GBM cell lines and secretes cytolytic cytokines during co-culture with cancer cells. CYNK-001 administered via the intracranial (IC) route exhibited *in vivo* antitumor activity in a U-87MG orthotopic mouse model. **Methods:** A Phase I/IIa clinical trial is enrolling IDH1 wild-type GBM patients at first or second recurrence with contrast-enhancing measurable disease (per RANO criteria) who are candidate for surgical resection. Screening MRI scans for inclusion are performed within 14 days prior to Day -5 lymphodepletion with Cyclophosphamide 900mg/m^2 and fludarabine 30mg/m^2 plus mesna. Using a standard 3+3 dose escalation schema, patients will receive the first cycle of CYNK-001 intravenously (IV) at an initial dose of 2.4 x10^9 cells on Days 1, 8 and 15 after lymphodepletion. Cell supportive IL-2 at 6M IU administered SQ on Days 1, 3, 5, 8, 10, 12, and 15 within 3 hours prior to CYNK-001 IV infusion where applicable. Cycle 2 begins with surgical resection on Day 22 in which CYNK-001 is administered directly into the tumor cavity wall at an initial dose of 100 x10^6 NK cells and an Ommaya catheter placement. Subsequent CYNK-001 IC administrations via the Ommaya are on days 29 and 36 with 6M IU IL-2 SQ. DLT is evaluated for all dosing cohorts from day 1 to 7 days post last dose of cycle 2. Once a maximum tolerated dose is identified, a safety lead-in cohort with an additional 3 cycles of CYNK-001 IC will be administered prior to initiating the Phase IIa portion of the study. Endpoints: The primary endpoint is dose-limiting toxicity for the Phase I analysis and 6-month progression free survival post tumor resection for the Phase IIa component. Post-resected tumor tissue will be characterized for effector immune cell function and immune suppression with assessments directed at CYNK-001 tumor distribution using methodology developed at Celularity Inc. Approximately 66 patients are planned for this Phase I/IIa study. Approximately 66 patients are planned for this Phase I/IIa study. Clinical trial information: NCT05218408. Research Sponsor: Celularity Inc.

TPS2081 **Poster Session**

Bortezomib sensitization of recurrent glioblastoma with unmethylated *MGMT* promoter to temozolomide, a phase II study (NCT03643549). *First Author: Dorota Goplen, Department of Oncology, Haukeland University Hospital, Bergen, Norway*

Background: Patients with glioblastoma with functional O6 methylguanine DNA methyltransferase (*MGMT*) DNA repair enzyme gain limited benefit from temozolomide (TMZ). Bortezomib depletes the MGMT enzyme, restoring the tumor s susceptibility to TMZ, if the chemotherapy is administered in the precise schedule. Additionally, bortezomib inhibits the tumor growth by blocking autophagy flux. Thus, pre-treatment with bortezomib prior to temozolomide leads to DNA repair enzyme depletion and blockade of autophagy-induced survival signals. **Methods:** The academic, industry independent, multicenter, open label, single arm, non-randomized phase II trial is designed to investigate the survival benefits for patients treated with bortezomib 48hrs prior to TMZ. Efficacy of this therapy will be compared to historical cohorts receiving standard management. The study will include 53 patients with recurrent or progressive, MGMT unmethylated glioblastoma. The additional 10 patients were treated in the phase IB. All patients will receive a combination of bortezomib 1.3mg/m2 administered IV on days 1, 4, 7, during each 4-week chemotherapy cycle with PO TMZ at 200mg/m2 5 days/week q4w starting on day 3. Dose reduction of TMZ is allowed if reduced bone marrow tolerance is present. Major eligibility criteria include histologically confirmed glioblastoma with unmethylated MGMT promoter, MRI evidence of recurrence within 14 days prior to enrolment, age ≥ 18 years with life expectancy > 8 weeks, KPS ≥ 70, radiologically (MRI) confirmed tumor relapse/progression ≥ 12 weeks since completed radiotherapy, tumor not available for radiosurgery, adequate bone marrow, renal and liver function, no contraindications for bortezomib and/or TMZ. Endpoints: Estimation of the median progression free survival (PFS) and overall survival (OS) of patients with recurrent or progressed glioblastoma as well as progression free rate at 6 months. Secondary objectives: Therapy response assessed by contrast enhanced MRI (RANO criteria) and neurological examination (NANO criteria) as well as identification of novel biomarkers that correlate with treatment response. Twenty-four of the planned 53 patients are enrolled. Five of them receive treatment. The prespecified activity goal for the first stage of the study was met. Discussion: Patients with glioblastoma harboring active MGMT enzyme have median survival of 12.7 months, compared to 21.7 months for patients with the *MGMT* gene promoter silenced by methylation. This dismal prognosis for the approx. 55% of GBM patients underscores the unmet need for novel combination therapies that sensitize the tumors to chemotherapy. Results from this trial will serve as preliminary evidence of the role of bortezomib administered in a precise manner to abolish the temozolomide resistance of GBM with unmethylated MGMT promotor. The study is currently active and recruiting. Clinical trial information: NCT03643549. Research Sponsor: National Program for Clinical Therapy Research in the Specialist Health Service, Norway.

TPS2082 **Poster Session**

Window-of-opportunity study of ONC201 in pediatric patients with diffuse intrinsic pontine glioma (DIPG) and thalamic glioma. *First Author: Yazmin Odia, Miami Cancer Institute, Baptist Health South Florida, Miami, FL*

Background: H3 K27M-mutant diffuse midline glioma is a universally fatal malignancy primarily affecting children and young adults; while radiotherapy (RT) provides transient benefit, no effective systemic therapy is currently available. ONC201, a first-in-class imipridone, is an oral, blood-brain barrier penetrating, selective small molecule antagonist of dopamine receptor D2/3 and agonist of the mitochondrial protease ClpP. Previously, ONC201 monotherapy demonstrated durable objective responses in adults with recurrent H3 K27M-mutant glioma. This phase 1 trial was designed to evaluate ONC201±RT in pediatric patients with H3 K27M-mutant midline glioma DIPG. **Methods:** This multicenter, open-label, dose escalation and expansion phase 1 study of ONC201 is comprised of eight arms that will evaluate the recommended phase 2 dose (RP2D) of ONC201, biomarkers, and pharmacokinetics (PK) of ONC201±RT in various treatment settings. Arm G previously defined the RP2D for ONC201 administered twice weekly on consecutive days in patients with H3 K27M-mutant glioma who had completed radiotherapy. Arm H, for which enrollment is ongoing, will estimate the influence of tumor location and blood-brain barrier integrity on PK and intratumoral ONC201 exposure in biopsy-eligible pediatric tumors (DIPG or contrast-enhancing thalamic glioma). Patients eligible for Arm H will be aged 2-≤19 years, ≥2 weeks from last RT administration, and have a Karnofsky/Lansky performance score ≥50; prior confirmation of H3 K27M mutation is not required. In Arm H, single-agent ONC201 administration will occur on two consecutive days each week during each 21-day cycle at the RP2D defined in Arm G. Evidence of disease progression is not required; as such, ONC201 may be administered in the maintenance setting or for recurrent disease. Arm H has a planned enrollment of 27 patients. Each patient will undergo biopsy at a single prespecified biopsy window, which will be assigned at enrollment (Table); plasma for PK analysis will be collected from all patients at all time points shown in the Table, with additional collection pre-dose and 0.5 h post first dose. Clinical trial information: NCT03416530. Research Sponsor: Chimerix, Inc, U.S. National Institutes of Health, Making Headway Foundation, Fly A Kite Foundation.

Arm H: tumor biopsy collection schedule.

Cohort	Cycle 1, Day 1:1-3 h post first dose	Cycle 1, Day 1:22-26 h post first dose[a]	Cycle 1, Day 2:1-3 h post second dose	Cycle 1, Day 2:6-10 h post second dose	Cycle 1, Day 2:22-26 h post second dose
Thalamic	n = 3	n = 3	n = 3	n = 3	n = 3
DIPG	n = 3	0[b]	n = 3	n = 3	n = 3

[a]Prior to second dose.
[b]Previously collected in another arm of the trial.

TPS2083 **Poster Session**

Design and initiation of an adaptive, randomized, controlled study of berubicin, a topoisomerase 2 poison that crosses the blood brain barrier (BBB), for the treatment of recurrent glioblastoma multiforme (GBM) after first-line therapy. *First Author: Sandra Silberman, Cortice Biosciences, New York, NY*

Background: Berubicin (also known as WP744) is a patented doxorubicin (Dox) analog with evidence that it crosses the BBB and has significant central nervous system (CNS) uptake. Induction of apoptosis and DNA damage by Berubicin was compared with Dox and showed much greater potency of Berubicin in all tested cancer cells, also significantly and consistently showing higher cytotoxicity than Dox. In models of intracranial orthotopic gliomas, Berubicin prolonged survival when compared to temozolomide, currently a standard of care in GBM. Evaluation of these models also showed that Berubicin had greater infiltration into the tumor compared to normal tissue, providing additional justification for its observed improved efficacy. Based on this data, a Phase 1 dose escalation study was conducted in patients with recurrent primary brain tumors. Berubicin was well tolerated, with myelosuppression (neutropenia and thrombocytopenia) as dose-limiting toxicities. Of 25 patients evaluable for efficacy, there was 1 complete response (14+ years), 1 partial response durable for 12 weeks, and 9 patients with stable disease over 6 weeks for a clinical benefit rate of 44%. **Methods:** CNS Pharmaceuticals, Inc. ("CNSP") has licensed Berubicin and initiated a randomized, controlled clinical trial of Berubicin vs. Lomustine in adults with recurrent GBM after first line therapy. The primary endpoint of this study, being conducted in the United States and Europe, is overall survival (OS), with a projected 243 patients enrolled in a 2:1 randomization design (Berubicin:Lomustine). This study has pharmacokinetic (PK) evaluations of all patients enrolled, with at least 15 patients undergoing complete PK assessments throughout the initial dosing period (3 days of IV administration of Berubicin over 2 hours, repeated every 3 weeks). Patients will be stratified on the basis of MGMT methylation, there will be documentation of IDH WT status, and no prior administration of bevacizumab will be allowed. An interim analysis will evaluate the comparative effectiveness of these treatments, an adaptive design intended to demonstrate that Berubicin's efficacy is at least equal to that of Lomustine such that continuation of the study is in patients' best interests (futility analysis). The overall survival endpoint and sample size have been calculated to be able to show a statistical difference between the two therapies as second line treatment for GBM. Additional studies in malignant diseases of the CNS (e.g., pediatric brain tumors, primary CNS lymphoma, metastatic tumors) are also being explored based on the potential for anthracycline activity in these indications. For the present study posted on clinicaltrials.gov as, additional details and contact information is available. Clinical trial information: NCT04762069. Research Sponsor: CNS Pharmaceuticals, Inc.

TPS2084 **Poster Session**

The PROTECT Study: A phase II, open-label trial of prophylactic skin toxicity therapy with clindamycin and triamcinolone in patients with glioblastoma treated with tumor-treating fields. *First Author: Mario E. Lacouture, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Glioblastoma Multiforme (GBM), is the most common and aggressive brain tumor. Tumor Treatment Fields (TTFields) is a noninvasive, regional antimitotic treatment modality approved for the treatment of recurrent and newly diagnosed GBM by the US Food and Drug Administration. TTFields delivers low intensity (1-3 V/cm), intermediate frequency (100-300 kHz), alternating electric fields to the tumor through noninvasive transducer arrays placed on the skin, around the region of the body containing the tumor. During mitosis, TTFields disrupt the formation of the mitotic spindle during metaphase resulting in apoptosis. Dermatologic adverse events (AEs) to TTFields include dermatitis and infections and were reported in 54% of patients in a phase III trial. Topical triamcinolone and clindamycin have demonstrated anecdotal benefit because of their anti-inflammatory and antimicrobial activity. Pre-clinical studies have shown no negative effect on impedance when applied onto skin under the arrays. The effect of topical triamcinolone and clindamycin for the prevention of skin AEs to TTFields has not been studied prospectively. **Methods:** We are conducting a phase II multicenter clinical trial in patients receiving standard-of-care TTFields therapy for GBM to determine the efficacy of a prophylactic intervention: topical clindamycin 1% solution and triamcinolone 0.1% lotion in preventing grade ≥2 epicutaneous device-related events. Eligible patients must be ≥18 years of age, newly diagnosed with GBM and initiating TTFields within 7 days of study enrollment. The primary objective is to determine the effect of topical clindamycin 1% and triamcinolone 0.1% on the prevention of grade ≥2 device-related skin AEs. Secondary objectives include investigating the effect of study agents on skin-related quality of life (using the PRO-CTCAE modules for rash, ulcer, and pruritus), evaluating the efficacy of study agents applied to the scalp at every array change by standardized photography evaluated by a blinded investigator, measuring the duration of skin toxicities and usage of the TTFields device, measuring the duration of treatment interruptions and time to first grade ≥ 2 skin events, determining the bacterial flora of scalp infections, and determining the effect of study agents on TTFields' impedance. Patients will be on study for 90 days. An end-of-study assessment will occur on day 90, and a post-treatment visit will occur on day 120. The first patient was enrolled on October 21, 2020 and hitherto, 8 patients have been consented. Participating sites include Memorial Sloan Kettering Cancer Center, Columbia University Medical Center, Tufts University Medical Center, Northwestern University, Washington University, University of Cincinnati, and John Theurer Cancer Center - Hackensack Meridian Health. Clinical trial information: NCT04469075. Research Sponsor: NOVOCURE LTD.

2500 **Oral Abstract Session**

Nemvaleukin alfa monotherapy and in combination with pembrolizumab in patients (pts) with advanced solid tumors: ARTISTRY-1. *First Author: Ulka N. Vaishampayan, University of Michigan Cancer Center, Ann Arbor, MI*

Background: Nemvaleukin alfa (nemvaleukin, ALKS 4230) is a novel, engineered cytokine that selectively binds to the intermediate-affinity interleukin-2 (IL-2) receptor (IL-2R) to preferentially activate antitumor $CD8^+$ T cells and natural killer (NK) cells with minimal expansion of immunosuppressive regulatory T cells. It is sterically occluded from binding to the high-affinity IL-2R, leveraging antitumor effects of the IL-2 pathway but mitigating toxicity associated with preferential binding of IL-2 to the high-affinity IL-2R. **Methods:** ARTISTRY-1 (NCT02799095) is a 3-part, first-in-human, phase 1/2 study of IV nemvaleukin alone and in combination with pembrolizumab in pts with advanced solid tumors. Parts A (dose escalation to 10 μg/kg/day), B (monotherapy in pts with melanoma or renal cell carcinoma [RCC]), and C (combination) included nemvaleukin 3 or 6 μg/kg/day ´5 and pembrolizumab every 21 days. Investigator-assessed antitumor activity (confirmed responses as per RECIST v1.1) and safety are reported as of 29 October 2021. **Results:** In Part A (N = 46), nemvaleukin recommended phase 2 dose was 6 μg/kg/day IV; maximum tolerated dose not reached. One pt had dose-limiting toxicity (grade 4 acute kidney injury) at 10 μg/kg. Pts in Parts B and C were heavily pretreated (1–9 prior lines of therapy, including prior checkpoint inhibitor therapy). Durable antitumor activity was observed for nemvaleukin monotherapy, including in RCC (objective response rate [ORR], 18.2% [4/22]) and in melanoma (ORR, 8.7% [4/46]), with 2 partial responses (1 unconfirmed) in 30 pts with cutaneous melanoma (ORR, 6.7%) and 2 PRs (1 unconfirmed) in 6 pts with mucosal melanoma (ORR, 33.3%). Durable antitumor activity was also observed for combination therapy (ORR, 16.1% [22/137]; disease control rate [DCR], 59.9%), including in platinum-resistant ovarian cancer (PROC; ORR, 28.6% [4/14]; DCR, 71.4%), with 2 complete responses and 2 PRs (1 unconfirmed) in 14 pts. Forty-three pts remain on therapy. The most frequent grade 3/4 treatment-related adverse events in Parts B and C, respectively, were anemia (9%, 10%), neutropenia (34%, 9%), and decreased neutrophil count (12%, 9%). Safety was consistent with previous reports. In pharmacodynamic studies, nemvaleukin monotherapy induced robust expansion of CD8+ T and NK cells, with minimal effect on regulatory T cells. **Conclusions:** ARTISTRY-1 showed proof of principle for preferential expansion of $CD8^+$ T cells and NK cells by nemvaleukin. Nemvaleukin was generally well tolerated and demonstrated promising efficacy. Durable responses were observed with monotherapy and combination therapy in heavily pretreated pts across a range of tumors, warranting further investigation. The US FDA granted nemvaleukin Fast Track designation for treatment of mucosal melanoma and PROC, and Orphan Drug designation for mucosal melanoma. Clinical trial information: NCT02799095. Research Sponsor: Alkermes, Inc.

2501 **Oral Abstract Session**

First-in-human study of SRF388, a first-in-class IL-27 targeting antibody, as monotherapy and in combination with pembrolizumab in patients with advanced solid tumors. *First Author: Aung Naing, Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The immunoregulatory cytokine IL-27 upregulates inhibitory immune checkpoint receptors (eg, PD-L1, TIGIT) and downregulates proinflammatory cytokines (eg, IFNγ, TNFα). SRF388 is a fully human IgG1 blocking antibody to IL-27 with potential to promote immune activation in the tumor microenvironment. A phase 1 study was conducted to establish the preliminary safety of SRF388 and to identify recommended phase 2 doses (RP2D) suitable for monotherapy and combination expansions (NCT04374877). **Methods:** The dose-escalation study (accelerated single patient followed by standard 3+3) enrolled patients (pts) with advanced treatment-refractory solid tumors. Upon RP2D selection, monotherapy and combination expansions opened for treatment-refractory clear cell renal cell cancer (ccRCC), hepatocellular cancer (HCC), and non-small cell lung cancer. SRF388 was administered IV every 4 weeks (wks) as monotherapy and every 3 wks with pembrolizumab. Tumor response was assessed by RECIST1.1. **Results:** The monotherapy dose-escalation enrolled 29 pts with doses ranging from 0.003 to 20 mg/kg. Median age was 64 years. Most pts were female (62%) with ECOG PS of 1 (72%). Approximately 80% had prior PD-(L)1 blockade, and 48% had ≥4 prior therapies. Treatment-related adverse events (TRAEs) occurred in 21%, and all were low grade. Fatigue was the only TRAE reported in ≥10% (n = 3). No dose-limiting toxicities (DLTs) or Grade ≥3 TRAEs were observed. Median time on study was 9 wks (range 0–59). One patient with highly treatment-refractory NSCLC experienced a confirmed partial response (PR) at 8 wks that was durable for 20 wks. Nine pts (31%) experienced disease stabilization at 8 wks, with 6 of 9 exhibiting durable disease control at 6 months. Of the 7 pts with ccRCC in the dose-escalation portion of the trial, 3 (43%) experienced durable disease control for ≥20 wks (range: 20-32). With doses up to 20 mg/kg, SRF388 PK remain linear with an estimated $T_{1/2}$ of 10-12 days. PK characteristics and safety profile support dosing every 3 or 4 wks. Based on safety, tolerability, PK, peripheral pSTAT1 inhibition, and preliminary efficacy, 10 mg/kg was selected as the RP2D. Both the pembrolizumab safety cohort (n = 10) and Stage 1 of the ccRCC monotherapy expansion (n = 17) have fully enrolled. Of the 10 evaluable pts with ccRCC, 1 confirmed monotherapy PR has been reported, enabling Stage 2 initiation. Changes in several serum cytokines and chemokines were observed after SRF388 administration, including expected increase in circulating IL-27 levels. **Conclusions:** Results of IL-27 pathway blockade with a first-in-class therapeutic demonstrates that SRF388 has good tolerability with encouraging preliminary antitumor activity as a monotherapy. Updated data, including safety and clinical outcomes as well as correlative biomarker analyses, will be presented. Clinical trial information: NCT04374877. Research Sponsor: Surface Oncology, Cambridge, MA, USA;.

2502 **Oral Abstract Session**

Interim safety and efficacy results from AURELIO-03: A phase 1 dose escalation study of the IL-2/IL-15 receptor βγ superagonist SOT101 as a single agent and in combination with pembrolizumab in patients with advanced solid tumors. *First Author: Elena Garralda, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain*

Background: SOT101 (previously SO-C101) is a fusion protein of IL-15 and the IL-15 receptor α sushi+ domain. Synergistic effects of SOT101 and an anti-programmed cell death protein 1 antibody have been validated in various tumor mouse models inducing a protective memory response. **Methods:** In this phase 1 study, safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of increasing doses of SOT101 administered subcutaneously were investigated in patients (pts) with advanced solid tumors as monotherapy (Part A) and in combination with pembrolizumab every 3-week cycle (Part B). Dose escalation followed a standard 3+3 design. Data cut-off was 26 January 2022. **Results:** Overall, 51 pts were treated: 30 in Part A monotherapy at 0.25 to 15 μg/kg SOT101 and 21 in Part B combination therapy (Tx) at 1.5 to 12 μg/kg SOT101. The median (range) number of previous lines of Tx was 3 (1-9) in Part A and 2 (1-6) in Part B. In Part A, 19 (63.3%) pts had previous check-point inhibitor (CPI) Tx, of whom 9 (30 %) were refractory, 5 (16.7%) relapsed. In Part B, 11 pts (52.4%) had previous CPI Tx, and the outcome was 9 (42.9%) pts relapsed, 1 (4.8%) refractory. The most common treatment-emergent adverse events (TEAEs) were transient, and included pyrexia, chills, lymphopenia, anemia, transaminase elevation and vomiting. Most TEAEs were ≤ Grade 2. No treatment-related death was reported. For both monotherapy and combination Tx, the recommended phase 2 dose of SOT101 was determined to be 12 μg/kg. In Part A, in 13 pts at 6 to 12 μg/kg SOT101, the observed clinical benefit rate was 38%. A partial response (PR) was confirmed in 1 pt with skin squamous cell carcinoma, CPI refractory, PR duration 46 days (d), on treatment 154 d. Four pts (all CPI pretreated) had stable disease (SD), range 33-183 d. Final median duration on treatment was 84 d, range 43-183 d. The median duration of clinical benefit was 190 d. In Part B, the observed clinical benefit rate across all SOT101 doses was 63%. A complete response (CR) was confirmed in 1 pt with mesothelioma, CPI naïve, starting at the first tumor assessment, and the pt is ongoing in cycle 5. Three pts, 2 CPI pretreated, had a PR, range 51-232 d, 2 ongoing with PR, and 1 Tx discontinuation while still on PR. Five pts, 3 CPI pretreated, had SD, range 92-340 d, 2 ongoing with SD. The 3 CPI pretreated pts had SD range 41-340 d, 1 pt ongoing. The preliminary median duration on combination Tx was 113 d, range 7-429 d. The preliminary median duration of clinical benefit was 131 d. **Conclusions:** SOT101 as monotherapy and in combination with pembrolizumab showed a favorable safety profile. Highly promising efficacy signals with one ongoing CR and several long-lasting PRs were reported in CPI-naïve and CPI pretreated pts, including CPI-resistant tumors. Clinical trial information: NCT04234113. Research Sponsor: Sotio Biotech AG.

2503 **Oral Abstract Session**

Dose escalation of a phase 1b/2 study of modakafusp alfa, an immune-targeting attenuated cytokine, in patients (pts) with metastatic solid tumors. *First Author: Melissa Lynne Johnson, Sarah Cannon Research Institute, Nashville, TN*

Background: Modakafusp alfa (TAK-573) is a first-in-class immune-targeting attenuated cytokine designed to deliver attenuated interferon alpha-2b (IFNα2b) moieties to CD38-expressing cells. It consists of two attenuated IFNα2b molecules genetically fused to the Fc portion of a humanized, anti-CD38, IgG4 monoclonal antibody. Specificity for CD38 and reduced IFN receptor binding affinity of the attenuated IFNα2b molecules significantly reduces the potential for off-target binding and toxicity. Modakafusp alfa has demonstrated immune cell activation and antitumor activities in preclinical mouse models, including tumor models that do not express CD38, and has shown strong clinical responses and immune activation in pts with refractory/relapsed multiple myeloma. The dose-escalation phase of this phase 1b/2 study (NCT04157517) investigated safety, pharmacokinetics, immunogenicity, pharmacodynamics (PD), and preliminary efficacy of modakafusp alfa in metastatic solid tumors. **Methods:** Adult pts with advanced/metastatic solid tumors received modakafusp alfa IV on day 1 of a 21-day cycle (Q3W). Dose escalation started at 0.1 mg/kg and proceeded based on cycle 1 safety data via a Bayesian model with overdose control principles. **Results:** Twenty-one pts were dosed in the escalation phase at 0.1 (n = 3), 0.2 (n = 3), 0.4 (n = 3), 0.75 (n = 3), 1.0 (n = 3), and 1.5 mg/kg (n = 6) Q3W; median age 63 y (range 42–80); male 57.1%; GI malignancies 71.4%; median prior lines of therapy 3 (range 2–7). Two pts had dose-limiting toxicities in cycle 1 at 1.5 mg/kg; 1 pt with baseline bone infiltration had grade 4 thrombocytopenia and 1 pt had grade 3 confusion. As of Nov 2021, across all doses, pts received a median of 2 treatment cycles (range 1–11). Modakafusp alfa treatment-related adverse events (TRAEs) reported in 81% of pts included infusion-related reactions (52.4%), chills (47.6%), and nausea (33.3%). Grade ≥3 TRAEs reported in 42.9% of pts included neutropenia (14.3%) and hypertension (9.5%). There was a greater than dose proportional exposure increase in the dose range 0.1–1.5 mg/kg, with no exposure accumulation after Q3W dosing. Incidence rate of post-treatment anti-drug antibody (ADA) was 100%. PD data suggested saturation of peak IFN pathway modulation at ≥0.2 mg/kg in the peripheral blood with duration of modulation increasing with dose. Among the 14 response-evaluable pts, 7 had best response of stable disease, including 1 with cutaneous melanoma who had 21% target lesion reduction. **Conclusions:** Modakafusp alfa had a manageable safety profile in the dose range 0.1–1.5 mg/kg in pts with solid tumors. Proof of mechanism was validated. The recommended phase 2 dose was determined as 1.0 mg/kg Q3W based on assessment of holistic data and will be tested in combination with a checkpoint inhibitor in selected tumor types. Characterization of ADA and its impact is ongoing. Clinical trial information: NCT04157517. Research Sponsor: This study was funded by Takeda Pharmaceutical Company Limited.

2504 **Oral Abstract Session**

Phase 1 trial of TIM-3 inhibitor cobolimab monotherapy and in combination with PD-1 inhibitors nivolumab or dostarlimab (AMBER). *First Author: Gerald Steven Falchook, Sarah Cannon Research Institute at HealthONE, Denver, CO*

Background: TIM-3 expressed on tumor-infiltrating T cells is associated with T-cell suppression. AMBER (NCT02817633) is evaluating cobolimab (TSR-022/GSK4069889) monotherapy and with PD-1 inhibitors in advanced solid tumors. **Methods:** Multi-center, open-label study conducted with the following escalation arm (Parts 1A–C primary analysis reported here): (1A) cobolimab (IV Q2W) monotherapy at 7 doses (6 weight-based [0.03–10 mg/kg] and 1 flat [1200 mg] dose); (1B) cobolimab (1 mg/kg) + nivolumab (3 mg/kg IV Q2W); and (1C) cobolimab (100, 300, or 900 mg) + dostarlimab (500 mg IV Q3W). Primary endpoints were safety, tolerability, and recommended phase 2 dose (RP2D, monotherapy and combination). **Results:** 104 patients (pts) were included: 1A (n=46), 1B (n=7), or 1C (n=55); 4 pts from 1A crossed over to 1C (included in 1A and 1C safety and efficacy analyses). Most common cancers were non-small cell lung cancer (NSCLC) and melanoma (1A), NSCLC (1B), and NSCLC, skin, and peritoneal mesothelioma (1C). In 1A, 30.4% had ≥5 lines (L) of prior therapy; 42.9% had 3L in 1B; 33.3% had 2L in 1C. Treatment-related treatment-emergent adverse events (TR-TEAE) occurred in 67.4% (1A), 85.7% (1B), and 67.3% (1C); most commonly in 1A (n≥4) fatigue (13.0%) and nausea (8.7%); 1B (n≥3) diarrhea (57.1%) and nausea and vomiting (42.9% each); and 1C (n≥8) fatigue (20.0%) and rash (14.5%). Grade (Gr)≥3 TR-TEAEs occurred in 4.3% (1A), 28.6% (1B), and 14.5% (1C). There were no Gr5 TR-TEAEs or TR-TEAEs leading to dose delay. Serious TR-TEAEs occurred in 2.2% (1A), 0% (1B), and 12.7% (1C). TR-TEAEs led to discontinuation in 2.2% (1A), 28.6% (1B), and 9.0% (1C). Dose limiting toxicities (DLTs) occurred in 3.0% (1/33) in 1A (Gr3 lipase increased [10 mg/kg]); 40.0% (2/5) in 1B (Gr3 diarrhea and ALT and AST elevation); and 0% in 1C. Cobolimab serum exposure increased in a dose proportional manner at the therapeutic dose range. Preliminary mean terminal phase $t_{1/2}$ ranged from 2.5–5.8 days for 0.03–0.3 mg/kg and 6.9–10.2 days for 1–10 mg/kg doses (1A), 6.9 days for 1B, and 9.5–12.3 days for 1C. **Conclusions:** Cobolimab + dostarlimab was well tolerated and showed preliminary anti-tumor activity, warranting further investigation of the RP2D + docetaxel in a randomized, phase 2 study. Funding: GSK (213348). Clinical trial information: NCT02817633. Research Sponsor: GlaxoSmithKline.

Efficacy by cobolimab dose.

n (%)	1A* (cobolimab): 1 mg/kg N=9	1A*: 10 mg/kg N=13	1A*: 1200 mg N=7	1B (cobolimab + nivolumab): 1 mg/kg N=7	1C (cobolimab + dostarlimab): 100 mg N=13	1C: 300 mg N=20	1C: 900 mg N=22
ORR	0	0	0	3 (42.9)	1 (7.7)	5 (25.0)	3 (13.6)
DCR	1 (11.1)	4 (30.8)	1 (14.3)	3 (42.9)	2 (15.4)	14 (70.0)	9 (40.9)

4 pts in 1A crossed over to 1C (included in 1A and 1C analyses). *ORR and disease control rate (DCR) were 0% in 0.03, 0.1, 0.3 (n=3 each) and 3 mg/kg (n=8) groups.

2505 **Oral Abstract Session**

Phase 1 first-in-human study of anti–ILT3 mAb MK-0482 as monotherapy and in combination with pembrolizumab in advanced solid tumors: Dose escalation results. *First Author: Martin Gutierrez, Hackensack University Medical Center, Hackensack, NJ*

Background: Immunoglobulin-like transcript 3 (ILT3) is an inhibitory receptor associated with immune tolerance and T-cell suppression within the tumor microenvironment. MK-0482, a novel humanized IgG4 mAb targeting ILT3, is undergoing phase 1 evaluation ± pembrolizumab (pembro) in advanced solid tumors (NCT03918278; MK-0482-001). Dose escalation data are presented. **Methods:** Eligible patients with advanced solid tumors were enrolled into sequentially escalating dose cohorts of MK-0482 monotherapy (0.2-2250 mg) or MK-0482 (7.5-2250 mg) + pembro 200 mg; both were administered IV Q3W for up to 35 cycles or until progressive disease (PD), unacceptable toxicity, death, or withdrawal. Patients receiving MK-0482 monotherapy could cross over to MK-0482 + pembro after PD. Primary objectives were safety, tolerability, and determination of the recommended phase 2 dose (RP2D). Secondary and exploratory objectives included assessing pharmacokinetics (PK), blood receptor occupancy (RO), anti–drug antibodies (ADA), and objective response rate (ORR) per RECIST v1.1 by investigator assessment. **Results:** Seventy-five patients were enrolled (n = 29, MK-0482 monotherapy; n = 46, MK-0482 + pembro); 8 patients crossed over to receive the combination. Median age was 63 years (range, 34-86); 73% had ECOG PS 1, 72% received ≥2 lines of prior anticancer therapy, and 32% received prior PD-1/PD-L1 inhibitors. Treatment-related AEs (TRAEs; any-grade/grade 3 or 4) were reported in 34%/7% of patients with MK-0482 monotherapy, 67%/4% with MK-0482 + pembro, and 50%/13% in those who crossed over. The most common TRAEs (≥10% of all patients) were pyrexia (10%) with MK-0482 monotherapy; fatigue (24%) and arthralgia, diarrhea, hyperthyroidism, hypothyroidism, and pruritus (11% each) with MK-0482 + pembro; and arthralgia (25%), hyperthyroidism and hypothyroidism (13% each) for patients who crossed over. Dose-limiting toxicities occurred in 2 patients who received MK-0482 + pembro: 1 grade 5 myositis (MK-0482 750 mg; the only TRAE leading to death) and 1 grade 2 myositis (MK-0482 2250 mg). Preliminary PK and blood RO data suggested that target-mediated drug disposition of MK-0482 was likely saturated in blood mononuclear cells at doses ≥75 mg. ADA to MK-0482 was observed in ~20% of patients, but no clear impact on MK-0482 PK was observed. A confirmed ORR of 15% (8 PR) was observed in patients who received MK-0482 + pembro, including patients who crossed over; no confirmed responses were observed in patients who received MK-0482 monotherapy. MK-0482 750 mg + pembro was selected as the RP2D based on the totality of data. **Conclusions:** MK-0482 ± pembro was generally well tolerated, and combination therapy provided modest antitumor activity in patients with heavily pretreated advanced solid tumors. The RP2D of MK-0482 + pembro is under further evaluation in tumor-specific cohorts. Clinical trial information: NCT03918278. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

2506 **Oral Abstract Session**

A phase 1b, multicenter, dose-escalation study of subasumstat (TAK-981) in combination with pembrolizumab in patients (pts) with advanced solid tumors. *First Author: Sanjay Goel, Rutgers Robert Wood Johnson Medical School, Bronx, NY*

Background: SUMOylation is a post-translational modification with a role in limiting type 1 interferon (IFN-1)-dependent immune responses. Subasumstat is a small-molecule inhibitor of SUMOylation with the potential to increase antitumor immunity and overcome tumor resistance to checkpoint inhibitors (CPI) by inducing IFN-1 signaling. Preclinical data suggest that subasumstat enhances antigen cross-presentation, promoting T cell dependent antitumor responses; subasumstat plus an anti-PD-1 CPI has shown synergistic tumor growth inhibition and activation of CD8+ T cells and natural killer cells in syngeneic mouse models. We report data from the dose escalation part of a phase 1b study of subasumstat with pembrolizumab in pts with relapsed/refractory, CPI-exposed, non-squamous non-small-cell lung cancer (NSCLC) or microsatellite-stable colorectal cancer (MSS-CRC). **Methods:** Pts received escalating doses (40, 60, 90, and 120 mg) of subasumstat IV in 3 dosing schedules: days 1 and 8 (QW), days 1, 4, 8, and 11 (BIW), or days 1, 8, and 15 (90 mg only) of 21-day cycles, plus pembrolizumab 200 mg IV on day 1 of each cycle for 2 years or until disease progression or unacceptable toxicity. Dose escalation was guided by Bayesian optimal interval design. Phase 1b primary objectives were safety, tolerability, and the recommended phase 2 dose of subasumstat with pembrolizumab. **Results:** As of October 13, 2021, 43 (35 MSS-CRC; 8 NSCLC) pts had received ≥1 dose of subasumstat (22 BIW [40–120 mg]; 15 QW [90–120 mg]; 6 on days 1, 8, 15 [90 mg]). Median number of treatment cycles was 3; 28 (65%) pts had discontinued treatment, 21 (49%) due to progressive disease. Median age was 58 years (range 34–77); 56% of pts were male. One pt had a dose-limiting toxicity of grade 3 angioedema at 120 mg BIW. The maximum tolerated dose was not identified. Treatment-emergent adverse events (TEAEs) occurred in 38 (88%) pts; subasumstat-related TEAEs occurred in 34 (79%) pts, and included chills in 20 (47%), pyrexia in 16 (37%), fatigue in 9 (21%), anemia in 6 (14%), and stomatitis in 5 pts (12%; 3 [50%] in the 120 mg BIW cohort). Grade ≥3 TEAEs occurred in 24 (56%) pts; subasumstat-related grade ≥3 TEAEs reported in 10 (23%) pts included anemia, pyrexia, and increased aspartate aminotransferase (2 [5%] pts each). Pharmacokinetic activity of subasumstat was linear and decreased in a tri-phasic manner. Subasumstat exerted pharmacodynamic activity including target engagement, SUMOylation inhibition and increased IFN-1 signaling. Partial responses were observed at ≥40 mg dose levels in pts with NSCLC and MSS-CRC. **Conclusions:** Subasumstat plus pembrolizumab showed a favorable safety profile and promising anti-tumor activity in pre-treated NSCLC and MSS-CRC pts. Updated data will be presented at the meeting. Subasumstat plus pembrolizumab is currently in phase 2 clinical development (NCT04381650). Clinical trial information: NCT04381650. Research Sponsor: Takeda Development Center Americas, Inc. (TDCA).

2507 **Oral Abstract Session**

Single-cell profiling of human heart and blood in immune checkpoint inhibitor-associated myocarditis. *First Author: Steven Michael Blum, Massachusetts General Hospital and Dana-Farber Cancer Institute, Boston, MA*

Background: Myocarditis due to immune checkpoint inhibitors (ICIs) is uncommon; however, myocarditis due to ICIs leads to severe morbidity and even death in 20-40% of cases. The molecular underpinnings of ICI-associated myocarditis are poorly understood, and there is an unmet clinical need to identify therapeutic targets and biomarkers that can aid in disease management. **Methods:** Heart tissue was obtained through endomyocardial biopsy or autopsy of patients receiving ICIs and was profiled with paired single-cell RNA sequencing (scRNA-seq) and T cell receptor sequencing (TCR) using the 10x Genomics Chromium system. A control dataset was constructed using scRNAseq data of heart tissue from patients receiving ICIs but without myocarditis and a published dataset from healthy patients not receiving ICIs. Peripheral blood mononuclear cells (PBMCs) were collected at the time of myocarditis diagnosis in a larger cohort of patients and analyzed with ICI-treated controls. The CITE-Seq protocol was used to measure paired scRNA-seq, TCR, and surface proteomics in PBMCs, using serial timepoints where available. **Results:** Heart tissue from 13 patients with myocarditis, including three fatal cases, and seven controls yielded 77,712 single cells. Blood profiling from 27 patients with ICI myocarditis and ICI-treated controls across 54 samples yielded over 230,000 cells. ICI myocarditis tissue demonstrated an increased T cell infiltrate (OR 8.94, FDR = 0.0021). Expression of multiple inflammatory pathways, most notably interferon responses, was up-regulated across multiple immune and non-immune cell types in the setting of myocarditis, providing important pathophysiological insights. T cell clones were also found to be shared between blood and heart, enabling the identification of putative pathogenic T cell subsets. **Conclusions:** Increased intramyocardial T cells and the activation of interferon response gene networks were seen in the setting of ICI myocarditis. These preliminary findings highlight potential pathological pathways in ICI myocarditis that could serve as biomarkers or therapeutic targets. Research Sponsor: U.S. National Institutes of Health.

2508 **Oral Abstract Session**

Major adverse cardiac events (MACE) with immune checkpoint inhibitor (ICI)-based therapies for cancer: A pooled analysis of investigational clinical trials sponsored by the National Cancer Institute Cancer Therapy Evaluation Program (NCI-CTEP) in the United States and Canada. *First Author: Abdul Rafeh Naqash, Medical Oncology/ TSET Phase 1 Program, Stephenson Cancer Center, University of Oklahoma, Oklahoma City, OK*

Background: MACE due to ICIs are infrequent immune-related adverse events (irAEs) that comprise a spectrum of cardiac toxicities with variable manifestations. ICI-related MACE can lead to significant morbidity and mortality, hence the need to better define presentations of MACE and their association with non-cardiac irAEs in ICI-treated patients. **Methods:** We conducted a retrospective pooled analysis of MACE captured in the serious adverse events reporting database of the NCI-CTEP for NCI-sponsored investigational clinical trials between 6/2015-12/2019. Patients (pts) were eligible if they had been treated with anti-programmed cell death protein-1/programmed death-ligand 1 (anti-PD-[L]1) alone or in combination with additional anti-cancer therapies. **Results**: A total of 6,925 pts received anti-PD-(L)1-based therapies; 48% (n = 3354) were treated with single-agent anti-PD-(L)1 therapy. Of 6925 pts, 0.6% (n = 40) qualified as ICI-related MACE. Myocarditis accounted for 45% (n = 18/40) of total ICI-MACE. Approximately 77.5% (n = 31/40) of MACE were ≥ grade 3. Multi-system organ involvement with other non-cardiac irAEs was seen in 65% (n = 26/40). Most pts with myocarditis (83%, n = 15/18) had one or more non-cardiac irAEs associated; non-cardiac irAEs were observed in 50% (n = 11/22) of non-myocarditis MACE. Incidence of MACE was higher with anti-PD-(L)1 + targeted therapies vs. anti-PD-(L)1 + anti-CTLA-4 (2.1% vs. 0.09%,*p = 0.08*). Most of these were non-myocarditis MACE. There was a significantly higher incidence of myocarditis with anti-PD-(L)1-based combinations vs. single-agent anti-PD-(L)1 therapies (0.39%, n = 13/3341 vs. 0.14%, n = 5/3566, *p = 0.04*. Most pts with myocarditis had been treated with anti-PD-1-based combinations (72%, n = 13/18); the most common combination being anti-PD1+ anti-CTLA-4 (92%, n = 12/13). Pts with myocarditis presented after a median of 2 ICI doses and after a median of 35 days from the initial ICI administration. In pts with myocarditis, a concurrent or preceding history of myositis was present in 53% (n = 8/15). Deaths related to myocarditis were identified in 22.5% (n = 4/18). All four patients who died had concurrent myositis, with three having concurrent transaminitis. **Conclusions**: Our results represent the first report of a comprehensive pooled analysis of ICI-MACE obtained from NCI CTEP-sponsored investigational clinical trials. Based on our results, increasing patient and prescriber awareness in understanding patterns of ICI-MACE and associated non-cardiac irAEs should be emphasized. Furthermore, better characterization of the risk and patterns of non-myocarditis MACE with the use of anti-PD(L)-1 ICIs concurrently with non-ICI-based anti-cancer therapies is needed. Research Sponsor: U.S. National Institutes of Health.

2509 **Clinical Science Symposium**

Efficacy of anti-PD1/PD-L1 immunotherapy in non–small cell lung cancer is dependent upon Immunoscore IC CD8 and PD-L1 status. *First Author: Jerome Galon, HalioDx, Marseille, France*

Background: Anti-PD1 and PD-L1 antibodies (mAb) are immune checkpoint inhibitors (ICIs) to treat patients with metastatic non–small cell lung cancer (NSCLC). Unfortunately, only a handful of patients respond to ICIs. **Methods:** A cohort of patients with metastatic NSCLC (n=133) treated with anti-PD1 or anti-PD-L1 mAb in two independent care centers was evaluated. An independent cohort of 132 patients from another hospital was used as a validation. Immunoscore IC, an in vitro diagnostic test (CE-IVD), was used on a routine single FFPE slide, and duplex immunohistochemistry CD8 and PD-L1 staining was quantified using digital pathology. Quantitative and spatial parameters related to cell location, number, proximity, and clustering were analyzed. An Immunoscore IC–based model discriminated patients into 2 categories or 3 categories. **Results:** Anti–PD-L1 clone (HDX3) had similar characteristics as other anti–PD-L1 clones (22C3, SP263) with a mean overall agreement above 95%. Intra- and inter-laboratory concordances for classifying patients at 1% cut-off according to digital anti–PD-L1 (HDX3) were 100% and 94%, respectively. Routine laboratory evaluation of PD-L1 expression showed an agreement with digital anti–PD-L1 quantification of 92% and 97% at 1% and 50% cut-offs, respectively. Using univariate Cox model after FDR correction, 5 pathological dichotomized variables were significantly associated with PFS (all $p < 0.0001$). These variables included: CD8 free of PD-L1, CD8 clusters, CD8 cells in proximity of PD-L1 cells, CD8 number, PD-L1 cells in proximity of CD8 cells. Similar results were found using univariate Cox analysis on continuous variables (all $p < 0.003$) in two independent cohorts of patients. Using multivariate Cox model Immunoscore IC classification improved the discriminating power of prognostic model, which included clinical variables and pathologist PD-L1 assessment. In two categories, the Immunoscore IC risk score was significantly associated with both patients' PFS ($p < 0.0001$) and OS ($p < 0.0001$) in the training cohort and in the validation cohort (PFS: $p = 0.0047$, OS: $p < 0.0001$). Further increased hazard ratios were found when stratifying patients into 3 categories of Immunoscore IC. At 6 months, PFS rates were 10% versus 60% in the training cohort and 20% versus 62% in the validation cohort for high-risk and low-risk Immunoscore IC score, respectively. All patients (100%) with high-risk Immunoscore IC score relapsed in less than 18 months, in contrast to 34% and 33% of low-risk Immunoscore IC patients who did not relapse for more than 36 months in the training and validation cohorts, respectively. **Conclusions:** These data underline that Immunoscore IC is a potent tool to predict the efficacy of ICIs in patients with NSCLC. Immunoscore IC characterized patients who are resistant to ICIs. Research Sponsor: Veracyte, Other Foundation, Other Government Agency.

2510 **Clinical Science Symposium**

External validation of the VIGex gene-expression signature (GES) as a novel predictive biomarker for immune checkpoint treatment (ICT). *First Author: Alberto Hernando-Calvo, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: VIGex is a 12- gene GES classifier initially developed on the Nanostring platform and validated for RNA-seq. VIGex classifies samples into Hot, intermediate-Cold (I-Cold) and Cold subgroups. The Hot subgroup as defined by VIGex has been associated with better (PFS) in patients (pts) treated on phase 1 ICT trials at Vall D'Hebron Hospital (VH) (ESMO2020). We investigated the performance of VIGex in pts treated with Pembrolizumab (P) in the INSPIRE clinical trial (NCT02644369) at Princess Margaret Cancer Centre (PM) and compared VIGex with other predictive ICT biomarkers. **Methods:** Pts with advanced solid tumors were treated with P 200 mg IV Q3wks. RNA-seq from baseline biopsies was performed using the Illumina NextSeq550 platform. Tumor RNA-seq data were transferred from PM to VH and classified by the VIGex algorithm blinded to clinical data. Bespoke circulating tumor DNA (ctDNA) was assayed at baseline (B) and start of cycle 3 (C3) using a pt-specific amplicon-based NGS assay (Signatera). Tumor mutational burden (TMB) was defined as the number of non-synonymous mutations per megabase and PD-L1 was assessed by immunohistochemistry (22C3). Hot subgroup (HOT) was compared to I-Cold + Cold (COLD). We defined 4 groups based on the combination of VIGex subgroups and the change in ctDNA at cycle 3 from baseline (ΔctDNA). Survival times were calculated with the Kaplan–Meier method and Cox proportional-hazard models were constructed. **Results:** Out of 76 pts, median age was 55y (range 21-81y), M:F 31:45, all ECOG 0-1, 16 High-grade serous ovarian, 12 triple negative breast, 12 head and neck, 10 melanoma and 26 other. Median no. of P cycles was 3 (range 1–35); follow up was 14m (range 1-67); Median PFS 10.9m and median overall survival (OS) 14m. Overall response rate (RECIST 1.1) was 24% in HOT and 10% in COLD ($p = 0.22$ two-sided Fisher's exact test). The HOT subgroup was significantly associated with higher OS and PFS when included in a multivariate model adjusted by tumor histology, TMB and PD-L1 (HR 0.43; 95%CI 0.23-0.81; $p = 0.009$) and (HR: 0.48; 95%CI 0.25-0.95; $p = 0.036$) respectively. A total of 57 pts had both VIGex and ΔctDNA data. The addition of ΔctDNA further improved the predictive performance of VIGex for OS (Table). **Conclusions:** VIGex maintained its predictive power for ICT outcomes when applied to an independent external dataset using RNA-seq. The predictive information provided by VIGex was independent of PD-L1 and TMB. Our data indicates that the addition of ΔctDNA to baseline VIGex may refine prediction for ICT outcomes. Research Sponsor: Drug only from MERCK and study is supported in part by Princess Margaret Cancer Foundation.

Subgroup	Median OS (months) [95CI%]	HR (95%CI)	P value
COLD + ↑ ΔctDNA	4.8 [3.02-NA]	Reference	NA
HOT + ↓ ΔctDNA	46 [27.5-NA]	0.16 (0.06 - 0.43)	**< 0.001**
COLD + ↓ ΔctDNA	22 [17.6-NA]	0.36 (0.12 – 1.04)	0.059
HOT + ↑ ΔctDNA	13 [6.6-NA]	0.34 (0.14 - 0.81)	**0.015**

2511 **Clinical Science Symposium**

Identifying gut microbial signatures associated with B cells and tertiary lymphoid structures (TLS) in the tumor microenvironment (TME) in response to immune checkpoint blockade (ICB). *First Author: Elise F Nassif, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: While ICB has significantly improved clinical outcomes across several cancer types, only 15-20% of patients develop a durable response. Thus, novel and targetable biomarkers are needed. There is increased appreciation of the role of the gut microbiome, and TLS and B-cells in the TME in response to ICB. Here, we investigate the association between these two determinants of response in patient specimens from three randomized phase 2 neoadjuvant ICB trials of nivolumab +/- ipilimumab (melanoma (MEL; NCT02519322; n=23), non-small-cell lung cancer (NSCLC; NCT03158129; n=31), sarcoma (SARC; NCT02301039; n=17). **Methods:** Patients were categorized as responders (R) or non-responders (NR) based on major pathologic response, as defined in each histotype (MEL and NSCLC viable tumor ≤10%; SARC hyalinization>30%). Baseline fecal samples were profiled via 16S rRNA gene sequencing from all three cohorts to assess the composition of patient gut microbiomes. Transcriptional profiles of biopsies collected pre-ICB for MEL and SARC, and post-ICB for MEL, SARC, and NSCLC were used to assess TLS (CXCL13, CCL18, CCL19, CCL21) and B-cell (PAX5, CD79B, CR2, MS4A1) signatures in the TME, by calculated mean values of normalized gene expressions. Comparison between samples were carried out using the Wilcoxon signed-rank test. **Results:** There were 21 R overall (NSCLC n=9; MEL n=9; SARC n=3). Despite significant differences in alpha and beta diversity across cohorts, relative abundance of *Ruminococcus* was significantly higher in R (p=0.003; NSCLC p<0.001; MEL p=0.049; SARC p=0.7). B-cell signature was significantly higher post-ICB in R (R vs NR, post, TLS p=0.13; B-cell p=0.003), with consistent trends in each cohort. Longitudinal evaluation of transcriptional profiles showed that expression of TLS and B-cell signatures increased with treatment in R (pre vs post, MEL and SARC; TLS p=0.0098; B-cell p<0.001) but not NR (pre vs post; TLS p= 0.87; B-cell p= 0.15), with consistent trends in sarcoma and melanoma subgroups. Combined correlative analysis with matched specimen showed that patients with higher pre-ICB relative abundance of *Ruminococcus* (above median) had significant increase in B-cell signatures (pre vs post, MEL and SARC; TLS p=0.052; B-cell p=0.002) which was not seen in patients with low abundance (below median) of *Ruminococcus* (pre vs post, MEL and SARC; TLS p=0.56; B-cell p=0.69). **Conclusions:** Unifying signatures in the gut microbiome are associated with response to ICB and increased B-cell infiltration and TLS formation in the TME. We expect these findings to energize mechanistic studies and new microbiome-based interventional approaches to improve clinical outcomes with ICB. Clinical trial information: NCT02519322, NCT03158129, NCT02301039. Research Sponsor: None.

2512 **Poster Discussion Session**

Phase I/IIa study of PM8001, a bifunctional fusion protein targeting PD-L1 and TGF-β, in patients with advanced tumors. *First Author: Ye Guo, Oncology, Shanghai East Hospital, Tongji University, School of Medicine, Shanghai, China*

Background: PM8001 is a bifunctional protein composed of the extracellular domain of the TGF-β RII receptor (a TGF-β "trap") fused to a humanized anti-PD-L1 IgG1 single-domain antibody. This is the first dose escalation and expansion phase I/IIa study to evaluate the safety and preliminary anti-tumor activity of PM8001 in advanced tumors. **Methods:** This study is comprised of a standard 3+3 dose escalation (Part A: 1, 3, 10, 20, 30, and 45 mg/kg Q2W) followed by dose expansion (Part B). Primary endpoints include safety for Part A, and ORR per RECIST 1.1 for Part B. Secondary endpoints include pharmacokinetics (PK), immunogenicity, DCR, PFS, and OS. **Results:** As of 16 December, 2021, a total of 108 subjects had received at least 1 dose of PM8001 with 25 subjects in Part A (0.3 mg/kg [n = 1], 1 mg/kg [n = 3], 3 mg/kg [n = 3], 10 mg/kg [n = 4], 20 mg/kg [n = 7], 30 mg/kg [n = 3], and 45 mg/kg [n = 4]) and 83 subjects in Part B (10 mg/kg Q2W [n = 1], 20 mg/kg Q2W [n = 63], 20 mg/kg Q3W [n = 11]), and 30 mg/kg Q3W [n = 8]). In Part A, only 1 DLT occurred in the 20 mg/kg dose group. MTD was not reached. Finally, 20 mg/kg Q2W was recommended as the RP2D for Part B. Of the 108 subjects, the median duration of PM8001 exposure was 6.9 weeks (range, 1.4-71.9). Any-grade TRAEs occurred in 84 subjects (77.9%), with 18 subjects (16.7%) reported with ≥ Grade 3. The most commonly reported ≥ Grade 3 TRAEs were anemia and rash (3 subjects each). Any-grade irAEs occurred in 66 subjects (61.1%), with 13 subjects (12.0%) reported with ≥ Grade 3. The most commonly reported ≥ Grade 3 irAEs were anemia (3 subjects). PK analysis showed a nearly linear dose-exposure relationship with PM8001 dosing from 1 to 45 mg/kg. Pharmacodynamic analysis demonstrated close to 100% PD-L1 target occupancy on PBMCs from the 20 to 45 mg/kg groups after multiple doses. An adequate inhibition to below the limit of quantitation of TGF-β1 was observed in the 1 mg/kg and higher dose groups. Of the 108 enrolled subjects, 67 subjects completed at least one efficacy evaluation. The ORR per RECIST 1.1 by investigator was 10.4% (7/67; 95% CI, 4.3%-20.4%), with 7 subjects achieving PR; the DCR was 53.7% (36/67; 95% CI, 41.1%-66.0%). Four additional PRs were observed after the data cut-off date. Of the total 11 PRs, 4 PRs occurred in patients who previously progressed after anti-PD-1 treatment. Most responses (10/11) occurred within 6 infusions, which indicates a rapid response towards PM8001 treatment. To date, 8 responders are still on treatment. **Conclusions:** PM8001 showed an acceptable safety profile and promising anti-tumor activity in advanced solid tumors, especially in patients previously treated with checkpoint inhibitors, which supports further studies to explore the safety and efficacy of PM8001 as a monotherapy and in combination with other anti-tumor agents. Global Phase II monotherapy and combination studies are currently ongoing. Clinical trial information: ChiCTR2000033828. Research Sponsor: Biotheus Inc.

2513 **Poster Discussion Session**

A phase 1 trial of the bifunctional EGFR/TGFβ fusion protein BCA101 alone and in combination with pembrolizumab in patients with advanced solid tumors. *First Author: Philippe L. Bedard, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: BCA101 is a first-in-class bifunctional fusion protein consisting of an anti-EGFR monoclonal antibody (mAb) and TGFβ receptor 2 extracellular domain (TGFβRII-ECD). Herein, we report the safety, pharmacokinetic (PK), pharmacodynamic (PD), and preliminary efficacy data of BCA101 as monotherapy and in combination with pembrolizumab among patients (pts) with advanced solid tumors refractory to standard therapies. **Methods:** Pts received BCA101 as a single agent (SA) or in combination with pembrolizumab at escalating doses in a parallel 3+3 design starting at 64 mg intravenously (IV) weekly (qw); and at 240 mg IV qw with pembrolizumab 200 mg IV q3w. Primary endpoint: safety and tolerability (CTCAE v5.0); dose limiting toxicity (DLT) period: 21 days. Secondary endpoints: overall response rate (ORR), PK/PD profile, progression-free survival (PFS), and changes in plasma and intra-tumoral TGFβ signaling assessed by SMAD2 phosphorylation. **Results:** As of 08-Feb-2022, 60 pts have received BCA101 (part A). Forty-five pts (colorectal, n=14; pancreatic, n=7; head and neck squamous cell carcinoma [HNSCC], n=6) received SA BCA101 at doses up to 1500 mg IV weekly. Fifteen subjects (SCC of the anal canal [SCAC], n=8; HNSCC, n=7) received BCA101 doses ranging from 240 to 1500 mg IV qw in combination with pembrolizumab. Maximum tolerated dose has not been reached. Common adverse events (AEs) attributed to BCA101 include rash (70%), fatigue (23%), pruritis and epistaxis (17% each); all grade (G)2 or less. One DLT was observed at the 1250 mg SA dose (G3 anemia, hematuria). No drug-related G4 AEs or deaths were observed. At data cutoff, best response in the SA arm was stable disease (SD) in 15/39 (39%) evaluable pts. In combination, partial response (PR) was observed in 3/11 (27%) evaluable pts (2 in SCAC, 1 in HNSCC) and a disease control rate (DCR) of 9/11 (82%). Two of 3 responders have been on study >4 months; including 1 confirmed PR in a HNSCC pt refractory to anti-PD-1 therapy and cetuximab. Saturation of the EGFR target was observed at BCA101 doses ≥750 mg. Dose proportional increase in Cmax and AUC were observed with doses of BCA101 750-1500 mg. Prolonged neutralization of plasma TGFβ1 was achieved at all doses ≥500 mg. Among paired tumor biopsies (n=23), pSMAD2 reduction up to 62% was observed at doses ≥500 mg. **Conclusions:** BCA101 is well tolerated and clinically active as a SA and in combination with PD-1 blockade with a predictable PK/PD profile. A recommended dose of 1500 mg both as SA and in combination has advanced to the part B expansion phase for pts with HNSCC, SCAC, and cutaneous SCC. Clinical trial information: NCT04429542. Research Sponsor: Bicara Therapeutics.

2514 **Poster Discussion Session**

Efficacy and safety of NT-I7, long-acting interleukin-7, plus pembrolizumab in patients with advanced solid tumors: Results from the phase 2a study. *First Author: Aung Naing, Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Checkpoint inhibitors (CPIs) are usually ineffective in patients (pts) with immune-cold microsatellite stable colorectal cancer (MSS-CRC) or pancreatic cancer (PDAC) and in those who progressed on previously treated with antibodies against PD1 or PD-L1. Here, we report the combination of NT-I7 plus pembrolizumab (pembro) on CPI-naïve MSS-CRC and PDAC cohorts, and patients (pts) with CPI-treated triple-negative breast cancer (TNBC), non-small cell lung cancer (NSCLC), and small cell lung cancer (SCLC) cohorts of this ongoing phase 2a trial. **Methods:** Pts with CPI-naïve relapsed/refractory (R/R) MSS-CRC and PDAC, and CPI-treated R/R TNBC, NSCLC, and SCLC, were enrolled. NT-I7 (efineptakin alfa) 1200 μg/kg intramuscularly every 6 weeks and 200 mg pembro intravenously every 3 weeks were administered until disease progression/unacceptable toxicity. The primary endpoint of the Phase 2a is the objective response rate (ORR), assessed by RECIST v1.1 and iRECIST. The secondary endpoints are duration of response (DoR), disease control rate, progression-free survival, and overall survival. **Results:** As of 14 Jan 2022, 92 pts with metastatic or locally advanced cancer who had received a median of 3 prior treatments were enrolled in the study; 32 in PDAC, 28 in MSS-CRC, 22 in NSCLC, 6 in TNBC, and 4 in SCLC. The median age was 62 years [29-81], ECOG PS 0 in 23 (25%), 1 in 68 (74%) and 2 in 1 (1%). Among 71 evaluable pts, the median follow up (months) was 7.7, 5.3, 5.0, 3.7, and 2.4 in TNBC, MSS-CRC, NSCLC, PDAC and SCLC, respectively. The ORR was 50% (1/2) in SCLC, 12% (3/25) in MSS CRC, 8% (2/26) in PDAC 6% (1/16) in NSCLC and 0% (0/2) in TNBC per iRECIST; and 50% (1/2) in SCLC, 4% (1/25) in MSS CRC, and 4% (1/26) in PDAC per RECIST 1.1. All 7 responders are ongoing. The two PDAC pts had DoR over 1.35 months (mos) and 6.64 mos with the best tumor reduction 100% and 72% respectively. The one SCLC pt had DoR over 1.5 mos with the tumor reduction 67%. The one NSCLC pt had DoR over 2.73 mos with the tumor reduction 60%, and the three MSS-CRC pts had DoR 6.34, 2.96, and 0.03 mos with the tumor reduction 60%, 56%, and 43% respectively. A sustained and significant (approximate 3X from baseline) increase of peripheral lymphocytes in all arms was observed as shown in our previous report. Among 92 treated pts, NT-I7-related adverse events (AEs) occurred in 67 (72.8%) pts, including 52 (56.5%) Grade (G)1-2, 13 (14.1%) G3, and 2 (2.2%) G4. There were no NT-I7 related G5 AEs. Additional updated efficacy, safety and biomarker data will be presented. **Conclusions:** The combination of NT-I7 and pembro demonstrated antitumor activity and manageable toxicity profile in heavily pretreated pts with CPI-naïve MSS-CRC and PDAC and CPI-treated TNBC, NSCLC, and SCLC, suggesting that the addition of NT-I7 to CPI can overcome the primary resistance to CPI in the former group and acquired resistance in the latter. Clinical trial information: NCT04332653. Research Sponsor: Neoimmunetech, Inc.

2515 **Poster Discussion Session**

First clinical and immunogenicity results including all subjects enrolled in a phase I study of Nous-209, an off-the-shelf immunotherapy, with pembrolizumab, for the treatment of tumors with a deficiency in mismatch repair/microsatellite instability (dMMR/MSI). *First Author: Marwan Fakih, City of Hope Comprehensive Cancer Center, Duarte, CA*

Background: Defective DNA mismatch repair (dMMR) leads to high levels of microsatellite-instability (MSI-H) and insertions or deletions in coding regions, triggering the generation of tumor-specific frameshift peptides (FSPs). We selected 209 shared FSPs among subjects with dMMR/MSI-H cancers, to generate an off-the-shelf vaccine for the treatment of dMMR/MSI-H tumors. Those FSPs were cloned into four proprietary Great Apes Adenoviral (GAd) and four Modified Vaccinia Ankara (MVA) vectors to create a polyvalent viral vectored vaccine named Nous-209 *[Leoni, G. et al. Cancer Res, 2020. 80(18): p. 3972-3982.]*. **Methods:** This phase 1 first in human (FIH) study (NCT04041310) evaluates safety and tolerability of two dose levels of the Nous-209 in combination with pembrolizumab, assesses immunogenicity and detects preliminary evidence of anti-tumor activity. Nous-209 is administered intramuscularly, concomitantly with pembrolizumab: one prime (GAd-209-FSP) at the 2nd pembrolizumab infusion and three boosters (MVA-209-FSP) at subsequent infusions each 3 weeks apart. The study is composed of two sequential cohorts i.e. dose escalation and dose expansion. **Results:** All evaluable subjects with 1st- or 2nd-line metastatic dMMR/MSI-H colorectal (CRC), gastric or gastroesophageal junction (GEJ) cancers enrolled in this phase I (n = 20) were evaluated as of February 03, 2022. Three subjects enrolled in dose level (DL) 1 (2 CRC and 1 GEJ cancer) showed durable confirmed partial responses (PRs). In DL 2 (12 CRC and 5 gastric cancers), 7 subjects had PRs, 6 had stable disease (SD) and 4 had progressive disease (PD) as best response. Most progressors progressed at the 1st CT and none of the responders have progressed. The median follow-up for subjects in DL1 is 24.7 months (22.3-26.7), and 7.6 months (0.9-19.4) in DL 2. The median progression free survival (PFS) and median duration of response (DoR) have not been reached. No dose limiting toxicities (DLTs) were observed. Vaccine immunogenicity was demonstrated in periphery by *ex-vivo* interferon-gamma ELISpot in 67% of subjects in DL 1, and 82% of subjects with evaluable samples in DL 2. The intratumoral TCR repertoire on pre/post tumor biopsies was analyzed in 3 evaluable subjects with PR and in 1 with PD: expansion and diversification of T cells post treatment with Nous-209 was noted only for the former. Vaccine-reactive TCR clones infiltrating the tumor biopsy post treatment were found in the only subject evaluated to date, with a long-term response. **Conclusions:** The combination of the Nous-209 and pembrolizumab is safe and well tolerated, and shows signs of clinical efficacy. Nous-209 elicits a neoantigen-specific T cell response expanding within the tumor, possibly contributing to the clinical outcome. Clinical trial information: NCT04041310. Research Sponsor: Nouscom Srl.

2516 **Poster Discussion Session**

Phase I trial of adjuvant autogene cevumeran, an individualized mRNA neoantigen vaccine, for pancreatic ductal adenocarcinoma. *First Author: Vinod P. Balachandran, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Pancreas ductal adenocarcinoma (PDAC) is a lethal cancer that claims ~90% of patients in <24 months of diagnosis. PDAC is also refractory to immunotherapy as most tumors exhibit an immune excluded/desert phenotype. However, although characterized by low mutation rates, most PDACs harbor mutations that can generate immunogenic neoantigens. Here, we report the results of a phase-I trial of autogene cevumeran, a systemic RNA-lipoplex individualized neoantigen-specific immunotherapy (iNeST) vaccine, to stimulate immunity against neoantigens in resected PDAC patients. **Methods:** We conducted an investigator-initiated, single-center, phase-I trial of adjuvant autogene cevumeran containing up to 20 neoantigens in each individualized vaccine, identified from resected PDACs using real-time next generation sequencing and bioinformatic neoantigen discovery. Following surgery, patients received atezolizumab (1 dose; week 6), autogene cevumeran (8 weekly doses starting week 9; doses 9,10 – weeks 17, 46), and modified (m) FOLFIRINOX (12 cycles; starting week 21). Primary endpoint: safety. Other endpoints: feasibility (actual vs. target treatment time), vaccine response (responder = positivity by two independent blood assays: IFNg ELISpot and T cell clonal expansion), and recurrence-free survival (RFS). Target accrual: n=20. **Results:** n=19 patients underwent surgery and received atezolizumab at 6.3 weeks (median; 95% CI 6.0–6.57) after surgery with no ≥ grade 3 (Gr3) adverse events. n=16/19 patients (84%) received autogene cevumeran at 9.4 weeks (median; 95% CI 9–10) after surgery. n=1/19 (5%) had insufficient neoantigens for vaccine manufacture. n=1/16 (6%) developed a vaccine-related Gr3 fever and hypertension. n=15/16 vaccinated patients (94%) received mFOLFIRINOX (median 12 cycles; 95% CI 7–12). Autogene cevumeran expanded polyclonal (median 7.5 clones, 95% CI 2–28), IFNg-producing neoantigen-specific $CD8^+$ T cells in 50% (n=8/16) of patients from undetectable levels to large fractions (median 2.9%, Table) of all blood T cells. At an early median follow-up of 15 months, vaccine responders (n=8) had a longer RFS vs. non-responders (n=8) (median not reached vs. 13.7 months, HR 0.08, 95% CI 0.01-0.5, $P = 0.007$). **Conclusions:** Autogene cevumeran is safe, feasibly manufactured in a clinically relevant timeframe, and immunogenic in PDAC. Vaccine induced neoantigen-specific immunity preliminarily correlates with improved PDAC outcome. Further clinical trials in PDAC are warranted. (This imCORE Network project was funded by Genentech Inc and BioNTech; additional funding from Stand Up To Cancer, Lustgarten Foundation). Clinical trial information: NCT04161755. Research Sponsor: Genentech Inc, BioNTech, Other Foundation.

Vaccine-induced T cells.

	Median % of all blood T cells (95% CI)		
	Pre-vaccine	*Post-vaccine*	*P* value
Non-responders (n=8)	0 (0-0)	0 (0-0.6)	0.001
Responders (n=8)	0 (0-0)	2.9 (0.2-10.4)	

2517 **Poster Discussion Session**

Recommended phase 2 dose (RP2D) of HB-200 arenavirus-based cancer immunotherapies in patients with HPV16+ cancers. *First Author: Siqing Fu, Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Treatment options are limited for patients with recurrent or metastatic human papillomavirus 16 positive (HPV16+) cancers. Generation and maintenance of HPV16+ cancers requires stable expression of HPV16-specific E7 and E6 oncoproteins, which are also a source of tumor-specific immunogenic neoantigens. HB-201 and HB-202 are replicating live-attenuated vectors based on lymphocytic choriomeningitis virus and Pichinde virus, respectively, which express the same non-oncogenic HPV16 E7E6 fusion protein and infect antigen presenting cells to induce tumor-specific T cell responses. The Phase 1 part of this study of HB-200 therapy (HB-201 single-vector therapy and HB-202/HB-201 two-vector alternating therapy) was conducted to determine RP2D for further exploration alone or in combination with pembrolizumab. **Methods**: The Phase 1 part used a 3+3 dose escalation design with up to 3 dose levels (DLs) of HB-201 and 4 DLs of HB-202/HB-201 explored. Patients with HPV16+ head and neck squamous cell carcinoma (HNSCC) or with other HPV16+ cancers were evaluated. Safety, tolerability, immunogenicity, and preliminary antitumor activity by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 or immune RECIST were assessed to determine RP2D. **Results**: As of January 2022, 65 patients with a median of 3 prior anticancer treatments have been enrolled in the Phase 1 part of the study. All had HPV16+ confirmed genotype; the most common primary site was oropharynx, followed by anal and cervix. Adverse events were generally mild or moderate. For HB-201, 3 DLs, 2 dosing schedules and 2 administration routes were assessed across 40 patients. At DL3 of HB-201 administered intravenously (IV), dose-limiting toxicity (DLT) occurred in 1/6 patients in the HNSCC group (Grade 4 encephalopathy, fully recovered) and 1/2 patients in the non-HNSCC group (Grade 3 rash, fully recovered). Preliminary safety, efficacy, and immunogenicity data support IV injection of DL3 (5×10^7 units) every 3 weeks (Q3W) as the RP2D for HB-201 single-vector therapy. For HB-202/HB-201, 4 DLs and 2 administration routes were assessed across 25 patients. At DL4 of HB-202/HB-201 IV, 1/5 subjects in the HNSCC group reported a DLT (Grade 4 hepatitis, recovering at time of discontinuation). RP2D for HB-202/HB-201 will be determined in the very near future. Tumor control, including partial response, have been observed in subjects treated with either HB-201 or HB-202/HB-201 as monotherapy. **Conclusions**: HB-201 and HB-202/HB-201 were generally well tolerated and showed preliminary antitumor activity in heavily pre-treated patients with HPV16+ solid tumors. DL3 was selected as RP2D for HB-201 monotherapy. In the Phase 2 part of the study a combination of HB-201 at 5×10^6 units IV Q3W with pembrolizumab is being tested in HPV16+ HNSCC patients. Clinical trial information: NCT04180215. Research Sponsor: Hookipa Biotech Gmbh.

2518 **Poster Discussion Session**

Phase II evaluation of the combination of PDS0101, M9241, and bintrafusp alfa in patients with HPV 16+ malignancies. *First Author: Julius Strauss, Laboratory of Tumor Immunology and Biology, National Cancer Institute, National Institutes of Health, Bethesda, MD*

Background: More than 630,000 cases of HPV related cancer occur worldwide annually. About 15-20% of cases respond to PD-(L)1 inhibitors and about 30% respond to dual PD-L1/TGF-β blockade including 10% of checkpoint refractory pts, but for the majority of pts with checkpoint refractory disease there is no effective standard therapy. Preclinical studies show that the combination of PDS0101, a therapeutic vaccine targeting HPV 16 E6/E7, M9241, a tumor-targeting IL-12 immunocytokine, and bintrafusp alfa (BA), a bifunctional fusion protein targeting TGF-β and PD-L1, resulted in maximum T cell infiltration and tumor reduction compared to any 1 or 2 of these agents alone. Prior clinical data suggests that the combination is preferentially active in HPV 16+ disease. **Methods:** 30 pts with advanced HPV 16+ cancer were treated with PDS0101, M9241 and BA (NCT04287868). Pts received BA at 1200 mg IV q2wks, M9241 at 16.8 mcg/kg SC q4wks or 8 mcg/kg SC q2wks, and PDS0101 as two 0.5 ml SC injections q4wks. Dose reductions or skipped doses for toxicities of BA and M9241 were allowed. 5 pts had surgical resection of tumor for disease control and were censored for PD but not survival. **Results:** 30 pts (9 cervical, 2 vaginal/vulvar, 6 anal, 13 oropharyngeal) were treated. 13/30 had grade 3 treatment related AEs including grade 3 anemia in 9 pts associated with grade 3 hematuria in 3 pts and grade 3 GI bleeding in 3 pts. 2 pts had grade 3 AST/ALT elevation. Grade 3 flu like symptoms and grade 3 hemophagocytic lymphohistiocytosis were each seen in 1 pt. One pt had grade 3 lymphopenia/leukopenia plus grade 4 neutropenia and one pt had grade 4 AST/ALT elevation. There were no grade 5 treatment related AEs. 7/8 (88%) pts with checkpoint naïve disease had objective responses (OR) including 1 delayed response after initial PD with 4/7 (57%) responses ongoing (median 17 months follow up). 10/22 (45%) with checkpoint refractory disease have had disease reduction including 6/22 (27%) with OR and 4/6 (67%) responses ongoing (median 12 months follow up). 6/8 (75%) pts with checkpoint naïve disease and 17/22 (77%) pts with checkpoint refractory disease are alive after a median of 17 and 12 months follow up respectively. For checkpoint refractory pts, M9241 dosing appears to affect response rates. 5/8 (63%) pts receiving M9241 at 16.8 mcg/kg had an OR compared to 1/14 (7%) who received M9241 at 8 mcg/kg with an OR. However, despite differences in response rates with higher vs lower M9241 dose, survival outcomes were similar irrespective of M9241 dose (p = 0.99 by Kaplan Meier analysis). **Conclusions:** The combination of PDS0101, M9241 and BA appears to have a manageable safety profile along with early evidence of clinical activity for pts with checkpoint naïve and refractory advanced HPV 16+ cancer. Moreover, growing data suggest that all 3 drugs in the combination contribute to the encouraging outcomes being observed. Clinical trial information: NCT04287868. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

2519 **Poster Discussion Session**

Identifying mechanisms of acquired immune escape from sequential, paired biopsies. *First Author: F. Stephen Hodi, Dana-Farber Cancer Institute, Boston, MA*

Background: Resistance to immune checkpoint blockade (ICB) can manifest as disease progression either at the initiation of treatment (primary resistance) or after some initial response (acquired resistance). To better understand the mechanisms underlying acquired resistance, the imCORE Network is conducting a study (NCT03333655) to examine changes in tumor biology from pre-treatment to disease progression across cancer types. **Methods:** Eligible patients included those experiencing clinical benefit on ICB (defined as objective response or stable disease longer than 6 months) and had evaluable tissue samples from both pre-treatment and within 30 days of progression. Samples were subjected to whole exome sequencing (WES), RNA sequencing (RNA-Seq), and immunohistochemistry (IHC). Whole blood samples or adjacent normal tissue were used as a reference for tumor variant calling. **Results:** As of December 3rd, 2021, 24 enrolled patients have complete sample pairs. Of those, melanoma, bladder, and lung were most common (n = 7, 6 and 5 pairs, respectively), but our cohort also included patients with breast cancer, squamous head & neck, and renal cell carcinoma. IHC data unexpectedly showed a modest, but consistent increase in tumor infiltrating CD8+ T cells at progression. In addition, IHC evidence of a decrease in MHC-I proteins (HLA-A and B2M) suggest that in 5 out of 24 cases, key proteins needed for antigen presentation are lost. Global differential gene expression analysis showed that immune gene expression was significantly increased at progression, including numerous chemokines and significant enrichment in gene sets responsible for antigen presentation machinery. Protein-altering mutations at progression appeared in B2M in one patient, and CXCL9 in another. However, in most cases it is unclear what genetic alterations are responsible. We do not observe evidence of consistent IFNγ and Jak/stat signaling loss or antigen presentation loss. **Conclusions:** While ICB resistance is thought to be associated with a lack of immune response within the TME, we found that acquired resistance is usually associated with either maintenance or an increase in immune infiltration. Multiple alterations that are unique to individual patients also continue to emerge. Our data shows ICB resistance is multifactorial and associated with dynamic changes to markers amid immune activation and inhibition. Clinical trial information: NCT03333655. Research Sponsor: Roche/Genentech.

2520 **Poster Discussion Session**

Effect of intratumoral INT230-6 on tumor necrosis and promotion of a systemic immune response: Results from a multicenter phase 1/2 study of solid tumors with and without pembrolizumab (PEM) [Intensity IT-01; Merck KEYNOTE-A10]. *First Author: Jacob Stephen Thomas, Division of Oncology, USC Keck School of Medicine, Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: INT230-6 is a new product with a unique dual anti-cancer mechanism. The drug is comprised of cisplatin (CIS) and vinblastine (VIN) co-formulated with an amphiphilic molecule that enables drug dispersion throughout a tumor and passive diffusion into cancer cells following intratumoral (IT) delivery. A neoadjuvant study in breast cancer confirms that a single injection can kill 95% of an injected tumor and recruit TILs. **Methods:** INT230-6 treatments are Q2W for up to 5 treatments followed by maintenance dosing every 9 weeks. Dose is set by the tumor's longest diameter or volume. One arm received INT230-6 plus PEM 200mg IV Q3W. Biopsies from injected tumor are taken pretreatment and Day 28 for immunohistochemistry (IHC) analysis. **Results:** Sixty-two subjects received INT230-6 alone (median age 61, with 4 prior treatments), and 21 INT230-6 + PEM (median age 70, with 3 prior treatments). To these subjects over 575 image guided INT230-6 IT injections were given (320 to visceral tumors such as lung, liver, pancreas). Doses ranged from 0.14 to 175mL (87.5 mg of CIS, 17.5 mg VIN - higher than typical IV doses). Pharmacokinetic data shows > 95% of the INT230-6 active agents remain in the tumor. The most common (> 25%) adverse events (AEs) related to INT230-6 were localized pain (58%), nausea (40%), and fatigue (29%). The most common AEs attributed to the PEM combination were nausea (62%), localized pain (57%), vomiting (57%), decreased appetite (43%), fatigue (43%) and constipation (29%). The incidence of grade 3 AEs for the INT230-6 arm was 11% and for the PEM combination was 14%. There were no related grade 4 or 5 AEs in the INT230-6 arm; and one grade 4 neutrophil count decrease was seen on the PEM combination. There were no dose limiting adverse events. No patient discontinued therapy due to toxicities related to either drug or injection procedure. The monotherapy arm enrolled patients from 17 tumor types; while the PEM combo recruited primarily pancreatic, CRC, triple negative breast, or bile duct cancer. IHC results confirm a marked reduction in proliferating tumor cells with influx of CD4 and CD8 T-cells. Seven of the INT230-6 monotherapy patients had non injected tumor shrinkage in 9 visceral/deep lesions. Estimated median overall survival (mOS) was over 1 year for both arms. **Conclusions:** In this clinical trial, deep and superficial tumor injections into patients with widely metastatic disease was feasible and well tolerated. Biopsies confirm the dual anti-cancer mechanism, and study patients live longer than would be expected for these refractory populations. INT230-6's rapid tumor killing and immune activation properties may offer an alternative to control refractory patients (even those that are chemotherapy refractory) and the product is moving into randomized controlled registration trials. Clinical trial information: NCT03058289. Research Sponsor: Intensity Therapeutics, Inc.

2521 **Poster Discussion Session**

First-in-human dose escalation and expansion study of MT-6402, a novel engineered toxin body (ETB) targeting PD-L1, in patients with PD-L1 expressing relapsed/refractory advanced solid tumors: Interim data. *First Author: Eugene R Ahn, Cancer Treatment Centers of America Chicago, Zion, IL*

Background: MT-6402 is a unique and potent PD-L1-targeted engineered toxin body (ETB) capable of directly killing PD-L1 expressing tumor and immune cells by internalization of a fused Shiga-like toxin A subunit (SLTA) resulting in permanent SLTA-mediated ribosomal inactivation. The targeting of PD-L1 expressing tumor cells may directly drive tumor regression whereas targeting of PD-L1 expressing immune cells may release immunosuppression and drive immune recognition of the tumor. MT-6402 also delivers an HLA-A*02 restricted cytomegalovirus (CMV) class I antigen into PD-L1 expressing cells (antigen seeding) that can be recognized by existing CMV-specific cytotoxic T cells. **Methods:** A first-in-human dose escalation and expansion study in patients with PD-L1-expressing advanced solid tumors was initiated in 2021. As of 1 Jan 2022, 6 patients received at least one dose of MT-6402, 4 of whom were eligible for Dose Limiting Toxicity (DLT) assessment in Cohort 1. **Results:** A significant reduction in CD14+ monocytes starting in cycle 2 was observed in patients on therapy after each MT-6402 administration, indicating an HLA-independent PD effect consistent with preclinical observations. 5 of 6 patients had a marked decrease in Monocytic Myeloid Derived Suppressor Cells (MDSC). The reduction in MDSC and monocytes in the periphery overlapped with increased CCL2 levels, a chemokine that directs movement of myeloid cells. One patient with osseous metastases from non-small cell lung cancer (NSCLC) who is HLA-A*02 and CMV+ showed complete CMV-specific T-cell extravasation at day 8 and serum cytokine signatures consistent with antigen dependent responses and T cell mobilization. This patient had reduced tracer uptake of metastatic bone lesions with 3/4 lesions resolving completely. A second HLA A*02 CMV+ patient followed a similar trend towards loss of peripheral CMV-specific T cells with a concurrent increase in total CD8 T cells. The CD8 T cells from these 2 patients had elevated T-bet expression from baseline, indicating antigen specific TCR stimulation and expansion. The activated immune response was also accompanied by increased IP-10 and IL-2 cytokine signatures in the serum. Consistent with these findings, one of these two patients had transient (1-12 h) grade 2 infusion related reaction and the other had transient (1-12 h) grade 2 cytokine release syndrome, both on Day 15. These results describe a novel approach to checkpoint modulation by MT-6402, that adds antigen seeding to PD-L1 directing mechanisms. MT-6402 was well tolerated and no DLT was observed in Cohort 1 (16 μg /kg, QW in 4-week cycles). **Conclusions:** Dose escalation is ongoing. The results hold promise for development of MT-6402 for solid tumors, including in the R/R setting. Data for additional patients will be presented at the meeting. Clinical trial information: NCT04795713. Research Sponsor: Molecular Templates, Inc.

2522 **Poster Discussion Session**

The association of pre-existing autoimmune disease and immune-related adverse events secondary to immune checkpoint inhibition therapy in a UK multicenter cohort. *First Author: Anna Claire Olsson-Brown, Clatterbridge Cancer Centre, Liverpool, United Kingdom*

Background: Pre-existing autoimmune disease (AID) potentially increases the propensity for the development of immune related adverse events (irAE) in response to oncological immune checkpoint inhibitors (ICIs) is biologically plausible and clinically observed. However, due to consistent clinical trial exclusion of those with pre-existing AID, the impact on the frequency and severity of irAEs is uncertain. Here we analyse this relationship in a large, real-world, UK multi-centre cohort. **Methods:** A retrospective analysis of 2049 patients treated with ICIs over a two year period was undertaken across 12 National Health Service centres by the UK National Oncology Trainees Collaborative for Healthcare Research (NOTCH). Patients received ICIs as standard of care for malignant melanoma, non-small cell lung cancer and renal cell carcinoma. The presence of pre-existing AIDs was assessed and classified as either autoantibody driven or autoinflammatory then correlated with clinically significant irAEs (i.e. ≥grade 2 or all-grade endocrinopathies). Statistical analyses included T-test, Mann-Whitney and Chi-squared. For overall survival (OS) Kaplan-Meier and log-rank tests were utilised. **Results:** Pre-existing AID were present in 13% (n = 257) of the overall cohort. Pre-existing endocrinopathies (30%; n = 76) were most common followed by rheumatological AIDs (18%; n = 46). In the pre-existing AID cohort there was a female predominance (48% vs 39%; p = 0.006) but no difference in smoking history (p = 0.074) or ethnicity (p = 0.12). There was no difference in ICI treatment between those with and without pre-existing AID (p = 0.2800). IrAEs occurred in 45% (n = 117) patients with pre-existing AID vs 33% (n = 583) without (p£0.001). The median time to onset of irAEs was similar. IrAEs with an increased incidence in the pre-existing AID cohort were colitis (p = < 0.001), arthralgia (p = 0.008) and dermatological irAEs (p = 0.014). There was no difference in the incidence of irAEs in patients with autoantibody driven vs autoinflammatory pre-existing AID (44.0 % vs 44.8%, p = 0.905). In the overall cohort, those with pre-existing AIDs had a median OS of 20.4 months (95% CI: 19.4-21.7) vs 14.1 months (95% CI: 12.8-16.3) in those without pre-existing AID (p = 0.004). **Conclusions:** This large multi-centre ICI-treated cohort demonstrates that pre-existing AID is a predisposing factor for the development of irAEs, however the incidence is lower than previously quoted. The pathological basis of pre-existing AID did not differentially affect irAE manifestation. Patients with pre-existing AID had improved OS compared to those without which has not been observed in previously reported studies. ICI treatment should be considered in those with pre-existing AID but further studies are needed to determine how best to optimise outcomes whilst mitigating the impact of irAEs. Research Sponsor: None.

2523 **Poster Discussion Session**

Preexisting autoantibodies as predictor of immune-related adverse events for advanced solid tumors treated with immune checkpoint inhibitors. *First Author: Arthur Daban, APHP, Paris, France*

Background: Immune checkpoint inhibitors (ICIs), used alone or as a combination are standard of care in many cancers. Generally well tolerated, they can generate immune-related adverse events (irAEs). No biomarkers are available to identify patients who are more likely to develop irAEs. The aim of this study was to assess the association between preexisting autoantibodies, occurrence of irAEs and survival outcomes. **Methods:** We performed a prospective study including 221 patients receiving ICIs for advanced solid tumors between May 2015 and July 2021. Autoantibodies testing (anti-neutrophil cytoplasmic, anti-nuclear, thyroid peroxidase and thyroglobulin) was performed before ICIs initiation. The associations among preexisting autoantibodies, the occurrence, the severity, the delay of irAEs and the survival outcomes, including progression-free survival (PFS) and overall survival (OS) were analyzed. Statistical analyses were performed with T-test, Cox regression models, univariate and multivariate analyses and Kaplan-Meier's method. **Results:** Of the 221 patients, 151 (68%) were men, the median age was 66,5 (range 21-90) years and 103 (81%) had an ECOG-PS of 0 or 1. Seventy-three percent (n=162) received an anti-PD-(L)1 in monotherapy, 27% (n=59) an anti-PD-(L)1 in combination, for a renal cell carcinoma in 45% (n=99) and a lung carcinoma in 41% (n=90). In total, 129 (58%) patients had preexisting antibodies. IrAEs were significantly more frequent in patients with preexisting autoantibodies: 64 patients (50%) in the positive group vs. 20 patients (22%) in the negative group, OR = 3.5 (95%CI=1.8 - 6.8), p=0.00002. Median time interval between ICI initiation and irAE was shorter in the positive group vs. the negative group, 13 weeks (IQR=43weeks) vs. 28.5 weeks (IQR=12weeks) respectively (p=0.01). Twelve patients (9.4%) experienced multi toxicities in the positive group vs. two (2%) in the negative group, OR=4.5 (95%CI0.98-36), p=0.04. ICIs exposure was identical in preexisting and non-preexisting autoantibodies groups. After a median follow-up of 25 months (95%CI=19-31), median PFS and OS were significantly longer among patients experiencing irAE: 12.6 months (95%CI=11-22.7) vs 5 months (95%CI=4.2-7.0), p= 0.0003 and 30 months (95%CI= 22.7-NR) vs 21 months (95%CI=15-34.6), p= 0.016. In multivariate analyses irAEs remain statistically associated with survival outcomes. Preexisting autoantibodies were not associated with survival outcomes. **Conclusions:** The presence of preexisting autoantibodies is significantly associated with the occurrence of irAE in patients treated with ICIs. Earlier and multiple irAEs were observed in the presence of preexisting autoantibodies. Thus, these biomarkers could help to identify patients at risk of irAEs and would prompt us to closely monitor them. Research Sponsor: None.

2524 **Poster Session**

Safety and efficacy results from the expansion phase of the first-in-human study evaluating TGFβ inhibitor SAR439459 alone and combined with cemiplimab in adults with advanced solid tumors. *First Author: Debbie Robbrecht, Erasmus MC Cancer Institute, Rotterdam, Netherlands*

Background: SAR439459 (SAR459) is a human anti-TGFβ monoclonal antibody that neutralizes all isoforms of TGFβ. In preclinical models, combining SAR459 with an anti-PD-1 showed improved anti-tumor activity compared to SAR459 single agent. In the dose escalation, acceptable tolerability was observed, the MTD was not reached and the preliminary RP2D was 22.5mg/kg Q3W when combined with cemiplimab (CEMI; S. Williamson et al. J Clin Oncol 39, 2021[suppl 15; #2510]). Reduction of plasma TGFβ was ≥90% at doses ≥0.25mg/kg Q2W, with a trend of a decrease in intra-tumoral TGFβ (D. Robbrecht et al. JITC 2021;9 [suppl 2; #250]). Here we report safety and efficacy results of the dose expansion. **Methods:** The expansion phase of this open-label, phase 1/1b study aimed to determine the optimal dose of SAR459 (7.5 mg/kg or 22.5 mg/kg Q3W) in patients (pts) with advanced melanoma (MEL) resistant to anti-PD(L)1 therapy (Part 2A); and the ORR (confirmed responses) in all treated pts with SAR459 22.5 mg/kg + CEMI 350 mg Q3W in pts with MEL, Non-small Cell Lung Cancer (NSCLC), or Hepatocellular Carcinoma (HCC), resistant to anti-PD(L)1; as well as in pts with mesenchymal Colorectal Cancer (CRC) or Urothelial Cancer (UC), anti-PD(L)1 naïve (Part 2B). **Results:** From October 2019 to September 2021, 109 pts with ECOG PS 0-1 enrolled in Part 2A (14) and Part 2B (95). Overall, the median age was 63 years and 83% of pts received up to 3 prior treatment lines for advanced disease (range 1-8). Based on preliminary data, the ORR in Part 2B was 8% (Table). No significant association between clinical response and plasma TGFb level at baseline or modulation upon treatment was observed. The correlation between tumor TGFb level and clinical benefit is inconclusive due to limited number of tumor biopsies. No response was observed in Part 2A. Overall, 100% of pts had at least one treatment emergent adverse event (AE), 67% were G≥3, 34% related G≥3, 17% G5, and 4% related G5. The limited number of patients treated with SAR459 alone at the RP2D did not allow to demonstrate added toxicity due to the combination. Overall, 51 pts (47%) reported hemorrhagic AE of any grade, 8 pts (7%) had G≥3 and 5 pts (5%) had fatal outcome. The rate of bleeding and severe hemorrhagic AE was higher in HCC pts compared to the other cohorts: 11/14 (79%) pts had a hemorrhagic AE, of which 3 (21%) G≥3 and fatal. An exploratory analysis showed a trend for higher frequency of any grade SAR459-related and fatal hemorrhagic AE in patients with higher exposure. **Conclusions:** The NCT03192345 study was discontinued due to a lack of efficacy, and a high bleeding risk particularly in pts with HCC. Clinical trial information: NCT03192345. Research Sponsor: Sanofi.

Part 2B objective response rate.

	MEL	NSCLC	HCC	CRC	UC	Part 2B all cohorts
N	25	17	14	24	15	95
ORR n(%)	2(8)	1(6)	1(7)	1(4)	3(20)	8(8)
PR	2	1	1	1	3	8
SD	6	7	4	5	3	25
PD	16	7	6	16	9	54
Not evaluable	1	2	3	2	0	8

2525 **Poster Session**

The impact of COVID-19 infection on immune-related adverse events in patients with cancer receiving immune checkpoint inhibitors. *First Author: Mengni Guo, AdventHealth Orlando, Orlando, FL*

Background: Immune checkpoint inhibitors (ICIs) can cause a variety of inflammatory autoimmune tissue damage, referred to as immune-related adverse events (irAEs). COVID-19 is associated with increased amounts of proinflammatory cytokines, which may synergistically affect the outcome of irAEs. Data are limited regarding the impact of COVID-19 on irAEs in ICI-treated cancer patients. **Methods:** We retrospectively analyzed adult patients with malignant solid tumors treated with ICIs at AdventHealth Orlando between August 2020 and August 2021. All COVID-19 infections were confirmed by PCR. Patients who had the most recent ICI treatment over one month before or after the positive COVID-19 test were excluded from the study. For COVID-19 positive group, only the irAEs that developed after COVID-19 infection were considered as events. **Results:** A total of 579 patients were included in our study, with 46 (7.9%) in COVID-19 positive group, and 533 (92.1%) in COVID-19 negative group. The baseline characteristics of patients in the two groups were similar in terms of age, ethnicity, ECOG, cancer histology, and type of ICI. With a median follow-up of 10 months (1-73 months), no differences in the time from ICI initiation to irAE onset, corticosteroid use, or additional immunosuppressant use were seen. A trend in higher incidence of all-grade diarrhea/colitis (8.7% vs. 3.0%, p=0.07) and grade 3 and 4 hepatitis (4.3% vs. 0.8%, p=0.08) was noted in the COVID-19 positive group, however the difference was not statistically significant. No significant difference in the incidence of pneumonitis (2.2% vs. 1.1%, p=0.44), nephritis (2.2% vs. 0.8%, p=0.34) or dermatitis (6.5% vs. 6.4%, p=1.00) were noted between COVID-19 positive and negative groups. We noticed a higher incidence of all-grade irAEs in the COVID-19 positive group (30.4% vs. 19.9%, p=0.18), but the difference was not statistically significant. The incidence of grade 3 and 4 irAEs was significantly higher in the COVID-19 positive group (10.9% vs. 3.2%, p=0.02). Nine COVID-19 related death occurred while no irAE-related death was noted in the entire cohort. **Conclusions:** Our study suggested that COVID-19 may pose a risk of severe irAEs in cancer patients receiving ICIs. Close monitoring and possible delaying ICI administration could be considered when cancer patients were infected with COVID-19. Research Sponsor: None.

Clinical features of the irAE between COVID-19 positive and COVID-19 negative groups.

Variable	COVID-19 positive N=46	COVID-19 negative N=533	P-value
All grades irAE, n (%)	14 (30.4)	106 (19.9)	0.18
Grade 3-4 irAE, n (%)	5 (10.9)	17 (3.2)	0.02
Corticosteroid use for irAE, n (%)	8 (57.1)	60 (56.6)	0.78
Use of additional immunosuppressant for irAE	0 (0.0)	4 (3.8)	1.00
Time to irAE, median (range)			
Treatment cycle	6 (2-72)	6 (1-56)	0.54
Days	255.5 (48-1662)	153.5 (7-1415)	0.25
Death related to irAE, n (%)	0 (0.0)	0 (0.0)	1.00

2526 **Poster Session**

A multicenter, randomized, double-blind, phase III trial comparing denosumab biosimilar QL1206 and denosumab in patients with bone metastases from solid tumors. *First Author: Huiping Li, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/ Beijing), Department of Breast Oncology, Peking University Cancer Hospital and Institute, Beijing, China*

Background: This phase III study compared clinical efficacy, safety of the first biosimilar QL1206 with denosumab in solid tumor patients with bone metastases. **Methods:** Patients aged 18-80 years, with bone metastatic solid tumors and ECOG performance status of 0-2 were randomly assigned 1:1 to receive subcutaneous QL1206 or denosumab (120 mg Q4W, both) based on stratification factors (tumor types, previous skeletal-related event [SRE], and current systemic anti-tumor therapy). The primary efficacy endpoint was the percentage changes from baseline to week 13 in urinary N-telopeptide/creatinine ratio (uNTX/uCr); Clinical equivalence would be confirmed if the two-sided 90% confidence intervals (CI) of the least-squares mean (LSM) difference of natural log-transformed ratio of week 13 uNTX/uCr to baseline calculated by analysis of covariance were within the margins of ±0.135. The secondary endpoints included the percentage changes from baseline to week 25 and 53 in uNTX/uCr, the percentage changes from baseline to week 13, 25 and 53 in serum bone-specific alkaline phosphatase (s-BALP) and the time to on-study SRE. Adverse events (AE), immunogenicity (IG) and pharmacokinetics (PK) were also assessed. Population PK was analyzed using nonlinear mixed effects model. **Results:** 717 patients were randomized to the QL1206 (n = 357) and denosumab (n = 360) groups, respectively. The median percentage changes at week 13 in uNTX/uCr were -75.2% for QL1206 and -75.8% for denosumab. LSM of natural log-transformed ratio of week 13 uNTX/uCr to baseline were -1.429 (standard error 0.130) and -1.441 (0.130) in the two groups. The LSM difference between the two groups was 0.012 (90% CI -0.078 to 0.103; P = 0.8208), within the equivalence margins. Analyses for subgroups of sex, age, and randomization strata showed almost no significant differences. The secondary endpoints were also similar between the two groups (median percentage changes in s-BALP from baseline to week 13: -38.0% vs -37.1%; hazard ratio of time to SRE: 1.264 [95% CI 0.670 to 2.383]; both P > 0.05). In the safety set, treatment-emergent AE occurred in 332 of 356 patients (93.3%) in the QL1206 group and 348 of 361 (96.4%) in the denosumab group. The proportions of positive anti-drug antibody (14/345 [4.1%] vs 16/352 [4.5%]), neutralizing antibody (three [0.9%], each), and PK characteristics were similar between the two groups. **Conclusions:** The results suggest that QL1206, the first biosimilar denosumab, is similar to denosumab with respect to clinical efficacy, acceptable safety, IG, and PK characteristics. The totality of evidence supports clinical equivalence of QL1206 and denosumab. Clinical trial information: NCT04550949. Research Sponsor: Qilu Pharmaceutical Co., Ltd.

2527 **Poster Session**

Safety, tolerability, and preliminary efficacy of nadunolimab, a first-in-class monoclonal antibody against IL1RAP, in combination with pembrolizumab in subjects with solid tumors. *First Author: Shekeab Jauhari, Sarah Cannon Research Institute, Florida Cancer Specialists and Research Institute, Lake Mary, FL*

Background: Interleukin-1 Receptor Accessory Protein (IL1RAP) is expressed on cancer and stromal cells of many solid tumors. IL1RAP interacts with IL-1R1, modulating downstream factors (e.g. IL-6, IL-8) and CRP level. Nadunolimab (CAN04), a fully humanized ADCC-enhanced IgG1 antibody, targets IL1RAP and blocks IL-1α and IL-1β. IL-1 promotes an immune suppressive microenvironment, e.g. by recruitment of MDSC which may induce checkpoint inhibitor resistance. Here, initial data are reported from the phase Ib clinical trial CIRIFOUR, evaluating nadunolimab combined with pembrolizumab in solid tumor patients (pts) progressed on prior anti-PD-(L)1 therapy. **Methods:** Primary objective was evaluating safety and tolerability of nadunolimab combined with pembrolizumab in pts with metastatic NSCLC (n = 5), head and neck squamous cancer (n = 9) or malignant melanoma (n = 1), progressed on prior anti-PD-(L)1 therapy of ≥12 weeks (wks). Dosing started with a priming dose of 0.5 mg/kg nadunolimab on Day -7, followed by 5 mg/kg nadunolimab weekly combined with standard pembrolizumab dosing. A safety lead-in phase 3+3 design was employed. Secondary objectives included preliminary efficacy and responses based on RECIST/iRECIST. Serum biomarkers and tumor biopsies were also analyzed. **Results:** Fifteen pts received at least one dose of 5 mg/kg nadunolimab with pembrolizumab: median age 63 years (50-79), 27% female, 100% Stage IV, 93% and 7% received prior pembrolizumab or nivolumab respectively, 7% ECOG 0, 93% ECOG 1. The pts had received a mean of 2.3 (range 1-6) previous lines of treatment. SAE were reported in 47% with one considered treatment-related (febrile neutropenia). Two treatment-related grade 3 AE were reported: one febrile neutropenia (DLT), one pneumonitis. No pts discontinued treatment due to treatment-related AE. One patient (7%) had unconfirmed PR as best response, 8 (53%) showed SD, and 6 (40%) iUPD. At time of analysis, 5 pts (33%) received ongoing treatment. Of these, two pts had received therapy for over 31 wks, another two for over 49 wks. Decreased IL-6 was observed after four wks and persisted during treatment. Reduced neutrophil-lymphocyte ratio (NLR) was observed throughout the study, appeared after first treatment, and was driven by a moderate reduction in circulating neutrophils. Decreased IL-6 and NLR were most pronounced in pts with longest disease control duration. IL1RAP expression on cancer and stromal cells was confirmed in tumor biopsies. **Conclusions:** The nadunolimab and pembrolizumab combination was considered safe and tolerable with preliminary evidence of prolonged disease control. The favorable safety provides basis for evaluation of further therapy with this combination. Next, nadunolimab and pembrolizumab will be assessed with carboplatin/pemetrexed in non-squamous NSCLC. Clinical trial information: NCT04452214. Research Sponsor: Cantargia AB.

2528 **Poster Session**

Customized autoantibodies (autoAbs) profiling to predict and monitor immune-related adverse events (irAEs) in patients receiving immune checkpoint inhibitors (ICI). *First Author: Sofia Genta, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Using a customized microarray, we previously reported that patients (pts) who develop irAEs grade (G)≥2 and those who do not, have different median fluorescent intensity (MFI) levels of specific autoAbs at baseline (pre-ICI). Leveraging a larger dataset, we evaluated whether overall baseline autoAbs elevation and early increases in autoAbs after ICI can predict irAEs as well as if steroid treatment can reduce autoAbs. **Methods:** Plasma was obtained from pts receiving ICI in two clinical trials (MET4-IO, NCT03686202 and INSPIRE, NCT02644369) and from healthy controls (hc). Collection time points in MET4-IO and INSPIRE studies included: baseline, 3-4 weeks (w), 6-8 w, 24 w and at the end of treatment and baseline and 6 w respectively. Arrays with 162 autoAg customized for frequent irAEs were incubated with plasma and probed with Abs to detect IgG and IgM reactivity. AutoAbs with MFI >500 per individual were compared between hc and pts with and without irAEs G≥2 by the Student-t test. **Results:** Samples from 114 pts and 14 hc were analyzed (pts characteristics are summarized in the Table). G≥2 irAEs included: hypothyroidism (13), pneumonitis (10), colitis (7), hepatitis (4), skin toxicity (7), infusion reaction (2), pancreatitis (2), meningitis (1), hypophysitis (1), corneal ulcer (1), high creatinine (1), myocarditis (1), myositis (1), diabetes (1), mucositis (1), myasthenia (1) and adrenal failure (1). Hc had less autoAbs with MFI >500 as compared to pts at baseline (median 32 vs 62 $p<0.001$). IgG with MFI >500 were higher at baseline in pts who developed G≥2 irAEs vs those without G≥2 irAEs (median 39 vs 33, $p=0.03$). In 23 pts with plasma collected at the time of irAEs, we observed a significant increase of autoAbs with MFI>500 from baseline (median 84 vs 77 $p= 0.009$). Paired samples at the time of irAEs and after steroids were available for 9/23 pts, showing lower autoAbs after steroid treatment (54 vs 79 $p=0.006$). No differences in autoAbs with MFI>500 pre and post ICI were seen in pts without G≥2 irAEs (baseline vs first post ICI collection median 58 vs 60, $p=0.13$). **Conclusions:** We observed a higher number of IgG with MFI >500 at baseline and a greater increase after ICI administration in individuals with irAEs compared to those without irAEs. Steroid treatment resulted in a decrease in autoAbs. A prospective study is ongoing to validate the potential role of autoAbs for risk stratification and monitoring of irAEs. Research Sponsor: Dr. Spreafico's research founding.

Pts characteristics.

	MET4-IO	INSPIRE	TOTAL
N of pts	30	84	114
Median age	67(24-81)	59 (21-81)	61(21-81)
Gender			
M	19 (63%)	39 (46%)	58 (51%)
F	11 (37%)	45 (54%)	56 (49%)
irAES≥G2			
Yes	18 (60%)	19 (23%)	37 (32%)
No	12 (40%)	65 (77%)	77 (68%)
Tumor type			
Melanoma	14 (47%)	11 (13%)	25 (23%)
HNSCC	14 (47%)	19 (23%)	33 (29%)
Other tumor types	2 (7%)	52 (64%)	56 (49%)
Type of ICI			
Anti PD1	18 (60%)	84 (100%)	102 (89%)
Anti PD1 + anti-CTLA4	12 (40%)	0 (0%)	12 (11%)

2529 **Poster Session**

Initial findings from a first-in-human, multicenter, open-label study of ATOR-1017, a 4-1BB antibody, in patients with advanced solid malignancies. *First Author: Gustav J. Ullenhag, Department of Radiology, Oncology and Radiation Science, Section of Oncology, Uppsala University, Uppsala, Sweden*

Background: ATOR-1017 is a human agonist Fcγ-receptor cross-linking dependent IgG4 antibody targeting the co-stimulatory receptor 4-1BB (CD137). ATOR-1017 activates T cells and natural killer cells in the tumor environment, leading to immune-mediated tumor cell killing. **Methods:** In this first-in-human, dose escalation, multicenter, phase 1 study (NCT04144842), adult patients with solid tumors refractory to standard therapy were enrolled in single patient cohorts for doses up to 40 mg, and thereafter in cohorts of 3-6 patients, to receive ATOR-1017 in a 21-day cycle. Intra-patient dose escalation of ATOR-1017 is allowed depending on the occurrence of Dose-Limiting Toxicities (DLTs) during cycle 1. ATOR-1017 is administered intravenously as monotherapy every three weeks until unacceptable toxicity, progressive disease, or withdrawal of consent. The primary objectives of the study are to determine the maximum tolerated dose, assess adverse events (AEs), evaluate DLTs, and to determine the recommended phase 2 dose. Secondary objectives include pharmacokinetics (PK), immunogenicity, and clinical efficacy, assessed with CT scans using Immune Response Evaluation Criteria in Solid Tumors (iRECIST). Exploratory objectives include assessment of pharmacodynamic (PD) biomarkers. **Results:** 22 patients (18 females), median age 55 years (34-76) with solid tumors, previously treated with median of 4 (0-6) lines of chemotherapy and/or 2 (0-3) lines of immunotherapy, were included and received at least one cycle ATOR-1017. Nine dose levels have been evaluated; 0.38 mg, 1.5 mg, 5 mg, 15 mg; 40 mg, 100 mg, 200 mg, 360 mg, and 600 mg and dose escalation is ongoing. Treatment-related (TRAEs) were reported in 12 out of 22 patients (54.5%); most common (≥10%) were fatigue (13.6%) and neutropenia (13.6%). Five patients experienced a grade 3-4 TRAE; neutropenia (n = 2), febrile neutropenia (n = 1), chest pain (n = 1), increased liver enzymes (n = 1) and leukopenia/thrombocytopenia (n = 1). No patients discontinued due to TRAEs, no DLTs were observed, and the maximum tolerated dose has not been reached. The median time for patients in the study was 12 weeks (range 4-67). As per data cut-off, January 18, 2022, four patients remained on treatment and 18 patients had discontinued treatment. The reasons for discontinuation include confirmed disease progression (n = 10), clinical deterioration (n = 4), withdrawal of consent (n = 1), death due to disease progression (n = 3). Preliminary PK data showed dose-proportional kinetics. Dose-dependent increase in PD biomarkers demonstrated target-mediated biological activity and proof-of-mechanism. The best response was stable disease observed in a total of 10 patients (45%). **Conclusions:** ATOR-1017 is safe and well-tolerated at doses up to 600 mg and has shown biologic activity. No DLTs have been reported so far and dose escalation continues. Clinical trial information: NCT04144842. Research Sponsor: Alligator Bioscience.

2530 **Poster Session**

Novel platform for identifying multiple cancer-specific antigens. *First Author: Danielle Mor, Augusta University, Augusta, GA*

Background: Virtually all cancer treatments that kill cancer cells also adversely affect normal cells and often have debilitating side effects. A key challenge has been to identify antigens that are suitable for antibody-based targeted therapeutics. We have developed a novel platform to detect and identify multiple cell surface antigens that are unique to human cancers. **Methods:** Breast Cancer cells (Hs578T) or Melanoma cells (Hs895.T) were injected into rabbits to generate polyclonal xeno-antibodies. The resulting serum against each cancer was then incubated with normal cells of the same tissue type derived from the same patients; Breast Epithelium (matched-pair Hs578Bst) or Skin Fibroblasts (matched-pair Hs895.Sk) in order to absorb antibodies that cross-react with antigens on normal tissue (U.S. Patent Application No. 16/243,161). Flow cytometry was used for measuring the binding capacity of the unfiltered serum and filtered serum (lacking cross-reacting antibodies) on both the cancer cells and normal cells. Cytotoxicity assays were performed using a secondary ADC (anti-rabbit IgG specific antibody conjugated to MMAF), to determine the cytotoxicity of the unfiltered antibodies and filtered antibodies on normal and cancer cells. **Results:** Flow cytometry revealed, for antibodies against breast cancer, there was 90.3% and 88.6% binding to breast cancer cells and normal breast epithelial cells, respectively, pre-filtration; and 78.9% and 23% binding, respectively, post-filtration. For antibodies against melanoma, there was 89.2% and 86.6% binding to melanoma cells and normal skin fibroblasts, respectively, pre-filtration; and 55.1% and 0% binding, respectively, post-filtration. The Table summarizes the cytotoxicity of unfiltered and filtered antibodies on cancer cells and normal cells. Remarkably, there was preferential killing of all the cancer cells tested by both unfiltered and filtered antibodies, while there was no cytotoxicity in the normal cells using filtered antibodies. Cytotoxicity was also observed when antibodies generated against one type of cancer were incubated with other cancer types. **Conclusions:** This data suggests that our xeno-antibody based method can detect cancer-specific sites, not found on normal cells, and diverse cancer types may share a common antigenic signature. These findings are significant for identifying unique antigens on cancer cells and designing targeted therapies against cancer. Research Sponsor: Cancer Antibodies Inc.

Antibodies against:	Incubated with:	% Cytotoxicity with Unfiltered Antibodies	% Cytotoxicity with Filtered Antibodies
Breast Ca (Hs578T)	Breast Cancer (Hs578T)	93.8 ± 4.2	61.27 ± 11.33
	Normal Breast Epithelium (Hs578Bst)	87.1 ± 8.9	1 ± 1.6
	Breast Cancer (MDA-MB-231)	80.15 ± 2.150	79.5 ± 0.5
Melanoma (Hs895.T)	Melanoma (Hs895.T)	66.96 ± 7.775	59.02 ± 7.530
	Normal Skin Fibroblasts (Hs895.Sk)	21.87 ± 11.96	0
	PBMCs	0	0
	Prostate Ca (PC3)	19.83 ± 10.81	38.03 ± 6.894
	Prostate Ca (LNCaP)	77.85 ± 9.850	73.95 ± 15.35
	Prostate Ca (DU145)	52.93 ± 1.870	41.6 ± 7.308

2531 **Poster Session**

Phase I clinical trial of NEO-201, an anti-tumor-associated CEACAM-5/6 monoclonal antibody in solid tumors. *First Author: Christopher Cole, Women's Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD*

Background: NEO201 is a humanized IgG1 monoclonal antibody generated against tumor-associated antigens from colorectal cancer which binds specifically to tumor-associated CEACAM-5 and CEACAM-6 variants without binding CECAM 5/6 on normal epithelial tissues. NEO-201 reactivity is positive in the majority of adenocarcinomas including colon (85%), pancreas (86%), lung (79%), and breast (53%). Preclinical data showed that NEO-201 exerts anti-tumor activity through antibody dependent cellular cytotoxicity and complement dependent cytotoxicity. Here we present outcomes from a phase I trial of NEO-201 in advanced solid tumors (NCT03476681). **Methods:** This was a classic 3+3 dose escalation trial, with cohort expansion at the RP2D. NEO-201 was administered intravenously every two weeks in a 28-day cycle. The primary objective was to assess the MTD/RP2D of NEO-201 in patients with advanced solid tumors. The secondary objective was to assess the preliminary antitumor activity and exploratory objectives assessed pharmacokinetics and the effect of NEO-201 administration on immunologic parameters and possible relationships with response. Of 17 patients enrolled, 11 had colorectal, 4 had pancreatic and 2 had breast cancer. 4 patients received NEO-201 at dose level (DL) 1 (1 mg/kg), 6 patients at DL 1.5 (1.5 mg/kg) and 7 patients at dose DL 2 (2 mg/kg). **Results:** At the time of data cutoff, all patients had discontinued therapy. 11 of 14 evaluable patients discontinued due to disease progression and 3 patients discontinued due to DLT (grade 4 febrile neutropenia and prolonged neutropenia, each in 1/6 patients at DL2, and grade 3 febrile neutropenia in 1/6 patients at DL 1.5). Most common grade 3/4 toxicities were neutropenia (94%), white blood cell decrease (59%), lymphocyte decrease (29%), and febrile neutropenia (24%). Protocol was modified to allow administration of G-CSF and based on safety and PK data the RP2D was established as 1.5mg/Kg. Median number of doses received was 4.7. 13 subjects were able to undergo disease assessment after two cycles. The best response observed was stable disease (SD) in 5/9 evaluable patients with colorectal cancer. Minor CA-19-9 reductions were observed in two pancreatic cancer patients at DL 1.5. Correlative endpoints revealed that all patients enrolled in the trial expressed NEO-201 target antigen on their tumor tissue. Analysis of soluble factors in serum revealed that a high level of soluble MICA at baseline was correlated with a downregulation of NK cell activation markers and progressive disease. Unexpectedly, flow cytometry showed that NEO-201 also binds to circulating T regulatory cells and depleted these cells especially in patients with SD. **Conclusions:** NEO-201 was safe and well tolerated at the MTD of 1.5 mg/kg. Depletion of T regulatory cells suggests that the combination of NEO-201 with immune checkpoint inhibitor should be tested in future clinical trials. Clinical trial information: NCT03476681. Research Sponsor: U.S. National Institutes of Health.

2532 **Poster Session**

In-vivo reprogramming macrophages and dendritic cells with Allocetra-OTS: Successful mono- and combination-antitumor therapy. *First Author: Dror Mevorach, Hadassah Medical Center, Jerusalem, Israel*

Background: Chimeric antigen receptor (CAR) T cells can activate an immune response to a cancer-specific antigen but is less effective in solid tumors. Immune check point inhibitors (ICI) revolutionized the treatment of solid tumors, however, in many tumors only partial response is achieved. Here we questioned the role of synergistic effect of Allocetra-OTS (cellular therapy for in-vivo reprogramming macrophages and dendritic cells, Enlivex Therap.) on solid tumor progression. **Methods:** To follow tumor growth *in vivo*, HeLa-CD19 cells were stably transduced with pLenti-PGK-V5-Luc-Neo. For CAR preparation, fresh mononuclear cells (MNC) were transfected with CD19-CAR plasmids. For the intraperitoneal solid tumor model, SCID-Bg mice were injected intraperitoneally (IP) with human HeLa-CD19 or HeLa-CD19-luciferase cells, 10×10^6 allocetra-OTS or vehicle, and 10×10^6 CD19-CAR T cells or mock T cells. In an immune-competent model, Balb/c mice were treated IP with AB12 (mesothelioma) with pLenti-PGK-V5-Luc-Neo and treated with anti-CTLA4 with or without Allocetra-OTS. Mice were monitored daily for clinical signs and peritoneal fluid accumulation and weekly for tumor growth. Kaplan-Meier log rank test was done for survival. Peritoneal cells were evaluated using single cell analysis and flow cytometry. Tumors were examined for bacterial presence by immunohistochemistry staining with antilipoteichoic acid (LTA) and antilipopolysaccharide (LPS). For allocetra-OTS preparation, enriched mononuclear fractions were collected by leukapheresis from healthy eligible human donors and induced to undergo early apoptosis. **Results:** SCID mice survived 30±5 days (range 27–37) and were sacrificed or died from solid tumor in the peritoneal cavity after accumulation of bloody peritoneal fluid and clinical deterioration. Results were verified using IVIS of intraperitoneal HeLaCD19-Luc cells. CAR T cell therapy significantly ameliorated survival to 55±11 days ($p < 0.05$ vs MOCK) but Alloctra-OTS further ameliorated survival to 75±10 ($p < 0.001$) with 20-40% complete remission. In AB12 model, anti CTLA4 therapy significantly ameliorated survival from 26±5 to 38 ±9 days ($p < 0.05$). However, Allocetra-OTS monotherapy ameliorated survival to 45 ±12 days ($p < 0.02$) and combinational therapy to 75±9 days ($p < 0.0001$) with complete remission in 60-75% of mice. Single cell analysis revealed that restoration of large peritoneal macrophages (LPM), were associated with antitumor activity. **Conclusions:** During intraperitoneal tumor progression, allocetra-OTS as monotherapy or combinational therapy with CAR or anti-CTLA4 significantly reduced tumor size and enable complete remission in up to 75% treated mice. Based on excellent safety profile in > 30 patients treated for sepsis and Covid19, human phase I/II of allocetra-OTS plus ICI, for peritoneal metastases, is planned for 2022. Research Sponsor: Enlivex Ltd.

2533 **Poster Session**

A phase 1, first-in-human (FIH) study of the anti-HER2 CAR macrophage CT-0508 in subjects with HER2 overexpressing solid tumors. *First Author: Kim Anna Reiss, University of Pennsylvania Abramson Cancer Center, Philadelphia, PA*

Background: Most solid tumors are resistant to immunotherapy. In pre-clinical studies, CAR-M infiltrate tumors, phagocytose tumor cells, activate the tumor micro environment (TME), recruit T cells, and present tumor antigens to T cells leading to robust anti-tumor immunity. CT-0508 is a first in class CAR-M, comprised of autologous monocyte derived macrophages expressing an anti-HER2 CAR. Here we present preliminary clinical results from the CT-0508 Phase 1 FIH study. **Methods:** This multi-center, open-label study is evaluating CT-0508's safety, tolerability, and manufacturing feasibility in 18 participants (pts) with advanced solid tumors overexpressing HER2 who have progressed on prior therapies. Monocytes are isolated from mobilized apheresis products, differentiated into macrophages and engineered with an anti-HER2 CAR. Group 1 pts (n = 9) receive a fractionated dose (D1, D3, D5) and Group 2 pts (n = 9) receive the full dose on D1. CT-0508 is administered without preparative chemotherapy (bridging is permitted). Serial blood samples, 1 pre and 2 post-treatment biopsies are collected to investigate safety, pharmacokinetics and mechanism of action. **Results:** Seven pts (4F/3M), median age 64 (49-73), have been treated [breast (2), esophageal (2), cholangiocarcinoma, ovarian and parotid gland cancers]. A median of 3 (2-10) prior lines of therapy have been administered, most pts (85.7%) received prior anti HER2 therapy. CT-0508 was successfully manufactured with high viability, purity and CAR expression, and was well tolerated with no dose limiting toxicities or AEs leading to discontinuation or dose modification. Two related SAEs were reported in the same pt (Grade 1 CRS, hospitalized for monitoring and Grade 2 infusion reaction, resolved within 1h). Three other pts had Grade 1-2 CRS; resolved within 4d with no use of tocilizumab needed. There were no major organ toxicities and no on-target off-tumor toxicities. Post-infusion cytokines were transiently elevated in most pts and were self-limiting. Among the 4 pts who reached week 8, the best overall response was stable disease (n = 3) and 1 pt progressed, with a median follow up of 8w. CT-0508 rapidly egressed from peripheral blood. CT-0508 CAR mRNA was detected in all tumor biopsies of the first 2 pts. CT-0508 activated the TME, with increased myeloid cell activation, T cell infiltration, activation and proliferation. TCR sequencing demonstrated peripherally expanding T cells enriched for tumor infiltrating lymphocyte clones, suggesting expansion of tumor reactive T cells. Correlative data from additional pts will be presented. **Conclusions:** In 7 pts, CT-0508 was safe and feasible to manufacture. Early correlative data demonstrate trafficking, TME modulation, and potential induction of anti-tumor T cell immunity. The study is actively enrolling. Clinical trial information: NCT04660929. Research Sponsor: Carisma Therapeutics.

2535 **Poster Session**

Antitumor activity of T cells expressing a novel anti-folate receptor alpha (FOLR1) costimulatory antigen receptor (CoStAR) in a human xenograft murine solid tumor model and implications for in-human studies. *First Author: Owen R. Moon, Instil Bio, Inc., Dallas, TX*

Background: ITIL-306 is an autologous tumor-infiltrating lymphocyte (TIL) therapy that integrates T-cell receptor (TCR)-specific antigen recognition (Signal 1) with robust costimulation via the novel CoStAR transgene upon engagement with FOLR1 (Signal 2; Sukumaran, et al. *JITC.* 2021;9:198). Here, we assessed IL-2 independent effector function by anti-FOLR1 CoStAR T cells in vitro and evaluated activity in a novel, more representative murine solid tumor model. **Methods:** For in vitro studies, healthy donor T cells were manufactured to express anti-FOLR1 CoStAR or left nontransduced (NTD). Product cells were stimulated with a single (Day [D]0; ±IL-2) or serial (D0, 7, 14, 21; no IL-2) addition of target cells expressing membrane-anchored OKT3 (Signal 1) and FOLR1 (Signal 2). T-cell activation and proliferation were measured. For in vivo studies, the carcinoembryonic antigen (CEA)-positive (Signal 1) H508 cell line was engineered to express FOLR1 (Signal 2) and injected into 6 mice/group (D–21). NTD or healthy donor T cells expressing HLA-A*02-restricted anti-CEA TCR only, anti-FOLR1 CoStAR only, or dual TCR+CoStAR were given intravenously (D0), and compared with PBS control. Tumor growth, survival, and T-cell expansion were assessed in 2 donors to D96. **Results:** After single and serial stimulation, only anti-FOLR1 CoStAR T cells showed sustained proliferation without exogenous IL-2. PD-1 positivity was low (< 10%) on anti-FOLR1 T cells up to D24. In vivo, T-cell persistence on D14 was increased in dual TCR+CoStAR vs anti-CEA TCR only mice (P< .001) and all other groups (P< .01-.001). Tumor growth up to D58 was significantly lower in dual TCR+CoStAR (< .5 cm^3) vs all other groups (each > 2 cm^3; P< .0001). Survival was significantly longer in dual TCR+CoStAR (P< .01) vs all other groups; only dual TCR+CoStAR mice were alive at D58, with 5/6 alive at D96. The second donor showed similar tumor control irrespective of exogenous IL-2 in responder mice, with > 50% alive at D96, and robust T-cell expansion in dual TCR+CoStAR mice. **Conclusions:** When combined with TCR-specific binding, CoStAR significantly enhanced T-cell proliferation, persistence, and antitumor activity in vivo vs TCR alone, resulting in tumor control and prolonged survival. Effects were not observed with CoStAR alone, underscoring that signaling through CoStAR alone does not induce T-cell effector function. The sustained proliferation of anti-FOLR1 CoStAR T cells without exogenous IL-2 support in vitro and in vivo supports a clinical TIL regimen free of high-dose IL-2. These results suggest that CoStAR may improve the clinical performance and benefit/risk profile of TILs, whereby fewer toxicities are expected with the removal of post-TIL IL-2 support. This will be explored in an upcoming first-in-human clinical study with ITIL-306. Research Sponsor: Instil Bio, Inc.

2536 **Poster Session**

Efficacy and safety of autologous expanded tumor infiltrating lymphocytes (TILs) in multiple solid tumors. *First Author: Rodabe Navroze Amaria, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: TIL therapy has been used extensively in metastatic melanoma patients for many years, now with ongoing efforts to commercialize treatment. The efficacy of TIL outside of melanoma is largely unknown thus we designed and implemented a trial using TIL manufactured at a single academic center for treatment refractory metastatic colorectal (CRC), pancreas (PDAC) and ovarian (OVA) cancers. **Methods:** Patients with CRC, PDAC and OVA refractory to standard therapies with ECOG PS 0-1 and normal organ function were eligible for TIL harvest. Ex vivo TIL expansion and manufacturing was conducted at the MD Anderson TIL lab under conditions that included IL2 and 41BB stimulation (using urelumab). All patients received a lymphodepletion regimen consisting of cyclophosphamide 60mg/kg days -7 and -6 and fludarabine 25mg/m2 days -5 through day -1, followed by infusion of pooled *ex-vivo* expanded TIL. Patients received up to 6 doses of high dose IL-2 (600,000 IU/kg) after TIL infusion. The primary endpoint was evaluation of the objective response rate (ORR) using RECIST 1.1 criteria with secondary endpoints including disease control rate, duration of response, PFS, OS and safety. **Results:** A total of 17 patients underwent TIL harvest and 16 were treated on protocol; including 8 CRC, 5 PDAC and 3 OVA. Median age was 57.5 (range 33-70) and 50% were females. Median number of lines of prior therapy was 2 (range 1-8). Median number of TIL infused was 76 X 10^9 (range 20.3 x 10^9-150 x 10^9). Median doses of cyclophosphamide and fludarabine administered were 2 (range, 2-2) and 3 (range, 1-5), respectively. Median doses of IL-2 administered was 6 (range, 1-6). There were no responders. Best response included prolonged SD in a patient with PDAC lasting until 18 months. Grade 3 or higher toxicities attributable to therapy was seen in 14 subjects (87.5%; 95% CI: 61.7 – 98.4) with the majority of toxicities representing expected pancytopenia from lymphodepletion. Infusion product analysis showed the presence of effector memory cells with high expression of CD39 irrespective of tumor type. Early on-treatment biopsy of PDAC patient with prolonged SD showed presence of proliferating (KI67+) CD4+ and CD8+ TIL. **Conclusions:** Generation of TIL at a single academic center for CRC, PDAC and OVA is feasible and treatment is associated with no new safety signals. For these tumor types, further research is required to identify host factors associated with resistance to TIL therapy and optimize manufacturing processes to create more effective TIL cell therapy. Clinical trial information: NCT03610490. Research Sponsor: Iovance.

2537 **Poster Session**

Examination of mutation signature and mutation spectrum as predictors of response to immune checkpoint blockade therapy. *First Author: Danae Bowen, UC Riverside School of Medicine, Riverside, CA*

Background: In recent years, there has been promising progress in the use of immune checkpoint blockade (ICB) as a treatment for various cancer types such as lung, kidney, bladder, skin, colon, and breast cancer. In order for this modality to have increased success, more precise selection tools are needed to predict which patients will benefit from treatment. Tumor Mutational burden (TMB) has been implicated as a biomarker for ICB response due to the increased tumor immunogenicity present in high TMB samples. However, we hypothesize that the quality of mutations may also have an impact in determining immune response, rather than just the quantity of mutations alone. **Methods:** A retrospective analysis of 2041 patients across multiple solid tumor types was conducted using an open-access, open-source cancer genomics database (Gao, Sci Signal, 2013), with the goal of assessing the influence of mutational signature on patient response to ICB (including CTLA-4, PD-1, and PDL-1). Patient demographics, treatment variables/outcomes, and tumor variables, including mutation spectrum, and mutation count, were evaluated. A paired two sample test for means was used to analyze data with $p < 0.05$ considered statistically significant. Response outcomes were determined per RECIST v 1.1. **Results:** Our data demonstrate that mutational spectrum profiles show distinct patterns when considering response to ICB, independent of TMB. Patients with breast invasive ductal carcinoma who responded to ICB had less C > A mutations ($p = 0.020$) and more C > T mutations ($p = 0.017$) compared to non-responders. Lung adenocarcinoma responders had less C > T mutations ($p = 0.003$) and more C > A mutations ($p = 0.0003$) compared to non-responders. Furthermore, both head and neck squamous cell carcinoma and glioblastoma multiforme responders had more T > A mutations ($p = 0.047$ and $p = 0.011$, respectively) than non-responders. However, in other cancer types studied (urothelial, colon, renal, lung squamous, and melanoma), there were no obvious trends to distinguish responders from non-responders. Preferentially mutated gene targets were also considered for all 10 cancer types (including CARD11, SMARCA4, GLI1, PIK3R1, PTPRT, among others), many of which were also tied to the unique mutational signatures observed and which may be separately identified as novel ICB therapy targets. **Conclusions:** We found that specific mutation type may impact response to ICB in at least 4 cancer types, including breast, lung adenocarcinoma, head and neck squamous cell carcinoma and glioblastoma multiforme. Of note, this trend was not found in other cancer types which are typically found to have higher TMB. Moving away from solely considering the magnitude of mutations in tumor samples and towards identifying specific mutational signatures may aid in providing necessary specificity for selecting patients for ICB cancer therapy. Research Sponsor: The program above is funded through the following: National Cancer Institute R25 grant CA225513, the Concern Foundation for Cancer Research, and Tri Delta.

2538 **Poster Session**

Multicenter phase Ib trial in the U.S. of salvage CT041 CLDN18.2-specific chimeric antigen receptor T-cell therapy for patients with advanced gastric and pancreatic adenocarcinoma. *First Author: Gregory P. Botta, UCSD Moores Cancer Center, La Jolla, CA*

Background: Claudin 18.2 (CLDN18.2) is a highly selective cell lineage marker with limited expression in normal gastric tissues and significantly higher expression in primary gastric, pancreatic tumors and their metastases. Anti-CLDN18.2-targeted CAR T cells, termed CT041, were developed to evaluate tumor response and patient-reported outcomes in the gastric and pancreatic cancer. Preliminary results of the trial (NCT03874897) showed an objective response rate (ORR) of about 60% in gastric cancer from a non-Western population. Here we report the results of CT041 for metastatic gastric cancer after ≥ 2 prior lines of systemic therapy or pancreatic cancer ≥ 1 prior line from six centers in the United States. **Methods:** This single-arm, open-label, phase Ib study (NCT04404595) investigated autologous CT041 CAR T cells in patients with CLDN18.2 positive advanced gastric (including diffuse, signet-ring) or pancreatic adenocarcinoma. All patients completed a conditioning regimen consisting of fludarabine, cyclophosphamide, and nab-paclitaxel prior to CT041 CAR T cells. The primary objective was to assess the safety, efficacy and cytokinetic profile of CT041. Adverse Events (AEs) were graded according to CTCAE 5.0, and tumor response was assessed per RECIST 1.1. **Results:** As of February 15, 2022, 11 patients (5 gastric and 6 pancreatic) with a median of 2 prior lines of therapy (range 1- 4) were treated with CT041 at a dose between 2.5 and 4 x 10^8 cells. There were no dose limiting toxicities, treatment-related deaths, severe cytokine release syndrome (CRS), immune effector cell-associated neurologic syndrome (ICANS), or severe gastrointestinal (GI) related AEs. All CRS were grade 1 or 2. Only one patient received tocilizumab. No grade 4 AEs were observed except for hematologic toxicities related to conditioning. The first eight patients were evaluable for response by the date of data cut-off: 1 patient achieved a complete response after two CT041 doses (gastric), 2 had partial response (gastric), 2 had stable disease with tumor shrinkage (pancreatic) and 3 (pancreatic) had progression of disease after an initial biochemical response. ORR was 37.5% (3/8) in all patients including 100% (3/3) in the gastric subgroup (all ≥ 3 prior lines). The last three patients had not reached the time for response assessment. CAR T cell expansion correlated with ctDNA reduction. The median duration of response and the progression-free survival had not been reached. **Conclusions:** These preliminary results indicate that CT041 therapy was safe and had therapeutic efficacy in patients with advanced GI cancers. In heavily pre-treated gastric cancer, CT041 may have significantly improved anti-tumor activity compared to historical treatment regimens. Clinical trial information: NCT04404595. Research Sponsor: CARsgen.

2539 **Poster Session**

The addition of fludarabine to cyclophosphamide for lymphodepleting chemotherapy enhances the persistence of infused NY-ESO-1 TCR anticancer therapy TBI-1301. *First Author: Marcus O. Butler, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Adoptive transfer of T cell receptor (TCR) gene-engineered T cells can induce durable anti-cancer responses. TBI-1301 is a novel gene therapy produced by engineering autologous lymphocytes to express an NY-ESO-1-specific TCR using a retrovirus vector that encodes siRNA to silence endogenous TCR. In this study, we examined a repeat infusion of TBI-1301 and the addition of fludarabine to cyclophosphamide for pre-infusion lymphodepletion. **Methods:** Eligibility included informed consent, HLA-A*02:01 or A*02:06 haplotype, and NY-ESO-1 expression by IHC. Eligible patients underwent harvest of PBMC which were processed at the treating site to generate engineered TBI-1301 cells. The study design infused 5x10^9 cells on day 0 and day 14 to patients following lymphodepletion with cyclophosphamide (CY; 750 mg/m^2 on day -7 and -6) plus fludarabine (FLU; 30 mg/m^2 on day -7 and -6). Repeat infusions were performed in two cohorts: Cohort B - patients who had previously received NY-ESO-1 TCR-transduced cells and Cohort C - NY-ESO-1 TCR treatment naïve patients. Endpoints included safety, efficacy, and biological correlates for persistence of NY-ESO-1-specific T cells post infusion. **Results:** Ten patients were enrolled in cohorts B and C. Nine patients in total are evaluable for response and toxicity, and no DLTs have been observed. In cohort B, 5 patients (5 synovial sarcoma) were treated, and 5 have received the target dose. In cohort C, 5 patients (3 synovial sarcoma, 2 melanoma) were treated, and 4 have received the target dose. One patient received a single infusion due to bacteremia on week 2. One of 5 patients in cohort B was previously treated with TBI-1301 cells in cohort C. In each cohort, 4 patients experienced grade 1-2 cytokine release syndrome. Best overall response by RECIST v1.1 was 3 stable disease, and 2 progressive disease in cohort B; and 2 stable disease and 2 progressive disease in cohort C. When compared to the earlier cohort, biomarker analysis demonstrated substantially longer persistence of transferred TBI-1301 cells in infused patients who received fludarabine (up to 372+ and 460+ days), and the cells displayed a less differentiated phenotype. **Conclusions:** Repeat infusions of TBI-1301 following lymphodepletion appears to be safe and to possess anti-tumor activity. Addition of FLU to the lymphodepletion regimen may contribute to longer persistence of gene-engineered T cells. Clinical trial information: NCT02869217. Research Sponsor: Takara Bio, Other Foundation.

2540 **Poster Session**

Predictors of severe CRS in longitudinal CAR T-cell clinical trial data. *First Author: Caleb Strait, Acorn AI at Medidata, A Dassaults Systems company, New York, NY*

Background: Cytokine release syndrome (CRS) is a life-threatening toxicity of chimeric antigen receptor (CAR) T-cell therapy and there is a limited understanding of its risk factors. Known markers of severe CRS lack specificity or require central lab facilities, making them unsuitable for safety surveillance during trials. Using data from anti-CD19 CAR-T trials from the Medidata Enterprise Data Store (MEDS) we analyzed laboratory tests with repeated measurements to identify differences in trends that persist across a variety of study designs, sponsors and indications. Our aim was to capture the dynamic response to lymphodepletion (LD) and CAR-T infusion events in the time course values of laboratory markers and compare these in the severe CRS (grade 3 and higher) and non severe CRS groups. **Methods:** Subjects in the anti-CD19 CAR-T trials obtained from MEDS had relapsed or refractory disease in one of the following: B Acute Lymphoblastic Leukemia (B-ALL), Mantle Cell Lymphoma (MCL), Non-Hodgkin Lymphoma (NHL) and Diffuse Large B-cell Lymphoma (DLBCL). Laboratory markers with repeated measurements across all studies were included in the analysis. Response to LD, CAR-T infusion and the onset of hematologic recovery was modeled with piecewise linear splines with knots at the boundaries of the pre LD (-18d to LD), the LD - infusion and post infusion (1d to 6d and 6d to 18d) intervals using linear mixed effects regression. **Results:** The dataset consisted of 542 patients: 24.1% B-ALL, 44.4% NHL, 16.8% MCL, 14.6% DLBCL; mean age 54.8 (SE = 0.021) years, 67.7% males. 27.3% had CRS 3+ with a median time-to-event of 4.5 days. Average rates of change (units per day) for the severe CRS subjects in the pre LD, LD-infusion and post infusion intervals relative to the rest are shown (table). None of the markers had a significant relative rate of change prior to LD. The average change in Albumin, Platelets and Hematocrit was consistently lower in severe CRS patients. **Conclusions:** Longitudinal laboratory marker data may be used to derive predictors of severe CRS in patients undergoing anti-CD19 CAR-T therapy. While some of the laboratory markers discussed above corroborate earlier findings, modeling the pre and post infusion kinetics can yield novel markers with improved precision in severe CRS prediction and better patient safety. Research Sponsor: None.

PARAM	Pre LD (-18d - LD)	LD-Infusion (LD - 1d)	Post infusion (1d - 6d)	Post infusion (6d - 18d)
Albumin (g/L)	-14.15	-13.61 (p < 0.001)	-16.83 (p < 0.001)	-14.78 (p < 0.001)
Basophils/Leukocytes (%)	-1.28	-1.26	-1.36 (p = 0.04)	-1.29
Hematocrit (%)	-18.24	-18.97 (p = 0.01)	-18.79 (p = 0.02)	-19.28 (p = 0.005)
Hemoglobin (g/L)	-72.40	-73.71 (p = 0.02)	-73.09	-75.95 (p = 0.006)
Platelets (10 ^ 9/L)	-86.09	-83.15 (p = 0.02)	-94.86 (p < 0.001)	-88.07 (p = 0.002)
Leukocytes (10 ^ 9/L)	-0.73	-1.38 (p = 0.001)	-0.37	-1.09 (p = 0.03)

2541 **Poster Session**

STRIvE-01: Phase I study of EGFR806 CAR T-cell immunotherapy for recurrent/refractory solid tumors in children and young adults. *First Author: Catherine Michelle Albert, Seattle Children's Research Institute, Seattle, WA*

Background: The epidermal growth factor receptor (EGFR) is a cell surface tyrosine kinase receptor associated with cell proliferation and differentiation. EGFR expression and activating mutations are associated with aggressive neoplastic disease, chemotherapy resistance, and increased metastatic potential. Published data and EGFR immunohistochemistry (IHC) performed on tissue microarrays indicate that 15-40% of pediatric solid tumors (ST) express EGFR. The unique EGFR monoclonal antibody (mAb) 806 selectively binds to an epitope that is conformationally hidden when EGFR is tethered but revealed when tethering is perturbed as occurs with EGFR overexpression, truncation, or through extra-cellular domain missense mutations. **Methods:** Children and young adults (CYA) with EGFR-expressing recurrent/refractory (R/R) ST were enrolled on a Phase 1 trial to examine the safety and feasibility of administering autologous chimeric antigen receptor (CAR) T cells derived from autologous T cells genetically modified to express a second generation EGFR806-specific scFV-IgG4hinge-CD28tm/cyto-4-1-BB-zeta and EGFRt tracking/suicide contract. All subjects received lymphodepleting chemotherapy with fludarabine and cyclophosphamide prior to the administration of cryopreserved CAR T cells a the prescribed dose level. The biologically effective dose (BED) or maximum tolerated dose was determined based upon observed toxicity through day 28 from initial CAR-T infusion and using a 3+3 statistical design. **Results:** Eleven subjects (n=10 evaluable, age range 9-25, median 18) were enrolled and received either dose level (DL) 1 (0.5×10^6 CAR-T/kg, n=4) or DL2 (1×10^6 CAR-T cells/kg, n=7). CAR T were manufactured successfully in all subjects. Most common toxicities were fatigue, tumor-related pain and cytokine release syndrome (n=2, maximum CTCAE grade 1). Dose limiting toxicity of CTCAE grade 4 transaminase level and hyperbilirubinemia occurred at DL2 (n=1). Maximum circulating CAR-T expansion was 29.66 cells/uL (range 0.05-29.66 cells/uL) with median persistence of 28 days (range 0-90). Two subjects on DL1 and one subject on DL2 demonstrated mixed response on day 28 and tolerated additional CAR T infusion without dose limiting toxicity. **Conclusions:** EGFR806 directed CAR-T cells have an acceptable toxicity profile in CYA with R/RST and demonstrate anti-tumor activity in some patients. Additional analyses are ongoing to identify biomarkers of response and toxicity. Clinical trial information: NCT03618381. Research Sponsor: Seattle Children's Therapeutics.

2542 **Poster Session**

Development of B-cell maturation antigen (BCMA)-specific $CD8^+$ cytotoxic T lymphocytes using induced pluripotent stem cell technology for multiple myeloma. *First Author: Jooeun Bae, Dana Farber Cancer Institute, Boston, MA*

Background: A strategy for reversal of T cell exhaustion is reprograming of antigen-specific CTL to early lineage memory T cells with selective anti-tumor activities. To accomplish this goal, we epigenetically reprogrammed BCMA-specific $CD8^+$ CTL to a pluripotent state through key defined transcription factors, established "induced Pluripotent Stem Cells (iPSC)" exhibiting transcriptional and epigenetic features, re-differentiated them back into antigen-specific CTL and evaluated their properties and functional activities against multiple myeloma (MM). **Methods:** Functionally activeIFN-g producing HLA-A2 heteroclitic $BCMA_{72\text{-}80}$ (YLMFLLRKI)-specific $CD8^+$ CTL were applied for iPSC via transduction of four reprogramming factors (OCT3/4, SOX2, KLF4, c-MYC). Upon characterization of the BCMA-specific iPSC with high pluripotency potential, embryoid body was formed from the iPSC and further polarized into mesoderm layer development as evidenced by upregulation of transcriptional regulators (ABCA4, BMP10, CDH5, FOXF1, HAND1, PLVAP, SNAI2, TBX3). Next, BCMA-specific embryoid body-derived hematopoietic progenitor cells (HPC; $CD34^+$ $CD43^+$/$CD14^-$ $CD235a^-$) were sorted and induced to undergo T cell differentiation in the presence of Fc-DLL4 signaling and rectonectin. **Results:** Our RNAseq analyses demonstrated unique transcriptional profiles of HPC from different iPSC clones committing to $CD8^+$ T cells or other cell lineages (monocytes/granulocytes, B lymphocytes/NK cells). Principal component analyses demonstrated a high similarity and low variability of transcription profiles within the replicates of HPC committed to the same cell lineage. In addition, distinct genome-wide shifts and differential gene expression profiles were detected in HPC committed to each specific cell differentiation pathway. Specifically, the HPC commit to $CD8^+$ T cells utilized a diverse repertoire of modulators promoting development of T cell maturation, specific immune response regulation, memory T cells, cytotoxicity and interferon induction, which were significantly higher than shown in HPC that differentiate to other cell lineages. In parallel, specific repression genes were identified in the HPC commit to $CD8^+$ T cells, which develop TGF-β receptor, rearrangement of Ig heavy chain genes and inhibitory receptors. The T cells differentiated were mainly $CD45RO^+$ memory CTL and fully rejuvenated without immune checkpoints expression and regulatory T cells and with high anti-MM activities. **Conclusions:** These findings identify genetic and epigenetic mechanisms and regulatory elements, which play key roles during lineage specific commitment of HPC developed in iPSC into $CD8^+$ CTL and help to further design a next generation of regenerative medicine that provide the appropriate signals for T cell lineage commitment from progenitor cells. Research Sponsor: Donation.

2543 **Poster Session**

CD19/CD20 bispecific chimeric antigen receptor (CAR) in naïve/memory T cells for the treatment of relapsed or refractory non-Hodgkin lymphoma. *First Author: Sarah Marie Larson, University of California, Los Angeles, Los Angeles, CA*

Background: Although chimeric antigen receptor (CAR)-T cells produce impressive outcomes in B-cell malignancies, a substantial fraction of patients with relapsed/refractory B-cell leukemia and lymphoma treated with anti-CD19 CAR-T cell therapy (CART19) either do not respond to treatment or relapse, with poor CAR-T cell persistence or CD19 antigen escape being two key factors that limit durability of response. In order to address these factors, we initiated a clinical trial with naïve/memory T ($T_{N/MEM}$) cells engineered to express bispecific anti-CD19/CD20 CARs (CART19/20) (NCT04007029). **Methods:** This trial is a Phase 1, first-in-human, dose-escalation trial enrolling patients with relapsed or refractory follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle-cell lymphoma (MCL) and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Following lymphodepletion chemotherapy with fludarabine and cyclophosphamide, patients received CART19/20 cell doses ranging from 50×10^6 to 200×10^6 CAR-positive cells. The primary endpoint was to evaluate the safety of CART19/20 as measured by adverse events and dose limiting toxicities. Secondary endpoints were efficacy as assessed by disease response, progression-free survival (PFS), overall survival (OS), and CAR transgene persistence. **Results:** As of February 7, 2022, dose-escalation has been completed with 9 patients enrolled and 8 patients infused (3 FL, 4 DLBCL including 2 transformed follicular and 1 primary mediastinal B cell, and 1 MCL). with CART19/20 cells on this study. The median age at the time of CART19/20 infusion was 59 and median prior lines of therapy was 3.5. All patients had stage IV disease and 7 of 9 patients required bridging therapy. Grade-1 cytokine release syndrome (CRS) occurred in 6 of 8 patients, and no patient experienced immune effector cell-associated neurotoxicity syndrome (*ICANS*). Among all patients, only one dose of tocilizumab was administered to one subject, and no steroids were given. With a median follow-up of 12 months from time of CART19/20 infusion (range: 4+ to 24+ months), 7 of 8 of patients remain in a complete remission. Median PFS and OS were not reached, and all patients with a complete remission demonstrate ongoing B-cell aplasia. **Conclusions:** This study demonstrates that CART19/20 cells are safe and effective in patients with relapsed/refractory NHL and potentially obviates the challenges of the commonest causes of relapse after CAR-T cell therapy by means of modifying $T_{N/MEM}$ cells and dual-antigen targeting, respectively. Given the strong safety and response observed, dose escalation was completed with the second dosing level (DL2) of 200×10^6 CAR-positive cells, and DL1 of 50×10^6 CAR-positive cells was chosen as the therapeutic dose for future trial expansion. Clinical trial information: NCT04007029. Research Sponsor: Parker Institute for Cancer Immunotherapy, The Kaplan Family Foundation, UCLA.

2544 **Poster Session**

Changes in circulating tumor DNA (ctDNA) and outcomes in solid tumors treated with immune checkpoint inhibitors (ICIs). *First Author: Laith Al-Showbaki, Princess Margaret Cancer Care Centre, Toronto, ON, Canada*

Background: Quantification of ctDNA levels can be a reliable prognostic tool in several malignancies. More recently, detection of genomic alterations in ctDNA have been validated as a predictive biomarker to guide treatment planning. Dynamic changes in ctDNA levels over time and in response to treatment may also provide prognostic information. However, less is known about the value of changes to ctDNA levels in response to immune checkpoint inhibitors (ICIs). **Methods:** We searched MEDLINE (host:PubMed) and reviewed trials exploring outcomes of patients with advanced solid tumors receiving ICIs in which outcomes were reported based on changes to ctDNA levels. ctDNA clearance was defined as reported in individual trials. Typically, this was defined as either >50% reduction or a reduction to undetectable levels. We extracted progression free survival (PFS) and/or overall survival (OS) values, related 95% Confidence intervals (CI) and/or p-values. Data were then included in a meta-analysis utilizing the generic inverse variance and random effects model. Variation in effect size was examined using random effects meta-regression analysis. **Results:** A total of 17 trials were included in the meta-analysis; ctDNA levels were detectable in all participants in all studies prior to initiation of ICIs. Method of detection included next generation sequencing and/or droplet digital polymerase chain reaction assays . Overall, low to undetectable ctDNA levels, measured 6-16 weeks after starting treatment was associated with significantly better PFS, (HR 0.20 95% CI, 0.14-0.28; p<0.001). Similarly, OS was superior in patients with substantially reduced or undetectable ctDNA levels after receiving ICIs, (HR 0.18, 95% CI, 0.12-0.26; p<0.001. The results were consistent across all disease sites, lines of treatment, level of change (undetectable vs. >50% reduction) and whether treatment exposure comprised single or multiple ICIs (see Table). **Conclusions:** In unselected advanced solid tumors, a substantial fall in ctDNA levels in response to ICIs is associated with substantial improvements in both PFS and OS. ctDNA change is an early response biomarker which may allow for de-escalation of cross-sectional imaging in patients receiving ICIs, or support treatment de-escalation strategies. Further research is needed to quantify variations in sensitivity between the available NGS assays, as well as differences discovery range between assay platforms. Research Sponsor: None.

Subgroups/outcome	Hazard Ratio	95% CI	Subgroup difference P
All patients (overall survival)	0.18	0.12-0.26	NA
Disease site			
Melanoma	0.20	0.12-0.33	0.27
Lung	0.16	0.08-0.31	
Others	0.05	0.01-0.26	
Treatment			
Single agent	0.14	0.07-0.31	0.45
Multiple/mixed	0.20	0.12-0.32	
Treatment line			
First line	0.22	0.13-0.36	0.31
Second or later line	0.14	0.07-0.28	
Level of ctDNA change			
>= 50% reduction	0.17	0.05-0.62	0.93
Undetectable levels	0.18	0.12-0.27	

2545 **Poster Session**

Baseline peripheral T-cell composition in relation to radiographic phenotypes of immune-related pneumonitis. *First Author: Brian S. Henick, Columbia University Medical Center, New York, NY*

Background: Pneumonitis is one of the most morbid complications from immune checkpoint inhibitor (ICI) treatment, but pathogenic mechanisms are unclear and no biomarkers permit pre-treatment risk assessment. We sought to characterize peripheral T cell subsets of pneumonitis patients on the single cell level. **Methods:** Blood was collected before and during ICI treatment in 24 patients. Cells were processed for single cell RNA sequencing (scRNAseq) employing CITEseq methodology using multiplexed cell surface markers labelled with a cocktail of oligonucleotide-tagged Total-Seq anti-human antibodies against CD4, CD8, CD45RA and CD27 followed by Chromium 10X sequencing. Principal Component Analysis was performed with iCellR, K-nearest-neighbor-based Network graph drawing Layout, and PhenoGraph clustering to assign cell types. CT scans were performed per standard of care and were reviewed by an experienced thoracic radiologist. **Results:** Seven of 24 patients developed pneumonitis; 9 did not experience an immune-related adverse event, and the remainder experienced arthritis (4), thyroiditis (3), or neurotoxicity (1). Pneumonitis patients had expanded proportions of TH2 $TCF7^+$ T cells at baseline as compared to the other patients. Radiographically, two patients' pneumonitis manifested as Chronic Hypersensitivity Pneumonitis (CHP), and four had Organized Pneumonia (OP). At baseline, CHP patients had significantly lower levels of $CD8^+$ TCM cells (CXCR3+), double-positive T cells, gamma-delta T cells, and higher levels of naïve-like $CD4^+$ TN $TCF7^+LEF1^+$ and $CD4^+$ TH1/2 $CXCR3^+GATA3^+$ cells compared to OP. Gene expression levels also distinguished between these radiographic phenotypes. **Conclusions:** The peripheral T cell composition of patients who developed pneumonitis was distinct from those who did not in our cohort and unique by radiographic manifestation, suggesting potential pathogenic mechanisms and a prelude to circulating predictive markers of ICI toxicity. Research Sponsor: U.S. National Institutes of Health.

2546 **Poster Session**

Early circulating tumor DNA (ctDNA) kinetics using a tumor-naïve assay as a predictive biomarker in early-phase immunotherapy (IO) clinical trials. *First Author: Enrique Sanz Garcia, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: ctDNA kinetics with tumor-informed assays can predict treatment outcome in patients (pts) treated with anti-PD1 IO (*Bratman et al*, Nature Cancer 2020). We evaluated whether early ctDNA kinetics with a tumor-naïve assay were associated with clinical outcomes in advanced solid tumor patients treated on early phase IO trials. **Methods:** Advanced solid tumor pts treated with investigational IO agents at the Princess Margaret Phase I program were enrolled. Baseline (B) and pre-cycle 2 (C2) (3-4 weeks after first dose) plasma samples were prospectively collected via an institutional liquid biopsy program (LIBERATE, NCT03702309). ctDNA was assessed using the tumor-naïve 425-gene Geneseeq Prime panel in a clinical laboratory. Mutations in each gene detected in ctDNA were measured as Variant Allele Fraction (VAF). Mean VAF from all mutations was calculated. Radiological response was measured per RECIST criteria and correlated using ROC curves. Hyperprogression (HPD) was defined using VHIO criteria (*Matos et al*, CCR 2020). Survival outcomes were estimated using the Kaplan Meier method. **Results:** From 12/2017 to 3/2020, 162 plasma samples from 81 pts with 25 different tumor types were collected. Pts were treated within 25 different IO phase I/II trials, 72% of which involved a PD-1/PD-L1 inhibitor. Median age was 58y (range 21 – 79), 54% female, 76% ECOG1. Sarcoma and colorectal (11%, each) followed by breast (8%) and melanoma (7%) were the most frequent tumors. Median follow up was 10.3 months (m) (1.8-46.9). CR 4% (n = 3), PR 6% (n = 5), HPD 11% (n = 9). Clinical benefit (CB) rate (CR+PR+SD > 6 months) was 20% (n = 16). ctDNA was detected in 122/162 samples (75.3%) (60 at B, 62 at C2). The most frequent mutations were *TP53* (32%), *PI3KCA* (12%), *PKHD1* (11%), and *KRAS* (9%). Mean VAF at B below median was not associated with OS (HR = 0.68 95%CI 0.4-1.16; p = 0.16) or PFS (HR = 0.93 95%CI 0.56-1.54; p = 0.77). Mean VAF change (difference between mean VAF at B and at C2) was associated with response (AUC = 0.99) and CB (AUC = 0.86). A decrease in mean VAF from B to C2 was seen in 24 pts (37.5%) and was associated with longer PFS (median PFS 2.7 vs 1.8 m; HR: 0.43, 95%CI 0.24-0.77; p < 0.01) and OS (median OS 10.8 vs 9.1 m; HR: 0.54; 95%CI 0.3-0.96; p = 0.03) compared to an increase in mean VAF. These differences were more marked if there was > 50% decrease in mean VAF from B to C2 (n = 11, 17%) compared to decrease < 50% or increase: median PFS 3.6 vs 1.8 m (HR: 0.29, 95%CI 0.13-0.62; p < 0.01) and median OS not reached vs 9.6 m (HR: 0.23, 95%CI 0.09-0.6; p < 0.01). No differences in mean VAF change were seen between HPD and PD pts. **Conclusions:** In a pan-cancer solid tumor early phase trial IO cohort, a decrease in ctDNA within 4 weeks of treatment was associated with increased CB, OS and PFS. HPD pts did not show greater increases in ctDNA. Tumor-naïve ctDNA assays may be useful to identify early treatment benefit in phase I/II trials with IO. Research Sponsor: Princess Margaret Cancer Centre, Pharmaceutical/Biotech Company.

2547 **Poster Session**

Pharmacogenomic prediction of immune-related adverse events from immune checkpoint inhibitors among Asian patients. *First Author: Yiqing Huang, Department of Haematology Oncology, National University Cancer Institute Singapore, Singapore, Singapore*

Background: Immune checkpoint inhibitors (ICIs) have ushered in a unique entity known as immune-related adverse events (IrAEs) that can be debilitating and challenging for physicians. Given that genomic variation underlies both disease susceptibility and drug response, there is reasonable cause to believe that genomic markers are predictive of IrAEs. We perform a pioneering pharmacogenomic study to uncover genomic biomarkers associated with IrAEs from ICIs. **Methods:** Since March 2018, we recruited cancer patients treated with ICIs from the National University Cancer Institute Singapore and Tan Tock Seng Hospital. IrAEs were clinical characterized and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5. DNA was extracted and genotyped by Infinium Global Screening Array (700K markers). Statistical analyses were performed using SVS/HelixTree. Genetic association was performed by logistic regression. Bonferroni corrected $P < 7.1E-08$ was considered statistically significant. **Results:** We conducted a pilot pharmacogenomic genome-wide association study (GWAS) on 307 patients of Asian Ancestry. Median age was 62. Majority were male (68.1%), Chinese (75.9%), ECOG PS 0-1 (91.6%), stage IV cancer at diagnosis (64.6%). Non-small cell lung cancer (36.2%), renal cell carcinoma (12.4%) and hepatocellular carcinoma (7.2%) were the three most common cancers. Top four ICIs used were pembrolizumab, nivolumab, atezolizumab and durvalumab, respectively (44.6%, 26.1%, 10.1% and 10.1% respectively). Nine percent of patients received dual ICIs concurrently. Median duration of treatment was 152 days and median follow up was 212 days. IrAEs were seen in 50.5% of patients. Skin (21.8%), endocrine (6.8%) and hepatotoxicity (5.9%) were the most common IrAEs. Eight percent of patients had CTCAEv5 grade ≥3 toxicity, of which hepatotoxicity (2.6%), skin (1.6%) and pulmonary toxicities (1.3%) were the most common. A preliminary pharmacogenomic investigation revealed one potential novel genetic locus associated with IrAEs: *LOC105373202* rs5915369; Unadjusted P= 6.6E-08, OR (95%CI) = 27.8 (3.7-206.5), minor allele = A, 10.7% in cases vs 0.4% in controls. We also identified an additional 3 independent SNPs (rs167609, rs2341687, *DMD*rs5928214) with nominal significance ($7.1E-0-8 \leq P < 5.0E-7$). **Conclusions:** This pilot pharmacogenomics GWAS uncovered 4 potential novel genetic loci predictive of IrAEs from ICIs amongst Asian patients. Further pharmacogenomic discovery/replication and functional validation studies are currently onongoing to identify specific genomic biomarkers that predispose individual patients to IrAEs. Research Sponsor: National Research Foundation, Singapore and National Medical Research Council (NMRC), Singapore under its NMRC Centre Grant Programme (NMRC/CG/M005/2017_NCIS).

2548 **Poster Session**

Circulating *KRAS* variant-specific shedding and association with survival in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) receiving chemoimmunotherapy. *First Author: Jacob E. Till, University of Pennsylvania Abramson Cancer Center, Philadelphia, PA*

Background: Circulating tumor DNA (ctDNA) is increasingly used as a prognostic marker with high ctDNA shedding associated with poor survival. Gene-, but not variant-specific, differences in ctDNA shedding have been reported. Tumor burden, mitotic rate, and cell death rate have been proposed as contributors to ctDNA shedding. Here we investigate associations of ctDNA shedding for the two most common mPDAC *KRAS* variants, G12D and G12V, with tumor burden, mitotic score, and overall survival (OS). **Methods:** Pretreatment (baseline) ctDNA was analyzed by droplet digital PCR for 86 (including 44 G12D, 30 G12V) patients with mPDAC receiving front-line chemoimmunotherapy in a randomized open-label Phase II study (NCT03214250). Baseline tumor burden in total, within the pancreas, and distally, was assessed by sum of RECIST target lesion diameters. Tumor tissue variant allele fraction (tVAF) and mitotic score (geometric mean expression of 65 mitosis-associated genes) were calculated from DNA and RNA sequencing. **Results:** ctKRAS shedding (dichotomized at median mutant copies/mL) was associated with OS for G12D bearing tumors (p = 0.03) but not G12V (p = 0.17, log-rank test). To identify variant-specific features of shedding, we examined the Spearman correlation for total tumor burden and ctKRAS shedding; G12D but not G12V shedding was correlated with tumor burden (p = 0.01 and p = 0.22 respectively). However, the higher tVAF in G12V compared to G12D tumors (p = 0.048, Mann-Whitney test) could result from differences in purity, ploidy, and *KRAS* copy number. Thus, we used tVAF as a scalar to calculate an adjusted tumor burden which was significantly correlated with both G12D and G12V ctDNA shedding (p = 0.004 and 0.02, respectively). When a patient's distal vs. pancreatic lesions were analyzed separately, pancreatic tumor burden was not correlated with G12D or G12V shedding (p = 0.10 and 0.33, respectively) but distal burden was correlated with both (p = 0.001 and 0.02, respectively). While there was no difference by *KRAS* variant for the correlation between adjusted tumor burden and shedding, these results do suggest that, in patients with mPDAC, distal rather than primary tumor burden may drive ctDNA shedding. Finally, tumor mitotic rate was combined with adjusted total tumor burden in a linear regression model; both were significant for predicting G12D shedding (p = 0.007 and p < 0.0001, respectively) but not for G12V (p = 0.045 and p = 0.16, respectively). **Conclusions:** These data suggest that ctDNA shedding and survival associations may be *KRAS* variant-specific in mPDAC. Tumor mitotic score and location of tumors may explain some variant-specific differences in shedding. As clinical ctDNA tests become more widely used, further investigation of variant-specific shedding in *KRAS* and other genes may be key for proper interpretation of ctDNA tests. Research Sponsor: Parker Institute for Cancer Immunotherapy, Other Foundation, Pharmaceutical/Biotech Company.

2549 **Poster Session**

Circulating cytokines as predictors of response to immune checkpoint inhibitors (ICIs) in patients (pts) with melanoma (Mel) and non–small cell lung cancer (NSCLC). *First Author: Giulia Pasello, Medical Oncology 2, Istituto Oncologico Veneto IOV-IRCCS, Department of Surgery, Oncology and Gastroenterology, University of Padova, Padua, Italy*

Background: ICIs lead to durable response and a significant survival improvement in a limited number of advanced stage Mel and NSCLC pts. The identification of predictive circulating biomarkers could be a promising tool to optimize pts' selection and outcome for ICIs treatment. **Methods:** This is a prospective real-world study enrolling advanced stage Mel and NSCLC pts referred to four Italian Centers and treated with ICIs. The primary endpoint is to verify the presence of an association between circulating cytokines (IL-1b, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, TNFα, GM-CSF) and disease control rate (DCR), progression free survival (PFS) and overall survival (OS). Pts undergo a blood collection, before every cycle for 6 cycles (T1-T6) and at tumor assessment till disease progression (PD) or for 2 years. Biomarker levels were assessed by Luminex xMAP based technology using R&D High Sensitivity kits. Each marker was categorized according to high and low levels by maximizing its discriminative ability, and the association with the outcome was tested in univariate and multiple analyses. **Results:** We report preliminary results on the T1-T2 blood samples from the first 78 enrolled pts (32 females/46 males; 43 Mel/35 NSCLC; median age 69 years). Serum IL-6, IL-8 and IL-10 were significantly higher at T1 and T2 in pts with PD (Kruskal-Wallis test). The median relative increase (RI) of IL-8 was 32% and 2% in pts with PD and disease control (DC), respectively (p = 0.0001). At multiple logistic analysis, IL-6 and IL-8 at T2 and the RI of IL-8 were independent factors predicting the probability of DC, with an overall accuracy of 83.8%. High levels of IL-6 and IL-8 at T2 were significantly associated with a low probability of DC (OR = 0.13, 95%CI: 0.03-0.52 and OR = 0.09, 95%CI: 0.02-0.37, respectively), and the RI showed a significantly lower probability of DC (OR = 0.14, 95%CI: 0.02-0.58). With a median follow-up of 10.6 months (m), mPFS and mOS were 5.8 m, 95%CI: 2.3-7.4 and 8.3 m, 95%CI: 4.0-13.8 for NSCLC; 6.9 m, 95%CI: 2.8-15.9 and 12.6 m, 95%CI: 4.7-NE for Mel pts, respectively. In the multiple Cox model, elevated IL-6 and IL-8 at T1 (HR = 3.03, 95%CI: 1.55-6.37, HR = 2.86, 95%CI: 1.46-5.63), elevated IL-10 at T2 (HR = 2.86, 95%CI: 1.39-5.94), and a RI of IL-8 (HR = 4.22, 95%CI: 1.85-11.21) remained significantly associated with a worse PFS. Higher levels of IL-6 (HR = 3.85, 95%CI: 1.13-20.0) and IL-8 (HR = 4.29, 95%CI: 1.98-9.83) at T2 and a RI of IL-8 (HR = 3.06, 95%CI: 1.43-6.72) remained significantly associated with a worse OS. **Conclusions:** High serum levels of IL-8 and IL-6 at T2 of ICI, combined with an increase of IL-8 from baseline, are strong predictors of PD, PFS, OS, in pts with advanced Mel and NSCLC. The role of the other cytokines tested, their time fluctuations and associations with clinical prognostic factors, gender, and immuno-related adverse events will be presented at the meeting. Research Sponsor: RF-2018-12367604 MoH; 2018 5x1000 Istituto Oncologico Veneto.

2550 **Poster Session**

Methylated circulating tumor DNA (cfMeDIP) as a predictive biomarker of clinical outcome in pan-cancer patients (pts) treated with pembrolizumab (P). *First Author: Enrique Sanz Garcia, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Bespoke mutation-based circulating tumor DNA (ctDNA) predicts response to P but relies on availability of tumor tissue and presence of mutations. Cell-free methylated immunoprecipitation and high-throughput sequencing (cfMeDIP-seq) may overcome these limitations and be applied to more pts. **Methods:** Pts with mixed solid tumors divided into 5 cohorts received P 200 mg Q3wks in the investigator-initiated INSPIRE trial (NCT02644369). cfMeDIP-seq was performed at baseline (B), pre cycle 3 (C3) and later cycles. Methylation probability was inferred from read depths in 300 bp bins. cfMeDIP score was the probability-weighted sum of 3270 pan-cancer differentially-methylated regions in the TCGA PanCanAtlas. ctDNA concentration was assayed using tissue-informed bespoke targeted NGS (Signatera). ΔctDNA and ΔcfMeDIP denote the change in ctDNA or cfMeDIP between B and C3, respectively. Association with OS or PFS was assessed using Cox proportional hazards model, adjusting for cohort (aHR). Multivariable analysis (MVA) also included tumor mutation burden and PD-L1 status. **Results:** 194 plasma samples from 87 pts were analysed with cfMeDIP-seq (84 at B, 55 at C3, 55 at later cycles). Demographics: male 33%; median age = 61 yrs (34–82); Cohorts: triple negative breast (26%), ovarian (25%), head & neck (21%), melanoma (12%), others (15%). Median follow-up = 10.6m (0.6–64.4); Median PFS = 1.9m; Median OS = 10.6m. cfMeDIP at B below median was associated with better OS (aHR = 0.51, 95%CI 0.29-0.91; p = 0.02) in MVA. ΔcfMeDIP was evaluable in 53 pts; any decrease in ΔcfMeDIP was predictive for OS (aHR = 0.36, 95%CI 0.18-0.72; p < 0.01) and PFS (aHR = 0.42, 95%CI 0.22-0.82; p = 0.01). Both ΔctDNA and ΔcfMeDIP were evaluable in 51 pts; decrease in ΔctDNA and ΔcfMeDIP predicted for longer OS (aHR = 0.45, 95%CI 0.23-0.86; p = 0.02 vs aHR = 0.39, 95%CI 0.19-0.80; p = 0.01); and PFS (aHR = 0.44, 95%CI 0.23-0.83; p = 0.01 vs aHR = 0.5, 95%CI 0.25-0.99; p = 0.04), respectively. When both ΔctDNA and ΔcfMeDIP are integrated in MVA, ΔcfMeDIP was predictive for OS (aHR = 0.48, 95%CI 0.23-1; p = 0.05). A decrease in ΔcfMeDIP and/or ΔctDNA was associated with longer OS (aHR = 0.2, 95%CI 0.09-0.45) and PFS (aHR = 0.27, 95%CI 0.13-0.58) compared to an increase in both assays (p < 0.01) (Table). **Conclusions:** We applied for the first time cfMeDIP-seq and mutation-based ctDNA analysis concurrently in pan-cancer pts treated with checkpoint blockade. ΔcfMeDIP correlated strongly with OS and PFS, representing a promising plasma-based predictive epigenetic biomarker in pts treated with P. ΔctDNA and ΔcfMeDIP can complement each other to predict outcomes, demonstrating that they may capture different biological changes. Clinical trial information: NCT02644369. Research Sponsor: BMO Chair in precision cancer genomics, Pharmaceutical/Biotech Company.

Group	OS-12m (%) (95%CI)
$\downarrow\Delta$ctDNA $\downarrow\Delta$cfMeDIP (n = 16)	87.5 (72.7-100)
$\downarrow\Delta$ctDNA $\uparrow\Delta$cfMeDIP (n = 10)	70 (46.6-100)
$\uparrow\Delta$ctDNA $\downarrow\Delta$cfMeDIP (n = 8)	62.5 (36.5-100)
$\uparrow\Delta$ctDNA $\uparrow\Delta$cfMeDIP (n = 17)	29.4 (14.1-61.4)

2551 **Poster Session**

The FLARE score, circulating neutrophils, and association with COVID-19 outcomes in patients with solid tumors. *First Author: Elia Seguí, Medical Oncology, Hospital Clínic de Barcelona, Spain, Barcelona, Spain*

Background: Inflammation and neutrophils play a central role in severe Covid-19 disease. In previous data, we showed that the FLARE score, combining both tumor and Covid-19-induced proinflammatory status (proinflam-status), predicts early mortality in cancer patients (pts) with Covid-19 infection. We aimed to assess the impact of this score in a larger cohort and characterize the immunophenotype (IF) of circulating neutrophils. **Methods:** Multicenter retrospective cohort (RC) of pts with cancer and Covid-19 infection across 14 international centers. Circulating inflammatory markers were collected at two timepoints: baseline (-15 to -45d before Covid-19 diagnosis) and Covid-19 diagnosis. Tumor-induced proinflam-status was defined by high dNLR (neutrophils/(leucocytes-neutrophils)>3) at baseline. Covid-19-induced proinflam-status was defined by +100% increase of dNLR between both timepoints. We built the FLARE score combining both Tumor and Infection-induced inflammation: T+/I+ (poor), if both proinflam-status; T+/I- (T-only), if inflammation only due to tumor; T-/I+ (I-only), if inflammation only due to Covid; T-/I- (favorable), if no proinflam-status. The IF of circulating neutrophils by flow cytometry was determined in a unicenter prospective cohort (PC) of pts with cancer during Covid-19 infection and in healthy volunteers (HV). Primary endpoint was 30-day mortality. **Results:** 524 pts were enrolled in the RC with a median follow-up of 84d (95%CI 78-90). Median age was 69 (range 35-98), 52% were male and 78% had baseline PS <1.Thoracic cancers were the most common (26%). 70% had active disease, 51% advanced stage and 57% were under systemic therapy. dNLR was high in 25% at baseline *vs* 55% at Covid-19 diagnosis. The median dNLR increase between both timepoints was +70% (IQR: 0-349%); 42% had +100% increase of dNLR. Pts distribution and mortality across FLARE groups is resumed in the Table. Overall mortality rate was 26%. In multivariate analysis, including gender, stage and PS, the FLARE poor group was independently associated with 30-day mortality [OR 5.27; 1.37-20.3]. 44 pts were enrolled in the PC. Median circulating neutrophils were higher in pts with cancer (n=10, 56.7% [IQR: 39-78.4%]) vs HV (n=6, 35.8% [IQR: 25.6-21%]), and particularly higher in pts with cancer and severe Covid-19 infection (n=7, 88.6% [IQR: 80.9-94%] (p=0.003). A more comprehensive characterization of the IF of circulating neutrophils, including Lox1/CD62/CD64, will be presented at ASCO. **Conclusions**: The FLARE score, combining tumor and Covid-19-induced proinflam-status, can identify the population at higher risk for mortality. A better characterization of circulating neutrophils may help improve the prediction of Covid-19 outcomes in pts with cancer. Research Sponsor: AMGEN.

	Distribution	30d mortality	
FLARE T+/I+	5% (n=19)	68%	p=0.001
FLARE T+/I-	20% (n=74)	39%	
FLARE T-/I+	37% (n=136)	33%	
FLARE T-/I-	38% (n=140)	3%	

2552 **Poster Session**

NK cell activity and methylated HOXA9 circulating tumor DNA as prognostic biomarkers in patients with non-small cell lung cancer treated with PD-1/PD-L1 inhibitors. *First Author: Sara Witting Christensen Wen, Department of Oncology, Vejle Hospital, University Hospital of Southern Denmark, Vejle, Denmark*

Background: PD-1/PD-L1 inhibitors have improved survival for patients with non-small cell lung cancer (NSCLC), but better prognostic biomarkers are needed. **Methods:** We prospectively collected plasma from 82 patients with NSCLC before initiating treatment with PD-1/PD-L1 inhibitors and before treatment cycles 2-4. We used the NK Vue assay to measure interferon gamma (IFNγ) as a surrogate for natural killer cell activity (NKA) with a cutoff of 250 pg/mL. Circulating tumor DNA (ctDNA) in the form of methylated HOXA9 was measured by droplet digital PCR. ctDNA status was classified as detectable or undetectable ctDNA. **Results:** Patients were classified into three groups according to IFNγ levels at the available time points. The NKA-low group had a persistently low level of IFNγ or dropped to and remained at a low level after baseline (<250 pg/mL, n=29), the NKA-mixed group experienced either an increase from low to normal levels or vice versa (n=34), while the NKA-high group maintained a normal level of IFNγ (≥250 pg/mL, n=13). The median PFS was 64 days (95% confidence interval (CI) 48-115 days), 228 days (95% CI 146-353 days), and 214 days (95% CI 101-693 days), respectively, for NKA-low, NKA-mixed, and NKA-high (p=0.003). The median OS was 170 days (95% CI 110-285 days), 487 days (95% CI 361-761 days), and 1,131 days (95% CI 235 days to not reached), respectively (p<0.001). Patients were divided according to detectable (ctDNA+, n=41) or undetectable (ctDNA-, n=32) ctDNA after one treatment cycle. Median PFS was 97 days (95% CI 58-192 days) and 228 days (95% CI 146-353 days), respectively, for ctDNA+ and ctDNA- (p=0.018). Median OS was 235 days (95% CI 170-525 days) and 544 days (95% CI 361-1158 days), respectively (p=0.007). A score combining NKA and ctDNA both measured after the first treatment cycle had a strong prognostic impact. Group 1 had a low level of IFNγ (<250 pg/mL) and detectable ctDNA (n=27), group 2 had either low levels of IFNγ and undetectable ctDNA or vice versa (n=29), and group 3 had normal levels of IFNγ (≥250 pg/mL) and undetectable ctDNA (n=15). Median PFS was 69 days (95% CI 48-213 days), 183 days (95% CI 102-235 days), and 307 days (95% CI 140-693 days), respectively, for group 1, 2, and 3 (p=0.022). Median OS was 221 days (95% CI 121-539 days), 419 days (95% CI 235-650 days), and 1,158 days (95% CI 250 days to not reached), respectively (p=0.002). Biomarker score 1 was a marker of poor prognosis for OS with a hazard ratio (HR) of 3.971 (95% CI 1.763-8.943, p=0.001) compared to biomarker score 3. It remained statistically significant with a HR of 5.560 (95% CI 2.359-13.101, n=71, p<0.001) when adjusting for PD-L1 status, histology, and performance status. **Conclusions:** A biomarker score combining the levels of NKA and ctDNA status after the first cycle of treatment may be used to stratify the prognosis in patients with NSCLC treated with PD-1/PD-L1 inhibitors. Research Sponsor: Dansk Kræftforskningsfond / Danish Cancer Research Fund, Other Foundation, Pharmaceutical/Biotech Company, Grants within the Department of Oncology, Vejle Hospital.

2553 **Poster Session**

Network analysis to determine association between immuno-related toxicities and immune soluble profile in patients treated with anti–PD-1. *First Author: Andrea Botticelli, Department of Radiological, Oncological and Anatomo-Pathological Science, "Sapienza" University of Rome, Rome, Italy*

Background: Immune checkpoint inhibitors (ICIs) have peculiar, immune-related adverse events (irAEs), as a consequence of interfering with self-tolerance mechanisms. The incidence of irAEs varies by ICI class, administered dose and treatment schedule. The aim of the study was to define a baseline (T0) immune profile (IP) predictive of irAE development. **Methods:** A prospective, multicenter study evaluating the IP of 79 patients with advanced cancer, treated with anti-PD-1drugs as a first- or second-line setting was performed. The results were then correlated with irAEs onset. The IP was studied by means of multiplex assay, evaluating circulating concentration of 12 cytokines, 5 chemokines, 13 soluble immune checkpoints and 3 adhesion molecules. IDO levels were evaluated through a modified liquid chromatography–tandem mass spectrometry. Data were first pre-processed by performing logarithmic transformation and Shapiro-Wilk-test. A connectivity heatmap was obtained by calculating Spearman correlation coefficients. Two different networks of connectivity were constructed, based on the toxicity profile. **Results:** Toxicity was predominantly of low/moderate grade. High-grade irAEs were relatively rare, while cumulative toxicity was high (23%). A positive and statistically significant correlation between the cumulative toxicity and IP10 and IL8, sLAG3, sPDL-2 sHEVM, sCD137, sCD27 and sICAM1 was found. Moreover, patients who experienced irAEs had a markedly different connectivity pattern characterized by disruption of most of the paired connections between cytokines (all the connections of the cytokine IL8, most of the connections between the pro-inflammatory chemokines, or all the connections of CD137, CD27, and CD28), while sPDL-2 pair-wise connectivity values seemed to be intensified. Network connectivity analysis identified a total of 187 statistically significant interactions in patients without toxicity and a total of 126 interactions in patients with toxicity. Ninety-eight interactions were common to both networks, while 29 were specifically observed in patients with toxicity. **Conclusions:** A peculiar pattern of immune dysregulation in patients who develop irAEs was defined. This immune serological profile could lead to the design of a personalized therapeutic strategy in order to prevent, monitor and treat irAEs at an early stage. Research Sponsor: None.

2554 **Poster Session**

Auto-reactive antibodies as predictive markers for immune checkpoint–induced pneumonitis. *First Author: Mehmet Altan, MD Anderson Cancer Center, Houston, TX*

Background: Certain immune-related adverse events (irAEs) that emerge with immune checkpoint blockade share clinical features of autoimmune conditions. Preexisting auto-reactive antibodies and their contribution to irAEs have not been well defined, and observations are limited. **Methods:** We longitudinally collected patient plasma samples from a clinical trial that combines immune checkpoint inhibitors, Ipilimumab, and Nivolumab (I+N) with subsequent radiation therapy (Lonestar, NCT03391869). Plasma samples were collected at baseline, after 12 weeks of I+N (induction), and at the time of Grade $\geq$ 2 pneumonitis (CTCAEv5.0). Auto reactive antibody profiles were analyzed using a fluorescence-based assay system that measures more than 130 antigens and is capable of assaying antibody reactivity for IgG and IgM fractions, including nuclear-cytosolic and tissue-specific antigens. Selected antibodies had a reportable result range, reference intervals, and reproducibility with quality controls. A paired t-test was used to compare the mean of longitudinally collected baseline and toxicity samples. An unpaired t-test was used to compare differences between groups. The False Discovery Rate was used to control the Type I error rate of multiple comparisons. **Results:** In the study cohort, G$\geq$2 pneumonitis was observed in 11 patients out of 194 (5.6%). Serum was collected at baseline for all 11 patients, and 9 of the 11 patients had a serum sample collected at the time of pneumonitis event. Longitudinal serum samples (baseline and post-induction) collected from 32 patients without any irAEs were used as control. At baseline AChR3 and calmodulin antibodies were elevated in patients who developed pneumonitis, compared with baseline samples from controls ($p \leq 0.05$). At the time of pneumonitis IgM antibodies against AChR3, CXCL10, NSE, BAFF, CA242, Cytokeratin 19 were noted to be elevated in serum for pneumonitis cases compared with post induction samples from control ($p \leq 0.005$). **Conclusions:** We identified auto reactive antibodies associated with a higher risk of immunotherapy associated pneumonitis in patients treated with ipilimumab and nivolumab. These included auto reactive antibodies against proteins associated with lung injury (AChR3), lung inflammation (BAFF, CXCL10) and against alveolar epithelium (Cytokeratin 19). Future studies are warranted to determine if auto-reactive antibodies can be used as pre-treatment risk markers or to diagnose pneumonitis and may offer insights into to mechanisms that predispose toward pneumonitis. Research Sponsor: LUNGevity foundation.

2555 **Poster Session**

Comprehensive transcriptomic analysis of immune checkpoint markers in a pancancer cohort: Implications for response and resistance. *First Author: Hirotaka Miyashita, Mount Sinai Beth Israel, New York, NY*

Background: Although immune checkpoint blockade (ICB) has revolutionized cancer treatment, not all patients with cancer benefit from ICB. One possible explanation for poor responders/resistance is the variable expression level of the target molecules (e.g., PD-1 and PD-L1) in the tumor microenvironment. There are recent or ongoing trials targeting variable pathways for immune evasion (e.g., LAG3 or IDO1). It is therefore of interest to know the expression levels related to variable immune checkpoints so that clinical trials can focus on the patients who can benefit from the cognate treatment. **Methods:** Overall, 514 patients with various solid tumors seen at the University of San Diego, Moores Center for Personalized Cancer Therapy were analyzed. The expression levels of checkpoint markers (ADORA2A, BTLA, CD276, CTLA4, IDO1, IDO2, LAG3, NOS2, PD-1, PD-L1, PD-L2, PVR, TIGIT, TIM3, VISTA, and VTCN) in the tumor samples were measured through RNA sequencing and normalized to internal housekeeping gene profiles, and ranked from 0 to 100 percentile based on a reference population. The expressions of each checkpoint marker were correlated with cancer types, microsatellite instability (MSI), tumor mutational burden (TMB), and programmed death-ligand 1 (PD-L1) status on immunohistochemistry. **Results:** In this cohort, 60% were female, median age of 60, and included 30 different tumor types, with colorectal cancer being the most common (27%). The rank values of all checkpoint markers were distributed broadly from 0 to 99 or 100. CD276 and NOS2 had the highest (68^{th} percentile) and lowest (13.5 percentile) median rank values, respectively. When rank values were categorized to "Low" (0-24), "Intermediate" (25-74), and "High" (75-100), 41.6% of patients showed high expression of CD276 while only 13% showed high expression of PD-L1. Each patient had a distinctive protfolio of the categorical expression levels of 16 checkpoint markers. Several checkpoint markers, especially NOS2, showed a significant correlation with cancer type. (median rank values in colorectal, stomach, pancreatic, and breast cancer were 79, 76, 5 and 0 respectively, $p < 0.001$) Five markers (IDO1, LAG3, PD-1, PD-L1, and TIGIT) showed significant correlation with MSI, while seven markers (CTLA4, IDO1, LAG3, PD-1, PD-L1, PD-L2, and TIGIT) were significantly associated with positive PD-L1 status. However, no significant association was seen based on TMB or tissue-specific grouping of patients. **Conclusions:** The expression of immune checkpoint markers varies from patient to patient, though transcript expression of several markers correlates with cancer type, MSI, and PD-L1 status. Clinical trials with patient selection based on the expression level of checkpoint markers matched to the corresponding ICB drug are warranted. Research Sponsor: None.

2556 **Poster Session**

The immune micro-environment of inflammatory breast cancer is characterized by an influx of CD163+ tumor-associated macrophages. *First Author: Christophe Van Berckelaer, Multidisciplinary Breast Clinic, Unit Gynaecologic Oncology, Antwerp University Hospital (UZA), Edegem, Belgium*

Background: Inflammatory breast cancer (IBC) is a rare form of breast cancer characterized by rapid progression. A specific immune response seems to be an important driver for the aggressive biological behavior. We previously demonstrated that the spatial composition of the tumor immune micro-environment (TIME) is associated with survival in IBC. However, it remains an enigma how the TIME can contribute to the IBC phenotype. Since the number of tumor-infiltrating lymphocytes (TILs) between IBC and non-inflammatory breast cancer (nIBC) is similar and PD-L1 expression is higher, the functional state or composition of the immune infiltrate might determine the fulminant course of IBC. In this study, we assess the composition of the TIME in both IBC and a cohort of subtype-matched nIBC patients. **Methods:** We collected clinicopathological variables, evaluated PD-L1 positivity (SP142, Ventana) and scored TILs in a cohort of 161 IBC and 115 molecular subtype-matched nIBC patients. Affymetrix data (for CIBERSORT analysis) was available for 30 IBC and 20 nIBC patients. Immunostainings for CD8+ cytotoxic T cells, FOXP3+ Tregs, CD79a+ activated B cells and CD163+ TAMs (Hematoxylin-DAB) were done according to validated protocols. All slides were were evaluated in Visiopharm to quantify the number (density) and area (relative marker area, RMA) of DAB+ immune cells in both the invasive margin (IM) and the tumor stroma (TS). **Results:** Patients with IBC presented with higher stage disease ($P < 0.001$), but there were no other significant differences in clinicopathological parameters. In both cohorts, TAMs were the most abundant immune subset followed by B cells, CD8+ T cells and Tregs. For every subset the number of immune cells was higher in the IM than in the TS. Independent of molecular subtype or stage, IBC patients had more infiltration with TAMs in the TS. This was shown using both density (Median IBC: 424/mm2 vs nIBC: 290/mm2, OR: 0.82, 95% CI 0.76 – 1.00, $P = 0.008$) and RMA (Median IBC: 1.02% vs nIBC: 0.73%, OR: 0.87, 95% CI 0.77 – 1.00, $P = 0.04$). As previously described, PD-L1 positivity was significantly higher in the IBC cohort ($P = 0.005$), but no other significant differences in TIME composition between IBC and nIBC were found. Gene expression of CD163 correlated with the number of CD163+ TAMs ($R = 0.38$, $P = 0.005$) and CIBERSORT analysis confirmed a profile enriched for macrophages in IBC. Interestingly, the number of M1 macrophages was also higher in IBC ($P = 0.03$) and there was a strong correlation between the number of CD163+ TAMs in the TS and the M1 macrophage CIBERSORT subset ($R=0.48$, $P < 0.001$), possibly indicating that not only the number but also the functional state of TAMs is different in IBC. **Conclusions:** Using an extensive immune-phenotyping protocol we demonstrate, in a large cohort of IBC patients, that IBC is characterized by a specific tumor micro-environment in which TAMs play an important role. Research Sponsor: FWO.

2557 **Poster Session**

Characterization of tumor antigen expression and myeloid immune profiles to inform the development of immune stimulating antibody conjugates (ISACs).

First Author: Lisa K. Blum, Bolt Biotherapeutics, Redwood City, CA

Background: Immuno-oncology (IO) has historically focused on T cell-driven effects, but a growing class of myeloid therapies are under investigation. This class includes immune-stimulating antibody conjugates (ISACs), which comprise a tumor-targeting antibody conjugated to an immune-stimulating payload. ISACs may require both tumor-associated antigens and tumor-resident myeloid cells for activity. As new IO strategies such as TLR-activating ISACs are developed, understanding the myeloid landscape is relevant for cancer biology and drug development. **Methods:** Tumor microarrays with formalin-fixed paraffin embedded sections of breast (BC), colorectal (CRC), gastric (GC), head and neck squamous cell (HNSCC), and non-small cell lung (NSCLC) cancers were analyzed by immunohistochemistry for tumor antigens (HER2, CEA, PD-L1), myeloid cell markers (CD68/CD163/CD11c/BDCA2), and CD8+ T cells. **Results:** Tumor infiltrating myeloid cells and CD8+ T cells varied across indications (Table). Low densities of intra-tumoral CD8+ T cells (<100/mm^2) were observed in CRC, with higher CD8+ T cell counts observed in other cohorts. In contrast to T cells, substantial myeloid infiltrates were observed across tumor types. While MSI status was associated with higher CD8+ T cell infiltration in CRC, myeloid cells were abundant in both MSI and MSS samples. Monocyte-derived (mDC) and conventional DCs (cDC), which respond strongly to TLR activation, were present in all indications, with highest numbers observed in NSCLC. HER2+ BC samples had high infiltration of plasmacytoid DCs, a key TLR7-responsive population. PD-L1 expression on immune cells was associated with higher CD8+ T cell and myeloid cell numbers. In contrast to HER2 and PD-L1, CEA expression was independent of immune infiltration. **Conclusions:** Abundant myeloid infiltrates were observed across solid tumors, independent of T-cell infiltration. The presence of myeloid cells in multiple tumor types offers broadscale therapeutic targets for ISACs and other myeloid-directed therapies that can activate the innate immune system as a bridge to adaptive immunity. Research Sponsor: Bolt Biotherapeutics.

Median density (interquartile range) of cells/mm^2.

	N	CD8+ cells	Macrophages *(CD68+BDCA2- or CD163+CD11c-BDCA2-)*	cDC & mDCs *(CD11c+ CD68-BDCA2-)*	Plasmacytoid DCs *(BDCA2+ CD68-CD163-)*
CRC: Total	245	99 (23, 228)	217 (84, 493)	50 (19, 193)	12 (4, 33)
CRC: MSI-L/H	38	224 (92, 405)	283 (132, 492)	41 (16, 210)	9 (4, 21)
CRC: MSS	157	68 (22, 187)	217 (98, 429)	49 (17, 171)	12 (4, 35)
BC: Total	178	140 (41, 384)	398 (215, 723)	96 (41, 215)	11 (4, 70)
BC: HER2+	37	212 (116, 780)	241 (166, 403)	20 (5, 62)	1423 (665, 2392)
BC: Triple Negative	70	187 (31, 593)	699 (346, 1117)	93 (44, 234)	10 (3, 31)
NSCLC	74	207 (74, 510)	549 (324, 787)	445 (246, 861)	7 (4, 17)
HNSCC	74	223 (77, 626)	585 (311, 879)	166 (59, 353)	9 (3, 20)
GC	98	109 (31, 473)	434 (234, 659)	204 (80, 339)	8 (5, 17)

2558 **Poster Session**

Assessment of a 4-chemokine signature in prediction of T-cell inflammation and response to immune checkpoint inhibition across tumor types.

First Author: Joan Miguel Romero, Research Institute of the McGill University Health Centre, Montréal, QC, Canada

Background: Immune checkpoint inhibitors (ICI) are highly effective in select cancers. Novel predictors of T cell-inflammation may identify a broader subset of tumors with ICI responsiveness. Our group has identified four chemokines (CCL4, CCL5, CXCL9, CXLC10) able to predict a T cell-inflamed phenotype in primary and metastatic pancreatic tumors. Here, we test whether this 4-chemokine signature can predict T cell-inflammation across additional tumor types and response to ICI. **Methods**: Using matched genomic and transcriptomic data from 6,455 patients spanning 25 tumor types from The Cancer Genome Atlas, we searched for associations between the 4-chemokine signature and metrics of antitumor immunity. Further, we tested the association of this signature with markers of DNA damage repair deficiency. We also investigated the ability of this signature to predict response to immunotherapy using real-world data from a pan-cancer cohort of 82 patients in the Personalized OncoGenomics Program who had received ICI. **Results**: The majority of tumor types displayed sub-populations with high expression of the 4-chemokines (4-chemokine^{hi}) and transcriptional hallmarks of the cancer-immunity cycle. Testicular germ cell tumors, cervical squamous cell carcinomas, and head and neck squamous cell carcinomas were the strongest expressors of the signature. Immunomodulatory genes, including *PD-L1*, *PD-1*, *TIM3*, *LAG3*, *TIGIT*, *CTLA-4*, and *FASLG*, were significantly overexpressed ($p<0.05$) in the 4-chemokine^{hi} cohorts. Genesets of processes involved in the cancer-immunity cycle, including MHC I expression and cytolytic activity, were upregulated in the 4-chemokine^{hi} cohorts ($p<0.05$). While a global relationship between tumor mutation burden (TMB) and 4-chemokine expression across tumor histological type was seen (rho=0.42, p=0.02), high TMB was associated with only a subset of 4-chemokine^{hi} tumors. Among patients treated with ICIs, those with 4-chemokine^{hi} tumors had a longer median time to progression (104 versus 71 days, p=0.013) and overall survival (391 versus 195 days, p=0.016). The 4-chemokine signature outperformed TMB for overall survival prediction. **Conclusions**: Subpopulations of T cell-inflamed patients exist across tumor types and may therefore respond favourably to ICI. The 4-chemokine signature has the potential to select a wider spectrum of patients that may benefit from ICIs. Research Sponsor: Terry Fox Research Institute, Other Foundation, Other Government Agency.

Multivariate cox proportional hazards model for TTP and OS.

	Metric	Group	N	HR	P value
TTP	TMB	<10	42	Reference	
		≥10	23	0.39 (0.18, 0.86)	0.020
	4-chemokine score	lo+med	39	Reference	
		hi	26	0.37 (0.19, 0.73)	0.004
OS	TMB	<10	42	Reference	
		≥10	23	0.59 (0.28, 1.26)	0.174
	4-chemokine score	lo+med	39	Reference	
		hi	26	0.37 (0.20, 0.72)	0.003

HR = Hazard Ratio. OS = Overall survival from ICI initiation. TTP = Time to progression from ICI initiation.

2559 **Poster Session**

FORTITUDE: Results of a phase 1a study of the novel transgene-armed and tumor-selective vector NG-350A with and without pembrolizumab (pembro).

First Author: Lee S. Rosen, UCLA Division of Hematology-Oncology, Santa Monica, CA

Background: Stimulating CD40 may support anti-cancer immune responses; however, on-target toxicity limits systemic dosing. NG-350A is a tumor-selective and blood stable adenoviral T-SIGn vector expressing a potent fully human IgG agonistic anti-CD40 antibody (mAb). NG-350A was designed to selectively deliver anti-CD40 to multiple tumor sites via IV delivery, driving immunological tumor re-engineering while avoiding systemic toxicity. We report results from a first-in-human trial after completion of enrollment. **Methods:** FORTITUDE (NCT03852511) is a phase 1 study of NG-350A ± pembro in patients (pts) with metastatic/advanced epithelial tumors. NG-350A monotherapy (mTx) was dose-escalated in separate intratumoral (IT; increasing numbers of doses) or IV (one cycle; three increasing dose levels) cohorts. IV NG-350A + pembro (200 mg Q3W for ≤8 cycles) was then assessed. **Results:** As of Jan 2022, 28 heavily pre-treated pts had received NG-350A, either as IT mTx (n=9; two dose levels), IV mTx (n=16; IV dose levels 1, 3 & 4) or IV + pembro (n=3; IV dose level 2). The MTD of NG-350A ± pembro was not reached, with no DLTs at the highest IT and IV dose levels. The safety profile of NG-350A was consistent with acute reactions to viral particles and asymptomatic aPTT prolongations (Table). No systemic CD40 transgene protein was detected at any dose level and the only SAE to occur in >1 pt was pneumonia. No objective responses were observed; however, 3/6 patients treated with NG-350A mTx at IV dose level 4 achieved stable disease (dose not yet tested with pembro). Dose-dependent specific increases in serum IL-12, IFNγ and IL-17a were detected in pts treated with IV NG-350A mTx from ~Wk 2. Increases were sustained at ≥5x baseline levels 7 wks after dosing in the majority of evaluable pts treated at higher IV dose levels. These responses did not occur with IT dosing (or in prior studies with an unarmed vector); further follow-up is ongoing for NG-350A + pembro. IV NG-350A also led to the expansion of T cell clones in blood; most of these were newly detected. **Conclusions:** NG-350A ± pembro was well-tolerated, with no evidence of CD40-related toxicity. NG-350A IV mTx led to specific and sustained cytokine responses consistent with the MoA of the encoded anti-CD40 Ab. Peak cytokine elevations were typically higher than reported with systemic anti-CD40 Abs, suggesting NG-350A can drive local immunological tumor changes while avoiding systemic toxicity. A further trial (FORTIFY, NCT05165433) will continue dose-escalation of NG-350A + pembro to identify a dose level for efficacy assessments. Clinical trial information: NCT03852511. Research Sponsor: PsiOxus Therapeutics Ltd.

n (%)	IT NG-350A mTx (n=9)	IV NG-350A mTx (n=16)	IV NG-350 + pembro (n=3)
Most common TEAEs			
aPTT prolongation	6 (67)	5 (31)	2 (67)
Pyrexia	4 (44)	6 (38)	0
Nausea	3 (33)	6 (38)	0
Chills	2 (22)	7 (44)	0
Any Grade ≥3 TEAE	4 (44)	6 (38)	3 (100)
Any TE-SAEs	3 (33)	8 (50)	2 (67)
Any treatment-related SAE	1 (11)	3 (19)	1 (33)
DLTs	0	1 (dose level 1)	0

2560 **Poster Session**

Dose escalation of davoceticept, a conditional CD28 costimulator and dual checkpoint inhibitor, in advanced malignancies (NEON-1).

First Author: Diwakar Davar, University of Pittsburgh Medical Center, Hillman Cancer Center, Pittsburgh, PA

Background: Strong preclinical rationale supports combining checkpoint inhibition (CPI) with T cell costimulatory agonists, particularly of CD28, a critical T cell costimulatory molecule recognized as a key target of checkpoint inhibition. Davoceticept (ALPN-202) is a variant CD80 vIgD-Fc fusion that mediates PD-L1-dependent CD28 costimulation and inhibits the PD-L1 and CTLA-4 checkpoints. It has demonstrated superiority to CPI-only therapies in multiple tumor models *in vitro* and *in vivo*, while demonstrating favorable preclinical safety. **Methods:** This is an open-label dose escalation and expansion study of davoceticept in adults with advanced solid tumors or lymphoma (NCT04186637). Patients with cancers refractory to standard therapies including CPIs, or cancers without available standard or curative therapy are eligible. Dose escalation studied two dose schedules, Q1W and Q3W. Objectives include safety and tolerability, PK, PD and preliminary anticancer activity. Disease assessments are evaluated by RECIST v1.1 for solid tumors. A prior presentation discussed the first 5 cohorts of the Q1W schedule; this presentation updates progress in dose escalation, including the Q3W schedule. **Results:** As of January 2022, 57 adults with various advanced solid tumors, most commonly colorectal and pancreatic, received davoceticept monotherapy, which was well tolerated through 10 mg/kg Q3W. It demonstrated dose-dependent PK and target saturation. Immune-related AEs (irAEs), occurred in 20/57 (35%), mostly of the skin, endocrine and gastrointestinal systems. All but 4 of the irAE were grade 1-2. Only one DLT (chronic active gastritis grade 3) was observed at 3 mg/kg Q3W. Among 48 evaluable patients, unconfirmed partial responses were observed in 2 (colorectal and renal cell). Stable disease, at first scan at 6 weeks, was observed in 23 (48%); 11 (23%) demonstrated volume reduction (target lesion ΔSLD < 0%); 2 had SD for > 6 months, and 1 had an ongoing SD at 8 months. At doses above 0.1 mg/kg, *ex vivo* analyses showed agonism of T cell CD28, and flow cytometry demonstrated increased circulating activated (ICOS+), proliferating (Ki-67+) and central memory T cells, and reduced regulatory T cells, consistent with CD28 engagement. **Conclusions:** Davoceticept was well tolerated at doses capable of engaging CD28 costimulation *in vivo*, with early signs of activity and peripheral immune activation in a largely treatment-refractory, non-immunogenic tumor population. These findings support an additive benefit of combining CD28 agonism with checkpoint inhibition and identify biologically active dose regimens of davoceticept for subsequent single agent development, and provide further rationale for combination study. Expansion cohorts, including cutaneous melanoma and PD-L1-positive cancers, are planned, and a combination study with pembrolizumab has initiated (NCT04920383). Clinical trial information: NCT04186637. Research Sponsor: Alpine Immune Sciences.

2561 **Poster Session**

LAG3 transcriptomic expression correlates with high levels of PD-1, PD-L1, PD-L2, and CTLA-4 checkpoints and with high tumor mutational burden across cancers. *First Author: Jacob J. Adashek, University of South Florida, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

Background: Lymphocyte Activation Gene 3 (LAG3) or CD223 is an immune checkpoint that can be found on various T cells: CD4+, CD8+, regulatory T cells (Tregs), natural killer T cells, natural killer cells, and plasmacytoid dendritic cells. The expression of LAG3 molecule acts to increase T-cell exhaustion, leading to decreased tumor killing as well as an increase in immune suppressive cytokine release. Many clinical trials of LAG3 inhibitors have had modest effects, but recent data suggests that the LAG3 antibody relatlimab together with nivolumab (anti-PD1) provided greater benefit than nivolumab alone in patients with melanoma. **Methods:** The RNA expression levels of 397 genes in various types of solid tumors from 514 patients seen at the UCSD Moores Cancer Center were analyzed at a CLIA-licensed laboratory, OmniSeq (https://www.omniseq.com/). Following removal of germline variants, synonymous variants, indels and SNVs with < 5% VAF, TMB is reported as mutations/megabase. Transcript abundance was normalized to internal housekeeping gene profiles and ranked (0-100 percentile) in a standardized manner to a reference population of 735 tumors spanning 35 histologies. Odds ratio for high LAG3 expression was calculated and Bonferroni corrected for multiple genes and cancer histologies with > 40 samples. **Results:** A total of 116 (22.6%) tumors had high LAG3 (≥75) across 32 different histologies. Cancers with the highest proportion of LAG3 were neuroendocrine (47%), uterine (43%), sarcoma (33%), breast (31%), ovarian (30%), pancreatic (24%), lung (20%), stomach (16%), and colorectal (15%). There was significant association for high LAG3 with high PD-L1 (adj P < 0.001), high PD-1 (adj P < 0.0014), high PD-L2 (adj P < 0.0014), high CTLA-4 (adj P < 0.0014), TMB ≥10 mt/mb (adj P = 0.0504). There was no significant association between histologies colorectal (adj P = 0.1834), breast (adj P = NS), ovarian (adj P = NS), pancreatic (adj P = NS), or gender (adj P = 0.272). **Conclusions:** High LAG3 was found in almost a quarter of tumor samples and significantly associated with other immune checkpoints with FDA-approved drugs. Ongoing studies combining LAG3 inhibitors and specific immune checkpoint inhibitors may yield more clinical benefit if individualized immunomic transcript interrogation is undertaken, rather than population-based approaches without employment of rationally combined agents matched to each patient's cancer. Research Sponsor: None.

2562 **Poster Session**

LB101, a conditionally tetravalent PD-L1xCD47 bispecific monoclonal antibody (mAb), combines tumor microenvironment (TME) targeted delivery (PD-L1) and a single biological high potency effector (CD47). *First Author: Jonny Finlay, LockBody Therapeutics, a Centessa Company, Cheshire, United Kingdom*

Background: Anti-PD-L1 antibodies are well-established as potent immune effectors in solid tumors expressing PD-L1 and demonstrate binding to these tumor cells within the TME. By contrast, due to the ubiquitous expression of CD47 on normal cells and tissues, anti-CD47 therapeutic agents with an active antibody Fc can lead to serious dose-limiting toxicities and profound biodistribution problems. To overcome these issues, we have generated LB101, a next-generation conditionally activated PD-L1xCD47 bispecific mAb with two anti-CD47 domains blocked by two further anti-PD-L1 domains, linked by two proprietary IgG-derived hinges, which inhibit CD47 interactions in the periphery, but are degraded in the PD-L1+ TME, thereby activating CD47 blockade to induce antibody-dependent cellular phagocytosis (ADCP). **Methods:** An IgG1-based, conditionally activated bispecific molecule was examined in binding, phagocytosis, PD-L1 blocking and flow cytometry assays. Efficacy analyses were performed in an hPD-L1+ syngeneic model in hPD-L1+/hPD1+ C57BL/6 mice, and preliminary safety and exposure analyses were completed in monkey. **Results:** In its intact locked form, LB101 exhibited anti-PD-L1 assay potency similar to atezolizumab. CD47 binding was only observed for LB101 after unlocking by hinge linker cleavage, leading to strongly enhanced ADCP by human CD14+ cells. In monkey, plasma stability of the locked construct was established with a PK profile mimicking that of a typical PD-L1 mAb. In the MC38 mouse model, systemically administered LB101 monotherapy delivered at equimolar dose to atezolizumab, led to no anemia, weight-loss, or overt toxicity. Monotherapy LB101 exhibited greatly improved efficacy and durability of response (14/16 tumors eradicated) over isotype control IgG (0/16) and atezolizumab (1/16). The CD47 naked parent IgG1 mAb was not tolerated in mouse, with 100% lethality above 2mg/kg. In rechallenge experiments, all naïve mice established tumors rapidly while none of the mice from groups with prior LB101-induced regressions exhibited tumor growth. **Conclusions:** Single agent LB101 immunotherapy delivered systemically in a difficult to treat syngeneic mouse model resulted in PD-L1 directed, local tumor-specific CD47 effector engagement leading to significant tumor regressions as compared to atezolizumab without overt toxicity. Future developments will focus on developing LB101 as a single agent therapeutic and exploring the potential of LockBody technology in improving the therapeutic index of other anti-cancer biological effectors through conditional activation within the TME. Research Sponsor: Centessa Pharmaceuticals.

2563 **Poster Session**

TransCon IL-2 β/γ, a novel long-acting prodrug with sustained release of an IL-2Rβ/γ-selective IL-2 analog, demonstrates improved pharmacokinetics and profound expansion of cytotoxic immune cells in non-human primates. *First Author: David Rosen, AscendisPharma, Redwood City, CA*

Background: Recombinant interleukin-2 (IL-2, aldesleukin) is an approved cancer immunotherapy but causes severe side effects including cytokine release syndrome (CRS) and vascular leak syndrome (VLS). This is believed to be due to activation of IL-2Rα^+ endothelial cells and inflammatory eosinophils as well as high C_{max} due to the short half-life requiring frequent high dose administrations. Also, potent activation of immunosuppressive IL-2Rα^+ regulatory T cells (Tregs) may limit IL-2's efficacy. TransCon IL-2 β/γ is a novel long-acting prodrug with sustained release of an IL-2Rβ/γ-selective IL-2 analog designed to optimally address these shortcomings. **Methods:** Naïve male and female cynomolgus monkeys received 2-3 doses of TransCon IL-2 β/γ intravenously Q2W. Blood samples were taken to assess plasma concentrations of IL-2 β/γ (active drug), serum cytokines, hematology and immunophenotyping. Histopathology was also performed. **Results:** Administration of TransCon IL-2 β/γ induced robust increases in absolute lymphocyte counts (ALC), with no/minor increases in eosinophil counts. The increase in ALC was primarily driven by potent activation and expansion of CD8$^+$ T cells, NK cells and $\gamma\delta$ T cells, relative to CD4$^+$ T cells and Tregs. At doses with maximum pharmacodynamic (PD) responses, TransCon IL-2 β/γ induced on average > 20-fold ALC increases, > 19-fold CD8$^+$ T cell increases, > 50-fold Effector Memory CD8$^+$ T cell increases, > 18-fold NK cell increases and > 400-fold $\gamma\delta$ T cell increases compared to pre-dose levels. These changes corresponded with a low C_{max} and a long effective half-life (> 30 hours) for IL-2 β/γ. A clear induction of soluble CD25 and chemokine MCP-1 was seen after dosing, while levels of IL-5, IL-6, IFN-γ and TNF-α remained low. Further, histopathology showed no signs of vascular damage, tissue necrosis, pulmonary edema or eosinophilia. **Conclusions:** In cynomolgus monkeys, TransCon IL-2 β/γ demonstrated remarkable PD responses in CD8$^+$ T cells, NK cells and $\gamma\delta$ T cells over Tregs and eosinophils. No signs of VLS or CRS were observed. These results are likely due to the selective IL-2Rβ/γ bias along with the slow and sustained release of IL-2 β/γ resulting in low C_{max} and long circulatory half-life enabled by the TransCon prodrug technology. The massive expansion of $\gamma\delta$ T cells, which are known to possess considerable anti-tumor activity, is to our knowledge a unique finding for TransCon IL-2 β/γ among IL-2 variants in clinical development. Altogether, the responses seen in monkeys are suggestive of a potentially substantial improvement in the therapeutic index beyond what has been achieved by aldesleukin or new IL-2 variants to date. TransCon IL-2 β/γ is currently being evaluated in a clinical Phase 1/2 trial as monotherapy and in combination with pembrolizumab (NCT05081609). Research Sponsor: Ascendis Pharma.

2564 **Poster Session**

A novel polymeric peptide delivery platform and association with targeted co-delivery of antigens and STING agonists with antitumor immune response. *First Author: Max Mu Wang, Medical Scientist Training Program, Northwestern University, Chicago, IL*

Background: Use of tumor antigens for the development of patient-specific cancer vaccines has been a promising therapeutic strategy. However, challenges remain in delivering subunit vaccine components in a coordinated fashion to elicit antitumor immune responses. To overcome these, we developed rationally designed vaccines using a novel nanoplatform called the Protein-Like Polymer (PLP), in reference to its globular structure reminiscent of native proteins, with unique characteristics that allow for sustained/targeted delivery of tumor antigens in conjunction with STING agonists. **Methods:** PLPs containing a model melanoma antigen were synthesized via ring-opening metathesis polymerization (ROMP) and characterized. A library of compounds were generated with different sidechain linkage chemistries (amide, ester, or disulfide), degrees of polymerization, and inclusion/exclusion of Oligo(ethylene glycol) (OEG) side chains. *In vitro* uptake and functional assays using gp100-specific T Cells were conducted with fluorescently-labeled and non-labeled polymers respectively. *In vivo* experiments were done using a B16F10 murine melanoma tumor model over-expressing gp100. Ability of PLPs to co-deliver immunomodulatory compounds was tested by electrostatically coupling a small molecule STING agonist 2'3' cGAMP which formed stable nanostructures. The optimized construct was also tested in an OVA system to prove generalizability. **Results:** Conjugating peptide antigens using a cleavable disulfide linkage, which reduces intracellularly in antigen presenting cells (APCs), resulted in increased endosomal localization and efficacy. Incorporating a diluent amount of OEG side chains increased resistance to enzymatic degradation while improving bioactivity and uptake by APCs. *In vivo* studies using PLPs conjugated with gp100 resulted in significant increases in survival time and reduced tumor burden in B16 melanoma. Increasing the DP, and therefore the density of antigen side chains, improved vaccine efficacy and resistance to proteolysis. Mice treated with STING-PLP complexes showed significantly smaller tumors vs control at day 14 (0.038g vs 0.76g; p < 0.0001) and allowed for subcutaneous administration of 2'3' cGAMP, which otherwise diffuses rapidly away from the injection site. OVA-PLPs behaved similarly in their cognate system but showed no activity when tested on gp100-specific cells and vice versa demonstrating antigen-specificity. **Conclusions:** This work validates the potential of PLPs to overcome major limitations in cancer vaccine development. The modularity of the platform allows for complex nano-architectures including systems capable of delivering challenging compounds, ie small molecule STING agonists, subcutaneously through electrostatic coupling. This technology has the potential to revolutionize cancer vaccinology. Research Sponsor: U.S. National Institutes of Health.

2565 **Poster Session**

Exploiting GLAAD molecules to drive an antitumor immune response in a colorectal cancer mouse model. *First Author: Yemi Adesokan, Gnubiotics Sciences SA, Epalinges, Switzerland*

Background: Only a minority of colorectal cancer (CRC) patients benefit from immune checkpoint inhibitors (ICI), with less than half of eligible patients responding to the treatment. Abnormal glycosylation of tumor cells is a signature of cancer development. Here, we described novel immunomodulatory molecules, named GLAAD (glycopeptides with adjuvant and tumor-associated antigen delivery). We hypothesized that GLAAD, by sharing similarities with aberrant glycans expressed in many cancers, may be a safe and effective treatment strategy to promote response and overcome resistance to ICI, thus addressing an urgent clinical need. Using a CRC mouse model, we tested whether two GLAAD candidates reduce tumor burden when orally administered alone or in combination with ICI. **Methods:** C57/BL6J mice were supplemented with 3% GNU-201 or 3% GNU-101 in the drinking water starting 14 days prior to tumor cell injection (d-14), while control mice received normal drinking water. On day 0, all mice were injected subcutaneously with MC38 CRC cells in each flank. On days 6, 9, 12, and 15, mice in each group received anti-PD1 antibody (aPD1) or an isotype control. Tumor size was measured every 3rd day. On day 18, the mice were sacrificed. **Results:** The aPD1 therapy alone showed a limited anti-tumor efficacy overall. Groups treated with GNU-201, GNU-101, GNU-201+aPD1 or GNU-101+aPD1 exhibited reduced growth, resulting in a significantly reduced tumor volume vs control on day 18. In contrast, GLAAD candidates alone significantly reduced tumor volume compared with control and led to a numerically larger decrease than aPD1 treatment alone, suggesting a higher efficacy. When analyzing tumor infiltrating myeloid cells on day 18, no differences were seen for neutrophils or dendritic cells but the proportion of macrophages was decreased in mice receiving GNU-201 or GNU-101. GNU-101 resulted in reduced serum levels of IL-10, a molecule participating in the suppression of antitumor immune responses. The tested GLAAD candidates stimulated robust anti-tumor T cell responses. GNU-201 and GNU-101 supplementation alone or in combination with aPD1 increased the proportion of T cells and among those CD8+ T cells, IFNγ producing CD4+ T cells, IFNγ+ and perforin+ CD8+ T cells. GNU-101 and GNU-201 elicited memory T cell responses after priming of the mice, measured as the *ex vivo* recall response (CD69 expression) of CD8+ T cells isolated from the tumor. **Conclusions:** GNU-201 and GNU-101 as standalone treatment induce a strong anti-tumor response that is as good as or even better than aPD1 alone. The therapeutic efficacy is associated with increased tumor infiltration and activation of T cells, in particular CD8+ T cells, highlighting the role of these GLAAD candidates as potent adjuvants in supporting specific tumor-associated antigen recognition by the immune system. Research Sponsor: Gnubiotics Sciences SA.

2566 **Poster Session**

Phase 1b study of GS-3583, a novel FLT3 agonist Fc fusion protein, in patients with advanced solid tumors. *First Author: Anthony W. Tolcher, Next Oncology, San Antonio, TX*

Background: We have previously shown that systemic administration of GS-3583, a Fms-like tyrosine kinase 3 (FLT3) agonist Fc fusion protein leads to expansion of conventional dendritic cells (cDC), both subtype 1 (cDC1) and subtype 2 (cDC2), in the periphery of healthy volunteers (Rajakumaraswamy N, et al. *J Clin Oncol.* 2021;39[suppl_15]:2559.). This mechanism may increase cDC in the tumor microenvironment and promote T cell mediated antitumor activity in patients with solid tumors. **Methods:** This ongoing, Phase 1b, open label study is investigating the safety, tolerability, immunogenicity, pharmacokinetics, and pharmacodynamics of escalating multiple doses of GS-3583 monotherapy in adult patients with advanced solid tumors using a standard 3 + 3 design. GS-3583 was administered intravenously on Days 1 and 15 of Cycle 1 and on Day 1 of each subsequent 28-day cycle for up to 52 weeks or until progressive disease or unacceptable toxicity. Dose-limiting toxicity (DLT) was evaluated during the first 28 days of GS-3583 therapy at each dose level. **Results:** At the time of the Dec 3, 2021 data cut-off, 9 patients have enrolled in 3 dose escalation cohorts. Median (range) age was 71 (44-79); 4 (44%) patients were male. Tumor types were pancreatic (n=3), ovarian (n=4), and rectal (n=2). To date, no DLTs or discontinuation due to adverse events (AE) have been observed. Three patients had Grade ≥3 AEs which were also recorded as serious AEs, none of which were considered related to GS-3583. Dose dependent increase in GS-3583 exposure was observed in the evaluated dose range 2 to 12 mg with target-mediated drug disposition appearing to be saturated at doses above Dose Level 2. GS-3583 accumulation was observed at higher dose levels. GS-3583 treatment resulted in expansions of cDC1 and cDC2 at all 3 doses (Table); a dose-dependent trend in the magnitude and the durability of cDC expansion was observed. At the highest dose evaluated, GS-3583 produced ≥100-fold expansion of both cDC1 and cDC2 at multiple time points. Dose escalation on the study is still ongoing. **Conclusions:** GS-3583 was safe and well tolerated and induced dose-dependent expansion of cDCs in the periphery in patients with advanced solid tumors up to doses of 12 mg. These findings support further dose escalation and clinical development of GS-3583 in combination with agents that would stimulate the expanded cDCs to produce anti-tumor responses. Clinical trial information: NCT04747470. Research Sponsor: Gilead Sciences, Inc.

Dose Level (mg GS-3583)	1 (2 mg)	2 (6 mg)	3 (12 mg)
Median peak cDC1 fold expansion (range)	124 (188 – 15)	83 (0)	191 (283 – 99)
Observation of peak cDC1 expansion	C1D24	C2D15	C2D1
Median peak cDC2 fold expansion (range)	147 (154 – 34)	201 (0)	217 (273 – 162
Observation of peak cDC2 expansion	C1D15	C2D15	C2D1

C = cycle; D = day.

2567 **Poster Session**

A phase II study to evaluate the safety and efficacy of radiotherapy combined with irinotecan liposome followed by camrelizumab and apatinib for advanced solid tumors that failed standard treatments. *First Author: Jie Shen, The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China*

Background: Liposomes deliver the drug to tumors based on enhanced permeability and retention (EPR) effects. Radiotherapy further prompts the distribution of liposomal drugs to tumor sites receiving radiotherapy by altering the tumor microenvironment. In addition, radiotherapy might enhance systemic antitumoral responses to immunotherapy. Herein, we aimed to explore safety and efficacy of radiotherapy in combination with irinotecan liposome, immunotherapy, and antiangiogenic therapy in advanced solid tumors patients (pts) that failed standard treatments. **Methods:** Anopen single-arm, multi-center, phase II study was conducted to enroll solid tumors pts who have failed standard treatments. Eligible pts would receive radiotherapy combined with irinotecan liposome followed by camrelizumab and apatinib. Radiotherapy of 24 Gy/3 fractions/3-10 days was given to the targeted lesions. Irinotecan liposome (80mg/m^2 i.v.) was administered once within 48 hours after radiotherapy and followed by camrelizumab (200mg i.v. q3w) and apatinib (250mg po qd) until disease progression or unacceptable toxicity. The primary endpoint was the objective response rate (ORR) of the irradiated lesions evaluated by the investigators as per RECIST V1.1. The secondary endpoints were disease control rate (DCR) and treatment-related adverse event (TRAE). **Results:** As of Dec 2021, 55 pts were enrolled includin 9 with biliary tract cancer, 8 with pancreatic cancer, 8 with sarcoma, 5 with lung cancer, 2 with liver cancer, 2 with cervical cancer, 2 with gastric cancer, and 22 with other cancer types. 26 (47.3%) pts failed at least 3 lines of therapy before enrollment. The median follow-up was 41 weeks and 42 pts can be evaluated. 15 partial response, 26 stable disease, and 1 progressive disease were achieved. The ORR and DCR of irradiated target lesions were 35.7% and 97.6%, respectively. The ORR and DCR of every cancer type are listed in table. TRAEs (all grades) occurred in 87.3% (48/55) pts. The most common grade 3-4 related TRAEs were lymphocyte count decreased (29.1%), white blood cell count decreased (10.9%), and anaemia (10.9%). **Conclusions:** The combination of radiotherapy, irinotecan liposome, camrelizumab, and apatinib demonstrated promising anti-tumor activity and well tolerance in various advanced solid tumors that failed standard treatments. Clinical trial information: NCT04569916. Research Sponsor: None.

Cancer types	Evaluable(N≥2)	ORR of theirradiated lesions	PR	SD
Biliary tract cancer	8	12.5%	1	7
Sarcoma	7	28.6%	2	5
Pancreatic cancer	4	0	0	3
Lung cancer	3	33.3%	1	2
Liver cancer	2	0	0	2
Cervical cancer	2	50.0%	1	1
Gastric cancer	2	100%	2	0
Other cancer types	14	57.1%	8	6

2568 **Poster Session**

Safety results of Q-1802, a Claudin18.2/PD-L1 bsABs, in patients with relapsed or refractory solid tumors in a phase 1 study. *First Author: Jifang Gong, Department of Gastrointestinal Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/ Beijing), Peking University Cancer Hospital and Institute, Beijing, China*

Background: Q-1802 is a humanized bispecific antibody that targets both the tumor -specific antigen CLDN18.2 and the immune checkpoint PD-L1. **Methods:** This is a first-in-human, phase 1a/1b, multicenter, dose escalation and dose expansion study of Q-1802 administered intravenously to adult pts with resistant/ refractory advanced or metastatic solid tumors who had failed standard therapies. Monotherapy of Q-1802 was conducted in 20-30 enrolled subjects. In the dose escalation phase (phase 1a), an accelerated titration followed by a 3+3 design was used to assess the safety and tolerability of Q-1802 monotherapy (dose range 0.1 mg/kg to 20 mg/kg); and determine the maximum tolerated dose (MTD). Q-1802 was administered Q3w on a 21-day treatment cycle and dose limiting toxicity (DLT) observation period. Tumor assessments per RECIST v1.1 were performed once every 6 weeks (2 cycles). Q-1802 PK and PD analyses were performed. **Results:** As of Jan 20, 2022, a total of 9 patients (median age 57y; most patients received ≥3 prior regimens) were enrolled in phase 1a with DLT evaluation of the 20 mg/kg cohort currently in progress. The most common tumor types were GI cancers. There were no DLTs up to 10 mg/kg of Q-1802, inclusive. Phase 1a with DLT evaluation of the 20 mg/kg cohort currently in progress. The most common treatment related adverse events (TRAEs) were Gastrointestinal AE (66.7%, 6/9), including nausea 6/9 (66.7%), vomiting 5/9 (55.6%), abdominal pain 2/9 (22.2%) and diarrhea 2/9 (22.2%). The second common TRAEs were IRR (infusion related reaction) (33.3%, 3/9), including Fatigue 3/9 (33.3%), Fever 2/9 (22.2%), Chill 2/9 (22.2%), face pain 1/9 (11.1%). There was G1/2 except for one patient experienced a G3 skin rash, and one patient reported with a G3 Gastrointestinal AE. Two SAEs (G2 fever and G3 Gastrointestinal AE) were reported, both were considered as possibly related to study drug, but recovered shortly. No death reported due to study related treatment. Safety evaluation of the 20 mg/kg dose level is in progress. One Gastric cancer patient (moderate CLDN18.2 expression at baseline) with prior heavily treatment observed clinical benefit and response with Non-CR/Non-PD at first tumor assessment at dose of 10mg/kg and continues the therapy. Q-1802 drug exposure increased with increasing dose. The elimination of Q-1802 appears to follow first-order elimination kinetics. **Conclusions:** Q-1802 bsABs has presented safe and well-tolerated profile up to doses of 10 mg/kg. The dose escalation is still in progress. Clinical trial information: NCT04856150. Research Sponsor: QureBio Ltd.

2569 **Poster Session**

Breath biopsy early detection of lung cancer using an EVOC probe targeting tumor-specific extracellular β-glucuronidase. *First Author: Christiaan Frederick Labuschagne, Owlstone Medical, Cambridge, United Kingdom*

Background: Lung cancer is a leading cause of mortality with 5-year survival less than 20%, largely a result of many cases being diagnosed late. Early detection can increase cancer survival up to 13-fold underscoring the need for effective screening. Targeted Low dose computed tomography (LDCT) has been shown to be effective but its impact to date has been limited due to slow adoption and variable uptake in high-risk populations. Breath analysis represents a non-invasive screening approach either alone or alongside LDCT. Numerous studies have investigated potential endogenous breath biomarkers of lung cancer. Many have produced promising results but to date, no validated biomarkers with clear connections to cancer metabolism have been revealed. We have explored an alternative, probe-based approach based around Exogenous Volatile Organic Compound Probes (EVOC Probes). The probes target tumour associated extracellular b-glucuronidase, a glycosidase enzyme that normally resides within lysosomes. **Methods:** We use a hydrophilic non cell permeable substrate probe D5-ethyl-βD-glucuronide (D5-EtGlu) that upon hydrolysis by the target enzyme releases D5-ethanol, a unique volatile reporter molecule detectable on breath. This provides a readout of tumour associated enzyme activity using breath analysis. **Results:** Administering D5-EtGlu to mice resulted in tumour specific release of D5-ethanol, enabling discrimination between healthy and tumour bearing animals. Increased expression of b-glucuronidase in lung cancer tissue and the tumour microenvironment was confirmed with immunohistochemistry (IHC) in clinical samples. A phase 1a clinical trial administered D5-EtGlu to healthy individuals in a single ascending dose study to establish safety and background D5-ethanol levels in healthy individuals. This resulted in no adverse events and low/no D5-ethanol signal verifying the inaccessibility of D5-EtGlu to intracellular b-glucuronidase. The next stage, currently ongoing, is a proof of mechanism in humans. D5-EtGlu is administered intravenously to confirmed lung cancer patients followed by breath analysis. D5-ethanol breath levels will be compared to cancer free individuals receiving the same dose of D5-EtGlu. **Conclusions:** Non-invasive breath testing has great potential to contribute to diagnosis for lung cancer including a potential role in screening. Our current work is evaluating the use of an administered probe to stimulate tumour-specific enzyme activity and produce a marker detectable on breath. Continued success could result in a sensitive and highly specific method for lung cancer early detection. Research Sponsor: Owlstone Medical.

2570 **Poster Session**

Artificial intelligence-powered pathology image analysis merged with spatial transcriptomics reveals distinct TIGIT expression in the immune-excluded tumor-infiltrating lymphocytes. *First Author: Gahee Park, Lunit Inc., Seoul, South Korea*

Background: TIGIT is a promising emerging immunotherapeutic target. However, the specific sources of TIGIT expression within the tumor microenvironment are largely unknown. Here, we present an AI-powered spatial tumor-infiltrating lymphocyte (TIL) analyzer, Lunit SCOPE IO, to integrate image analysis from whole slide images with single-cell molecular profiling. **Methods:** We used The Cancer Genome Atlas (TCGA) RNA expression data across 23 cancer types (n=6,930). Lunit SCOPE IO was developed, trained, and validated based on >17k H&E whole-slide images, to segment cancer area (CA) and cancer-associated stroma (CS) and to detect tumor cells and TILs. The intratumoral TIL, stromal TIL, and tumor cell purity (TCP) in the CA+CS area were calculated. The public spatial transcriptomics (ST) dataset for breast cancer was downloaded from the 10X Visium web page. Lunit SCOPE IO was applied to the associated H&E WSIs to match distinct TIGIT expression to single cells identified in the WSIs. **Results:** TIGIT was highly expressed in TGCT (3.45±0.11; median±SEM), LUAD (3.07±0.05), and HNSC (2.89±0.06), and was highly enriched in samples with microsatellite instability-high or tumor mutational burden-high (≥ 10/Mb) compared to those without them (fold change = 1.30, $p < 0.001$). At a macroscopic, bulk-level in the TCGA dataset, TIGIT expression was positively correlated with intra-tumoral TIL density (R=0.37, $p<0.001$) and stromal TIL density (R=0.42, $p<0.001$), but it was negatively correlated with TCP (R=-0.27, $p<0.001$). Lunit SCOPE IO analyzed the images from ST analysis and calculated intra-tumoral TIL, stromal TIL, and TCP of each region of interest, containing 2 (IQR 0-7) cells. Interestingly, at a microscopic, cell-level, TIGIT expression was still higher in areas of enriched stromal TIL ($P < 0.001$) and lower in tumor cell-dense areas, but it was not significantly correlated with enriched intra-tumoral TIL areas, meaning that TIGIT expression is likely derived from the excluded TILs in the CS area. **Conclusions:** Interactive analysis of spatial transcriptomics with AI-powered pathology image analysis revealed that TIGIT expression in the tumor microenvironment is exclusive to confined areas with stromal TIL enrichment, reflecting the exclusion of TIL from the tumor nest. Research Sponsor: None.

	Fold change of TIGIT expression	P value
TCGA: iTIL < mean versus iTIL ≥ mean	1.58	< 0.001
TCGA: sTIL < mean versus sTIL ≥ mean	1.55	< 0.001
TCGA: TCP < mean versus TCP ≥ mean	0.75	< 0.001
ST: iTIL < mean versus iTIL ≥ mean	0.47	< 0.001
ST: sTIL < mean versus sTIL ≥ mean	2.39	< 0.001
ST: TCP < mean versus TCP ≥ mean	0.28	< 0.001

2571 **Poster Session**

Evaluation of pharmacodynamic and patient enrichment biomarkers for SAR444881, a first-in-class anti-ILT2 monoclonal antibody for cancer immunotherapy. *First Author: Ilana Mandel, Biond Biologics, Misgav, Israel*

Background: Leukocyte Ig-like receptor B1 [LILRB1; ILT2] is an inhibitory receptor expressed on various immune cells. ILT2 binds to classical and nonclassical MHC class I molecules, with highest affinity to HLA-G. ILT2-mediated inhibition leads to impairment of immune cell proliferation, differentiation, phagocytosis, cytotoxicity and cytokine secretion. Antagonism of ILT2 signaling may serve as a novel target for anti-cancer immunotherapy. SAR444881 (BND-22) is a novel humanized IgG4 monoclonal antagonist antibody which selectively binds to ILT2 and blocks its interaction with MHC I molecules. SAR444881 induces robust macrophage and lymphocyte-driven anti-tumor activity in *in vitro* and *in vivo* models. To overcome the limitation that LILRB proteins are not expressed in rodents, we conducted a series of *in vivo* studies using humanized mouse models, cancer patient biopsies and *ex vivo* co-culture systems to interrogate the pharmacodynamic (PD) response of ILT2 antagonism as well as inform the combinatorial and patient enrichment strategies for SAR444881. **Methods:** SAR444881-induced modulation of PD biomarkers was evaluated in humanized xenograft models. Ex vivo co-culture system has been established using patient tumor tissues and isolated PBMC or other immune cells. Biomarker expression on immune cells and secreted soluble proteins were monitored by flow cytometry and ELISA, respectively. Procured tumor samples of patients with various advanced solid tumors, including Head and neck squamous cell carcinoma (HNSCC), Gastric Cancer (GC), Non-Small Cell Lung Cancer (NSCLC) and Colorectal Cancer (CRC) were utilized to evaluate protein or gene expression levels of potential predictive biomarkers (ILT2, HLA = G, PD-L1) using immunohistochemistry (IHC) and whole transcriptomic analysis (RNAseq). **Results:** 1) PD biomarkers: in murine models, SAR444881 modulates intra-tumoral sub-populations of CD8+ T cells, NK cells and Macrophage polarization; 2) Combination strategy: functional study in an *ex vivo* system showed that addition of an anti-PD-1 antibody induced an increased production of pro-inflammatory cytokines, including IFNγ and TNFα, compared to SAR444881 or anti-PD-1 alone. Concomitantly, combining SAR444881 with cetuximab resulted in increased phagocytosis compared to isotype control. 3) Predictive biomarkers: protein and gene profiling results suggest enriched expression of ILT2 in majority of biopsies from several tumor types including NSCLC, HNSCC and CRC. **Conclusions:** These data inform the PD response biomarkers, combination, and patient enrichment strategies for the clinical development of SAR444881 to maximize its benefits for cancer patients. An ongoing phase 1/2 trial of SAR444881 mono- and combination therapy in patients with advanced solid tumors is testing these concepts in the clinic (NCT04717375). Research Sponsor: Sanofi, Biond Biologics.

2572 **Poster Session**

Safety and tolerability of T-SIGn vectors when administered using "flat" versus "low-high-high" (LHH) dosing regimens. *First Author: Thomas Lillie, PsiOxus Therapeutics Ltd, Abingdon, United Kingdom*

Background: Tumor-selective viruses, particularly those dosed systemically to deliver transgenes, are potentially powerful cancer therapies. However, acute cytokine reactions to viral particle (vp) infusion may affect vector tolerability [Small 2006], thereby limiting the maximum tolerated dose (MTD) and subsequent transgene delivery. T-SIGn vectors (e.g. NG-641 and NG-350A) are transgene-armed variants of the epithelial tumor-selective adenovirus enadenotucirev (EnAd). Acute serum cytokine increases post-dosing have been seen at the MTD of EnAd ("flat" dosing of 3×10^{12} vp on Days [D] 1, 3 and 5) [Machiels 2019]. Following supportive preclinical data [McElwaine-Johnn 2019], we explored if a LHH dosing regimen, in which a lower dose is given on D1 prior to two higher doses on D3 and 5, may improve vector safety/tolerability thereby allowing higher cumulative doses to be given. **Methods:** Data were pooled from three Phase 1 dose-escalation studies in advanced/metastatic epithelial cancer: SPICE (EnAd + pembrolizumab/nivolumab; NCT02636036), FORTITUDE (NG-350A ± pembrolizumab; NCT03852511) and STAR (NG-641; NCT04053283). Serum cytokines were measured using a 17-analyte Luminex assay. IL-6/MCP-1 data for D1, 3 and 5 (pre- and 6-10 hrs post-dose) were analyzed to examine acute cytokine changes. TNFα/IFNγ were examined due to their association with cytokine release syndrome (CRS). Samples analyzed from SPICE/FORTITUDE were taken before PD-1 inhibitor administration. **Results:** 84 patients (SPICE n=51; FORTITUDE n=18; STAR n=15) were included in these analyses; 79 had cytokine data. AEs and Gr≥3 AEs within 1 wk of first dose, and DLTs at any time, were less frequent with a LHH vs flat dosing regimen (Tbl). Importantly, a LHH dose of 1-6-6 (1×10^{12} vp on D1; 6×10^{12} vp on D3 and 5; greater than the previous flat MTD) was tolerated. Acute increases in TNFα/IFNγ were limited and no severe CRS was seen. Increases in IL-6/MCP-1 with 1×10^{11} or 1×10^{12} vp flat dosing were negligible, whereas acute increases in IL-6/MCP-1 were seen after the first dose of 3×10^{12} vp when given as a flat dose (negligible increases on D3/5). Notably, cytokine responses with 1-3-3 dosing (1×10^{12} vp on D1; 3×10^{12} vp on D3 and 5), including after the first 3×10^{12} vp dose on D3, were negligible. Cytokine responses after the first dose of 6×10^{12} vp in the 1-6-6 regimen were similar to those seen with the first dose of the flat 3×10^{12} vp regimen. **Conclusions:** LHH dosing appears to induce a desensitization mechanism allowing higher cumulative doses of T-SIGn vectors to be given without the associated acute reactions to viral infusions. This finding may have implications for optimizing safety-efficacy profiles of viral vectors in cancer. Clinical trial information: NCT02636036, NCT03852511 and NCT04053283. Research Sponsor: PsiOxus Therapeutics Ltd.

Safety summary (% of patients).

	Flat 1×10^{11} (n=10)	Flat 1×10^{12} (n=26)	Flat 3×10^{12} (n=22)	1-3-3 and 1-6-6 (n=26)
Days 1-7				
AE	100	100	100	92
Gr≥3 AE	0	19	41	15
SAE	30	8	5	15
Related SAE	30	8	0	4
DLTs any time	10	15	14	4

2573 **Poster Session**

Micro-organospheres retain patient tumor microenvironment for precision immuno-oncology. *First Author: Shengli Ding, Xilis.Inc, Durham, NC*

Background: Current patient-derived organoid (PDO) models are largely devoid of immune components. We developed a precision microfluidic and membrane platform to generate patient-derived micro-organospheres (MOS) that retain tumor-resident immune and stromal components for personalized immuno-oncology (IO) assays. **Methods:** MOS were generated from lung, kidney, and colorectal cancer patients. The composition and function of patient tumor-resident immune cells in MOS were characterized by flow cytometry, single-cell RNA-seq, antibody staining, and TCR-seq. High-content and longitudinal imaging with AI analyses were used to quantify tumor cell death and immune cell dynamics inside MOS in response to IO therapies including checkpoint inhibitors, T cell bispecific antibodies, and adoptive tumor infiltrating lymphocyte (TIL) therapies, followed by single-cell analyses. **Results:** Tumor and stromal cells quickly form tissue niches inside MOS to sustain the viability and function of encapsulated immune cells. MOS derived from lung and kidney cancer patients respond to Nivolumab, indicated by the Annexin V apoptosis marker. ESK1* (TCB antibody targeting HLA-A2/WT1) induces killing in eight lung tumor patients derived MOS. We further developed a MOS T-cell potency assay as autologous TILs or PBMC efficiently infiltrate MOS from lung, kidney and CRC patients and induce tumor cell apoptosis. Adjunctive therapies combining TCB with TILs enhanced the potency of adoptive cell therapy against lung tumor. Based on the data, three ongoing and upcoming personalize IO clinical trials will further validate the ability of the MOS assay to predict patient response to TCB, checkpoint combinations, and adoptive cell therapy. **Conclusions:** MOS provide a rapid and scalable personalized platform for developing and testing IO therapies such as checkpoint inhibitors, bispecific antibodies, and T cell therapies on patient tumor models that still retain the original tumor microenvironments. Research Sponsor: None.

2574 **Poster Session**

Phase 1b study of the novel first-in-class G protein-coupled estrogen receptor (GPER) agonist, LNS8801, in combination with pembrolizumab in patients with immune checkpoint inhibitor (ICI)-relapsed and refractory solid malignancies and dose escalation update. *First Author: Carolyn Muller, University of New Mexico, Albuquerque, NM*

Background: LNS8801 is an oral, highly selective, small molecule agonist of the G protein-coupled estrogen receptor (GPER). LNS8801 normalizes c-Myc levels in cancer cells, inhibits proliferation, suppresses invasion, and enhances immune recognition. In preclinical models, LNS8801 has demonstrated increased activity with ICIs. In the first-in-human dose escalation study, LNS8801 was safe and tolerable alone and in combination with pembrolizumab in patients with metastatic solid tumors (NCT04130516). **Methods:** Patients who are relapsed and refractory (r/r) to PD-1/L1 ICIs and have measurable disease are enrolling in a Phase 1b cohort and receive LNS8801 (125 mg, QD, PO) and pembrolizumab (200 mg, Q3W, IV) (NCT04130516). The primary objective is safety and tolerability assessed according to NCI CTCAE v5.0. Secondary endpoints include pharmacokinetic, pharmacodynamics (eg., increase in serum prolactin over the initial 10 hours of dosing to assess GPER engagement), objective response rate and clinical benefit rate per RECIST v1.1. **Results**: Updates from the dose escalation portion of the study include long term benefit in a monotherapy patient with cutaneous melanoma on treatment for 2 years with RECIST stable, metabolically inactive disease by PET; a metastatic uveal melanoma patient on therapy for a year, and growing confidence in LNS8801's favorable safety profile and predictive systemic biomarkers. As of 2/1/22, 13 ICI r/r patients were treated with LNS8801 and pembrolizumab, including those who entered the study directly after confirmed progression on ICIs. Cancer types include lung (3), colorectal, vaginal, nasopharyngeal, neuroendocrine, uterine, and pancreatic cancer, mesothelioma (2), and cutaneous and uveal melanoma. 46% of patients had AEs possibly related to study drugs (31% grades 1-2 and 31% grade 3), with colitis (15%) and fatigue (23%) appearing in more than 10% of patients. Of the 10 evaluable patients, 7 had stable disease (SD), with 4 patients demonstrating tumor regression. At the data cut-off, duration of treatment ranged from 0.7–7.5 months with 4 patients treated between 4.8 and 7.5 months and 4 patients continuing on treatment. All evaluated patients with SD had a prolactin response indicative of systemic target engagement. **Conclusions**: The combination of LNS8801 and pembrolizumab is tolerable without unanticipated toxicities and demonstrates encouraging anti-tumor activity in patients that are r/r to ICIs, including patients who enrolled immediately after confirmed progression on pembrolizumab alone. These data, as well as continued follow-up on patients with long-term benefit from dose escalation, support further development of LNS8801 as a cancer therapeutic. Clinical trial information: NCT04130516. Research Sponsor: Linnaeus Therapeutics.

2575 **Poster Session**

Phase I study of epacadostat in combination with sirolimus in advanced malignancy. *First Author: Chao Hui Huang, University of Kansas Medical Center, Westwood, KS*

Background: Epacadostat (E) is an inhibitor of Indoleamine 2,3 dioxygenase-1 (IDO1) which is a rate-limiting enzyme in the catabolism of tryptophan to kynurenine. The inhibition of IDO1 leads to increase tryptophan and reversal of immunosuppression by increasing the proliferation of T cells, suppression of regulatory T cells (Tregs) and activation of mTOR which suppresses autophagy. Sirolimus (S) can reverse the mTOR activation induced by E, suppress the expression of PD-L1 and function of Tregs. We initiated a phase I trial to test the safety and tolerability of SE combination in patients with advanced solid tumors, with plans for an expansion phase II study in patients with advanced recurrent lung cancer once maximum tolerated dose (MTD) was defined. **Methods:** The phase I trial portion of the study used a modified 3+3 design in which the dose transition rule was similar to standard 3+3 design with the modification based on sirolimus PK data. S had a lead-in of 3mg/day(d) at day -7 followed by 1mg/d with E added on day 1 of Cycle 1 starting at 300mg bid in a 28d cycle at dose level 1; then S is escalated to 6mg/d followed by 2mg/d maintenance with E at 300mg bid at level 2. An additional level 3 was added with S at 6mg/d followed by 2mg/day with E at 400 bid based on results of E at 400-600 mg bid in combination with a checkpoint inhibitor with improved control of peripheral kynurenine and intra-tumoral kynurenine reductions. Enrollment continued until Dose limiting toxicity (DLT) which was defined as grade 3 hematologic toxicities or grade 3 or 4 non-hematologic toxicities up to Cycle 2 day 1. MTD was defined as DLT not exceeding 33% of subjects. **Results:** The phase I study enrolled 15 patients, with 9 patients evaluable. The types of cancers were non-small cell lung ca (1), colorectal (5), esophagus (1), gallbladder (1) and sarcoma (1). DLT was not observed up to level 3. Adverse events attributed to SE were Grade 1 Diarrhea (2), stomach pain (1); elevated liver enzymes (ELE) (1), decreased white blood cell (1), anorexia (1), hypokalemia (1), dizziness (1), skin rash (1); Grade 2 ELE (1), Anemia (1), Vertigo (1), Constipation (1), Nausea (2); Grade 3: Diarrhea (1), serotonin syndrome (1), dyspnea (1). The best response observed was stable disease in 3 patients, 5 patients had disease progression and 1 patient was not assessable for response due treatment discontinuation related to side effect of serotonin syndrome. The Expansion Cohort (Part 2) did not proceed since the sponsor decided to discontinue further development of E. **Conclusions:** The combination of SE is feasible, tolerable with mostly grade 1 and 2 toxicities. There were few grades 3 toxicities. SE produced stable disease as best response in 33% of patients. Research using the combination of SE as an immunomodulatory therapy in patients with lung cancer resistant to checkpoint inhibitor is worth additional exploration. Clinical trial information: NCT03217669. Research Sponsor: Epacadostat.

2576 **Poster Session**

Systemic TLR7/8 micelles trigger a novel and potent anti-tumor response by strong recruitment of neutrophils leading to massive tumor cell killing. *First Author: Simon Skjøde Jensen, MonTa Biosciences, Kgs Lyngby, Denmark*

Background: Clinical use of TLR7/8 agonists is currently restricted to topical application of Imiquimod for treatment of superficial basal cell carcinoma since systemic administration is prevented due to dose-limiting toxicity. Here, we present a novel micelle-based drug delivery technology containing a lipid-anchored TLR7/8 agonist for intravenous administration. The MBS8 formulation shows good efficacy in mouse cancer models, is well tolerated in rodents and non-human primates and is currently being tested in clinical studies (NCT04855435). **Methods:** MBS8 was tested in 12 syngeneic mouse cancer models as monotherapy or in combination anti-PD-1 and anti-PD-L1 antibodies. MBS8 was administered IV as slow bolus. Tumors and spleens were analysed using histology, immunohistochemistry, ELISPOT and flow cytometry. Phenotyping of tumor microenvironment was done using flow cytometry and Nanostring analyses. Safety and tolerability were tested in mice, rats and monkeys. Safety-related and PD biomarkers were identified in monkeys using a multiplex MSD technology and validated in whole human blood stimulated with MBS8 *ex-vivo*. **Results:** In several syngeneic mouse tumor models, MBS8 led to complete eradication of established tumors. The complete responders showed tumor rejection upon re-challenge. In these mice, a $CD8^+$-dependent tumor-specific immune memory response was evident. Tumors demonstrated a massive tissue necrosis (> 80%) within 24-48h after the first drug administration and showed massive neutrophil infiltration 6h after dosing. Antigen specific $CD8^+$ T-cells were detected in tumors 24 hours after treatment with increased $CD8^+$:T_{reg} cell ratio and enhanced antigen presentation in tdLN. MBS8 showed both additive and synergistic effect when combined with anti-PD-1 or anti-PD-L1 antibody treatment. Moreover, in tumors being resistant to anti-PD-1 treatment, co-administration of MBS8 reverted sensitivity to anti-PD-1 treatment in a synergistic manner. A panel of cytokines induced by MBS8 upon repeat dose administration in monkeys was identified in plasma as potential biomarkers. Ten of them were further evaluated in whole human blood treated with MBS8 *ex vivo*. Currently, these cytokines are being used in Phase I clinical studies. **Conclusions:** MBS8 showed significant anti-cancer activity in multiple *in vivo* solid tumor models when administered either as monotherapy or in combination with ICIs. MBS8 demonstrated a novel mode of action with neutrophils playing a central role as primary effector cells causing a rapid killing of tumors. Further, adaptive immune response was initiated including generation of tumor specific $CD8^+$ cells and establishment of the immune memory. MBS8 was well tolerated in rodents and cynomolgus monkeys at the dose levels above therapeutic effective doses identified in mice, thus providing a good therapeutic window. Research Sponsor: MonTa Biosciences.

2577 **Poster Session**

Phase I dose escalation of LAVA-051, a novel bispecific gamma-delta T-cell engager (Gammabody), in relapsed/refractory hematological malignancies. *First Author: Annemiek Broijl, Department of Hematology, Erasmus MC Cancer Institute, Rotterdam, Netherlands*

Background: LAVA-051 is a 27kD humanized bispecific single domain antibody (VHH) that directly engages CD1d and the Vδ2-TCR chain of Vγ9Vδ2-T cells and additionally stabilizes the interaction between CD1d and type 1 NKT cells (Nature Cancer 2020;1:1054-1065) to mediate potent killing of CD1d-expressing tumor cells. By engaging innate-like T cell subsets with inherent antitumor activity, namely Vγ9Vδ2-T and type 1 NKT cells, LAVA-051 has the potential to combine high therapeutic efficacy with limited off-tumor toxicity. CD1d is expressed by tumor cells in the majority of patients with CLL (chronic lymphocytic leukemia) and MM (multiple myeloma), while expression in AML (acute myeloid leukemia) is most pronounced on (myelo)monocytic subtypes. Tolerability studies in non-human primates with cross-reactive surrogate bispecific γδ-T cell engagers showed a good safety profile without signs of CRS (cytokine release syndrome). **Methods:** This is an open label, accelerated titration design, phase 1/2a study in patients with relapsed/ refractory CLL, MM, and AML (NCT04887259). The phase 1 study starts with single-patient cohorts for the first 3 dose levels followed by a 3+3 design. The primary objectives of the study are to investigate the safety and tolerability of LAVA-051 and to determine its recommended Phase 2a dose (RP2D). Secondary objectives of the study include evaluation of PK, PD, immunogenicity, and preliminary antitumor activity. The (flat) starting dose was determined to be 0.45 μg. LAVA-051 is administered by IV infusion over 2 hours twice a week. **Results:** As of Feb 14, 2022, a dose level of 45 μg has been reached with no reports of CRS (ASTCT grading) or dose limiting toxicities (DLTs). Six patients in total have been treated with LAVA-051; 4 patients (2 MM, 2 CLL) were evaluable for DLTs during cycle 1 at dose levels 0.45 μg, 3 μg, 15 μg and 45 μg. Treatment emergent AEs (TEAEs) (CTCAEv5.0) were predominantly of grade 1 and 2 severity (e.g. fever, chills, and headache) . One patient (45 μg) reported a grade 2 infusion related reaction (IRR) that lasted less than 12 hours following the first administration only. Frequency and severity of TEAEs did not increase with escalating doses and all TEAEs were reversible. One patient with CLL developed symptoms consistent with a tumor flare reaction during cycle 1, and continues on cycle 5 of treatment with stable disease at 15 μg. PK data indicate increasing drug exposure in correlation with increasing doses of LAVA-051, and PD data indicate a dose-dependent increase in LAVA-051 receptor occupancy of the Vγ9Vδ2-T cell receptor. Importantly, no consistent or significant changes in measured cytokines have been observed. Updated results will be presented at the congress. **Conclusions:** LAVA-051 has been well tolerated early in dose escalation with on-mechanism pharmacodynamics consistent with Vγ9Vδ2-T cell engagement. Clinical trial information: NCT04887259. Research Sponsor: LAVA Therapeutics N.V.

2578 **Poster Session**

Assessing PD-L1 without a biopsy and through PD-L1 PET imaging with 18F-BMS-986229. *First Author: Michael A. Postow, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Programmed death ligand-1 (PD-L1) is usually determined by immunohistochemistry (IHC). Determining PD-L1 status by whole body, non-invasive PD-L1 PET imaging with 18F-BMS-986229 tracer infusion may be a way to circumvent limitations to PD-L1 IHC such as poor tissue availability; discrepant PD-L1 IHC results among different tumors within the same patient; and inability to measure PD-L1 longitudinally given challenges with repeated biopsies. **Methods:** Within the prospective ADAPT-IT trial (NCT03122522) testing an abbreviated course of nivolumab (nivo) + ipilimumab (ipi) in patients with unresectable stage III or IV melanoma, we investigated PD-L1 PET imaging in a 10-patient expansion cohort at baseline and after 6 weeks of treatment. Maximum standard uptake value (SUV max) and mean of all SUV max for lesions for PD-L1 PET were calculated on a whole patient level for each target/ non target lesion. Standard treatment response was determined by RECIST v1.1 at weeks 6 and 12. PD-L1 IHC was scored using the E1L3N antibody by tumor proportion score (TPS), Immune Cell Score (ICS), and a Combined Positive Score (CPS). Comparisons between PD-L1 PET parameters and response were determined by complete or partial response (CR/PR); stable disease (SD), and progressive disease (PD) at respective imaging timepoints. Absolute changes in PD-L1 SUV mean and max were calculated between scans. The correlation between PD-L1 PET and IHC was estimated using Spearman's coefficient correlation. **Results:** Five patients (50%) had a PR to treatment at week 6; one of these PR became a CR at week 12 and one PR was not assessable at week 12. All RECIST responders at week 6 (n = 5) had baseline PD-L1 SUV mean ≥3.00, and all progressors at week 6 (n = 3) had baseline PD-L1 SUV mean ≤2.60 (Table). A similar trend was observed when assessing response at week 12 and when considering baseline PD-L1 SUV max. Patients had changes in their PD-L1 SUV levels between baseline and week 6. Baseline PD-L1 SUV mean (inclusive of all lesions within a patient) correlated with PD-L1 IHC by TPS, ICS, and CPS (r = 0.64, 0.5, 0.47, respectively). No patients had side effects from 18F-BMS-986229 tracer infusion. **Conclusions:** The signal of PD-L1 positivity by PET imaging with 18F-BMS-986229 at baseline appears associated with early efficacy from nivo + ipi in this small cohort and may offer additional information than PD-L1 IHC. The ability to assess PD-L1 on a whole patient level at multiple timepoints on treatment may have future implications in how best to sequence and combine immunotherapies but further study in larger patient cohorts is needed. Clinical trial information: NCT03122522. Research Sponsor: Bristol Myers-Squibb.

	PR[1], N = 5	SD[1], N = 2	PD[1], N = 3
Mean of Baseline PD-L1 SUV[2] (PD-L1 positive lesions only)	5.40 [3.00 – 8.60]	3.58 [3.15 – 4.00]	2.40 [2.20 – 2.60]
Max of Baseline PD-L1 SUV[2]	7.30 [3.20 – 8.60]	4.90 [4.60 – 5.20]	2.20 [0.00 – 2.60]

[1]Assessed at Week 6
[2]Median [Range]

2579 **Poster Session**

The effects of AVM0703 mobilization of endogenous gamma delta/invariant TCR+ bispecific natural killer T-like cells against solid tumors and blood cancers. *First Author: Theresa Deisher, AVM Biotechnology, LLC, Seattle, WA*

Background: Glucocorticoids (GC) are a common component of blood cancer regimens, typically at doses 40 mg or lower due to concerns of pancreatitis and hepatotoxicity (Walasik-Szemplińska et al. Thyroid Research. 2019;12:13; Ataallah et al. Cureus. 2020;12[7]) and neuropsychiatric effects. AVM Biotechnology has developed a high concentration, high volume, preservative-free, patent pending formulation of dexamethasone (AVM0703), that allows administration of up to 21 mg/kg (1470 mg for 70 kg) over a one-hour IV infusion. Prophylactic use of circadian physiologic hydrocortisone reduces the risk of GC neuropsychiatric side-effects (Warris LT, et al. J. Clin. Oncol. 2016;34:2287; Meijer & de Kloet Endocrinology. 2017;158:448). Acute supra-pharmacologic doses (>6 mg/kg) AVM0703 mobilizes endogenous bispecific gamma delta invariant TCR+ bi-specific Natural Killer T-like cells (AVM-NKT) (PCT/US21/19773), via a non-GC receptor, that rapidly home to diseased organs in preclinical models and are directly related to tumor killing, including Non-Hodgkin's Lymphoma, Melanoma, and Multiple Myeloma. **Methods:** Cancer cell lines and (mouse host) were i) immune-resistant mouse A20 B lymphoma (Balb/c), ii) xenografted human T-ALL CCRF-CEM (NCRnu), iii) mouse B16F10 melanoma (B62DF1), and iv) mouse MOPC315 (Balb/c). Cancer cell lines were inoculated into the flank either as single cell suspensions or encased in Matrigel. When tumor volume reached between 100-500mm^3 well-established tumors, mice were orally gavaged with a human equivalent dose (HED) of 15-18 mg/kg AVM0703 as monotherapy, or as a preconditioning prior to adoptive cell transfer (ACT), or in combination with chemotherapy. Responses were determined by tumor volume measurements, tumor immunohistochemistry or flow cytometry detection of residual cancer cells. **Results:** Immunohistochemistry analysis of tumors from AVM0703 treated mice demonstrated pseudoprogression similar to checkpoint inhibitors: *i.e.* tumors were measurable however in some cases all cancer cells had been eradicated. Therefore, subsequent tumor monitoring at end point was done by flow cytometry to quantify the total number of live cancer cells more accurately than tumor measurements by calipers or immunohistochemistry, due to pseudoprogression and limitations of examining only a few sections from each tumor. **Conclusions:** AVM0703 led to: i) complete response (CR) in 27% of immune-resistant mouse A20 tumors as monotherapy and CR in 60% when combined with 2 doses of cyclophosphamide/fludarabine (CyFlu); ii) tumor eradication and long-term memory against xenografted human T-ALL; iii) enhancement of ACT equivalent to CyFlu preconditioning in mouse melanoma; and iv) preliminary 95% CR against mouse multiple myeloma. Research Sponsor: AVM Biotechnology, U.S. National Institutes of Health.

2580 **Poster Session**

Radiotherapy-immunotherapy related pneumonitis prediction from pretreatment CT using a deep graph-based integrative model. *First Author: Linlin Yang, Shandong Cancer Hospital and Institute, Jinan, China*

Background: Early prediction of symptomatic pneumonitis (grade ≥ 2) could potentially assist the comprehensive management for non-small cell lung cancer (NSCLC) patients who received radiotherapy combined with immunotherapy. A more accurate integrative model for symptomatic pneumonia prediction using CT images is needed. **Methods:** This retrospective study contains 243 NSCLC patients (62 symptomatic pneumonitis) who underwent radiotherapy combined with immunotherapy between January 2015 and June 2021. Five-fold cross-validation was performed for training and testing. There were 195 cases in the training set (50 symptomatic pneumonitis) and 48 cases in the validation set (12 symptomatic pneumonitis) in each fold. The deep graph integrative model (DG) was composed of two pretrained 3D UNet encoders to extract deep features from tumor and lung volumes of pre-treatment CT images, respectively, and a graph attention layer (GAT) for integration and classification. The encoders were fine-tuned using manually segmented tumor and lung CT volumetric patches from the training set. Evaluation measures include area under ROC curve (auc), sensitivity (sen), and specificity (spe). **Results:** Our new DG achieved auc, sen, and spe of 0.823, 0.767, and 0.810, which outperformed conventional CT radiomics model (auc 0.743, sen 0.620, spe 0.752), 3D UNet based deep radiomics model (auc 0.761, sen 0.746, spe 0.737), and our model without GAT (auc 0.796, sen 0.762, spe 0.782). The improvement was statistically significant ($p < 0.001$). **Conclusions:** Our DG model improved symptomatic pneumonia prediction using CT images, which can be used as a tool to effectively improve the safety and personalized treatment of combined radiotherapy with immunotherapy for NSCLC patients. Research Sponsor: National Natural Science Foundation of China.

2581 **Poster Session**

Outcomes of patients (pts) treated with novel immunotherapy (IT) agents in phase 1 clinical trials (Ph1-CT) at early lines for advanced disease. *First Author: Juan Jose Soto Castillo, Medical Oncology Department-Phase 1 Functional Unit, Catalan Institute of Oncology (ICO), L'Hospitalet De Llobregat, Barcelona, Spain*

Background: The overall survival (OS) benefit observed with immune checkpoint inhibitors led to their approval in many tumor types. Given the large number of IT compounds in early clinical development, many pts are offered IT within Ph1-CT even before having exhausted standard of care (SOC) therapies. We assessed outcomes of pts receiving novel IT treatments within Ph1-CT at the Phase 1 Unit of Catalan Institute of Oncology (ICO), Barcelona, Spain. **Methods:** We retrospectively reviewed a correlative series of pts with advanced/metastatic solid tumors treated with IT within Ph1-CT at ICO from January 2018 to June 2021. Primary endpoint was to assess clinical outcomes measured by median progression-free survival (mPFS) and median OS (mOS) according to number of prior lines (PL) for recurrent/metastatic disease, grade 3-4 toxicity (G3-4 Tox) and age. Data on prior IT (yes vs no) and availability of alternative SOC were evaluated. Overall response rate (ORR) was assessed according to RECIST 1.1. Clinical benefit rate (CBR) was defined as complete/partial response + stable disease for ≥6 months (m). PFS/OS were calculated by Kaplan-Meier method. Log-rank test was used for comparisons. Median PFS of alternative SOC according to historical data was recorded by tumor type and line of treatment. **Results:** A total of 104 pts received IT within Ph1-CT: IT monotherapy = 39 (37.5%), IT combinations = 65 (62.5%) (IT+IT = 59 [90.8%], IT+targeted therapy = 6 [9.2%]). Median age was 54 y (42-77), 62.5% were men and all had ECOG 0-1. Four most frequent cancers were urothelial (19.2%), colorectal (15.3%), head & neck (12.5%) and glioblastoma (11.5%). Number of PL: 0 = 20 (19.2%) pts, 1 = 37 (35.6%) pts, ≥2 = 47 (45.2%) pts. Nine (8.6%) pts had received prior IT. G3-4 Tox rate for the overall population was 19.2% and for pts who had received prior IT was 33%. ORR was 11.5%; CBR was 24%. Overall mPFS and mOS were 2.7m and 8.6m, respectively. Pts with less PL had greater mPFS and mOS ($p < 0.05$) (Table). Pts with available alternative SOC had lower mPFS but similar mOS compared to historical SOC (2.6m vs 4.8m, 11.4m vs 11.8m, respectively). G3-4 Tox (yes vs no) and age (< 70 vs ≥70) did not significantly impact on mOS or mPFS ($p = 0.18$ and $p = 0.83$, respectively). At end of Ph1-CT treatment, 47 (45.2%) pts worsened their ECOG status, 15 (14.4%) pts were enrolled in a subsequent trial and 22 (21.1%) pts received SOC. **Conclusions:** In our cohort of pts treated with novel IT within Ph1-CT, overall clinical outcomes were modest in terms of mPFS, mOS, and CBR. However, pts with less pre-treated tumors seem to achieve higher survival benefit from early treatment with IT within Ph1-CT, although this benefit remains unclear in pts with alternative SOC. Research Sponsor: None.

Pts	PFS(m)	OS(m)
≤1 PL vs ≥2 PL	3.8 vs 2.5, **p 0.003**	14.1 vs 8.7, **p 0.002**
≤2 PL vs > 2 PL	3.6 vs 1.3, **p 0.002**	11.5 vs 1.7, **p 0.004**
Pts in IT Ph1-CT (with vs without available SOC)	2.6 vs 2.1, **p 0.048**	11.4 vs 4, **p 0.0083**

2582 **Poster Session**

A phase 1 first-in-human dose finding/randomized phase 2 study of IMM60 and pembrolizumab (PEM) in advanced melanoma and non–small cell lung cancer (NSCLC; IMP-MEL). *First Author: Nicholas Coupe, Oxford University Hospital, Oxford, United Kingdom*

Background: Invariant natural killer T-cells (iNKTs) share features of innate cells (NK-like) and T-cells (can prime and boost an adaptive immune response). The importance of this relatively rare lymphocyte subset has generated increased interest due to its dual ability to have a direct cytotoxic effect on CD1d expressing tumors and also its ability to induce long-lasting antitumor CD8 T cell responses mediated by cross priming and licensing of dendritic cells. Various clinical approaches involving the use of allogenic iNKT cells (both untransduced and CARs) are in development and here we describe initial clinical studies with IMM60, a synthetically derived agonist of iNKT cells which is formulated in a liposome(PORT-2). In preclinical studies, IMM-60 treatment results in maturation of DCs and B cells and a potent stimulation of iNKT cell-derived IFN-g. In efficacy studies, IMM60 demonstrated monotherapy activity in PD-1 resistant models, (eg., B16-F10), up-regulation of PD-L1 expression on cancer cells as a consequence of its priming effect, and was able to overcome resistance to PD-1 antibody therapy. **Methods:** IMP-MEL is an open-label first-in-man phase 1/2 study, currently enrolling adult subjects with advanced NSCLC and melanoma. IMM60 containing liposomes were administered IV Q3W at 3 escalating dose levels for 6 doses alone or with PEM 200mg Q3W. The study seeks to assess the safety and efficacy of IMM-60 alone and in combination with PEM. **Results:** 5 subjects have been enrolled in the monotherapy cohort having a median of 3 prior therapies (min 2, max 5). Median age was 64.5 years. No treatment related adverse events have been reported nor any objective disease responses in the evaluable monotherapy subjects (n=3) to date. **Conclusions:** IMM-60 is well tolerated when administered IV as monotherapy at the doses tested. The liposomal formulation leads to a favorable preliminary safety profile. Full results of the phase 1 will be reported at the meeting with analysis of circulating cytokines and flow cytometric analysis. The trial plans to transition to phase 2 testing IMM60-alone vs PEM monotherapy vs the combination of IMM60 with PEM. Clinical trial information: 80472712. Research Sponsor: iOX Therapeutics, University of Oxford.

2583 **Poster Session**

A phase 1 study of the novel immunotoxin MT-5111 in patients with HER2+ tumors: Interim results. *First Author: Brian Andrew Van Tine, Washington University in Saint Louis, St. Louis, MO*

Background: MT-5111 is a 55kD engineered toxin body (ETB) targeting HER2 in solid tumors that binds to an epitope distinct from trastuzumab and pertuzumab, offering potential combination strategies with other HER2-targeting agents. MT-5111 may demonstrate efficacy in patients (pts) resistant to other HER2-targeting agents, as its mechanism of action induces direct cell kill via enzymatic and permanent ribosome destruction. **Methods:** This is a phase 1 study in adults with advanced HER2+ solid tumors. The dose-escalation portion (Part A) enrolls pts into sequential dose cohorts, followed by Part B expansion cohorts for HER2+ breast cancer (BC), gastroesophageal adenocarcinoma (GEA), and any other HER2+ cancer (CA). MT-5111 is dosed weekly IV over 30 min in each 21-day treatment (tx) cycle until disease progression, unacceptable toxicity, death or withdrawn consent. **Results:** As of Jan 2022, 27 pts had enrolled in Part A cohorts (0.5 to 10 μg/kg/dose) with completed DLT assessments: 9 (33%) pts were male and 18 (67%) female, median age 67 and a median of 4 prior systemic and 2 prior HER2-targeting tx. Common tissue types were BC (9/30%), biliary CA (6/22%), GEA (4/15%). The following safety data reflect 33 treated pts to date including ongoing 13 μg/kg/dose Part A and 10 μg/kg/dose BC expansion cohorts. No Grade (G) 4/5 tx-emergent adverse events (AEs) or DLTs occurred. Tx-related AEs occurred in 17 (52%) pts, most commonly G1/2 fatigue (8/24%). 3 pts had G1 troponin elevations without clinical signs or symptoms of cardiac distress: 1 at 6.75 μg/kg/dose, 2 at 10 μg/kg/dose. 2 pts (3 and 4.5 μg/kg/dose) had reversible G2 and G1, respectively, infusion-related reactions (IRR)s. A comparison of cytokines from baseline to on-treatment timepoints reveals no evidence of significant changes, even in pts with IRR. Best response per RECIST thus far was stable disease (SD) in 7 pts or non-CR/non-PD in 2 pts: 1 pt had SD for 12 weeks (wks) (4.5 μg/kg, pancreatic CA); 1 pt (1 μg/kg/dose, BC) had non-CR/non-PD for 30 wks; 1 pt (10 μg/kg/dose, GEA) has ongoing SD for 18 wks. AUC_{last} data match PK simulations in non-human primate studies. C_{max} at 10 μg/kg/dose is ≥5 times the IC_{50} values of high HER2 expressing gastric CA and BC cell lines while approaching the IC_{50} of a moderately HER2 expressing liver CA cell line. **Conclusions:** MT-5111 is well tolerated to-date with no clinically significant immuno/cardiotoxicity. Dose escalation is ongoing at a dose of 13μg/kg, expected to be required for efficacious exposure. Clinical trial information: NCT04029922. Research Sponsor: Molecular Templates, Inc.

2584 **Poster Session**

Factors associated with acute kidney injury among patients with cancer treated with immune checkpoint inhibitor therapy: A population-based study. *First Author: Phillip S. Blanchette, ICES, London Health Sciences Centre, Western University, London, ON, Canada*

Background: Cancer immune checkpoint inhibitor (ICI) therapy may be associated with kidney immune-related adverse events (IRAEs) and other causes of acute kidney injury (AKI). In clinical trials, the frequency of AKI events was uncommon, however, further real-world study is warranted. **Methods:** We evaluated the proportion of AKI events among patients with advanced cancer (bladder, head and neck, lung, kidney and malignant melanoma) treated with ICI therapy in Ontario, Canada from 2012 - 2018. AKI was defined by a rise in the concentration of serum creatinine as per Kidney Disease: Improving Global Outcomes (KDIGO) criteria. A multivariable regression model was used to identify predictors of AKI while accounting for the competing risk of death. **Results:** A total of 4,380 patients received ICI therapy. In follow-up, 1,283 (29%) had recorded AKI event (any stage AKI) and 289 (7%) had a severe AKI event (≥ stage 2). Median time to AKI was 6 months (Interquartile Range 2-16 months) and ≤ 1 % of patients received dialysis therapy. Within 30 days of any observed AKI event, 853 (58%) discontinued ICI therapy, 372 (29%) were hospitalized and 266 (21%) died. Mortality was significantly higher among patients who experiencing a severe AKI event (≥ stage 2) as compared to patients with a less severe AKI event (stage 1) or no observed AKI event. Among patients alive at 30 days following an AKI event, 14% received an outpatient corticosteroid or immunosuppressive therapy prescription, 7% had a visit with a nephrologist. Characteristics associated with a higher risk of AKI included female sex, bladder or kidney cancer (reference malignant melanoma), history of hypertension or diabetes, higher Charlson comorbidity score, a baseline estimated glomerular filtration rate less than 30 mL/min/1.73 m^2, or outpatient prescription for either a proton pump inhibitor or non-steroidal anti-inflammatory drug. Among patients with an AKI event and treatment discontinuation, re-challenge of ICI therapy was infrequent (16%) with a significant risk of a recurrent AKI event (57%). **Conclusions:** In a population-based study among patients with cancer receiving ICI therapy, the rate of AKI was common (29%) but severe AKI was less frequent (7%). Rates of ICI discontinuation, hospitalization and death are substantial following an AKI event. Kidney function should be monitored carefully among patients undergoing ICI therapy who have common risk factors for developing renal disease. Nephrology consultation may be optimized among patients who develop a severe AKI event, especially among individuals who are considered for ICI therapy re-challenge. Research Sponsor: Medical Oncology Research Fund (MORF) London Regional Cancer Program.

2585 **Poster Session**

Systematic review and meta-analysis evaluating the impact of antibiotic use on the clinical outcomes of patients with cancer treated with immune checkpoint inhibitors. *First Author: Gerard Zalcman, Department of Thoracic Oncology, CIC INSERM 1425, Université de Paris, Hôpital Bichat, Paris, France*

Background: In recent years, the gut microbiome has increasingly emerged as influencing the response to immune checkpoint inhibitors (ICIs) and antibiotic (ABX) exposure has repeatedly been shown to impair clinical outcomes of patients suffering from different cancer types and treated with ICIs. We published in 2020 a meta-analysis confirming that ABX use hampered survival of non-small cell lung cancer (NSCLC) patients treated with ICIs. The present study aims to determine whether ABX use also reduces survival of patients receiving ICIs for other cancers. **Methods:** PubMed and major oncology conferences' proceedings were systematically searched to identify studies assessing the impact of ABX on the clinical outcomes of cancer patients treated with ICIs. Studies were included when reporting data on Overall Survival (OS), Progression-Free Survival (PFS), Overall Response Rate (ORR) and Progressive Disease Rate (PD), according to ABX exposure. Pooled Hazard Ratios (HRs) for OS and PFS and Odds Ratios (ORs) for ORR and PD were calculated, as well as HRs for OS and PFS according to different cancer types and different ABX exposure time windows (TWs). **Results:** Overall, 94 independent cohorts were included, representing 26,174 patients suffering from various types of cancer. The pooled HRs for PFS (61 cohorts, 13,224 patients) and OS (88 cohorts, 25,480 patients) were 1.47 [95% Confidence Interval (CI) 1.31-1.66] and 1.66 [95% CI 1.50-1.83], respectively, confirming a significant harmful impact of ABX on patient' survival, observed across all cancer types (Table). The analyses of OS and PFS based on ABX exposure TWs suggested a stronger deleterious effect of ABX when taken around ICI treatment initiation. The response to treatment among ABX users was also impaired: the pooled ORs for ORR (30 cohorts, 4,590 patients) and PD (33 cohorts, 4,972 patients) were 0.55 [95% CI 0.39-0.77] and 1.97 [95% CI 1.48-2.64], respectively. **Conclusions:** ABX were shown to impair the clinical outcomes of cancer patients treated with ICIs, regardless of cancer type. Research Sponsor: Da Volterra.

Impact of ABX use on the survival of cancer patients treated with ICIs.

Cancer Type	Number of Patients for OS (ABX Users)	Pooled HR OS [95% CI]	Number of Patients for PFS (ABX Users)	Pooled HR PFS [95% CI]
All Cancer Types	25,480 (6,994)	1.66 [1.50-1.83]	13,224 (4,142)	1.47 [1.31-1.66]
NSCLC	12,674 (2,834)	1.62 [1.38-1.90]	5,463 (1,368)	1.49 [1.26-1.76]
Urothelial Carcinoma	3,371 (1,545)	1.60 [1.09-2.34]	3,232 (1,499)	1.26 [0.84-1.90]
Melanoma	2,812 (339)	1.81 [1.27-2.59]	708 (111)	1.72 [0.95-3.10]
Renal Cell Carcinoma	1,029 (212)	1.84 [1.30-2.62]	529 (127)	2.04 [1.40-2.98]
Other Cancers*	2,285 (766)	1.74 [1.26-2.39]	1,983 (684)	1.55 [0.87-2.75]

*Head and neck cancer, esophagogastric cancer, Hodgkin's lymphoma, gynecologic cancers, and sarcoma.

2586 **Poster Session**

Outcomes of responders to PD-1/PD-L1 inhibitors who discontinue therapy after sustained disease control. *First Author: Harsh Sharma, University of New Mexico Hospital, Albuquerque, NM*

Background: PD-1/PD-L1 immune checkpoint inhibitors (ICIs) are widely used in the treatment of metastatic malignancies. Judiciously balancing disease control (DC) against development of immune-related adverse events (irAE) remains a crucial aspect of treatment. The effect of treatment discontinuation after sustained disease control (SDC) is unknown. The purpose of this analysis was to evaluate outcomes of responders to ICI who discontinue treatment after a minimum of 12 months (SDC). **Methods:** We retrospectively reviewed the database of the University of New Mexico Comprehensive Cancer Center between 2014 and 2021 and identified patients who had received ICI. Patients with metastatic solid tumors who had stopped ICI therapy after achieving SDC [stable disease, partial response, complete response (SD,PR,CR)] were selected and outcomes reviewed from their electronic health records. **Results:** We identified 204 patients who were treated with ICI for various solid cancers. Forty-four patients (21.6%) met the criteria, of whom 35 with follow-up data were included in the final analysis; including 11 melanoma, 5 non-small cell lung, 4 head & neck, 8 renal, 4 urothelial, 1 anal, 1 Merkel cell carcinoma, and 1 liposarcoma. Patients were divided into two groups: those who stopped ICI due to an irAE [irAE group, n=14, median treatment time (MTT), 16.6 mo] and those who stopped due to other reasons (eg completion of 2 years of therapy, n=20, non-cancer related surgery, n=1) (non-irAE group, n=21, MTT, 23.7 mo). Among the irAE group, the most common irAE included pneumonitis, rash, transaminitis, and fatigue. As of data cutoff date, 10 of 14 (71%) patients continued to show SDC. Only 4 of 14 (28.6%) patients in this group experienced progression of disease (PD), one of whom was re-challenged with nivolumab and achieved DC (median follow-up of 19.2 mo after last dose of treatment, range 3-50.2 mo). Among the non-irAE group, 13 of 21 (62%) continued to have SDC. Eight of 21 (38%) experienced PD after stopping treatment, 7 of whom received ICI rechallenge, with 2 of 7 achieving DC (median follow-up of 22.2 mo, range 3.6-54.8 mo). At a median follow-up of 21.3 mo from stopping ICI therapy (range, 3-54.8 mo), 10 patients (71%) from the irAE group and 13 (61.9%) from the non-irAE group are in DC and have not experienced PD. **Conclusions:** We demonstrate that 23 (66%) patients experienced SDC, regardless of cancer type or development of irAE. After including patients who were re-challenged with ICI due to PD, 26 (74%) remain in DC. Future prospective malignancy-specific trials such as NCT04637594 are warranted to evaluate optimal treatment duration. Research Sponsor: None.

Outcomes of ICI responders who discontinued therapy after ≥ 12 months.

Response to therapy	Non-irAE Group, n=21 (60%)	irAE Group, n=14 (40%)	Total, N=35 (100%)
Disease control	13 (61.9%)	10 (71.4%)	23 (65.7%)
PD	8	4	12
Rechallenge after PD	7	1	8
Disease control after rechallenge	2	1	3

2587 **Poster Session**

Efficacy and safety of dostarlimab in patients (pts) with mismatch repair deficient (dMMR) solid tumors: Analysis of 2 cohorts in the GARNET study. *First Author: Thierry Andre, Sorbonne University, Saint-Antoine Hospital, AP-HP, Paris, France*

Background: Dostarlimab is a programmed death 1 (PD-1) inhibitor approved in the US as a monotherapy in pts with dMMR solid tumors that have progressed on or after prior treatment, with no satisfactory alternative treatment options; or dMMR advanced/recurrent (AR) endometrial cancer (EC) that has progressed on or after treatment with a platinum-based chemo; and in the EU as a monotherapy in pts with dMMR/microsatellite instabilityhigh (MSI-H) AR EC that has progressed on or after treatment with a platinum-based chemo. Here we report on efficacy and safety in 2 expansion cohorts that enrolled pts with dMMR solid tumors. **Methods**: GARNET is a multicenter, open-label, single-arm phase 1 study. Cohort A1 enrolled pts with dMMR/MSI-H AR EC; cohort F enrolled pts with dMMR/MSI-H/POLε-mut non-EC solid tumors. Pts received 500 mg of IV dostarlimab Q3W for 4 cycles, then 1000 mg Q6W until PD, discontinuation, or withdrawal. Primary endpoints were ORR and DOR by BICR per RECIST v1.1. Biomarker status was based on local assessment. **Results**: For this third interim analysis, 153 pts with dMMR/MSI-H EC and 210 pts with dMMR/MSI-H/POLε-mut non-EC solid tumors (56% colorectal cancer, 11% gastric) were enrolled and treated. Efficacy analysis was performed for 143 dMMR/MSI-H EC and 204 dMMR/MSI-H/POLε-mut non-EC pts who had measurable disease at baseline and ≥6 mo of follow-up. ORRs were 45.5% (dMMR/MSI-H EC) and 43.1% (dMMR/POLε-mut non-EC solid tumors; Table). Probability of PFS at 6, 9, and 12 mo was 49.5%, 48.0%, and 46.4% in dMMR/MSI-H EC and 51.8%, 48.1%, and 46.4% in dMMR/MSI-H/POLε-mut non-EC. Median (m) DOR and mOS were not reached for either cohort. A total of 13 pts (8.5%) with dMMR/MSI-H EC and 12 pts (5.7%) with dMMR/MSI-H/POLε-mut non-EC solid tumors discontinued owing to a treatment-related adverse event (TRAE). TRAEs occurring in ≥12% of pts were diarrhea, asthenia, fatigue, nausea, and pruritis (dMMR/MSI-H EC) and diarrhea, asthenia, and pruritus (dMMR/MSI-H/POLε-mut non-EC solid tumors). 2 deaths (1 hepatic ischemia, 1 suicide) were attributed by investigators to dostarlimab in pts with non-EC solid tumors. **Conclusions**: Dostarlimab demonstrated durable antitumor activity across 16 tumor types in pts with dMMR solid tumors, confirming efficacy in a larger sample size with extended follow-up. The safety profile was acceptable, with manageable toxicities. Clinical trial information: NCT02715284. Research Sponsor: GlaxoSmithKline.

	dMMR/MSI-H EC N = 143	dMMR/MSI-H/POLε-mut non-EC N = 204
Median follow-up time, mo	27.6	27.7
ORR, n (%, 95% CI)	65 (45.5; 37.154.0)	88 (43.1; 36.250.2)
Response ongoing, n (%)	54 (83.1)	77 (87.5)
mDOR (range), mo	NR (1.18+ to 47.21+)	NR (2.76 to 41.49+)
mPFS (95% CI), mo	6.0 (4.118.0)	7.1 (3.619.5)
Estimated probability of PFS, % (95% CI)		
6 mo	49.5 (41.057.5)	51.8 (44.658.5)
9 mo	48.0 (39.456.0)	48.1 (40.954.8)
12 mo	46.4 (37.854.5)	46.4 (39.353.2)
mOS (95% CI), mo	NR (25.7NR)	NR (21.7NR)

NR, not reached.

2588 **Poster Session**

Extended duration of anti-PD-1 therapy, using reduced frequency dosing, in patients with advanced melanoma and Merkel cell carcinoma. *First Author: Lisa May Ling Tachiki, University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: Optimal duration of treatment (DoT) with immune checkpoint inhibitors (ICI) in patients with metastatic melanoma (Mel) and Merkel cell carcinoma (MCC) is unclear. ICI discontinuation in Mel patients, especially those without CR, may be associated with a higher rate of progression over time, as compared to ICI continuation. Thus, extending DoT could improve outcomes. However, indefinite continuation at standard frequency doses (SFD) is not logistically or financially viable. Based on data from phase I studies suggesting sustained PD-1 receptor occupancy beyond 3 months after a single dose of nivolumab, we employed reduced frequency dosing (RFD) of anti-PD-1 antibodies every 2-3 months, to extend ICI duration beyond 2 years. **Methods:** This retrospective study analyzes patients in our skin cancer clinic with metastatic Mel and MCC who experienced initial clinical benefit with anti-PD-1 administered at SFD and then transitioned to RFD. We analyzed safety and efficacy endpoints including progression free survival (PFS) and rates of immune-related adverse events (irAE) with RFD. We also compared the pharmaceutical costs and patient-centered costs between 2 years of treatment at SFD versus extended DoT at RFD. **Results:** From 2014 – 2021, 23 patients with either metastatic Mel (N = 18) or MCC (N = 5) received anti-PD-1 therapy at RFD. Median DoT at SFD in this cohort was 1.1 years (range 0.2 – 2.2) with best objective tumor responses of CR (N =6), PR (N = 11), SD (N = 6). Median DoT at RFD was 1.2 years (range 0.2 – 3.5). The median follow-up for the entire cohort is 3.7 years (range 0.7 – 6.3) after ICI initiation. The 3-year PFS in Mel patients was 100% in those with CR (3/3), 89% with PR (8/9), and 50% with SD (3/6). The 3-year PFS in MCC was 100% in all 5 patients, including patients with CR (3/3) and with PR (2/2). Any-grade irAEs occurred in 43% of patients by 3 years on RFD, and grade 3/4 irAEs presented in 15%. Among the subset of 15 patients with DoT >2 years (median 3.4 yr, range 2.0 – 5.0), total savings amounted to $1.1 million in drugs costs and 384 hours of clinic and travel time despite the increased DoT, as compared to the calculated values for 2-year DoT at SFD. **Conclusions:** RFD may provide an alternative approach to extending DoT in patients receiving ICI without additional logistical and financial burden, while preserving outcomes. Efficacy and safety data suggest sustained biologic activity of ICI with RFD administration. PK/PD analyses on patient samples are ongoing to further characterize the RFD approach. The RFD approach could be utilized to expand ICI access to communities with limited healthcare resources, thereby impacting cancer outcomes at a global scale. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

2589 **Poster Session**

The effect of circadian rhythm on clinical outcome in patients receiving pembrolizumab in the INSPIRE pan-cancer trial. *First Author: Helena Jacoba Janse van Rensburg, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: The molecular networks comprising circadian rhythm are expressed in immune cells where they affect immune-related processes. Within the emerging field of chrono-immunotherapy, it has been proposed that immunotherapies should be applied at certain times of day to optimize efficacy. Two recent reports have suggested that earlier administration of immune checkpoint inhibitors (ICIs) in non-small cell lung cancer and melanoma may offer improved survival outcomes (Karaboué et al. ASCO 2021, PMID 34780711). Whether this observation applies to other tumour types, or occurs in geographic regions with differing seasonality, is not known. **Methods:** We retrospectively analyzed the time of administration data from the INSPIRE single-centre, phase II, multi-cohort study of pembrolizumab (200 mg IV over 1 hour, q3w to maximum 35 cycles) in patients with advanced solid tumours (NCT02644369). Kaplan-Meier methods were used to estimate PFS and OS. Cox proportional hazards models were fitted to assess the association between time of administration and PFS or OS, adjusting for cohort. Fisher's exact test was used to test for association with immune-related adverse events (irAEs). **Results:** A total of 106 patients (19 head and neck squamous cell, 22 triple negative breast, 21 epithelial ovarian, 12 melanoma, 32 other solid tumours) were accrued between March 21, 2016, and May 9, 2018. Median time of follow-up was 11.5 months. Start of infusion times were obtained for 806 total doses. The median time of administration was 15h06 for the first dose and 15h11 for all doses (range 09h19 – 18h34). No differences in PFS or OS were observed between patients who received their first dose before or after noon, or before or after 15h06. Furthermore, no differences in PFS or OS were observed between patients who received ≥ 50% of their doses before or after noon, or before or after 15h11. There was also no difference in PFS or OS between patients who did or did not have a significant proportion of doses (≥ 20%) after 16h30 ("evening" in previous reports). There were no differences in the frequency of grade ≥ 2 irAEs amongst the various groups. No differences in efficacy were found when individual cohorts were evaluated separately. Finally, no differences in PFS or OS were observed when participants were grouped by season of first dose. **Conclusions:** Despite previous reports of improved survival with earlier ICI dosing, we did not identify any association of time of pembrolizumab administration with clinical outcomes. Our analysis is limited by small sample size and patient heterogeneity which may hinder identification of smaller associations. It is also unclear whether lower response rates in a pan-cancer population (relative to prior reports in lung cancer and melanoma) might impact correlation analysis. Further studies will be necessary to interrogate this phenomenon and ensure that ICI are optimally applied. Research Sponsor: Princess Margaret Cancer Foundation, Pharmaceutical/Biotech Company.

2590 **Poster Session**

A phase II study of pembrolizumab for HPV-associated papilloma patients with laryngeal, tracheal, and/or pulmonary involvement. *First Author: Sara I. Pai, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: Recurrent respiratory papillomatosis (RRP) is caused by human papillomavirus (HPV) types 6 & 11. RRP proliferates in the squamous epithelium lining the respiratory tract impacting breathing, swallowing, and voice and carries a 3-5% risk of malignant transformation. Given the multi-focality of the disease and tolerized host immune response against HPV, in part through upregulation of the PD1:PDL1 axis, the safety and efficacy of systemic pembrolizumab (pembro) as a novel treatment for this benign tumor patient (pt) population was evaluated in a phase II clinical trial. **Methods:** RRP pts > 12 years of age were treated with pembro 200mg every 3 weeks. Primary endpoints were best overall response (ORR) (measured by endoscopic lesional burden) and safety. Greater than 5 pts with disease response out of 21 (assuming > 1 of first n = 11 with disease in response) provided 86% power to distinguish between a 15% and a 38% ORR (one-sided 8% binomial test). HPV-specific CD8+ T cell frequency and functional states and biomarkers of response and immune resistance are being evaluated in serial tissue and liquid biopsies (up to 8 biopsies/patient over the 24 months of treatment). **Results:** The Simon two-stage, stage 1 criteria was met. A total of 21 patients were enrolled and all are now off treatment. Median age (range) was 45 (19-68), 57% (12/21) were male and 67% (14/21) were white. 48% (10/21) had Juvenile-onset (Jo)-RRP, 57% (12/21) had pulmonary RRP involvement, and 19% (4/21) had SCC derived from their RRP. 62% (13/21) completed 24 months of treatment. Reasons for discontinuation included disease progression (14%, 3/21), treatment related adverse event (TRAEs) (14%, 3/21), and study withdrawal (10%, 2/21). A partial response (≥25% reduction in endoscopic tumor burden score) was observed in 57% (12/21) (95% CI: 34%-78.2%) of pts (7 of 10 with Jo-RRP and 5 of 11 with Adult-onset (Ao)-RRP disease responded). Stable disease was observed in 33% (7/21). No complete responses were observed. Fatigue was the most frequent TRAEs; Grade 3 TRAEs included uveitis and hypophysitis, both of which were reversible upon pembro discontinuation and steroid use. At a median follow-up: 25.6 (6.2-38.1 months), the mean number of surgical interventions was reduced by 7 surgeries/year (p = 0.004) in pts treated on the trial for > 12 months, and, upon treatment completion, durable clinical benefit was observed with no additional treatment needed for the duration of the clinical trial follow-up for some pts. **Conclusions:** Pembro reduces the need for routine surgical interventions based on the durable response rates being achieved. Further study of pembro +/- other agents is warranted to achieve and sustain complete responses in this population. Clinical trial information: NCT02632344. Research Sponsor: Merck, Other Government Agency.

2591 **Poster Session**

Efficacy of immune checkpoint inhibitors in patients with non–small cell lung cancer harboring *ERBB2* exon 20 insertions and non-*ERBB2* exon 20 insertions. *First Author: Hai-Yan Tu, Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, School of Medicine, South China University of Technology, Guangzhou, China*

Background: Immune checkpoint inhibitors (ICIs) have suboptimal efficacy in non-small cell lung cancer (NSCLC) patients with *ERBB2* mutations, including *ERBB2* exon 20 insertions. This study aims to investigate the efficacy of ICIs and immune characteristics in NSCLC patients harboring *ERBB2* ex20ins and non-ex20ins mutations. **Methods:** Advanced NSCLC patients harboring *ERBB2* mutations were recruited from January 2016 to December 2020. Pre-ICI tumor tissue samples were collected and performed with targeted next-generation sequencing. Patients received ICIs were followed up every 3 months until November 2021. Genomic features were compared between patients with *ERBB2* ex20ins and non-ex20ins mutations. Progression-free survival (PFS), overall survival (OS), and tumor immune microenvironment (TIME) features characterized by multiplex immunohistochemistry (IHC) were further analyzed in patients receiving ICIs. Two-sample T-tests were performed to compare means; Cox models were fitted to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Two external datasets of *ERBB2*-mutant NSCLC patients, including TCGA (n = 23) and META (n = 33), were used for validation. **Results:** A total of 117 eligible patients were enrolled (median age: 59 [range: 24-82], males 57.3%, stage IV 68.4%, adenocarcinoma 93.2%), of whom 37 received subsequent ICI treatment. similar PD-L1 tumor proportion score (mean: 8.1% *vs.* 13.2%, $p = 0.25$) and significantly lower mutation number (mean: 3.0 *vs.* 6.2 muts/person, $p < 0.01$) were detected in patients with *ERBB2* ex20ins, compared to patients with *ERBB2* mutations other than ex20ins. Similarly, in the TCGA cohort, tumor mutation burden was significantly lower in *ERBB2* ex20ins patients (mean: 2.2 *vs.* 10.3 muts/Mb, $p = 0.02$). Of 37 patients receiving ICIs, *ERBB2* non-ex20ins patients displayed superior PFS (mPFS: 13.5 *vs.* 4.4 months, HR: 0.31, 95% CI: 0.14-0.71), relatively long OS (mOS: 27.5 *vs.* 8.1 months, HR: 0.47, 95% CI: 0.20-1.14), and a relatively high rate of durable clinical benefit (64.3% *vs.* 34.8%, $p = 0.10$) than ex20ins patients, consistent with what was observed in the META cohort (PFS, mPFS: 13.2 *vs.* 2.5 months, HR: 0.20, 95% CI: 0.06-0.68; OS, mOS: 23.3 *vs.* 8.0 months, HR: 0.32, 95% CI: 0.11-0.90). Moreover, the CD4+ T cell density appeared to be lower in the tumor stroma of *ERBB2* ex20ins patients than that of non-ex20ins patients (300.5 *vs.* 1288.0 /mm^2, $p = 0.08$), even though the general TIME features of ex20ins patients were similar to those of non-ex20ins patients. **Conclusions:** NSCLC patients carrying *ERBB2* ex20ins demonstrated worse clinical outcome under ICI treatment, similar PD-L1 expression and lower mutation number when compared to those with non-ex20ins mutations. Genomic and TIME characteristics should be further investigated to elucidate the efficacy of ICIs in lung cancer patients carrying *ERBB2* mutations. Research Sponsor: Guangdong Provincial People's Hospital Young Talent Project (Grant No. KY012021191 to Yang-Si Li).

2592 **Poster Session**

Updated efficacy and safety results from the phase 2 study of serplulimab, a novel anti-PD-1 antibody, in patients with previously treated unresectable or metastatic microsatellite instability-high or mismatch repair-deficient solid tumors. *First Author: Jin Li, Shanghai East Hospital, Shanghai, China*

Background: Serplulimab is a novel humanized monoclonal antibody against PD-1. At ASCO 2021, we have presented the results from the phase 2 serplulimab study (NCT03941574) in patients with unresectable/metastatic microsatellite instability-high or mismatch repair-deficient (MSI-H/dMMR) solid tumors who have progressed on or been intolerant to standard therapies with a median follow-up of 7.7 months. Here, we report the updated efficacy and safety results together with the results from sensitivity analysis after another 6-month follow-up. **Methods:** In this single-arm, open-label, multicenter, phase 2 study, patients aged 18–75 years with histologically or cytologically confirmed unresectable or metastatic MSI-H/dMMR solid tumors were enrolled to receive 3 mg/kg of intravenous serplulimab every two weeks for up to two years. The primary endpoint was objective response rate (ORR) assessed by an independent radiological review committee (IRRC) per RECIST v1.1. Secondary endpoints included ORR assessed by the investigators, duration of response (DoR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** As of July 10, 2021, 108 patients had received at least one dose of study treatment and were included in the safety set (SS). Among them, 68 patients with confirmed MSI-H (by local sites or central lab) were included in the main efficacy analysis population (MEAP); 58 patients with confirmed MSI-H (by central lab) and had no major protocol deviations were included in the sensitivity analysis population (SAP). The median follow-up duration was 13.5 months in the MEAP and 14.0 months in the SAP. IRRC-assessed ORR per RECIST v1.1 was 39.7% (95% CI 28.0–52.3; 3 complete response [CR]) in the MEAP and 43.1% (95% CI 30.2–56.8; 2 CR) in the SAP. Investigator-assessed ORRs were 38.2% (95% CI 26.7–50.8; 1 CR) and 41.4% (95% CI 28.6–55.1; 1 CR) in the MEAP and the SAP, respectively. Median DoR, PFS, and OS were not reached; 12-month OS rate was 74.5% (95% CI 62.2–83.3) in the MEAP and 82.4% (95% CI 69.7–90.1) in the SAP. In the SS, 57 (52.8%) patients had grade ≥3 treatment-emergent adverse events, most commonly anemia (9.3%). Thirteen (12.0%) patients had grade ≥3 immune-related adverse events. Three (2.8%) deaths (2 progressive disease and 1 intestinal obstruction) that might be related to serplulimab were reported. **Conclusions:** The encouraging antitumor activity and the manageable safety profile sustained after a longer duration of follow-up, supporting the further development of serplulimab as a potential tissue-agnostic antitumor treatment. Clinical trial information: NCT03941574. Research Sponsor: Shanghai Henlius Biotech, Inc.

2593 **Poster Session**

Preliminary data from an ongoing phase 1 dose-escalation study of CCX559, an orally administered small molecule PD-L1 inhibitor, in patients with advanced solid tumors. *First Author: Gonzalo Tapia-Rico, ICON Cancer Centre, University of Adelaide, Adelaide, SA, Australia*

Background: The novel small molecule CCX559 is a highly potent and selective PD-L1 inhibitor that induces the dimerization and internalization of cell-surface PD-L1. CCX559, when orally administered in animal models, demonstrated anti-tumor efficacy, including the ability to induce complete responses (Li C, et al. Cancer Res 2021;81(13_Suppl): Abstract nr 1274). Safety pharmacology and toxicology studies in animals demonstrated an acceptable safety profile for CCX559. Taken together, the preclinical data supports the initiation of human trials in patients with advanced solid tumors. PD-(L)1 therapies have been shown to increase peripheral T cell activation and cytokines such as IFNγ and CXCL9 in patients (Herbst RS, et al. Nature.2014; 515(7528):563–567). **Methods:** This phase 1, first-in-patient, multicenter, open-label, dose-escalation study evaluates safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary anti-tumor activity of CCX559 in patients with refractory, locally advanced or metastatic solid tumors. CCX559 is dosed orally once daily with a starting dose level of 30 mg. Dose escalation/de-escalation is based on the Bayesian Optimal Interval (BOIN) design. PBMC and plasma samples were collected from patients over the first 2 cycles (6 weeks) of treatment, and PD assays were performed, including measurement of cytokines and T cell proliferation. **Results:** As of February 1, 2022, one patient per cohort was enrolled at the 30 mg and 60 mg levels, and 9 patients were enrolled in the 120 mg dose cohort. Of the 11 patients enrolled, 5 patients (all 120 mg cohort) remain on treatment. No DLTs, treatment-related SAEs, or severe (Grade 3 or higher) treatment-related AEs have been reported. PD assays have been performed with samples from the 30 mg (n=1), 60 mg (n=1), and 120 mg (n=3) cohorts. Patients in all three cohorts showed increased peripheral CD4 and CD8 T cell proliferation starting in the first cycle (21 days) of treatment, as measured by Ki67 positivity. Increases in plasma IFNγ, CXCL9, CXCL10, and CXCL11 levels were observed, in particular in one patient (120 mg cohort) starting 15 days after treatment initiation. **Conclusions:** Initial results from the phase 1 dose-escalation study of CCX559 indicate on-target PD effects consistent with PD-L1 inhibition. Updated PD data, together with the safety and PK profile, will be presented. Clinical trial information: ACTRN12621001342808. Research Sponsor: ChemoCentryx, Inc.

2594 **Poster Session**

Cancer PD1/PD-L1 inhibitor efficacy as stratified by smoking status: A population large database study. *First Author: Zachary D. Urdang, Departments of Otolaryngology and Clinical/Experimental Pharmacology - Thomas Jefferson University, Philadelphia, PA*

Background: Delineating clinical factors that predict immune checkpoint inhibitor (ICI) cancer therapy response is a pressing need and smoking is a known factor. In this study we leveraged a large international (heavily US) database to perform the largest study to date for all cancers and major cancer sub-sites/types. **Methods:** Utilizing the TriNetX electronic health records database with 84.3M patients we tested the hypotheses that ICI response stratifies based on smoking, and continued smoking after ICI. Queries were constructed using billing codes for all cancer types treated with an ICI with and without smoking. The smoking cohort was subsequently sub-stratified for continuing vs cessation of smoking after ICI. Next, using ICI therapy as the index event, odds ratios (OR) with 95% confidence intervals for death, and treatment related secondary outcomes were calculated between 0.5-5 years after ICI treatment. Statistics were calculated using TriNetX's integrated statistical platform before and after 1:1 propensity score matching (PSM) for smoking related co-morbidities. **Results:** The OR for death after ICI therapy for smokers (*n* 13336) vs non-smokers (*n* 38973) for any cancer type was 1.27(1.21-1.34) and decreased to 1.11(1.04-1.19) after PSM. Further substratifying the smoking cohort for continued vs cessation of smoking yielded ORs of 1.13(1.03-1.24) and 1.12(1.01-1.24) before and after PSM respectively. Secondary outcomes included ablative surgery, chemotherapy, radiation, and secondary neoplasm. ORs for receiving chemotherapy, and developing secondary neoplasm were most consistently statistically significant across comparisons. **Conclusions:** Smoking adversely potentiates cancer outcomes after ICI therapy. PSM for smoking related comorbid conditions decreased the magnitude of this association although the findings remained clinically and statistically significant. This highlights the key role in smoking related co-morbid conditions as prognostic clinical characteristics. Furthermore, this suggests that smoking affects ICI on a mechanistic/biological level beyond increasing burden of medical comorbidities. Lastly, as smoking cessation also improved outcomes after PSM this further suggests that washout of smoke toxins has a mechanistic/biological effect on ICI activity. Research Sponsor: None.

Propensity score matching corrected	Alive	Deceased (between 0.5-5yrs after ICI)
Smoker	9,379	2,754
Non-Smoker	9,337	2,540

Odds ratio = 1.11(1.04-1.19)

2595 **Poster Session**

Extended interval dosing in patients with cancer receiving immune checkpoint inhibitors: Safety analysis from the EDICI study. *First Author: Luca Cantini, Department of Pulmonary Medicine, Erasmus MC Cancer Institute, Rotterdam, Netherlands*

Background: Healthcare costs and need of frequent patients' (pts) access to oncology departments led to an increasing interest in alternative immune check-point inhibitors (ICIs) administration schedules able to offer longer dose intervals. The extended interval dosing (ED) of nivolumab and pembrolizumab was approved based on pharmacokinetic data, the relationship of exposure to efficacy, and the relationship of exposure to safety. We aimed to investigate real-life immune-related adverse events (irAEs) incidence in pts treated with ED-ICIs. **Methods:** Clinicopathological and treatment characteristics of all consecutive solid cancer pts treated with ICIs (pembrolizumab, nivolumab) monotherapy who received at least one cycle of the ED (pembrolizumab 400 every 6 weeks or nivolumab 480 mg every 4 weeks) were identified from patient electronic records of 37 oncology departments across Europe and entered into a prospectively maintained database. **Results:** Among 756 pts enrolled in the EDICI study, 733 pts (229 treated with pembrolizumab, and 504 with nivolumab) were included in the final safety analysis (median follow up time: 24.7 months). 476 pts were males, with melanoma (441, 60%) and non-small cell lung cancer (151, 20%) being the prevalent tumor types. Median age was 67 years old, and 589 (80%) pts received ICIs in the advanced setting. 501 (68%) of the enrolled pts started ICIs with canonical interval dosing (CD, median number of cycles administered: 13) and subsequently switched to ED after a median time interval of 210 days. During CD-ICI, 197 pts (39%) developed irAEs of any grade and 14 patients (3%) G3/G4 events; after switching to ED-ICI treatment, which was administered for a median of 7 cycles and 336 days, irAEs of any grade and G3/G4 events were experienced by 155 (36%) and 20 (5%) pts, respectively; 73 (47%) cases of any grade-toxicity and 12 (60%) of G3/G4-toxicity were *de novo.* 33 (7%) pts switched back to CD, in 45% of the cases due to toxicity. Pts who started *up-front* with ED (n = 232, 32%) were exposed to the drug for a median of 7 cycles; 56 of them (25%) developed irAEs of any grade and 9 (6%) G3/G4 irAEs. Skin (12% of patients), endocrine (11%), rheumatic (10%) and gastrointestinal (9%) were the most common irAEs during ED; 42% were "multiple-site" irAEs, showing no difference with CD (p = 0.21). Lower creatinine values before switch to ED (adjusted odds ratio [aOR], 1.24; 95%CI, 1.03-1.48; P = 0.02) and previous toxicity during CD (aOR, 1.20; 95%CI, 1.08-1.33; P < 0.01) were independent risk factors for development of irAEs during ED. **Conclusions:** Despite similar exposure time, the safety profile of ED treatment did not differ from CD, confirming that ED-ICI administration is a safe and feasible option also in cancer pts outside of clinical trials. Future investigations are needed to explore efficacy data and economic impact of this strategy. Research Sponsor: None.

2596 **Poster Session**

Identification of super-exhausted T cells: A novel population predictive of response to immunotherapy. *First Author: Florent Peyraud, Institut Bergonié, Bordeaux, France*

Background: Given that most of cancer patients treated with anti-PD1/PD-L1 immune checkpoint blockers (ICB) do not derive benefit, there is a crucial need to identify reliable predictive biomarker of response. Besides PD-1, several key immune checkpoints, such as CTLA4, LAG3, TIM3 and TIGIT, are associated with a T cell exhausted phenotype and play a crucial role in leading to cancer immune evasion. The impact of simultaneous expression by T cells of distinct inhibitory receptors on outcome of patients treated with ICB is still unknown. **Methods**: We analyzed the tissue samples, collected before ICB initiation, from patients with solid tumors and included in an institutional molecular profiling program (NCT02534649). We used multiplexed-immunohistofluorescence with the following panel CD3/PD1/TIM3/LAG3/TIGIT/CTLA4, and performed immune cell characterization using multispectral images analysis. We then investigated the correlation between coexpression of T cell-associated exhaustion markers, clinical response rate, progression-free survival (PFS) and overall survival (OS) by Cox proportional hazards models. **Results**: Four hundred thirty five patients were included in the analysis (NSCLC: n=207, 47.6%; sarcoma: n=42, 9.7%; urothelial: n=30, 6.9%; others: n=156, 35.9%). Digital pathology analysis allowed us to identify a population of "super-exhausted" T cells characterized by the co-expression of PD1, LAG3, TIGIT and TIM3 which was enriched in 125 cases (28.7%), and was significantly associated with better PFS (HR 1.60, CI95 1.26-2.04, p<0.001) and OS (HR 1.42, CI95 1.07-1.89, p=0.016) in the whole cohort. Patients with super-exhausted high tumors had higher objective response rate (38.4%) compared to super-exhausted low tumors (19.7%, p<0.001). The presence of super-exhausted T cells was significantly higher in responders (10%) versus non responders (4%, p<0.001). Correlation with better outcome was observed whatever the subgroup considered (NSCLC vs other tumors, CD8 T cells density and presence of tertiary lymphoid structure [TLS]). In multivariate analysis (n=372, 85.5%), increased tumor infiltration by super-exhausted T cells (>1 %) was significantly associated with better PFS (HR 0.61, CI95 0.46-0.81, p<0.001, Table) and OS (HR 0.68, CI95 0.48-0.97, p=0.033, Table). **Conclusions**: The presence of super-exhausted T cells may represent a new predictive biomarker of response to ICB and pave the way for the development of effective ICB combinations. Data from an independent validation cohort will be presented at the meeting. Research Sponsor: None.

Patients	Endpoint	PFS			OS		
372	Subgroup	HR	CI	p-value	HR	CI	p-value
	Super Exhausted T cells (>1.09%)	0.61	(0.46-0.81)	<0.001	0.68	(0.48-0.97)	0.033
	TLS positive	0.72	(0.56-0.94)	0.014	0.66	(0.48-0.90)	0.010
	CD8 density (<152 cells/mm^2)	1.11	(0.88-1.42)	0.74	1.06	(0.80-1.41)	0.69
	Performance Status (>1)	1.60	(1.15-2.24)	0.006	2.19	(1.51-3.19)	<0.001

2597 **Poster Session**

Novel, small molecule inhibitors of PD-1/PD-L1 pathway. *First Author: Luca Rastelli, Jubilant Therapeutics, Bedminster, NJ*

Background: Programmed Cell Death 1 (PD-1) protein plays a key role in inhibiting immune responses and enhancing self-tolerance via modulation of T-cell activity, inducing T-cell apoptosis and inhibiting apoptosis of regulatory T cells. PD-L1 also plays an important role in various malignancies where it can attenuate the host immune response to tumor cells thereby favouring tumor progression and metastasis. High expression of PD-L1 in glioblastoma tumor tissues is associated with poor survival of patients, and PD-L1 may act as a prognostic predictor and an effective therapeutic target for glioblastoma. A number of monoclonal antibodies targeting PD-1/PD-L1 have approved for various malignancies. Still, efficacy of these antibodies in glioblastoma and brain metastasis continues to be moderate potentially owing to lack of or poor brain penetrance of these agents. Therefore, there is still a need for potent, selective small molecule PD-1/PD-L1 inhibitors with enhanced brain penetration in the treatment of such cancers. **Methods:** Rational design approaches were used to design novel small molecule PD-1/PD-L1 pathway inhibitors; potency of these inhibitors was assessed in an *in-vitro* TR-FRET assay. Checkpoints signalling reporter assays as well cell based PD-L1 dimerization assays were used to assess the mechanistic and functional effects. *In vivo* efficacy was assessed in orthotopic GBM as well as in syngeneic and humanized subcutaneous tumor models in mice. **Results:** Our lead PD-L1 inhibitor JBI-2174 showed strong *in vitro* IC50 of ~1 nM in TR-FRET assay that measures interaction between hPD-1 and hPD-L1 and a picomolar IC50 against monkey PD-L1. In selectivity assays for immunooncology targets, JBI-2174 was highly selective for PD-L1. JBI-2174 also inhibited PD-L1/PD-1 mediated signalling essential for T-cell modulation. JBI-2174 induced dimerization of PD-L1 as observed by size exclusion chromatography, which was confirmed by co-crystal structure and recapitulated in cell based dimerization assay. Elucidation of the co-crystal structure, clearly demonstrated that JBI-2174 clearly interacts with multiple amino acids on PD-L1 that are critical for PD-1 binding. JBI-2174 showed excellent oral bioavailability across pre-clinical species and sustained brain exposure. In the in vivo efficacy studies, JBI-2174 showed comparable efficacy to the anti-PD-L1 antibody or Atezolizumab in syngeneic (4T1, CT-26) and in partially humanized models (MC-38/hPD-L1). Further, oral administration of JBI-2174 resulted in statistically significant increase in survival (Day 27 in control vs day 38 in treated, $p < 0.05$) in a mouse glioma orthotopic model. **Conclusions:** The oral bioavailability and brain exposure of this molecule will make it attractive for cancers with unmet medical needs such as GBM and brain metastasis. IND enabling studies are being initiated for this compound. Research Sponsor: Jubilant Therapeutics.

2598 **Poster Session**

Association between body mass index and treatment efficacy with immune checkpoint inhibitor therapy: A retrospective study. *First Author: Hannah Wang, Baylor College of Medicine, Houston, TX*

Background: Increased body mass index (BMI) has been associated with improved efficacy of immune checkpoint inhibitor therapy (ICI) in cancer patients. We aimed to retrospectively assess the relationship between patient BMI and response to ICI at two unique health care systems in our institution **Methods:** We identified patients treated with ICI from 2015-2021 at the Michael E. DeBakey Veterans Affairs Medical Center (MEDVAMC) Cancer Center and Baylor St. Luke's Medical Center (BSLMC), a private hospital-based cancer center, both academic affiliates of Baylor College of Medicine. Clinical details, including BMI, and treatment efficacy were collected. We defined BMI categories as follows: underweight (< 18.5), normal weight (18.5-24.9), overweight (25-29.9), and obese (≥30). Progression free survival (PFS), overall survival (OS), and overall response rate (ORR) were the primary end points calculated for treatment efficacy. Survival curves were generated using the Kaplan-Meier method, and intergroup comparisons were performed with log-rank test. Cox regression analysis was used to determine whether BMI at ICI initiation was associated with survival. Chi-square testing was used to determine any association between BMI and ORR. **Results:** We identified 430 patients treated with ICI, 257 (60%) from BSLMC and 173 (40%) from MEDVAMC. 341 patients (79%) were male and 89 (21%) female. Cancer types included 127 (30%) lung, 49 (11%) kidney, 40 (9.3%) bladder, 38 (8.8%) melanoma, and 38 (8.8%) mesothelioma, 34 (7.9%) head and neck, and 104 (24%) other. 160 (37%) patients had a normal BMI at ICI initiation, 37 (8.6%) underweight, 132 (31%) overweight, and 101 (23%) obese. Mean BMIs of different cancer types were as follows: lung (24.7), kidney (29.2), bladder (26.0), melanoma (29.9), mesothelioma (25.25), head and neck (23.7). 292 (68%) patients were treated with ICI monotherapy. The ORR for patients with normal vs. obese BMIs treated with ICI were 28% and 42%, respectively ($p = 0.03$). In a subset of patients evaluable for survival ($n = 322$), patients with an obese BMI had a significantly improved median PFS compared to those with normal BMI (36.4 vs. 23.5 months, respectively, $p < 0.0001$). Multivariable analysis demonstrated that patients with an obese BMI had significantly improved overall survival compared to patients with a normal BMI (HR 0.64, 95% CI 0.44-0.91, $p = 0.014$). This relationship was also seen in the subset of patients treated with ICI monotherapy (HR 0.66, 95% CI 0.45-0.95, $p = 0.029$). This association was noted regardless of health care systems. **Conclusions:** Increased BMI in cancer patients treated with ICI may predict better treatment efficacy and survival outcomes. More research is needed to define this relationship more clearly. Research Sponsor: None.

2599 **Poster Session**

Cisplatin (Cis) combined with sintilimab (Sint) and niraparib (Nir) in advanced solid tumors: Updated results. *First Author: TAO Haitao, Department of Oncology, Chinese PLA General Hospital, Beijing, China*

Background: PARP inhibitors or chemotherapy combined with PD1/PDL1 inhibitors resulting in enhanced antitumor activity. We previously reported the part 1 result of a phase Ib study exploring the safety and efficacy of Cis plus Sint and Nir. Here we presented the updated survival and safety data. **Methods:** Eligible pts will receive Sint and Cis on D1, plus Nir on D1-21, every 21-day for up to 4 cycles, following Sint and Nir until disease progression or intolerable toxicity. Part 1 was dose escalation phase followed 3+3 model, and part 2 was dose expansion phase enrolled more patients based on part 1. The primary objective was to determine maximum tolerated dose (MTD)/ recommended part 2 dose (RP2D). Secondary endpoints include objective response rate (ORR) per RECIST v1.1, and safety based on CTCAE v5.0. **Results:** PR2D of Cis and Nir were 60 mg/m^2 and 100 mg, respectively when combined with sint 200mg. From 7/2019 to 9/2021, 22 pts (13 pts in part2) were enrolled, including 12 small cell lung cancer (SCLC), 7 lung squamous cell carcinoma (LUSC), 2 ovarian cancer (OC) and 1 cervical squamous cell carcinoma (CSCC). Most were male (77.3%, n=17), ECOG=1 (63.6%, n=14), current smoker(68.2%, n=15) and PDL1 < 1(50%, n=11). 36.4% (8/22) and 27.3% (6/22) had brain and liver metastasis at baseline, separately. Median follow-up was 6.2 months (range 2.5-10.8). ORR was 27.3% (6/22), DCR was 59.1% (13/22). Median progression-free survival (PFS) was 3.3 months (95%CI 1.9-3.9), and PFS rates at 6 months and 12 months were 28.8% and 10.8%. Median overall survival (OS) was 8.0 months (95%CI 4.9-14.1), 12 months OS rates was 28.5%. Median treatment duration was 4.7 months (range 1.9-15.1). The most common treatment-related adverse events included anemia (90.9%, 20/22, [5 Grade 3/4]), fatigue (77.3%, 17/22, [1 Grade 3/4), γ-glutamyl transpeptidase increased (72.7%, 16/22, [0 Grade 3/4]), leukopenia (68.2%, n=15, [4 Grade 3/4]) and neutropenia (59.1%, n=13, [5 Grade 3/4]). **Conclusions:** In this updated analysis, Cis combined with Sint and Nir showed clinically meaningful efficacy and an adequate safety profile in previously treated advanced solid tumors. Data need longer follow-up. Clinical trial information: ChiCTR1900024488. Research Sponsor: None.

2600 **Poster Session**

Study to evaluate intraperitoneal (IP) ONCOS-102 with systemic durvalumab in patients with peritoneal disease who have epithelial ovarian (OC) or metastatic colorectal cancer (CRC): Phase 2 results. *First Author: Dmitriy Zamarin, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Locoregional treatment with oncolytic viruses may be used to improve the efficacy of immune checkpoint inhibitors at both treated and distant tumor sites. This study evaluated the combination of IP-administered ONCOS-102, an oncolytic adenovirus encoding for granulocyte macrophage colony stimulating factor (GM-CSF), with systemic durvalumab (durva) in patients (pts) with advanced OC or CRC who have failed prior chemotherapy. **Methods:** This open-label study (NCT02963831) evaluated ONCOS-102 (IP 3 x 10^{11} VP in 500ml saline [recommended phase 2 dose] weekly x 6) + durva (IV 1500 mg every 4 weeks x 12). One dose of cyclophosphamide was given prior to first ONCOS-102 dose. Phase 2 evaluated the activity of the combination using Simon's 2-stage MINIMAX design. In MINIMAX stage 1, if ≥ 5 of 18 OC pts or ≥ 1 of 13 CRC pts met the efficacy criteria (progression free at end of week 24), 15 additional OC pts or 14 additional CRC pts were to be enrolled in stage 2. The efficacy endpoint would be met if ≥ 11 OC pts or ≥ 4 CRC pts remained progression free at 24 weeks. Safety, response rate and progression-free survival (PFS) by RECIST 1.1, overall survival (OS), and immunologic effects in tumors were evaluated. ITT population = all pts who received at least one dose of durva or ONCOS-102; per protocol (PP) population = all pts who received at least 60% of ONCOS-102 doses and at least 1 durva dose in the first 2 cycles. **Results:** In MINIMAX stage 1, the OC cohort did not meet the efficacy criteria and was closed. For CRC, stage 1 efficacy criteria were achieved and the cohort was opened for stage 2. As of the 14 Dec 2021 cutoff, CRC enrollment was complete, and all pts were followed for 24 weeks or until progression or off study. Two pts were progression free at 24 weeks (see table). Treatment-related adverse events (TRAEs) occurring in > 30% pts were vomiting, nausea, fatigue, chills, and pyrexia. There were no grade 4 or 5 TRAEs. Grade 3 TRAEs were reported in 8 pts, 2 in the OC cohort and 6 in CRC. All grade 3 TRAEs occurred in no more than 1 pt for each AE except abdominal pain, which occurred in 2 pts. **Conclusions:** The combination of IP ONCOS-102 and durva was well tolerated. The study did not meet its efficacy endpoint. Evaluation of pre- and on-therapy translational parameters is ongoing. Clinical trial information: NCT02963831. Research Sponsor: Ludwig Institute for Cancer Research, Other Foundation, Pharmaceutical/Biotech Company.

	CRC Completed Stage 2		OC Closed after Stage 1	
Population	**ITT (36)**	**PP (28)**	**ITT (19)**	**PP (15)**
Sex, n (%)	F 21 (58.3) M 15 (41.7)	F 18 (64.3) M 10 (35.7)	F 19 (100.0)	F 15 (100.0)
Median age (range) years	58.5 (39 - 74)	58.5 (44 - 74)	67.0 (49 - 77)	68.0 (49 – 77)
Progression free at week 24	2 (5.6%)	2 (7.1%)	0	0
Best response	0 CR, 0 PR, 9 SD, 22 PD, 5 missing	0 CR, 0 PR, 7 SD, 19 PD, 2 missing	0 CR, 0 PR, 4 SD, 15 PD, 0 missing	0 CR, 0 PR, 4 SD, 11 PD, 0 missing
Median PFS (95% CI) months	1.8 (1.6, 1.9)	1.8 (1.6, 1.9)	1.8 (1.2, 1.9)	1.9 (1.6, 1.9)
Median OS (95% CI) months	7.1 (5.4, 11.5)	7.1 (5.4, 11.5)	6.6 (3.6, 19.7)	7.5 (4.4, 19.8)

2601 **Poster Session**

PRaG regimens (PD-1 inhibitor combined with radiotherapy and GM-CSF with or not IL-2) rechallenge for patients with acquiring resistance to PD-1/PD-L1 inhibitors in refractory advanced solid tumors. *First Author: Meiling Xu, The Second Affiliated Hospital of Soochow University, Suzhou, China*

Background: Immune checkpoint inhibitors, especially PD-1/PD-L1 inhibitors can promote tumor regression and long-term survival in patients with advanced solid tumors. Despite the characteristic durability of response to ICI, unfortunately some patients may develop acquired resistance after an initial response. The underlying mechanism and effective measure are remarkably limited, perhaps restraining development of immunotherapies. The PRaG trial as a salvage therapy in patients with refractory metastatic solid tumors has obtained satisfactory results(Yuehong Kong et al. ASTRO 2021). With great surprise we found that patients with PD-1/PD-L1 inhibitors acquired resistance are more likely to benefit from the PRaG regimens. This is the PRaG regimen rechallenge that could represent an attractive option in advanced solid tumors. We retrospectively analyzed the clinical efficacy and safety of PRaG regimen (PD-1 inhibitors combined with radiotherapy and GM-CSF with or not IL-2) rechallenge to treat immunotherapy-refractory patients with advanced solid tumors. **Methods:** This is a retrospective analysis of patients who showed initial resistance to PD-1/PD-L1 inhibitors were retrospectively collected from PRaG serial trails (ChiCTR1900020175 and NCT04892498). Patients received SBRT or HFRT (2-3 doses of 5-8Gy) to a target metastatic site, PD-1 inhibitor was dosing intravenously within one week after completion of SBRT or HFRT, and GM-CSF subcutaneous (SC) injection once daily for 14 days after radiotherapy(the PRaG 2.0 regimen, GM-CSF 200μg SC d1-7, sequentially IL-2 2million IU d8-14.). The specific PRaG regimens had been reported at the meeting of 2020 ASCO. Pooled analysis of response rate (ORR), median progression-free survival (mPFS), and treatment-related adverse events were calculated. **Results:** A total of 15 multi-metastatic patients were enrolled between October 2020 and February 2022. Thirteen patients showed acquired resistance and underwent at least one assessment, 5 patients were lung cancer, 3 patients were renal cancer, 2 patients were liver cancer, 2 patient was colon cancer, 1 patient was sarcoma. The ORR was 18.2%, and the disease control rate (DCR) was 90.9%. The median PFS was 8.87 months (95%CI, 1.41 to 16.33 months). One lung cancer achieved complete remission, with PFS over 17 months. Treatment-related adverse events of any grade occurred in 11 of 15(73.3%) patients, while there was no grade 3 or higher adverse events. **Conclusions:** Our preliminary results suggested that PRaG regimens rechallenge maybe an active and feasible strategy in PD-1/PD-L1 inhibitors acquired resistance. The therapy was well tolerated and had acceptable toxicity. A phase III prospective study is being planned to clarify the role of rechallenge after acquired resistance. Clinical trial information: ChiCTR1900020175 and NCT04892498. Research Sponsor: None.

2602 **Poster Session**

A first-in-human phase I dose escalation of YH001, an anti-CTLA-4 monoclonal antibody (mAb), in combination with toripalimab (anti-PD-1 mAb) in patients with advanced solid tumors. *First Author: Vinod Ganju, PSEHOG, Frankston, VIC, Australia*

Background: YH001 is a humanized anti-hCTLA-4 IgG1 mAb that relieves CTLA-4-mediated immunosuppression, and thereby enhances the T-cell-mediated anti-tumor immune response. Pre-clinical data have shown potent anti-cancer activity when combined with anti-PD-1 mAb. **Methods:** This is an ongoing phase 1 dose-escalation study conducted in Australia. Patients (pts) with advanced solid tumors received YH001 by IV administration at 0.05 to 6.0 mg/kg for 1 cycle (21 days) then in combination with Toripalimab (anti-PD-1 mAb) at 240 mg Q3W for 4 cycles. An accelerated titration method followed by the standard "3+3" design was utilized to evaluate safety, tolerability and preliminary efficacy. **Results:** As of 31-Dec-2021 data cut-off, 24 pts with advanced solid tumors were enrolled and dosed at 0.05 mg/kg (n=2), 0.1 mg/kg (n=3), 0.3 mg/kg (n=3),1mg/kg (n=5), 2mg/kg (n=5), 4mg/kg (n=3) and 6mg/kg (n=3). Baseline ECOG scores were 0 (n=14), 1 (n=10) with all pts progressed after a median of 2 prior lines of available standard therapy (range 1-5) including 5 pts progressed after prior immunotherapy of anti-PD-1 antibody. Overall, 6 cases of Grade(G) 3 or above treatment-related AEs (TRAEs) have been reported in 5 pts at 0.3 mg/kg, 4 mg/kg and 6 mg/kg dose level respectively, including 1 G3 colitis, 1 G4 thrombocytopenia, 1 G3 Enterocolitis, 1 G3 Rash, 1 G3 Pruritus and 1 G3 hepatitis. There were no death events due to TRAEs. 18 pts (75%) had 63 TRAEs of any level, including 28 G1 TRAEs, 29 G2 TRAEs. 2 of the first 3 pts at MAD (6mg/kg) met protocol defined DLT in Combo phase. Among the 23 pts having imaging tumor assessment by RECIST v1.1, 4 achieved PR and 9 achieved SD in Best of Response. 1 subject with gastroesophageal junction carcinoma at 0.3 mg/kg has achieved PR since the 2nd tumor assessment, target lesion decreased by up to 84.5% from baseline. 1 subject with urothelial carcinoma at 2 mg/kg progressed after prior anti-PD-1 antibody has achieved PR since the 2nd tumor assessment, target lesion decreased by up to 74% from baseline. 1 subject with uterine carcinosarcoma at 2 mg/kg has achieved PR since the 1st tumor assessment, target lesion decreased by up to 52.3% from baseline. 1 subject with vulva adenocarcinoma at 6 mg/kg has achieved PR since the 1st tumor assessment, target lesion decreased by up to 71.4% from baseline. ORR (CR+PR) and DCR (CR+PR +SD) were 17.4%, 56.5% respectively. **Conclusions:** YH001 was well tolerated up to 4 mg/kg dose levels when combined with toripalimab and has shown encouraging antitumor activity in patients with advanced solid tumors. Clinical trial information: NCT04357756. Research Sponsor: Eucure (Beijing) Biopharma Co., Ltd.

2603 **Poster Session**

A phase I open-label, dose escalation of YH003, an anti-CD40 monoclonal antibody, in combination with toripalimab (anti-PD-1 mAb) in patients with advanced solid tumors. *First Author: Jermaine Coward, ICON Cancer Centre, South Brisbane, QLD, Australia*

Background: YH003, a recombinant, humanized agonistic anti-CD40 IgG2 monoclonal antibody (mAb) specifically recognizes and agonizes CD40 on the antigen-presenting cells to enhance immune responses. Preclinical data have shown potent anti-cancer activity when combined with anti-PD-1 antibodies. **Methods:** This is an ongoing phase 1 dose-escalation study conducted in Australia using an accelerated "3+3" design. Patients (pts) with advanced solid tumors receive YH003 by IV administration Q3W as monotherapy at 0.03 to 3.0 mg/kg for the first cycle (21 days) then in combination with Toripalimab at 240 mg Q3W for the 4 subsequent cycles. Treatment continuation beyond cycle 4 is possible if subject is deriving an ongoing clinic benefit. The safety, tolerability and preliminary efficacy data will be analyzed. **Results:** Between 29 Jul 2020 and 30 Dec 2021, a total of 20 patients with various advanced solid tumors were enrolled including 0.03 mg/kg (n = 3), 0.1 mg/kg (n = 3), 0.3 mg/kg (n = 3), 1.0 mg/kg (n = 8) and 3.0 mg/kg (n = 3). The median age was 60 years (range 33-75). Baseline ECOG scores were 0 (13 pts) and 1 (7 pts). 8 pts had received prior immunotherapy (anti-PD-1/PD-L1 or anti-PD-1+CTLA-4mAb). Dose escalation has been completed and only one dose-limiting toxicity relating to YH003 was observed at 1.0 mg/kg (grade 3 transaminitis). The maximum tolerated dose (MTD) was not reached. 13 (65%) pts experienced any grade treatment related adverse events (TRAEs). The most common (≥ 10%) TRAEs were infusion reaction, pyrexia, fatigue, nausea, diarrhea, transaminitis. Most TRAEs were grade 1 or 2. Only 3 (15.0%) pts experienced Grade 3 TRAEs including one each of neutropenia (YH003 0.3 mg/kg), transaminitis (YH003 1.0 mg/kg) and elevated lipase (Toripalimab 0.1 mg/kg). Only 2 pts have permanently discontinued treatment due to TRAEs including grade 3 transaminases increased and grade 2 hepatitis. There were no ≥grade 4 TRAEs and drug related serious adverse events (SAEs) were not observed. Among 14 pts assessable for response, the overall response rate (ORR) was 14.3% (2/14) and disease control rate (DCR) was 35.7% (5/14). One partial response (PR) occurred in a pt with anti-PD1/anti-CTLA4 refractory ocular melanoma with liver metastases (YH003 0.1 mg/kg) who continued on treatment for > 1 year. The other PR occurred in a pt with Non-Small Cell Lung Carcinoma (YH003 1.0 mg/kg) who continued on treatment for almost 9 months. **Conclusions:** YH003 was well tolerated up to 3.0 mg/kg dose levels when combined with Toripalimab and has shown encouraging antitumor activity in patients with advanced solid tumors. Clinical trial information: NCT04481009. Research Sponsor: Eucure (Beijing) Biopharma Co., Ltd.

2604 **Poster Session**

A phase 1 multiple-ascending dose study to evaluate the safety and tolerability of XmAb23104 (PD-1 x ICOS) in subjects with selected advanced solid tumors (DUET-3). *First Author: Mehmet Akce, Winship Cancer Institute, Atlanta, GA*

Background: XmAb23104 is a bispecific antibody targeting T cells that simultaneously express PD-1, an immune checkpoint, and ICOS, a costimulatory molecule expressed after T cell activation. DUET-3 is a Phase 1, first-in-human, dose-escalation and expansion study in subjects with advanced solid tumors, designed to assess safety, tolerability and to identify the maximum tolerated dose (MTD) of XmAb23104. Secondary objectives are to assess pharmacokinetics (PK), immunogenicity, and preliminary anti-tumor activity. We report preliminary data from the completed dose-escalation phase. **Methods:** A 3+3 monotherapy dose escalation with 9 dose levels from 0.002 to 15 mg/kg has been completed. Subjects with measurable disease who progressed on prior standard therapy were eligible. A minimum 6-week washout from prior pembrolizumab was required. XmAb23104 was administered biweekly and RECIST 1.1 assessment was performed every 8 weeks. **Results:** Sixty-two subjects were treated in escalation at doses up to 15 mg/kg; no dose-limiting toxicities were observed and an MTD was not reached. These subjects had advanced disease, 92% were Stage IV at screening, the median number of prior therapies was 3, and 37% had previous checkpoint therapy. Thirty-seven subjects (59.7%) experienced a treatment-related adverse event (TRAE); the most common were diarrhea (9.7%), decreased appetite (9.7%), and fatigue (9.7%). The majority of TRAEs were Grades 1 or 2, with 6 subjects (9.7%) having a Grade 3 or higher TRAE. Thirteen immunotherapy-related adverse events (irAEs) occurred in 8 subjects; no individual irAE occurred in more than 1 subject. Most irAEs were mild (Grades 1 and 2) with 1 Grade 3 pruritus and 1 asymptomatic Grade 4 lipase elevation. Partial responses were observed in 3 subjects (sarcoma; prior PD-1 head and neck squamous cell carcinoma [HNSCC] and renal cell carcinoma [RCC]), and stable disease > 12 months was observed in 2 subjects with colorectal cancer (CRC; 1 MSS and 1 MSI-H). A dose of 10 mg/kg was selected after consideration of PK, safety, and clinical activity data in consultation with the investigators and continues to be evaluated in the expansion part of the study. **Conclusions:** The dose escalation part of this study indicates XmAb23104 was generally well tolerated at doses up to 15 mg/kg and has shown clinical activity in subjects with advanced solid tumors. CTLA4 blockade has been found to increase the frequency of ICOS-expressing T cells in prostate cancer, bladder cancer, melanoma, and hepatocellular cancer (Chen, 2009; Liakou, 2008; Wei, 2017) and may be applicable to other immunogenic tumor types. XmAb23104 is currently being studied alone or in combination with ipilimumab in expansion in non-squamous non-small cell lung carcinoma, melanoma, CRC, undifferentiated pleomorphic sarcoma, HNSCC, and RCC. Clinical trial information: NCT03752398. Research Sponsor: Xencor.

2605 **Poster Session**

Retrospective analysis of the effect of angiotensin receptor blockers and angiotensin converting enzyme inhibitors on the efficacy of anti-PD-1/PD-L1 immunotherapy in patients with advanced cancer. *First Author: Jason Suh, Valley-Mount Sinai Comprehensive Cancer Care, Paramus, NJ*

Background: Components of the renin angiotensin system (RAS) are expressed in tumors with activation leading to tumor and stromal cell release of immunomodulatory cytokines promoting an immunosuppressive microenvironment and increased infiltration of tumor associated macrophages. Angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) are anti-hypertensives that inhibit the RAS. It is unknown if ACEi and ARB treatment modulates the efficacy of anti-PD-1/PD-L1 immunotherapy. **Methods:** A retrospective chart review was conducted to identify patients with unresectable malignancies initiating treatment with a PD-1 or PD-L1 inhibitor based regimen between 1/1/13 and 6/1/19 at Valley Hospital in New Jersey. IRB approval was obtained. Efficacy of treatment was measured by medical oncologist documentation of clinical benefit (CB = stable disease / treatment response) versus disease progression. Chi-square tests were performed to assess relationship between ACEi or ARB exposure and immunotherapy benefit. To assess for a broader anti-hypertensive effect, the relationship in patients on a beta-blocker but not ACEi/ARB was assessed. **Results:** 197 patients were identified of which 190 had documentation of clinical outcome. The mean age was 72.8 years with 54% female and 46% male. 56 patients were exposed to ACEi (N = 28) or ARB (N = 28) and 141 patients to neither. 37 patients were exposed to beta blocker but not ACEi or ARB. 60 patients had nonsquamous NSCLC (16 on ACEi or ARB), 26 squamous NSCLC (7 on ACEi or ARB) and 24 melanoma (10 on ACEi or ARB). 71% of ACEi/ARB exposed patients had CB by clinician assessment as opposed to 47% in those not on ACEi or ARB (p = 0.003). In ACEi exposed patients, 71% had CB versus 51% in unexposed patients (p = 0.048). In ARB exposed patients, 70% had CB versus 51% in unexposed patients (p = 0.069). By contrast, 51% of beta-blocker treated patients had CB versus 55% in untreated patients (p = 0.72). 36% of ACEi/ARB exposed patients remained on treatment at 12 months versus 22% of ACEi/ARB unexposed patients. Subset analyses were performed on the 3 largest patient populations: squamous NSCLC, nonsquamous NSCLC and melanoma. ACEi/ARB exposed melanoma patients had CB rate of 70% versus 43% in those unexposed. ACEi/ARB exposed squamous NSCLC patients had CB rate of 86% versus 47% in unexposed patients. By contrast, ACEi/ARB exposed nonsquamous NSCLC patients had a 56% CB rate versus 48% in unexposed patients. **Conclusions:** Based on retrospective analysis, advanced cancer patients treated with anti-PD-1/PD-L1 regimens had a statistically significant increase in clinical benefit if administered in the context of renin angiotensin system blockade. Prospective disease specific trials can further validate these findings and define the degree of clinical benefit. Research Sponsor: None.

2606 **Poster Session**

First-line PD-1 inhibitors immunotherapy and chemotherapy combined with or without radiotherapy for patients with advanced non-small cell lung cancer. *First Author: Peng Ding, Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China*

Background: Immunochemotherapy has become a standard first-line regimen for advanced non-small-cell lung cancer (NSCLC). Several studies showed the synergistic effects of immunotherapy and radiotherapy on local and abscopal tumour control. But the data of first-line immunochemotherapy combined with radiotherapy for the advanced NSCLC is still scarce. **Methods:** Patients with advanced NSCLC receiving first-line PD-1 inhibitors immunotherapy plus chemotherapy in a single center were retrospectively analyzed in this study. They were divided into two groups according to whether they had received radiotherapy. The efficacy and safety of first-line immunochemotherapy combined with radiotherapy (ICRT group) and immunochemotherapy alone (ICT group) were investigated. **Results:** A total of 135 patients were included; 65 patients received PD-1 inhibitors plus chemotherapy and radiotherapy, while other 70 patients were treated with immunochemotherapy alone. The median interval time between radiotherapy and PD-1 inhibitors immunotherapy was 5 days (range, 0-96 days). The overall response rate (ORR) was 50.8% in the ICRT group and 40.0% in the ICT group, respectively. Patients in the ICRT group achieved significant longer progression-free survival (PFS, median 16.5 vs 10.4 months, P= 0.043) and overall survival (OS, median not reached vs 21.0 months, P= 0.030) compared with those in the ICT group. The addition of radiotherapy was the only prognostic factor for PFS (HR = 0.617, 95%CI: 0.385-0.989, P= 0.045) and OS (HR = 0.512, 95%CI: 0.277-0.947, P= 0.033) by univariate Cox regression analysis. Patients were well tolerated and the overall incidence of adverse events was similar between the ICRT group and ICT group. One patient in ICRT group stopped immunotherapy because of severe immune-associated pneumonia. 3.1% of grade 3-4 radiation-related adverse events were observed. **Conclusions:** Adding radiotherapy to first-line PD-1 inhibitors immunotherapy and chemotherapy improved outcomes of patients with advanced NSCLC and showed acceptable toxicity. Additional prospective studies exploring the first-line combination of immunochemotherapy and radiotherapy are warranted. Research Sponsor: National Natural Science Foundation of China (grant number 82103004).

2607 **Poster Session**

Resistance to anti-PD-1/anti-PD-L1: GB1211 reverses galectin-3 induced blockade of pembrolizumab and atezolizumab binding to PD-1/PD-L1. *First Author: Joseph Mabbitt, Galecto, Inc., Stevenage, United Kingdom*

Background: Galectin-3 (Gal-3) is a β-galactoside binding lectin highly expressed across many cancers (Li et al. Biomedicines, 2021) with high expression associated with poor response to the PD-1 inhibitor pembrolizumab (Capalbo et al., Int J Mol Sci, 2019). In addition, it has also been shown preclinically in in vivo mouse non-small cell lung carcinoma (NSCLC) models that inhibition of Gal-3 enhances the performance of checkpoint inhibitors targeting the PD-1/PD-L1 axis (Vuong et al., Cancer Res, 2019; Zhang et al., FEBS Open Bio, 2020). The mechanism by which Gal-3 negatively impacts the effect of PD-1/PD-L1 based checkpoint inhibitors is not fully understood. We investigated the hypothesis that anti-PD1/anti-PDL1 is induced by direct binding and blockade of Gal-3 to the PD-1/PD-L1 complex itself. **Methods:** SPR was used to investigate the effect of recombinant hGal-3 in combination with a Gal-3 inhibitor (GB1211) on the binding of recombinant hPD-L1 to hPD-1 in the absence and presence of either pembrolizumab or atezolizumab. SPR analysis was performed with a BIAcore (Cytiva, USA). hPD-1 was immobilized onto a CM5 Series S sensorchip via amine coupling and proteins, antibodies or small molecules flowed over in various combinations. Observations made at the protein level were further confirmed in cell binding assays using flow cytometry measuring pembrolizumab and atezolizumab binding to cells lines over expressing high levels of either PD-1 (Jurkat cells) or PD-L1 (RAJI-hPD-L1 cells), respectively. **Results:** Gal-3 potentiated the binding of PD-L1 to PD-1 with a 3-fold increase in its K_D observed and the efficiency of pembrolizumab and atezolizumab binding to and blocking the PD-1/PD-L1 axis was reduced. A 6-fold reduction in K_D of pembrolizumab for the PD-1/PD-L1 complex was observed in the presence of Gal-3. In addition, atezolizumab PD-L1 blockade was reversed in the presence of Gal-3 and dramatically improved by GB1211. Similarly, in cell systems expressing high levels of PD-1 or PD-L1, Gal-3 reduced the binding of pembrolizumab and atezolizumab to their respective targets on cell surfaces that was also reversed by GB1211. **Conclusions:** Gal-3 was shown to vastly reduce the binding of the checkpoint inhibitors pembrolizumab and atezolizumab, by potentiating the interaction between PD-1 and PD-L1. GB1211 restored the binding of the anti-PD1/anti-PDL1 therapeutics and may thus reduce tumor resistance to these agents. These findings harmonize excellently with *in vivo* and clinical data showing an association between Gal-3 expression and lack of efficacy of PD-1/PD-L1 targeted checkpoint inhibitors. Galecto is now investigating the safety and efficacy of GB1211 in combination with atezolizumab in NSCLC. Research Sponsor: Galecto, Inc.

2608 **Poster Session**

Actual immune checkpoint inhibitor drug use in U.S. patients with cancer. *First Author: Alia Rawji, OptumLabs, Minnetonka, MN*

Background: By 2018, seven Immune Checkpoint Inhibitor (ICI) drugs had gained FDA approval in nine cancers and the number of indications has continued to increase. Haslam et al. estimated that between 36.1 and 38.5% of US patients with cancer were eligible for ICI therapy in 2019. We report the use of ICI dugs in the first-line of therapy (LOT1) and second-line (LOT2) among enrollees treated for 9 cancers with an FDA indication approval in or before 2017. **Methods:** A cohort of patients treated for one of the nine most common cancers with an FDA indication for ICI drugs in 2017 was identified using de-identified data from the OptumLabs Data Warehouse, and clinical information from the Optum Cancer Guidance Program's electronic prior authorization (ePA) platform. De-identified administrative claims data were then linked to ePA information (cancer type & diagnosis date) at the patient level to identify details of treatment received. Eligible patients were enrolled in a commercial or Medicare Advantage (MA) plan and initiated treatment within six months of diagnosis, enrolled at least six months prior to diagnosis date (ensuring this was the LOT1) and at least thirty days after start of first identified treatment regimen (to identify the full treatment regimen). LOT1 treatment initiation ranged from 1/1/2017 to 12/31/2020 for those who were diagnosed before 6/30/2020. ICI regimens are defined as those with an ICI drug received within first thirty days of the LOT start date. **Results:** In this population, we identified 17,283 eligible patients treated for non-small cell lung cancer (4654), melanoma (705), renal cell carcinoma (554), bladder cancer (1974), colorectal (4502), hepatocellular carcinoma (673), gastric cancer (1786), head and neck cancer (1923), or Hodgkin lymphoma (512) in 2018, 2019, and 2020. Overall, 3,291 (19%) of these patients received an ICI in LOT1 with rates increasing over time. The highest rates of ICI use in LOT1 are for the treatment of melanoma, remaining consistent over time, while ICI use in LOT2 is highest for the treatment of non-small cell lung cancer although evidence from 2020 suggests this may be waning. Among patients being treated for renal cell carcinoma, ICI use in LOT2 decreased from 43% (2018) to 15% (2020) while LOT1 ICI use increased to 81% in 2020. **Conclusions:** Overall, ICI use has changed over time in both the first- and second-line setting. In particular, we observe a shift in ICI use from LOT2 to LOT1, consistent with the more recent FDA approvals in earlier lines of therapy. Research Sponsor: None.

Regimens containing immune checkpoint inhibitors.

	1st line			2nd line		
	2018	2019	2020	2018	2019	2020
Overall	14%	20%	22%	19%	18%	12%
Non-small cell lung cancer	35%	41%	42%	44%	42%	29%
Bladder cancer	2%	5%	10%	13%	14%	9%
Renal cell carcinoma	51%	77%	81%	43%	23%	15%
Melanoma	92%	95%	95%	38%	22%	11%
Hepatocellular carcinoma	5%	10%	14%	11%	12%	8%
Head and neck cancer	1%	4%	8%	13%	12%	6%
Other Cancers	1%	1%	2%	3%	5%	1%

*2020 data for those diagnosed through 6/30/2020.

2609 **Poster Session**

A prospective, multicenter, single-arm clinical trial of PD-1 inhibitors in combination with radiotherapy and GM-CSF, sequentially followed by IL-2 (PRaG 2.0) therapy in advanced refractory solid tumors. *First Author: Pengfei Xing, The Second Affiliated Hospital of Soochow University, Suzhou, China*

Background: It's been widely recognized that T cells play an essential role in immunotherapy of malignant tumors. Notably, in our previous PRaG trial, we observed that T cell decreasing occurred in some patients with advanced refractory solid tumors during PD-1 inhibitor combined with stereotactic body radiation therapy (SBRT) / hypo-fractionated radiotherapy (HFRT) and granulocyte macrophage-colony stimulating factor (GM-CSF) treatment which might be one of the reasons for their poor efficacy. To further improve the efficacy of immunotherapy combined with radiotherapy, we optimized the PRaG regimen and added interleukin-2 (IL-2), which amplifies and activates T cells. We conducted PRaG 2.0 trial to further explore the effect of T cells on efficacy. **Methods:** Patients with advanced refractory solid tumors who lacked or were intolerant to the available standard of care were enrolled to receive PRaG 2.0 regimen. A treatment cycle consisted of SBRT or HFRT (5 or 8Gy×2-3f) delivered for one metastatic lesion, PD-1 inhibitor dosing within one week after completion of radiotherapy, GM-CSF 200μg subcutaneous (SC) injection once daily for 7 days (d1-7), and then sequentially followed by IL-2 2million IU SC once daily for 7 days(d8-14). PRaG 2.0 regimen was repeated every 21 days for at least 2 cycles until no appropriate lesions for irradiation or reached the tolerance dose of normal tissues. Patients who could not continue radiotherapy and had not yet developed progression disease (PD) allowed PD-1 inhibitors to be continued as maintenance therapy until PD or unacceptable toxicity but no more than one year. The primary endpoint was Progression-Free Survival (PFS). This trial was registered at www.clinicaltrials.gov with identifier number NCT04892498. **Results:** With the cutoff date of 31 December 2021, a total of 34 patients were enrolled, in which 28 patients (82%) completed at least 1 tumor assessment with a median follow-up time of 5.5 months (95%CI: 4.4, 6.6). Median PFS and overall survival (OS) were currently not reached. The objective response rate (ORR) was 21.4%, and the disease control rate (DCR) was 71.4% by RECIST1.1. Compared to baseline, no significant decrease of T cells, including $CD3^+$, $CD4^+$, and $CD8^+$ T cells, have been observed in 19 patients who completed ≥ 4 treatment cycles. Treatment-related adverse events (TRAE) occurred in 28 of 34 (82.4%) patients, Grade ≥ 3 TRAEs occurred in three patients (8.8%). TRAEs leading to treatment interruption occurred in three patients (8.8%). **Conclusions:** These preliminary results of PRaG 2.0 trial demonstrate that PD-1 inhibitors in combination with radiotherapy, GM-CSF, and IL-2 could potentially maintain the T cells and improve clinical outcomes in patients with advanced refractory solid tumors with acceptable toxicity. Clinical trial information: NCT04892498. Research Sponsor: None.

2610 **Poster Session**

A phase 1/2 study of onatasertib, a dual TORC1/2 inhibitor, combined with the PD-1 antibody toripalimab in patients with advanced solid tumors (TORCH-2). *First Author: Pei Shu, Clinical Trial Center, National Medical Products Administration Key Laboratory for Clinical Research and Evaluation of Innovative Drugs, West China Hospital, Sichuan University, Chengdu, China*

Background: Pre-clinical studies suggest synergistic activity of the combination of inhibitors of mTOR with a PD-1 antibody in solid tumors. Here we report initial results of a phase 1/2 open-label, dose escalation and expansion trial of the oral TORC1/2 inhibitor, onatasertib (ATG-008) in combination with toripalimab (tori), a PD-1 monoclonal antibody, in patients (pts) with advanced solid tumors (NCT04337463). **Methods:** This study consists of two phases: dose escalation and dose expansion. The primary objective in the dose escalation phase was to evaluate safety and tolerability of onatasertib combined with tori, followed by a dose expansion phase to assess antitumor efficacy and verify the safety and tolerability profile of the combination therapy. Primary endpoints included maximum tolerated dose (MTD), recommended phase II dose (RP2D) and efficacy of the combination. Other endpoints included pharmacokinetics, and exploratory biomarkers of drug activity. Prior check point (anti-PD-1, anti-PD-L1, CTLA-4), mTOR and/or PI3K/AKT/mTOR inhibitor therapy was excluded, regardless of PD-L1 expression. Onatasertib was administered orally once a day (QD) at three dose levels (15, 20 and 30mg) in combination with tori at the approved dose of 240 mg, once every 21 days (Q3W). Efficacy assessments are reported based on RECIST1.1 criteria. **Results:** As of Dec 20, 2021 cut-off, 28 advanced solid tumor pts were enrolled in the study with 10 pts in the dose escalation phase and 18 pts in the dose expansion phase. Median age was 52 years. Baseline ECOG scores were 0 (4 pts) and 1 (24 pts) with a median of 2 prior lines therapy (0-7), 21 pts had stage IV disease. No dose-limiting toxicities were reported in dose escalation phase. The study did not reach MTD. All pts had ≥ 1 TEAEs; 19 (67.9%) pts had grade ≥ 3 TEAEs. The most common grade ≥ 3 TEAEs included lymphocyte count decreased (21.4%), rash (14.3%) and hyperglycemia (10.7%). AEs lead to discontinuation in 2 pts (7.1%). The RP2D for onatasertib was determined to be 15-20 mg in combination with the recommended dose of tori. Among the 21 efficacy evaluable (EE) pts, the ORR was 28.6% (6 pts, 5 confirmed) and DCR was 71.4% (15 pts). In 5 EE pts with cervical cancer, 1 complete response (CR) and 3 partial responses (PR) were observed (all confirmed). One cervical cancer pt with negative PD-L1 expression achieved CR and remains on treatment after 580 days. Two other PRs were seen (one nasopharyngeal carcinoma, one ovarian carcinoma). Median progression free survival (PFS) in the whole cohort was 3.52 months and 18-month PFS rate was 31.2%. **Conclusions:** Onatasertib in combination with tori is tolerable with encouraging response rates and disease stabilisation in subjects with advanced solid tumors, especially in cervical cancer. Expansion enrolment for cervical cancer is ongoing and updated information will be presented. Clinical trial information: NCT04337463. Research Sponsor: Antengene Corporation.

2611 **Poster Session**

Safety of dual checkpoint-blockade with PSB205, an anti-PD-1/CTLA4 monoclonal antibody combination, manufactured and dispensed as a single product: A phase 1 study. *First Author: Rashmi Chugh, University of Michigan, Ann Arbor, MI*

Background: PSB205 is a new biological agent consisting of two engineered monoclonal antibodies (anti-PD-1 IgG4 and anti-CTLA-4 IgG1) expressed in a fixed ratio (2:1) from a single cell-line, manufactured as one product and dispensed from a single vial. PSB205 was designed to optimally balance efficacy and safety through differential target coverage of PD-1 and CTLA-4: the anti-CTLA-4 antibody was engineered to have a shorter half-life to modulate exposure and lower risk of immune-related adverse events (irAEs). **Methods:** We report safety data from a first-in-human study, conducted in standard 3+3 Phase 1 dose escalation format, enrolling subjects with refractory solid tumors with mixed histologies, who had exhausted available standard treatments. Primary objectives were safety (including Dose Limiting Toxicities), tolerability and selection of a Phase 2 dose. Secondary objectives were PK and preliminary evaluation of effectiveness. Treatment was Q3 wks. Inclusive the 1st week following the 2nd infusion, the DLT-period was 28 days. **Results:**Nine US-centers enrolled 27 subjects, representing 19 tumor histologies, in 5 ascending dose cohorts ranging from 0.1 mg/kg to 5 mg/kg; an additional N = 49 pts were dosed in expansion cohorts at 5 mg/kg and 400 mg (fixed dose). Median number of prior systemic treatments for metastatic disease was 4. No DLT was observed at any of dose level evaluated. The most frequent Treatment-Related Adverse Events (TRAE) reported were diarrhea (9%), Infusion-Related Reaction (IRR) (5%) and fatigue (4%). Among the subset (N = 33) who completed at least 4 cycles of treatment, the most common TRAE were diarrhea (21%), IRR (12%), Fatigue (9%), and irAEs, specifically colitis, rash and arthralgia (6% each symptom). Most TRAEs were Grade 1 /2, with just 1 case each of diarrhea and colitis Graded as G 3/4. Tumor responses (all PRs) were observed at dose levels of 3 mg/kg and 5 mg/kg in 4 pts - 1 each with with RCC, SCLC, HNSCC and gastric cancer. **Conclusions:** PSB205 provides dual checkpoint blockade with a very tolerable side effect profile, with less AEs than typically noted in published studies of anti-PD1 and anti-CTLA-4 combination therapy. Further studies are ongoing to confirm this observation. Dose levels of 5 mg/kg and 400 mg fixed were selected for Phase 2, which has commenced enrollment. Clinical trial information: NCT03986606. Research Sponsor: Sound Biologics.

2612 **Poster Session**

Predictors of response to immune checkpoint inhibitors (ICI) rechallenge post-disease progression in solid tumors: A systematic review and meta-analyses. *First Author: Hassan Mohammed Abushukair, Jordan University of Science and Technology, Irbid, Jordan*

Background: Rechallenge with the same or different ICI has been proposed as a second line option in patients who progress on an initial ICI course. Considering rechallenge risks of limited benefit and further toxicity, identifying predictors for patients benefiting from rechallenge would provide much needed guidance for practice. We present a systematic review and meta-analyses of response predictors to ICI rechallenge after disease progression in solid tumors. **Methods:** A systematic search of PubMed, Cochrane database and ASCO meeting library was done for studies published up to Jan 2022 evaluating the efficacy of ICI rechallenge in patients with advanced solid tumors after disease progression on initial ICI. Predictors of interest included duration of the initial ICI course using a cutoff point of 6 months, and best overall response (BOR) to initial ICI: stratified into responders (complete or partial response or stable disease) and non-responders (progressive disease). Odds ratios (OR) for ICI rechallenge response were calculated & pooled in reference to initial ICI duration and its BOR using the fixed effects model. ORs with a 95% confidence interval [CI] not overlapping the null value (1) were considered statistically significant. **Results:** A total of 56 studies reporting on ICI rechallenge upon progression, comprising 3579 patients, of which 31 studies have switched their second ICI regimen. Initial ICI was anti-PD-1 in 37 studies, anti-CTLA-4 in 14 studies, and anti-PD-L1 in 10 studies. Involved solid cancers included melanoma (n = 30), NSCLC (n = 15), RCC (n = 6), and others (n = 5). Pooled objective response rate for rechallenge was 18.4% ([15.4-21.4], I^2 = 84.6%), with the highest being among melanoma patients (21.2% [17.2-25.2], I^2= 83.4%). For BOR, no significant difference was found for the entire cohort (OR = 1.34 [0.86 - 2.09], I^2 = 27.1%). In melanoma studies, response to ICI rechallenge was significantly higher in patients responding to the initial ICI prior to progression (OR = 1.87 [1.03-3.39], I^2 = 24.5%). For treatment duration, there was no difference in the entire cohort concerning ICI rechallenge (OR = 1.54 [0.86-2.75], I^2 = 14.2%), yet melanoma patients showed a significant difference favoring those who had longer response durations on initial ICI (OR = 2.05 [1.01-4.16], I^2 = 0.0%). **Conclusions:** Response to rechallenge in advanced melanoma patients was more common in initial ICI responders with a longer course duration (> 6 months). More homogeneous studies are needed to validate our findings and investigate other potential markers for rechallenge such as PD-L1 status & mutational burden. Research Sponsor: None.

	Total	Melanoma	NSCLC	RCC
# of studies/pts	15/439	7/230	5/83	3/126
BOR OR (95% CI)	1.34 (0.86-2.09)	1.34 (0.86-2.09)	0.65 (0.24-1.7)	1.17 (0.44-3.1)
# of studies/pts	10/236	6/168	4/68	
Duration OR (95% CI)	1.54 (0.86-2.75)	2.05 (1.01-4.16)	0.79 (0.27-2.31)	

2613 **Poster Session**

Association of proton pump inhibitor use with survival outcomes in patients with cancer treated with immune checkpoint inhibitors: A systematic review and meta-analysis. *First Author: BaoQing Chen, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Proton pump inhibitors (PPIs) were revealed to regulate gut microbiome alterations and further impact the response to immune checkpoint inhibitors (ICIs). Contradictory impacts on survival were observed in ICI-treated patients when concomitantly use PPI or not. We performed this systematic review and meta-analysis to analyze the association of PPI use with survival outcomes in ICI-treated cancer patients. **Methods:** EMBASE, MEDLINE/PubMed, Cochrane Library databases and major oncology conferences proceedings were comprehensively searched. Studies comparing overall survival (OS) and progression-free survival (PFS) between PPI use and PPI non-use in ICI-treated cancer patients were included. Data regarding the characteristics, ICI and PPI treatments and survival outcomes for patients were extracted. Hazard ratios (HRs) with 95% confidence intervals (CIs) were pooled using random-effect models. Subgroup meta-analyses and meta-regressions were performed to explore possible factors of heterogeneity among study results. **Results:** A total of 20 studies were included, comprising 2812 ICI- and PPI-treated patients and 3990 ICI-treated and PPI-free patients. The pooled HR is 1.30 (95% CI, 1.17-1.45; $P < .001$) for OS and 1.20 (95% CI, 1.08-1.34; $P < .001$) for PFS, indicating a significant negative association between PPI use and survival of ICI-treated patients. Subgroup meta-analyses by factors including cancer types, ICI types and time window of PPI use, revealed such associations were in patients with non-small cell lung cancer (OS: HR = 1.40, 95% CI = 1.23 to 1.59, $P < .001$; PFS: HR = 1.27, 95% CI = 1.16 to 1.40, $P < .001$) or urothelial cancer (OS: HR = 1.50, 95% CI = 1.26 to 1.80, $P < .001$; PFS: HR = 1.37, 95% CI = 1.17 to 1.60, $P < .001$), patients treated with anti-PD-1/PD-L1 (OS: HR = 1.41, 95% CI = 1.30 to 1.53, $P < .001$; PFS: HR = 1.29, 95% CI = 1.20 to 1.38, $P < .001$), patients receiving PPI as baseline treatment (OS: HR = 1.43, 95% CI = 1.21 to 1.69, $P < .001$; PFS: HR = 1.29, 95% CI = 1.16 to 1.44, $P < .001$) or 60 days before ICI treatment initiation (OS: HR = 1.28, 95% CI = 1.11 to 1.48, $P < .001$; PFS: HR = 1.27, 95% CI = 1.16 to 1.40, $P < .001$), rather than concomitantly with ICI initiation. **Conclusions:** PPIs use in patients treated with ICIs is associated with a shorter OS and PFS, especially in several specific subgroups of cancer patients. PPIs should be strictly controlled, and appear to not impact survival if given temporarily after ICIs initiation. These detailed observations could provide basis for clinical guidelines when concomitantly use PPIs and ICIs. Research Sponsor: National Natural Science Foundation of China (No.81902462), U.S. National Institutes of Health, U.S. Department of Defense (W81XWH2110030), and Berlin Institute of Health.

2614 **Poster Session**

A pan-cancer analysis of P21 activated kinase (PAK) family genes as potential biomarkers for immune checkpoint therapy. *First Author: Sun Gang, The Affiliated Cancer Hospital of Xinjiang Medical University, Xinjiang Cancer Center, Key Laboratory of Oncology of Xinjiang Uyghur Autonomous Region, Urumqi, China*

Background: PAK (P21 activated kinase) is a family of serine threonine kinases, that consist of 6 members, PAKs 1-6, which are positioned at an intersection of multiple signaling pathways implicated in oncogenesis. Recent studies have found relationship between mutations of some PAK family genes and antitumor immunity. Here, we explored the associations of PAK family gene mutations with ICI response based on multidimensional data from multiple solid tumors. **Methods:** An immunotherapy cohort (Broad/Dana-Farber, Nat Genet 2018, N = 249) within 7 types of tumors as discovery stage, was used to explore the association of PAK family genes mutations with tumor mutation burden (TMB) and efficacy of immunotherapy. To further validate the predictive value of PAK family genes, we employed another ICI-treated cohort, MSKCC cohort (Samstein, Nat Genet 2019, n = 1661), as a validation cohort. TMB was calculated as the total count of nonsynonymous mutations in coding sequence. **Results:** In discovery cohort, compared to that in the PAK-Wt group, longer OS was observed in the PAK-Mut group (mOS: 31.3 vs 15.4 months, HR = 0.59, 95% CI: 0.36 to 0.96, $P = 0.03$). In addition, PAK-Mut group had higher TMB ($P < 0.001$). Median TMB in PAK-Mut group and PAK-Wt group is 17.79 (IQR, 7.45-36.55) Mut/Mb and 5.47 (IQR, 2.46-9.09) Mut/Mb, separately. In validation cohort, PAK-Mut patients also achieved significant improved OS compared with PAK-Wt patients (mOS: 44.0 vs 17.0 months, HR = 0.51, 95% CI: 0.37 to 0.69, $P < 0.001$). Moreover, multivariable analysis of validation cohort demonstrated that PAK-Mut was associated with better OS (HR = 0.71; 95%CI, 0.52-0.98; P = 0.036), after adjusting for Age, Gender, Metastasis, Treatment, TMB, Cancer type. Compared with PAK-Wt group (median [IQR]: 5.90 [2.95-10.04]), PAK-Mut group (median [IQR]: 21.19 [11.81-43.29]) also had higher TMB ($P < 0.001$). **Conclusions:** The results indicated that PAK family genes mutation was associated with a higher TMB both discovery and validation cohort. Analysis of discover and validation immunotherapy cohort data showed PAK family was associated with better OS. These findings indicate that these genes mutation may serve as a potential predictive biomarker for ICI in solid tumor patients. Research Sponsor: None.

2615 **Poster Session**

***WDR49* mutation as a novel predictive biomarker in patients with non–small cell lung cancer with immune checkpoint inhibitors.** *First Author: Zhihui Shi, The Second Xiangya Hospital of Central South University, Changsha, China*

Background: Application of Immune Checkpoint Inhibitors (ICIs) has become the first-line therapy for advanced or metastatic non-small cell lung cancer (NSCLC). *WDR49* gene belongs to the WDR (WD40-repeat) protein family which participates in a wide range of biological processes, including DNA damage repair and immune regulation, etc. However, the correlation between *WDR49* mutation and immune efficacy is unclear. **Methods:** A total of three independent cohorts of NSCLC patients treated with immunotherapy were analyzed in this study: the Miao cohort (n = 56), the Rizvi cohort (n = 34), the Hellmann cohort (n = 75). Survival was estimated by Kaplan-Meier curves, with the p value determined by a log-rank test. HR was determined through the univariable and multivariable Cox regression. The CIBERSORT analysis relied on RNA-seq data in The Cancer Genome Atlas (TCGA) database. Two-sided P value < 0.05 was considered statistically significant. All the statistical analyses were conducted with R version 4.0.3. **Results:** In this merged cohort, the frequency of *WDR49* mutation (*WDR49*-mut) was 10.30% (17 in 165), and most patients with *WDR49* mutation were lung adenocarcinoma (LUAD) (11.85%, 16 in 135). Meanwhile, the frequency of *WDR49*-mut in TCGA database was 7.05 % and 3.84% in LUAD and lung squamous cell carcinoma (LUSC), respectively. The Kaplan-Meier curves survival analysis indicated that *WDR49*-mut was associated with longer progression free survival (PFS) (median PFS 23 months vs 5.2 months, hazard ratio [HR] = 0.17 [95% CI, 0.06–0.47], P < 0.001) and higher objective response rate (ORR) (76% vs 27%, P < 0.001). Furtherly, *WDR49*-mut was significantly related to higher tumor mutational burden (TMB) (median TMB 495 vs 149, P < 0.001), but it had nothing to do with the expression of PD-L1 (Proportion of PD-L1 positive 72.7% vs 68.5%, P = 1). The CIBERSORT analysis revealed that CD8+ T cell infiltration was significantly higher in *WDR49*-mut group than *WDR49* wildtype group (p < 0.05). **Conclusions:** Better treatment response and survival benefit in the mutant group suggest that the *WDR49* mutation may serve as a novel predictive biomarker in NSCLC patients with ICIs. The significantly higher TMB and CD8+ T cell infiltration in *WDR49*-mut group may be the potential mechanism. Research Sponsor: None.

2616 **Poster Session**

Molecular predictors of response among patients with MMRd tumors treated on NCI-MATCH Arm Z1D. *First Author: Jonathan Daniel Schoenfeld, Dana-Farber Cancer Institute, Boston, MA*

Background: On arm Z1D of the NCI-MATCH trial, the PD-1 inhibitor nivolumab was found to have activity among patients with mismatch repair-deficient (MMRd) tumors as defined by complete loss of MLH1 or MSH2 nuclear expression determined by immunohistochemistry, with 6-month progression free survival of 51%. We aimed to identify molecular predictors of response in this population. **Methods:** Among patients treated on NCI-MATCH Z1D, we evaluated genomic and tissue predictors of clinical benefit (CB), defined as patients with RECIST v1.1 complete or partial response or stable disease for ≥ 6months. WES files were processed and filtered using GATK best practices preceding TMB and MSI calculations according to MSI sensor score, a WES-based MSI rating system. Cutoffs were set to define TMB (TMB-Low: ≤10 mutation/Mb; TMB-High: >10) and MSI (MSS: ≤10% unstable loci; MSI-Low: $10 > x \leq 20$; MSI-High: >20). Multiplex immunofluorescence (mIF) used formalin-fixed paraffin-embedded slides stained using a BOND RX automated stainer. Expression analyses followed normalization in DEseq2's median of ratios method. Gene set enrichment analysis was conducted by "empirical phenotype-based permutation test." Additional RNA, WES, and mIF comparisons used the Wilcoxon rank-sum test. **Results:** Among 36 patients accrued to NCI-MATCH Z1D with pretreatment correlative samples available, 7 were unevaluable for response, and 1 was misclassified as having an MMRd tumor. Of the remaining 28, 15 had CB (2 CR, 10 PR, 3 SD ≤ 6 months) and correlative data were available for 26 (WES), 27 (RNAseq), and between 10-20 for mIF based on the marker assessed. According to MSI-sensor score, 11 were MSI-high, 8 were MSI-low, and 7 were MSS. MSI-sensor status, but not TMB was associated with CB (p=0.037 and p=0.185, respectively). Similar results were seen when using CR+PR vs SD+PD evaluation. Using RNAseq gene set enrichment analyses, CB patients had increased expression of interferon alpha (p=0.01), interferon gamma (p=0.03), PI3K-AKT-mTOR (p=0.02), cytotoxicity (p=0.05) and antigen processing (p=0.01) gene sets, while hedgehog signaling genes were increased in non-CB patients (p=0.04). The ESTIMATE immune index and infiltration of CD4+/PD1+/Ki67+ cell populations as determined by mIF were nominally higher in patients with CB (p=0.051 and p=0.075). **Conclusions:** Among patients with MMRd tumors treated with PD-1 checkpoint blockade, correlative analyses demonstrate associations between CB and MSI-sensor score as well as biomarkers indicative of immune infiltration and antigen presentation. This suggests that these measures may help differentiate patient response in MSI tumors. Clinical trial information: NCT02465060. Research Sponsor: U.S. National Institutes of Health.

2617 **Poster Session**

***PAPPA2* mutation as an indicator stratified patients benefit from immune checkpoint inhibitors in NSCLC and SKCM.** *First Author: Yiting Dong, National Cancer Center/National Clinical Research Center for Cancer/ Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: Pappalysin 2 (*PAPPA2*) mutation, most occurring in skin cutaneous melanoma (SKCM) and non-small cell lung cancer (NSCLC), is found to be related to anti-tumor immune response. However, the association between *PAPPA2* and efficacy of immune checkpoint inhibitors (ICIs) therapy remains unknown. **Methods:** Forty-one NSCLC patients receiving anti-PD-(L)1 (China cohort, n = 41) and seven public cohorts with whole-exome sequencing (WES) data were included to analyze the performance of *PAPPA2* mutation as an indicator stratifying patients benefit from ICIs, consolidating a discovery set (n = 34) and two validation sets (NSCLC validation set , n = 172 ; SKCM validation set, n = 210). The mechanism was analyzed in the Cancer Genome Atlas (TCGA) database (n = 1467). **Results:** In the discovery set, patients with *PAPPA2* mutation exhibited a significantly predominant PFS (HR, 0.11 [95% CI, 0.01-0.83]; P = 0.01), ORR (100.0% vs 21.4%; P < 0.001) and durable clinical benefit (DCB, 83.3% vs 32.1%; P = 0.012) compared to those with wide-type *PAPPA2*, consistent in NSCLC validation set (PFS, HR, 0.3 [95% CI: 0.16-0.56], P < 0.001; ORR, 70.8% vs. 20.9%, P < 0.001; DCB, 83.3% vs. 36.5%, P < 0.001) and SKCM validation set (OS, HR, 0.49 [95% CI: 0.31-0.78]; P = 0.002; ORR, 34.1% vs. 16.9%, P = 0.039; DCB, 50.0% vs. 30.7%; P = 0.036). Similar results were observed in multivariable models. In contrast, no association between *PAPPA2* mutation and OS or PFS was observed in TCGA datasets, suggesting that *PAPPA2* mutation may be a predictive but not a prognostic factor in ICI treatment for NSCLC patients. Based on CIBERSORT-inferred tumor infiltrating lymphocytes from TCGA, we found that *PAPPA2* mutation was significantly associated with higher activated CD4 memory T cells and lower Treg cells in tumor immune microenvironment, related with higher TMB ($P < 0.001$) and neoantigen load ($P < 0.001$). In addition, gene set enrichment analysis (GSEA) analysis revealed that *PAPPA2* mutation was correlated with upregulated DNA damage repair (DDR) signaling pathway. **Conclusions:** Our findings indicated that *PAPPA2* mutation could serve as a novel indicator to stratify beneficiaries from ICIs therapy in NSCLC and SKCM, warranting further prospective studies. Research Sponsor: CAMS Innovation Fund for Medical Sciences.

2618 **Poster Session**

Predictors of immunotherapeutic benefits in patients with advanced melanoma and other malignancies treated with immune checkpoint inhibitors utilizing ORIEN "real-world" data. *First Author: Ahmad A. Tarhini, Department of Cutaneous Oncology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

Background: Despite the significant improvements in treating cancer with immune checkpoint inhibitors (ICIs), many patients (pts) do not achieve disease control. Using Oncology Research Information Exchange Network (ORIEN) Avatar real-world data conducted under the Total Cancer Care protocol we investigate predictive biomarkers of ICI benefits in pts with advanced malignancies. **Methods:** Clinical data were normalized as part of ORIEN Avatar. RNA-seq was performed on tumor samples following the RSEM pipeline and gene expressions were quantified as Transcript Per Million (TPM). Gene expressions (GE) were log2(TPM+1) transformed. Mann-Whitney U-test was used to compute differences between groups, and Kaplan-Meier survival analysis was performed. **Results:** Pts (n=1214) with 27 cancer types treated with ICIs were retrieved from the database, where 1143 and 875 patients were profiled by WES and RNA-seq, respectively. 804 pts had both WES and RNA-seq data. The top six cancer types were renal cell carcinoma (n=206), non-small cell lung cancer (n=173), head and neck cancer (n=157), melanoma (n=154), sarcomas (n=99) and bladder cancer (n=87). The ICI regimens included therapy with atezolizumab (n=87), avelumab (n=12), cemiplimab (n=6), ipilimumab (n=47), nivolumab (n=424), pembrolizumab (n=525) and ipilimumab+nivolumab (n=113). Median overall survival (OS) for the entire cohort was 21.9 months. Patients had significant improvement in OS if ICI was given in the first line ($P<0.0001$). Previously published GE signatures were tested in the melanoma cohort. Signatures related to IFNg, effector T cells, chemokines, MHC II and Tertiary Lymphoid Structures were significantly prognostic and predictive of ICI benefits in advanced melanoma (Table). Analyses in the other cancer types are ongoing. **Conclusions:** GE data analyses validate the predictive value of immune related gene signatures following ICI immunotherapy in melanoma. Ongoing analyses are investigating these signatures in other malignancies and integrating the GE data with data related to TMB, somatic mutations and germline genetic variations. Research Sponsor: ORIEN Foundation and Community Foundation of Tampa Bay.

GE signatures and correlation with survival (>24 versus <24 months and overall survival) in cutaneous melanoma (n=123 pts).

Gene Signature Name	Description	Reference	Survival >24 vs <24 months; *P*-value	OS (log-rank test) *P*-value
IFNg-6	6-gene IFNg associated	Ayers 2017	0.0017	0.019
IFNg expanded immune 18	18-gene IFNg associated	Ayers 2017	0.0035	0.0031
Effector T cell	Effector T cell gene set	Bolen 2011	0.0013	0.0435
IFNg/Effector T cell	IFNg and effector T cell gene set	Fehrenbacher 2016	0.0009	0.0096
Chemokine	Chemokine gene set	Coppola 2011, Messina 2012	0.0073	0.0257
MHC II	13 MHC-II genes	Liu 2021	0.0185	0.0076
TLS	Tertiary lymphoid structures gene signature	Cabrita 2020	0.25	0.0031

2619 **Poster Session**

A deep learning approach utilizing clinical and molecular data for identifying prognostic biomarkers in patients treated with immune checkpoint inhibitors: An ORIEN pan-cancer study. *First Author: Payman Ghasemi Saghand, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

Background: Immune checkpoint inhibitors (ICIs) have made significant improvements in the treatment of cancer patients (pts), but many continue to experience primary or secondary resistance. Here, we leveraged clinical and genomic data to identify prognostic biomarkers in pts treated with ICIs utilizing a pan-cancer approach. **Methods:** Pts were enrolled to the Total Cancer Care protocol across 18 cancer centers within the Oncology Research Information Exchange Network (ORIEN). RNA-seq was performed on tumors following the RSEM pipeline and gene expressions were quantified as Transcript Per Million (TPM) and were logarithmically normalized. An Auto-Encoder Survival Deep Network (AE-SDN) architecture was developed that combined the reconstruction loss of AE with Cox regression for modeling time to event. For comparison, immunoscore for each pt was calculated based on the estimated densities of tumor CD3+ and CD8+ T cells (Galon, 2020) utilizing CIBERSORTx. The quality of overall survival (OS) predictions was assessed using Harrell's concordance index (C-index). Log-rank test was used to assess stratified group differences (by ICI or cancer histology) along with Kaplan-Meier (KM) survival analysis of AE-SDN and immunoscore. **Results:** Pts (n=522) with 4 cancer types including melanoma (n=125), renal cell carcinoma (n=149), non-small cell lung cancer (n=128) and head and neck cancer (n=120) treated with 6 ICI regimens were included in this analysis. ICI regimens were nivolumab (n=219), pembrolizumab (n=202), ipilimumab+nivolumab (n=69), ipilimumab (n=30), avelumab (n=1) and cemiplimab (n=1). The Table summarizes the overall C-index and associated 95% CIs and log-rank *P* values for the entire cohort (regardless of histology) resulting from our proposed AE-SDN model and the separate estimated immunoscore categorization. AE-SDN top selected genes were mostly related to immunity, carcinogenesis and tumor suppression. The corresponding KM plots showed significantly wider separations of the survival curves in favor of our proposed AE-SDN model relative to the immunoscore with more than 20% improvement in prediction power. **Conclusions:** Deep network machine learning analysis is a promising approach to identifying relevant prognostic biomarkers in cancer pts treated with ICI. This may lead to novel therapeutic predictive signatures and identification of mechanisms of ICI resistance. Our AE-SDN gene expression signature was significantly prognostic and outperformed the estimated CD3+, CD8+ T Cell immunoscore. Further refinements to our prediction power are ongoing along with more advanced neural network architectures to elucidate related functional pathways. Research Sponsor: ORIEN Foundation and Community Foundation of Tampa Bay.

	Avg. C-index	95% CI	Log-rank test p-value
AE Deep	0.6556	(0.6484 , 0.6629)	2.80E-14
Immuno-score	0.5402	(0.5345 , 0.5459)	8.20E-04

2620 **Poster Session**

Analysis of the contribution of macrophages to the overall tumor PD-L1 microenvironment using a screening multi-tumor tissue microarray and rapid multiplex fluorescence digital phenotyping approach. *First Author: Marie Cumberbatch, TriStar Technology Group LLC, Washington, DC*

Background: Programmed death ligand-1 (PD-L1) contributes to immune suppression in the tumor microenvironment (TME) by interacting with programmed cell death-1 (PD-1) on infiltrating T lymphocytes leading to tumor immune escape. Application of omics technologies has shed light on the relevance of the TME for response to immunotherapies and development of novel treatment options. Here we have applied a multi-plex immunofluorescence/multi-tumor tissue microarray (TMA) approach to examine the immunobiology of different TMEs with respect to the contribution by tumor cells and macrophages to overall PD-L1 expression. **Methods:** A TMA comprising 11 tumor types and a total of 144 different donors, each represented by two cores [1mm; 1 from invasive margin (IM) and 1 from tumor center (TC)], was stained using Ultivue's Immuno8 FixVUE panel (CD3, CD4, CD8, FOXP3, CD68, PD-1, PD-L1, pan-CK/SOX10). Whole slide images from two rounds of imaging (x20 magnification; four markers in each round) were aligned using Ultivue's UltiStacker software based on the nuclear counterstains from the two imaging rounds, to provide precise marker colocalization data. Cell phenotype data for each core was generated using Visiopharm software. **Results:** Overall PD-L1 positivity was greatest for NSCLC, SCLC, TNBC and gastric cancer ranging from approximately 600-1000 PD-L1+ cells/mm^2/core, compared with CRC, breast, pancreatic, liver, and gastric esophageal junction (GOJ) cancers (approx. 50-300 PD-L1+ cells/mm^2/core). Contribution by macrophages to overall PD-L1 expression (dual CD68+/PD-L1+) varied by tumor type representing 25-35% for NSCLC (SCC and ADC) and gastric cancer, whereas a converse pattern was apparent for SCLC, TNBC, breast (ER+ and Her2+) and pancreatic cancers where PD-L1+ macrophages accounted for a large proportion (approx. 60-85%) of overall tumor PD-L1 expression. Interestingly, as a proportion of total macrophage infiltration, approximately 65% of CD68+ macrophages were PD-L1+ for SCLC and TNBC, compared with less than 10% for pancreatic and liver cancer. Spatial analysis revealed PD-L1+ macrophage infiltration to be generally higher for IM versus TC, and the distribution between tumor (CK+) and stroma (CK-) remained similar despite exclusion of CD3+/CD8+ cytotoxic T cells from CK+ tumor regions for pancreatic and liver cancer. **Conclusions:** Taken together, these data illustrate the benefits of combining multiplexed immunofluorescence staining, with digital analysis of cell phenotypes within well characterized tumor samples to better understand the relative immunobiology of different TMEs. Here we demonstrate that the relative contribution of macrophages to the overall PD-L1 microenvironment varies between tumor types, which may help guide options for successful immunotherapy strategies. Research Sponsor: None.

2621 **Poster Session**

The inflamed immune phenotype (IIP): A clinically actionable artificial intelligence (AI)-based biomarker predictive of immune checkpoint inhibitor (ICI) outcomes across >16 primary tumor types. *First Author: Jeanne Shen, Department of Pathology, Stanford University School of Medicine, Stanford, CA*

Background: The IIP, defined by enriched intratumoral tumor-infiltrating lymphocytes (TIL), is a potential tumor-agnostic biomarker of responsiveness to ICI therapy. Here, we validate the IIP, as assessed by Lunit SCOPE IO, an AI-powered spatial TIL analyzer that runs on routine H&E-stained whole-slide images (WSI), for clinical outcome prediction in a large, multi-center international cohort of ICI-treated patients, demonstrating its utility as a practical biomarker to guide ICI treatment planning. **Methods:** Lunit SCOPE IO was developed using 17,849 H&E WSI of multiple cancer types, annotated by 104 board-certified pathologists (13.5×10^9 μm^2 area and 6.2×10^6 TIL). IIP+ tumors were defined as those with ≥ 20% of all 1 mm^2 tumor tiles in a WSI classified as having a high intratumoral TIL density. We evaluated the correlation between IIP and ICI treatment outcomes (overall response rate (ORR) and progression-free survival (PFS), assessed by RECIST v1.1) in a real-world dataset of 1,806 patients (> 16 primary tumor types) retrospectively collected from Stanford University Medical Center, Samsung Medical Center, Chonnam National University Hospital, Seoul National University Bundang Hospital, and Northwestern University. IIP status was sub-analyzed by PD-L1 22C3 tumor proportion score (TPS, n = 798), microsatellite status, and tumor mutational burden (TMB, n = 130). **Results:** The IIP+ phenotype (35.2%, 636 of 1,806) was highly enriched in nasopharyngeal carcinoma (68.0%), melanoma (56.3%), renal cell carcinoma (52.9%), and non-small cell lung cancer (NSCLC, 33.7%). The IIP+ proportion by PD-L1 TPS (< 1% / ≥ 1%) was 21.6% and 40.7%, respectively. While 33.3% of microsatellite unstable (MSI-H) or TMB-high (≥ 10/Mb) tumors were IIP+, a substantial proportion (26.1%) of microsatellite stable (MSS), TMB-low tumors were IIP+. The ORR in IIP+ patients was significantly higher (26.0% vs. 15.8% in IIP-, p < 0.001). Median PFS for IIP+ was 5.3 months (95% CI 4.6-6.9 m), significantly longer than that for IIP- (3.1 m, 95% CI 2.8-3.6 m), with a hazard ratio (HR) of 0.68 (95% CI 0.61-0.76, p < 0.001). The association held after excluding NSCLC patients (n = 909) (HR 0.69, 95% CI 0.59-0.81, p < 0.001). On subgroup analysis, IIP+ correlated significantly with prolonged PFS, regardless of ICI regimen (mono / combo therapy) or PD-L1 TPS (< 1% / ≥ 1%). Of note, IIP+ was predictive of favorable PFS only in the MSS, TMB-low group (n = 88, HR 0.56, 95% CI 0.33-0.96), but not in the MSI-H or TMB-high groups. **Conclusions:** The IIP, as evaluated by Lunit SCOPE IO, may represent a practical, clinically-actionable biomarker predictive of favorable ICI treatment outcomes across diverse cancer patient populations, including those with PD-L1 negative, MSS/TMB-low tumors, in whom predictive biomarkers are urgently needed. Research Sponsor: Lunit Inc.

2622 **Poster Session**

Dual *CDKN2A/MTAP* loss compared to *CDKN2A* loss alone and response to immune-checkpoint inhibitors (ICI) in advanced solid tumors. *First Author: Elio Adib, The Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute and Brigham and Women's Hospital, Boston, MA*

Background: We previously showed that *CDKN2A* genomic alterations (GAs) are associated with resistance to ICI (Adib E, Clinical Cancer Research, 2021). The majority of such GAs are homozygous deletions, which commonly (~50-80%) include *MTAP*, located 100kb telomeric of *CDKN2A*. MTAP loss leads to 5′-deoxy-5′-methylthioadenosine (MTA) accumulation and immunosuppressive effects in tumors. We examined combined *CDKN2A/MTAP* deletion vs. *CDKN2A* deletion/mutation alone as predictors of poor ICI response. **Methods:** We curated clinical data for cancer patients (pts) treated with ICI at Dana-Farber Cancer Institute through 6/2021, who had targeted panel sequencing. Inclusion criteria were: ICI in metastatic setting, ≥2 cycles, no concurrent systemic therapy, cancer type with > 50 pts treated. *CDKN2A/MTAP* GAs were defined as a deep deletion affecting both genes; *CDKN2A* only GAs included both homozygous deletions and truncating mutations. Hazard ratios (HR) for overall survival (OS) and time-to-treatment failure (TTF) were derived using multivariable Cox regression, adjusted for prior lines of therapy, treatment type (single vs. combination ICI), tumor mutational burden and ECOG PS. We also used a machine learning approach to quantify the density of tumor-infiltrating lymphocytes (TILs) in digital whole-slide H&E images of 144 melanoma pts with available genomic data. **Results:** 921 pts with 6 cancer types were studied: non-small cell lung cancer (NSCLC, n = 366), melanoma (mel, n = 228), urothelial carcinoma (UC, n = 120), esophagogastric carcinoma (EGC,n = 90), head and neck squamous cell carcinoma (HNSCC, n = 58), and renal cell carcinoma (RCC, n = 59). UC pts with *MTAP/CDKN2A* GAs had shorter OS and TTF than pts without GA in either gene (OS HR = 1.9[1.1-3.4], p = 0.005; TTF HR = 1.8[1.0-3.1], p = 0.0016) after adjusting for covariates. Similar results were seen for melanoma (OS HR = 2.5[1.4-2.6],p = 0.00065; TTF HR = 1.9[1.1-3.2],p = 0.018). There was no significant difference between pts with *CDKN2A* GA only and those without GA in either gene for OS or TTF in either UC or melanoma. *CDKN2A/MTAP* status was not associated with significantly shorter survival for NSCLC and EGC; while the analysis was confounded by HPV events for HNSCC, and underpowered for RCC. ML-based analysis of digital slides for melanoma, showed that tumors with *CDKN2A* GAs only (n = 42) had similar median density of TILs compared to tumors without GAs in either gene (n = 84; 920 vs. 943 TILs/mm2; p = 0.42). In contrast, tumors with co-occurring *CDKN2A/MTAP* GAs had lower TIL density (529 TIL/mm2, n = 17 vs. 925 TIL/mm2, n = 126 (pooled); p = 0.018, Wilcoxon rank sum). **Conclusions:** In this study, we showed that co-occurrence of *MTAP/CDKN2A* GAs, but not CDKN2A GA only, was associated with worse outcomes in pts with UC and melanoma treated with ICI. Lower TIL density was also seen in melanoma tissue samples with combined *MTAP/CDKN2A* GA. Research Sponsor: None.

2623 **Poster Session**

Comprehensive genomic and immune profiling defines immunotherapy treatment in patients with NSCLC with low PD-L1 IHC. *First Author: Sarabjot Pabla, OmniSeq, Inc., Buffalo, NY*

Background: Immune checkpoint inhibitors (ICIs) have emerged as effective treatments in non-small cell lung cancer (NSCLC). While the clinical utility of single agent ICI or in combination with chemotherapy has been well established, there remains an unmet need for the development of biomarkers that can better predict response. To address this need, we developed and applied a combination genomic and immune biomarker strategy to ICI-treated NSCLC patients which identified distinct patient subgroups with differential benefit among single agent or combination ICI treatment strategies. **Methods:** A discovery cohort (DC) of 5450 tumors across 37 histologies were evaluated by comprehensive genomic and immune profiling of the tumor immune microenvironment. Individual and combination biomarker assessment included PD-L1 IHC, TMB, tumor inflammation (TIGS), cell proliferation (CP) and cancer testis antigen burden (CTAB). From this cohort, combinations of molecular and immune biomarkers were identified and applied to a retrospective cohort (RC) of 225 metastatic NSCLC patients treated with pembrolizumab + chemo or pembrolizumab alone to correlate with response. Comparison of objective response rates (ORR) was performed using Chi-square test. Kaplan-Meir analysis was performed to test for differences in overall survival (OS) and 1-year OS. **Results:** Unsupervised analysis of the DC revealed four distinct biomarker combination groups that describe underlying tumor immunobiology: tumor dominant (CTAB, TMB, CP High), proliferative (CP High), inflamed (TIGS High), and checkpoint (PDL1, TIGS and TMB High). Application of these biomarker groups to the RC demonstrated significant differences in response to ICI regimens between groups (p = 0.04). Patients in the proliferative group (35.1%, 79/225; median PD-L1 = 20% TPS) treated with single agent pembrolizumab showed a significantly higher ORR (59%; 16/27) compared to pembrolizumab + chemo (27%; 14/52; p = 0.005), significantly improved 1-yr OS (p = 0.03), and trend towards better OS (p = 0.14). Importantly, patients in the inflamed group (16%, 36/225; median PD-L1 = 1% TPS), suggested that pembrolizumab + chemo (ORR 26.1%; 6/23) was not associated with ORR compared to pembrolizumab (ORR 31%; 4/13, p = 0.76), or OS (p = 0.37) and 1-yr OS (p = 0.57). **Conclusions:** Comprehensive genomic and immune profiling may identify PD-L1 low NSCLC patients who benefit from single agent pembrolizumab. PD-L1 low NSCLC patients with a proliferative phenotype may benefit from single agent pembrolizumab, whereas PD-L1 low cases with an inflamed phenotype may benefit from both single agent and combination pembrolizumab. Although further clinical validation of these predictive biomarker combinations is required, this data-driven approach demonstrates the potential to provide treatment decision support when selecting an ICI therapeutic strategy in lung cancer. Research Sponsor: Omniseq, Inc.

2624 **Poster Session**

Correlation between MSI, TMB, and RAS gene mutation in solid tumors. *First Author: Qingchang Li, The First Affiliated Hospital of China Medical University, Shengyang, China*

Background: RAS gene family encodes a protein that is a member of the small GTPase super family and plays an important role in the regulation of cell proliferation and promoting oncogenic events. Studies have reported that RAS gene shows a high mutation frequency in lung cancer, colorectal cancer and pancreatic cancer. However, the relation between RAS-mutant and RAS-wild type tumors in tumor mutation burden (TMB) and microsatellite instability (MSI) remain unclear in pan-cancer. **Methods:** We retrospectively analyzed 15188 Chinese patients with pan-cancer from laboratory of Simcere Diagnosis (Nanjing, China) during 2019-2021. Somatic mutations in tumor samples were assessed by next-generation sequencing (NGS). We evaluated RAS (KRAS, NRAS and HRAS) mutation frequency, TMB and MSI in RAS-mutant and RAS wild-type tumors. **Results:** RAS mutations were detected in 2663 (17.5%) samples, including 88.7% of KRAS mutations, 9.1% of NRAS mutations and 3.5% of HRAS mutations. The top 6 frequently cancers were colorectal cancer (829, 31.1%), lung cancer (747, 28.1%), pancreatic cancer (358, 13.4%), biliary tract cancer (210, 7.9%), liver cancer (78, 2.9%), and gastric cancer (73, 2.7%). We found that the incidence of MSI-H in patients with RAS-mutant solid tumors was 3.3% and the frequency of MSI-H was significantly higher in RAS-mutant gastric cancer than that in RAS wild-type (RAS-MUT vs RAS-WT, 20.5% vs 3.5%, p < 0.001). Contrary to our assumption, it was not observed in colorectal cancer (RAS-MUT vs RAS-WT, 5.8% vs 6.9%). In the analysis of TMB, RAS gene mutation was associated with higher TMB (P < 0.01). 27.4% of RAS-mutant gastric cancer and 10.8% RAS wild-type gastric cancer were classified as TMB-H (TMB ≥10 muts/Mb) (P < 0.01), while 13.4% of RAS-mutant colorectal cancer was TMB-H, with no significant difference between RAS wild-type. However, we did not observe a close association between MSI, TMB and RAS gene mutations in lung cancer, pancreatic cancer, biliary tract cancer, and liver cancer. **Conclusions:** We analyzed RAS gene mutations in Chinese patients with solid tumor. Our data showed that RAS mutations were associated with TMB-H and MSI-H in solid tumors, especially gastric cancer. In colorectal cancer, RAS mutations were associated with higher TMB, but not TMB-H. It was showed that RAS mutations in specific cancer types, such as gastric cancer and colorectal cancer, may be related to the efficacy of immunotherapy. Research Sponsor: None.

2625 **Poster Session**

Prevalence of high tumor mutational burden (TMB-H) and microsatellite instability-high (MSI-H) status in neuroendocrine neoplasms. *First Author: Sukhmani Kaur Padda, Samuel Oschin Cancer Center, Cedars-Sinai Medical Center, Los Angeles, CA*

Background: Neuroendocrine neoplasms (NENs) encompass a rare group of tumors arising in nearly any organ site. Patients with advanced-stage NENs have limited treatment options, and molecular profiling is not routinely performed in NENs. However, given tissue-agnostic FDA approvals for immunotherapy in biomarker-selected solid tumors, we sought to assess the frequency of TMB-H and MSI-H in NENs by organ site and in comparison to non-NEN counterparts. **Methods**: We retrospectively analyzed de-identified records from the Tempus database of NENs sequenced with the Tempus xT assay (DNA-seq of 595-648 genes at 500x coverage). Patients were included if their primary cancer arose in the lungs, GI tract (esophagus, stomach, small bowel, colon, rectum), pancreas, or prostate. Histologic diagnoses were grouped as NENs (including high grade or low/intermediate grade), and non-NENs (e.g. adenocarcinoma, squamous cell carcinoma) based on data abstracted from pathology reports. TMB-H was defined as ≥ 10 mutations/megabase. MSI-H was calculated as previously published (PMID: 31570899). Statistical comparisons were limited to groups of 10 or larger. **Results**: We characterized a total of 1,477 NENs from the following anatomic sites: lung (64%, N=951), pancreas (15%, N= 220), GI (15%, N= 224) and prostate (6%, N=82). TMB-H was most common in NENs arising in the lungs (17%, N=155), followed by the pancreas (5.4%, N=11), GI tract (4.8%, N=10), and prostate (3.8%, N=3) (p< 0.001). Overall, TMB-H was more common in high-grade NENs compared to low/int-grade NENs [17% (N=147) vs. 6.2% (N=31), P<0.001]. This was also observed in lung NENs [high-grade 19% (N=135) v low/int grade 10% (N=19), P=0.006], with other organ site analyses limited by sample size (although a similar trend was noted for GI NENs). The majority of patients with TMB-H lung NENs had a current or prior smoking history (94%, N=119). Overall, TMB-H was similar in NENs compared to non-NENs [13% (N=179) vs. 12% (N=3018), P=0.4]. However, in the pancreas, TMB-H was more common in NENs vs. non-NENs [(5.4% (N=11) v 1.6% (N=59), P<0.001] while the reverse was true in lung NENs [17% (N=155) v 22% (N=2006), P=0.001]. MSI-H was observed in only 0.9% (N=12) of NENs overall, including in 0.4% (N=4) of lung, 1.4% (N=3) of pancreas, 1.9% (N=4) of GI, and 1.2% (N=1) of prostate NENs. MSI-H status was less common in NENs compared to non-NENs [0.9% (N=12) vs. 2.5% (N=614), P<0.001]. **Conclusions**: In this real-world NEN cohort, the actionable molecular alterations of TMB-H (13%) and MSI-H (0.9%) were observed. Taken together, the data suggest that molecular profiling (regardless of grade) may help identify a small but meaningful subset of patients with NENs who may benefit from immunotherapeutic treatment approaches. Furthermore, the identification of MSI-H NENs has important implications related to germline testing. Research Sponsor: None.

2626 **Poster Session**

Automated tumor immunophenotyping and response to immunotherapy in non-small cell lung cancer using a spatial statistics approach. *First Author: Darya Orlova, Genentech, Inc., South San Francisco, CA*

Background: Based on the clinical success of immuno-oncology therapeutics, tissue-based, biomarker analyses have shifted from a focus on tumor cell phenotypes to spatial and functional analyses of the tumor immune environment. Distribution and composition of immune infiltrates have shown prognostic or predictive value in various studies; however, standardized approaches to categorize tumors into "Desert", "Excluded" or "Inflamed" immunophenotypes based on the density and pattern of immune infiltrates are missing. This categorization is typically based on visual inspection of a stained tissue section; it is labor-intensive and associated with poor inter-observer concordance. To eliminate these barriers we developed an automated approach that relies on a set of derived spatial features and named this analysis pipeline LATIS (metric Learning based Automated Tumor Immunophenotyping with Spatial statistics). **Methods:** We used two clinical trials, POPLAR (phase II; n=258) and OAK (phase III; n=623) that compared anti-PD-L1 treatment vs chemotherapy in patients with advanced non-small cell lung cancer to develop and validate this approach. LATIS utilizes scans of slides stained immunohistochemically for CD8 and cytokeratin (CK); images were tiled and classified according to CK status (positive/negative). First, CD8 positive and CK density was calculated for each tile. Twenty six spatial features were then extracted for each tiled image scan. We used a labeled (manual immunophenotype calls) POPLAR dataset to learn a metric that separates classes of labeled data best with respect of spatial features provided for each data point. Then, to co-embed OAK dataset with POPLAR dataset into the same space, we used that learned metric as a measure of distance between new unlabeled points (OAK data set). K-means clustering in the embedded space was used to identify clusters of data points followed by QFMatch to assign class labels ("Inflamed", "Excluded", "Desert") to each data point. **Results:** LATIS successfully relates spatial features to both, manual reads and patient response to therapy. In OAK, anti-PD-L1 treated patients experienced longer median overall survival (OS) when tumors showed intra-epithelial CD8+ cells (Inflamed) compared to tumors with a stromal pattern of CD8+ cells (Excluded) or a low density of CD8+ cells (Desert): 17.6 months vs 10.3 (Excluded) vs 12.1 (Desert) [p=0.0061]. Median progression-free survival (PFS) was 3.2 months (Inflamed) vs 2.6 (Excluded) vs 1.4 (Desert) [p=0.00058]. OS and PFS were not significantly different for the three categories in chemotherapy only arm. **Conclusions:** We suggest that tumor immunophenotype categories generated in an automated fashion by LATIS can serve as predictive biomarker for cancer immunotherapy. Research Sponsor: Roche/Genentech.

2627 **Poster Session**

Immuno-multiple reaction monitoring (iMRM) for quantitation of PD-L1 and PD-1-signaling proteins in non-small cell lung carcinoma (NSCLC). *First Author: Vincent Lacasse, Lady Davis Institute & McGill University, Montreal, QC, Canada*

Background: More accurate predictive biomarkers of response to checkpoint inhibitors (CPIs) still is a major unmet need in oncology. PD-L1 immunohistochemistry (IHC) limitations include its analytical variability and the post-translational modifications of PD-1 signaling-associated proteins like glycosylation. Moreover, PD-L1 IHC is an imperfect surrogate of the tumor immune microenvironment, and immunoscoring is important but difficult to assess in a clinical setting. Proteomic based technologies can overcome these challenges, but the low concentration of these proteins and the presence of high background noise in formalin-fixed paraffin embedded (FFPE) tumors were limiting obstacles. In this study, we evaluate the benefit of a new approach we used with anti-peptide antibodies to purify surrogate peptides, while liquid chromatography (LC) was coupled to multiple reaction monitoring mass spectrometry (iMRM) to improve specificity and precision of protein quantitation. **Methods:** To determine the concentration of PD-L1, PD-1, PD-L2, NT5E, LCK and ZAP70, we used unique and well detectable proteolytic peptides as surrogates. In a refined protocol, we optimized protein extraction and digestion, peptide immunoenrichment, LC and MRM parameters to maximize recovery, increase target-specific signal and reduce noise. Plus, we assessed the glycosylation status of PD-L1, PD-L2, and PD-1. The entire workflow was fully validated using 31 NSCLC FFPE tumors. PD-L1 quantitation by iMRM was compared to PD-L1 IHC clone 22C3. **Results:** On average, 71±29 μg (n = 52) of protein could be extracted from each 1–3 mm^3 NSCLC tumor FFPE core. The optimized iMRM method allowed the quantitation of PD-L1 and PD-1 down to 21 amol on-column. Inter- and intra-day repeatability were well below FDA guidelines (coefficients of variation [CV] < 20%) with average CVs of 5.2±4.0% (intra-day) and 4.5±2.6% (inter-day). Sample storage had no significant effect on peptide quantitation. The final multiplexed iMRM assay enables quantitation all targets and glycosylation states for > 40 samples in only 3 days (including external calibration and quality controls) and was used to quantify the PD-1/PD-L1 axis proteins successfully in all 31 NSCLC FFPE tumors. PD-L1 expression ranged from 2 amol/μg to 61 amol/μg of total protein. As expected, iMRM results correlated moderately ($R = 0.56$, $\rho < 0.001$) with PD-L1 IHC. PD-L1 glycosylation status ranged from 99.9±0.2%, and therefore did not explain the discrepancies between IHC and iMRM for these samples. **Conclusions:** Herein a robust iMRM workflow was developed for the quantitation of the PD-1/PD-L1 axis in FFPE. This proof-of-concept supports that MS-based assay can provide otherwise unavailable data (e.g., PD-L1 concentration, glycosylation status). CPI treated patient tumors are being currently processed to validate the predictive value of the assay. Research Sponsor: Genome Canada, Other Government Agency.

2628 **Poster Session**

The expression of aryl hydrocarbon receptor predicts responses to anti-PD-1 antibodies in non-small cell lung cancer. *First Author: Si-Chong Han, State Key Laboratory of Molecular Oncology and Department of Internal Medicine, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: Blockade of programmed cell death receptor 1 (PD-1) by antibodies such as pembrolizumab has revolutionized treatment for patients with non-small cell lung cancer (NSCLC). However, a significant number of patients achieve only marginal benefit. The predictive abilities of the frequently used biomarkers, including programmed cell death 1 ligand (PD-L1) and tumor mutation burden (TMB), are yet limited, highlighting the urgent need for more reliable biomarkers. Aryl hydrocarbon receptor (AhR) is a ligand-dependent transcription factor that controls the transcription of its targets including PD-L1. Whether AhR could be used as a predictive biomarker for response to PD-1 blockade immunotherapy in NSCLC warrants further investigation. **Methods:** We collected formalin-fixed, paraffin-embedded (FFPE) slides from 104 NSCLC patients before PD-1 blockade immunotherapy treatment, who had sufficient follow-up data for progression-free survival (PFS), and detected the expression of nuclear localized AhR (AhR^N) and membrane localized PD-L1 ($PD\text{-}L1^M$) with multiplex immunohistochemistry (mIHC). H-score was applied to characterize the specific value with the following formula [1 × (% cells intensity =1) + 2 × (% cells intensity = 2) + 3 × (% cells intensity = 3)]. Survival curve for each group was estimated by the Kaplan–Meier method and log-rank test. The diagnostic performance was assessed with the area under the receiver operating characteristic (ROC) curve (AUC), which was calculated based on the Wilcoxon rank-sum test. All statistical tests were two-sided and *P* values less than 0.05 were considered statistically significant. **Results:** Both AhR^N and $PD\text{-}L1^M$ could distinguish responders from non-responders, and patients with higher H-score had longer PFS than those with lower H score. The AUC of AhR^N was 0.804 (95 % CI: 0.721-0.881), higher than that of $PD\text{-}L1^M$ (0.714; 95 % CI: 0.618-0.811) and AhR^N+$PD\text{-}L1^M$ (0.743; 95 % CI: 0.649-0.837), indicating AhR^N might show better predictive capacity to the efficacy of PD-1 blockade immunotherapy than $PD\text{-}L1^M$. Besides, AhR^N exhibited the most significant accuracy in prognosis prediction, since the hazard ratio (HR) of AhR^N was 0.1529 (95 % CI: 0.07704-0.3033, *P*<0.0001), significantly higher than that of $PD\text{-}L1^M$ [HR:0.283 (95 % CI: 0.1525-0.525, *P*<0.0001)] and AhR^N+$PD\text{-}L1^M$ [HR: 0.2456 (95 % CI: 0.1309-0.4607, *P*<0.0001)]. Yet, among the 54 smokers, AhR^N+$PD\text{-}L1^M$ was the best classifier for the efficacy of immunotherapy, of which the AUC was 0.8937 (95 % CI: 0.816-0.971) and HR was infinitely approaching 0 (*P*<0.0001). **Conclusions**: AhR might be a reliable predictive biomarker for PD-1 blockade immunotherapy in NSCLCs. Research Sponsor: National Natural Science Foundation of China.

2629 **Poster Session**

Pan-cancer analysis of YAP1 expression as a predictive biomarker for cancer immunotherapy. *First Author: Taofeek K. Owonikoko, UPMC Hillman Cancer Center, Pittsburgh, PA*

Background: High YAP1 expression correlates with the 'T-cell inflamed' expression phenotype in small cell lung cancer (SCLC), but its association with other biomarkers of immune checkpoint vulnerability and in tumor types beyond SCLC is not known. We examined whether YAP1 expression correlates with other established markers of immune checkpoint blockade (ICB) efficacy (PDL1 expression and TMB) in a tumor agnostic manner to determine clinical relevance. **Methods:** Next-generation sequencing of DNA (592 gene panel or whole exome) and RNA (whole transcriptome) was performed for patient samples (n = 57,134), representing 13 cancer types, submitted to a CLIA-certified laboratory (Caris Life Sciences, Phoenix, AZ). The 'T-cell inflamed' signature (TIS) score was calculated as an 18-gene weighted coefficient composite value (Cristescu, 2018). PDL1 expression was assessed by immunohistochemistry (IHC) with cancer type-specific antibodies and thresholds, and high tumor mutational burden was defined as ≥10 mut/Mb. Patients were stratified into subgroups based on median YAP1 expression (YAP1-High/YAP-Low) within each cancer type. Significance was tested by Chi-square, Fisher's exact test, or Mann-Whitney U test. **Results:** YAP1-High tumors were associated with significantly increased TIS scores compared to YAP1-Low across all 13 cancer types examined, with the largest fold increase observed in SCLC (1.33-fold, $p < 0.0001$), followed by pancreatic cancer (1.28-fold, $p < 0.0001$), while the smallest occurred in melanoma (1.13-fold, $p < 0.0001$). Spearman correlation strength (range 0.23-0.57) between YAP expression and TIS scores was consistent with increased TIS scores in YAP1-High samples. TMB-High rates were similar in YAP-High and YAP1-Low subgroups for most cancer types, with slightly lower rates in YAP1-High tumors observed for endometrial (23.0 vs 26.6%, $p < 0.001$) and esophageal (7.0 vs 9.5%, $p < 0.05$) cancers. YAP1 expression was not significantly increased in PDL1+ (IHC) tumors for most cancer types. However, significantly decreased YAP1 expression was associated with PDL1+ samples in RCC (Renal Cell Carcinoma) (0.91-fold change, $P < 0.05$), MM (0.90-fold change, $P < 0.001$), and ENCA (0.80-fold change, $P < 0.0001$) **Conclusions:** Our analyses provide confirmation that YAP1 expression positively correlates with the 'T-cell inflamed' phenotype across many cancer types, including those with approvals for (ICB) therapy. YAP1 expression was independent of established markers of ICB response, including TMB and PDL1. Further analysis of YAP1 expression as an additional tumor agnostic predictive biomarker is warranted. Research Sponsor: None.

2630 **Poster Session**

A pancancer analysis of impact of *MDM2*/*MDM4* on immune checkpoint blockade (ICB). *First Author: Wafik S. El-Deiry, Cancer Center at Brown University, Providence, RI*

Background: *MDM2/MDM4* are implicated in hyperprogression after immune checkpoint blockade (ICB). Our preclinical studies showed reduced T-cell killing of *MDM2*-amplified tumor cells that was overcome by an MDM2 antagonist or gene knockdown, and we observed additional tumor killing by T-cells with MDM2 inhibition plus anti-PD1. We hypothesized that *MDM2/4* gene amplification/overexpression correlates with resistance to ICB and investigated the association of MDM2/4 alterations to overall survival (OS) following ICB across multiple solid tumors. **Methods:** Solid tumors tested at Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing on DNA (NGS) were analyzed. *MDM2/4* amplification (amp) was tested by NGS and determined as either amp4 (cutoff of >=4.0 copies) or amp6 (>=6.0) or amp8 (>=8.0). Real-world OS was obtained from insurance claims data and calculated from treatment start or tissue collection to last contact. Kaplan-Meier estimates were calculated for molecularly defined groups. X^2/Fisher-Exact were used and significance determined as P-value adjusted for multiple comparisons ($q<0.05$). **Results:** In a large cohort of TP53-wild type solid tumors, 2785 had *MDM2* amp4 (262 were ICB-treated), 2108 had *MDM2* amp6 (ICB: 192), 1721 had *MDM2* amp8 (ICB: 149); 1040 tumors had *MDM4* amp4 (ICB: 59), 293 had *MDM4* amp6 (ICB: 8) and 217 had amp8 (ICB: 4). NSCLC, GBM, breast, bladder cancer and liposarcoma had the highest *MDM2* amp and breast cancer, GBM, uterine, NSCLC and ovarian cancers had the highest *MDM4* amp. When all tumors were considered, *MDM2* amp4, 6 and 8 significantly associated with shortened OS (amp4: HR 1.31; amp6: HR 1.31; amp8: 1.29, all $p<0.0001$); similar results were seen with *MDM4* (amp4: HR 1.14, $p=0.004$; amp6: HR 1.51, $p<0.00001$ and amp8: HR 1.6, $p<0.00001$). Of note, *MDM4* amp4 but not *MDM2* amp4 was associated with significantly worse post-ICB survival (HR: 1.55, $p=0.009$).When comparing molecular differences between *MDM2* amp4 and *MDM4* amp4, significantly higher PDL1 expression was associated with *MDM2* amp (Ab clone 28.8: 58% vs. 28%; clone 22c3: 48% vs.25%, $q<0.05$); while higher mutation rates of *ARID1A*, *PIK3CA*, *PTEN*, *KRAS* and *CTNNB1* were associated with *MDM4* amp (all $q<0.05$). When investigating NSCLC, *MDM4* amp4 was associated with decreased post-ICB survival in NSCLC (HR: 2.59, $p=0.001$) but not *MDM2*; when comparing the molecular alterations, *MDM2* amp was associated with significantly higher PDL1 (22c3) (54% vs. 27%), *EGFR* mutation (36% vs. 14%) but less prevalent *KRAS* (15% vs. 50%), *STK11* (11% vs. 41%), *KEAP1* (2.5% vs. 27%) and *BRAF* (2% vs. 16%) mutations. The association with poor prognosis of *MDM2* amp4/6 (HR: 1.2 and 1.3, $p<0.05$) and *MDM4* amp4/6 (HR: 1.3 and 1.6, $p<0.05$) was seen in breast cancer, but not in NSCLC, GBM, bladder or uterine cancers. **Conclusions:** *MDM2* and *MDM4* amplification are negative prognostic factors in TP53-WT breast cancer while *MDM4* amp is associated with reduced survival in ICB-treated NSCLC. Research Sponsor: None.

2631 **Poster Session**

Systematic assessment of tumor mutational burden calculation across different sequencing platforms and cancer types and its implication in clinical decision-making. *First Author: Daqiang Sun, Tianjin Chest Hospital, Tianjin, China*

Background: Tumor mutation burden (TMB) has been validated as a biomarker to predict the response of immune checkpoint inhibitors (ICIs) treatment in various cancers. However, the effects of different sequencing platforms, cancer types and calculation methods on TMB as well as its cut-off value for predicting immunotherapy efficacy are still need to be further investigated. **Methods:** 4140 tumor samples were performed with targeted panel sequencing or whole exome sequencing (WES) in different platforms such as illumina and MGI. Public sequencing data from 3680 samples which contained targeted panel sequencing, WES and whole genome sequencing were obtained. The impact of different sequencing platforms, sequencing methods and calculation methods on the calculation of TMB were assessed. Further, targeted panel sequencing data from 71 sample of lung cancer patients treated with ICIs were used to determine the best cut-off value of TMB for predicting immunotherapy response. **Results:** TMB values calculated by different platforms and different sequencing methods were similar and there was no significant difference. The distribution of TMB at different sequencing depths and tumor purity were analyzed. We found that there was no significant difference in the distribution of TMB when the sequencing depth was greater than 500, the HE purity was greater than 0.1 or NGS purity was greater than 0.3. In addition, the correlation of TMB calculated from single-sample and paired-sample is 0.95. Further, the optimal cut-off value of TMB in lung cancer treated with ICIs was determined to be 8 through ROC curve analysis, and patients with TMB ≥ 8 had better outcomes than patients with TMB < 8. **Conclusions:** This study systematically analyzed the factors which influenced the TMB calculation, and verifies the feasibility of TMB calculation from single-sample. More importantly, the cut-off value of TMB for predicting immunotherapy efficacy in lung cancer was defined as 8 in East Asian populations, which can help in clinical decision-making. Research Sponsor: None.

2632 **Poster Session**

Association between tumor mutational burden (TMB) and mutational profile and its effect on overall survival: A post hoc analysis of patients with TMB-high and TMB-low metastatic cancer treated with immune checkpoint inhibitors (ICI). *First Author: Camila Bragança Xavier, Hospital Sírio-Libanês, São Paulo, Brazil*

Background: High-TMB was recently approved as an agnostic biomarker for pembrolizumab in advanced cancers. Still, several patients with high-TMB do not respond to ICI, while some patients with low-TMB benefit from immunotherapy. **Methods:** We collected genomic (MSK-IMPACTassay) and survival data from 1,661 patients and assessed OS (Kaplan-Meier method) according to the mutational status. To better qualify patients with TMB ≥ 10 mut/Mb (TMB-H) (N = 488, 29%) and TMB < 10 mut/Mb (TMB-L) (N = 1,173, 71%) for ICI treatment, we analyzed single gene alterations impacting OS ($P < 0.05$). For all genes exhibiting a correlation with OS, we conducted a Cox multivariate analysis stratified by median TMB, sex, median age, microsatellite instability (MSI) status, and histology. **Results:** Survival to ICI increased with higher TMB. Median OS was 42 and 15 months for TMB-H and TMB-L ($P < 0.05$), respectively. For TMB-H tumors, 5 genes (*STK11, KEAP1, CIC, E2F3, TP53*) exhibited reduced OS on ICI, and 22 genes (*NTRK3, TERT, NOTCH3, RNF43, TET1, PTPRD, NCOA3, TENT5C, ZFHX3, RIT1, CCNE1, PPM1D, GATA2, ALK, DNMT1, PTPRT, MET, EPHA7, BCL6, SMO, CDK6, MED12*) were associated with better OS, $P < 0.05$. Cox multivariate analysis confirmed a correlation between mutations in *STK11* and *E2F3* with worse OS, while mutations in *NTRK, PTPRD, RNF43, TENT5C, TET1,* and *ZFHX3* were associated with better OS ($P < 0.05$). Histology did not play a relevant role in ICI response except for melanoma (better OS; $P < 0.05$). MSI status did not significantly affect OS. For TMB-L tumors, 20 genes were related with reduced OS (*TP53, H3C2, DAXX, SMARC4, STK11, SOX17, RB1, PIK3CA, CTNNB1, KMT2D, HLA-A, FBXW7, CDH1, RBM10, KEAP1, IGF1R, H3C11, EGFR, RUNX1, B2M*), while 8 genes were associated with better OS (*VHL, SETD2, PBRM1, BRAF, KDM5C, MAP2K1, CSF1R, RET),* $P < 0.05$. Cox multivariate analysis confirmed 15 genes associated with superior (*KDM5C, PBRM1,* and *VHL*) and inferior (*CTNNB1, DAXX, FBXW7, H3C2, H3C1, IGF1R, KMT2D, PIK3CA, RB1, SMARC4, SOX17, TP53*) OS ($P < 0.05$). In the TMB-L context, melanoma histology and MSI status (except among VHL-mutated tumors) were independently associated with better OS. **Conclusions:** This pan-cancer analysis demonstrates that genomic alterations in single cancer genes can help define outcomes of TMB-H and TMB-L patients treated with ICI. Research Sponsor: None.

	BETTER OS	WORSE OS
TMB-H	*NTRK3*, TERT, NOTCH3, RNF43*, TET1*, PTPRD*, NCOA3, TENT5C*, ZFHX3*, RIT1, CCNE1, PPM1D, GATA2, ALK, DNMT1, PTPRT, MET, EPHA7, BCL6, SMO, CDK6, MED12*	*STK11*, KEAP1, CIC, E2F3*, TP53*
TMB-L	*VHL*, SETD2, PBRM1*, BRAF, KDM5C*, MAP2K1, CSF1R, RET*	*TP53*, H3C2*, DAXX*, SMARCA4*, STK11, SOX17*, RB1*, PIK3CA*, CTNNB1*, KMT2D*, HLA-A, FBXW7*, CDH1, RBM10, KEAP1, IGF1R*, H3C11*, EGFR, RUNX1, B2M*

*Genes that exhibited correlation with OS in both uni- and multivariate analysis.

2633 **Poster Session**

Age-associated differences in transcriptional expression and tumor immune microenvironment composition among older patients with cancer. *First Author: Khalil Choucair, University of Kansas School of Medicine, Wichita, KS*

Background: Older patients (pts) with cancer are underrepresented in registrational clinical trials for immune checkpoint inhibitor (ICI) therapies. There may be relevant differences in the makeup of the tumor microenvironment (TME) and in genomic signatures of cancer in older pts. This analysis explores differences in the genomic makeup of common cancers and their TME in pts ≥ 80 years (yr) of age, compared to younger pts. **Methods:** Next-generation sequencing of DNA (592 gene panel, NextSeq or whole-exome sequencing, NovaSeq) and RNA (whole transcriptome sequencing, NovaSeq) was performed for non-small cell lung carcinoma (NSCLC; n = 19,891), melanoma (MEL n = 2,899), and renal cell carcinoma (RCC; n = 1,333) pt samples submitted to a CLIA-certified laboratory (Caris Life Sciences, Phoenix, AZ). PD-L1 expression was assessed by immunohistochemistry (IHC), and high tumor mutational burden (TMB-H) was defined as ≥10 mut/Mb. Pts were stratified into age subgroups of ≥80 and < 80 yr for comparison of DNA damage response (DDR) gene alterations, gene expression profiling, and TME analysis (MCP-counter; Becht, 2016). *P-values* were adjusted for multiple hypotheses testing (Benjamini-Hochberg) unless noted as exploratory. **Results:** Pts ≥80 yr accounted for 16.0%, 19.9% and 5.3% of NSCLC, MEL and RCC pts, respectively. Compared to pts < 80 yr, NSCLC and MEL pts ≥80 yr had similar DDR gene mutation rates, while *BRCA1* mutations were more common in MEL pts ≥80 yr (2.1 *vs* 0.8%; exploratory-$p < 0.05$). NSCLC ≥80 yr TMEs had increased abundance of fibroblasts (1.09-fold, $p < 0.01$), dendritic cells (1.07-fold, $p < 0.01$) and macrophages (1.04-fold, $p < 0.01$), and MEL≥80 yr TMEs had fewer infiltrating T-lymphocytes (0.87-fold, $p = 0.02$). Increased expression of immune checkpoint (IC) genes *PDCDL1G2* (PD-L2; 1.11-fold), *HAVCR2 (*TIM-3; 1.11-fold*)*, and *CD80/86* (1.07/1.08-fold, $p < 0.05$) was seen in NSCLC pts ≥80 yr, while *IL-6* expression was decreased (0.88-fold; $p < 0.05$). The largest change in IC gene expression was for *IL-6* (1.24-fold, $p = 0.78$) in MEL, and *GZMB* (0.56-fold*;* $p = 0.17$) in RCC ≥80 yr. TMB-H was less common in NSCLC (29.7 vs 36.5%, $p < 0.001$) and more common in MEL pts ≥80 yr (65.7 vs 49.0%, $p < 0.01$), and PD-L1 (IHC-SP142, ≥2+l5%) expression was less frequent in RCC pts ≥80 yr (9.1 vs 19.4%, exploratory $p < 0.05$). Profiling of glutamine and glucose metabolism-related genes revealed increased *SLC38A5* (1.17-fold; $p < 0.0001$) and decreased *G6PC* (0.65-fold, $p < 0.01$) expression in NSCLC ≥80 yr. While not statistically significant, MEL and RCC pts ≥80 yr had opposite trends for *SLC38A5* and *G6PC* expression. **Conclusions:** Our analysis provides new insights to immune landscape of NSCLC, MEL, and RCC pts ≥80 yr. Differential gene expression and TME composition changes in this population suggest unique, cancer-specific therapeutic opportunities, and a potential to explore biomarkers of response to ICIs. Research Sponsor: None.

2634 **Poster Session**

Microsatellite-stable tumors with high tumor mutational burden in association with tumor response to immune checkpoint inhibitor therapy across solid tumors and correlation with specific oncogenic alterations. *First Author: Imran Nizamuddin, Northwestern University Feinberg School of Medicine, Chicago, IL*

Background: High tumor mutational burden (TMB-H) has shown promise as a predictive biomarker in certain tumors, but broad applicability across tumors is unclear. In 2020, pembrolizumab was approved for treatment refractory metastatic or unresectable solid tumors with TMB ≥10 mutations/megabase based on exploratory analysis of the KEYNOTE-158 study. Growing evidence suggest limitations of TMB-H across tumors. Our aim is to evaluate outcomes of patients (pts) with advanced microsatellite-stable (MSS) solid tumors with TMB ≥10 mutations/megabase treated with immune checkpoint inhibitors (ICIs) and identify genetic alterations that predict poor response to therapy. **Methods:** Pts treated between 01/2015 to 12/2020 at Robert H Lurie Cancer Center, Northwestern University, with ICIs and TMB ≥10 mutations/megabase on next generation sequencing by FoundationOne CDx, Tempus xT or Guardant360 CDx platforms were identified. Tumors other than carcinomas and microsatellite instability were excluded. Radiologic response was assessed using iRECIST criteria. Responders (CR/PR) were compared with non-responders (SD/PD). Subgroup analyses were conducted based on tumor type, genetic alterations within signaling pathways. Survival curves were calculated using Kaplan-Meier method. Multivariate analyses were performed to determine impact of clinical variables on response. **Results:** Of 119 pts, median age was 68 yrs, and 61% of pts were male. 15 tumor types were represented, most commonly melanoma (33%), NSCLC (28%), small cell lung carcinoma (5.9%), colorectal carcinoma (5%), and pancreatobiliary carcinoma (5%). When evaluating for efficacy (n = 106), ORR was 36% with CR 14%. Median PFS and OS overall were 10.9 mo and 29.9 mo. Lack of exposure to previous therapy was associated with response (p = 0.039). PD-L1 status, specific ICI regimen, age, and sex did not have prognostic significance. When comparing melanoma/NSCLC (n = 66) and other tumor types (n = 40) there was no significant difference in response (p = 0.3). When comparing response by specific gene mutations, *TP53* (p = 0.026) and *PIK3CA* (p = 0.025) were associated with worse response. Similarly, *ROS1* alteration trended to poorer response (p = 0.057). When evaluating genetic pathways, mutations within TP53 pathway were associated inferior response (p = 0.018). There was no significant difference in RTK/RAS, NRF2, PI3K, TGFβ, WNT, MYC, Cell Cycle, and Notch pathways. **Conclusions:** Growing evidence shows limitations of TMB-H as a predictive biomarker for ICI therapy in MSS tumors. Our data suggests alterations within *TP53* and its signaling pathway, *PIK3CA* mutations, and likely *ROS1* alterations are associated with non-responders in MSS TMB-H solid tumors. Further analysis of tumor-specific cohorts and genetic alterations will be presented. Research Sponsor: None.

2635 **Poster Session**

PD-L1 expression and microsatellite instability in tumors of unknown primary site. *First Author: Joao Neif, Barretos Cancer Hospital, Barretos, Brazil*

Background: Cancer of unknown primary site is a heterogeneous group of tumors for which the origin remains unknown, despite detailed investigation. Its clinical presentation occurs due to symptoms resulting from metastasis, which can be influenced not only by biological processes of the tumor, but also due to regulatory processes in the tumor microenvironment such as PD-L1. Microsatellite instability (MSI) is a predictive biomarker for cancer immunotherapy and its status as well as co-occurrence with PD-L1 expression is poorly evaluated. The aim of this study was to evaluate the expression of PD-L1 and the status of MSI in tumors of unknown primary site and their possible associations with clinical-pathological characteristics and clinical outcomes in patients with this type of tumor. **Methods:** The PD-L1 expression was evaluated using the immunohistochemistry technique and measured by CPS and TPS scores. MSI status was assessed using a hexa-plex marker panel by polymerase chain reaction followed by fragment analysis. Overall survival was analyzed using the Kaplan Meier method and comparisons of the curves using the log rank test. **Results:** Of the 121 conclusive cases for MSI status, only two cases (1,6%) were MSI-High. PD-L1 expression, assessed by both TPS and CPS, was positive in approximately 18% of 108 conclusive cases. PD-L1 expression is significantly less frequent in patients with a predominance of hepatic or bone metastasis and more frequent in patients with a predominance of nodal metastasis. The median overall survival was about 4 months, and the predominance of liver metastases was associated with a worse prognosis, while the use of chemotherapy and low ECOG-PS were associated with better survival. PD-L1 expression was associated with better overall survival. **Conclusions:** PD-L1 is expressed in a subset of patients with cancer of unknown primary site, while MSI is a rare event. It is necessary to better explore the microenvironment of this type of tumor as well as the role of immunotherapy to change such a dismal clinical outcome. Research Sponsor: Barretos Cancer Hospital - Research Institute.

2636 **Poster Session**

14-gene immunoglobulin (IGG) and proliferation signatures and association with overall survival across cancer-types. *First Author: Francesco Schettini, Hospital Clinic of Barcelona, Barcelona, Spain*

Background: The HER2DX prognostic assay in early-stage HER2-positive breast cancer integrates clinical variables and 4 gene expression signatures (GES) tracking IGG, tumor proliferation, luminal cell differentiation, and the expression of the HER2 amplicon. Here, we assessed the prognostic value across cancer-types of each of these four individual GES and a research-based version of the HER2DX risk-score. **Methods:** RSEM batch normalized RNA-sequencing gene expression data from The Cancer Genome Atlas (TCGA) project were downloaded from cBioPortal. The association between a research-based version of the HER2DX risk-score, and each GES, with overall survival (OS) was assessed as continuous variables using univariate Cox regression model. The research-based version of the HER2DX risk-score tested did not include clinical variables. The Cox model was applied to estimate hazard ratios (HR) with 95% confidence intervals. The threshold for statistical significance was set at $p< 0.05$. **Results:** Gene expression data from 9,852 patients representing 30 different cancer-types were evaluated. The proliferation, IGG, luminal and HER2 amplicon GES were significantly associated with OS in 40.0%, 33.3%, 23.0% and 6.7% of the cancer-types tested, respectively. The IGG GES was found significantly associated with a favorable OS in breast cancer (HR: 0.73, p < 0.001), cervical and head & neck squamous cell carcinomas (HR: 0.75, p = 0.021 and HR: 0.78, p < 0.001), lung adenocarcinoma (HR: 0.84, p = 0.020), skin melanoma (HR: 0.73, p < 0.001) and sarcomas (HR: 0.78, p = 0.029). Conversely, association of IGG GES with unfavorable OS was observed in uveal melanoma (HR: 1.74, p = 0.008), kidney clear cell and papillary cell carcinomas (HR: 1.29, p < 0.001 and HR: 1.44, p = 0.017, respectively), as well as brain low-grade gliomas (LGG) (HR: 1.56, p < 0.001). Finally, the research-based HER2DX risk-score was found significantly associated with OS in 11 of 30 (36.7%) cancer-types, including breast (HR: 1.42, p < 0.001) cervical and head & neck squamous cells cancers (HR: 1.36, p = 0.018 and HR: 1.30, p < 0.001), lung adenocarcinoma (HR: 1.34, p < 0.001), skin melanoma (HR: 1.34, p < 0.001), sarcomas (HR: 1.41, p = 0.003), adrenocortical carcinoma (HR: 2.31, p < 0.001), endometrial carcinoma (HR: 1.36, p = 0.005), hepatocarcinoma (HR: 1.26, p = 0.012), LGG (HR: 1.37, p = 0.001) and mesothelioma (HR: 1.48, p = 0.005). **Conclusions:** The 14-gene IGG and proliferation signatures are strong prognostic biomarkers across cancer-types. The opposite association of IGG with OS depending on the cancer-type warrants further investigation. Research Sponsor: None.

2637 **Poster Session**

Phase 1 studies of personalized neoantigen vaccine TG4050 in ovarian carcinoma (OC) and head and neck squamous cell carcinoma (HNSCC). *First Author: Jean-Pierre Delord, Department of Oncology, Institut Claudius Regaud, IUCT-Oncopole, Toulouse, France*

Background: Mutation-associated neoantigens (MANAs) constitute attractive antigens for the design of cancer vaccines. However, clinical implementation remains challenging because of the patient specific nature of MANAs, hereby requiring that a bespoke vaccine is designed for each subject. We developed a pipeline for the genomic characterization and the design of tailored vaccine using a modified vaccinia Ankara viral vector. **Methods:** Immunogenicity, safety and early clinical activity of personalized cancer vaccines are being assessed in two phase I trials, respectively in high grade serous OC and HPV-negative HNSCC. Patients (Pts) at high risk of relapse are enrolled in the study being in remission following surgical primary treatment. High risk is defined as stage IIIC or IVA for OC and stage III or IVA for HNSCC. A vaccine is manufactured for each patient. OC pts are treated at asymptomatic relapse based on radiological finding or elevation of CA-125 with the vaccine alone; HNSCC pts in complete remission after surgery and adjuvant therapy are randomized to receive the vaccine either at the end of locoregional treatment or in combination with standard of care at relapse. The vaccine was administered weekly for 6 weeks and a booster dose every three weeks over a year or until progression, whichever occurred first. **Results:** At the time of the data cut-off, a total of 8 pts were treated: 4 relapsing OC pts, 3 HNSCC pts in complete remission and 1 relapsing HNSCC pt. AE attributable to the vaccine were mainly grade 1 injection site reactions and fatigue. One OC pt displayed an objective response 6 weeks after initiation of vaccine and for 9 months with a normalization of CA-125 until death from an unrelated cause; 1 other OC pt remains on treatment with a stable radiological disease for 11 months. The 2 other OC progressed at the first evaluation on day 43. HNSCC pts treated in complete remission received respectively 20, 15 and 4 doses, and remain on treatment and disease free. One HNSCC patient received 9 doses of vaccine after relapse in conjunction with chemotherapy and anti-PD-1 therapy and remains on treatment with stable disease after 5 months. Immune monitoring demonstrates priming of a polyepitopic T cell response against class I and II antigens. Responses were observed regardless of HLA and without cross-reactivity to the germline protein. Adaptive response was associated with a shift of CD4 and CD8 T cells toward an effector phenotype and innate cellular immunity was activated with a strong maturation and activation of NK cells. Immune changes were stronger in pts with controlled disease versus progressors. **Conclusions:** Data demonstrate that TG4050 is safe, well tolerated and able to induce T cell responses whatever the HLA haplotype. Early signs of clinical activity were observed in OC pt. These data pave the way for further development and synergistic immunotherapeutic combinations. Clinical trial information: NCT04183166. Research Sponsor: TRANSGENE.

2638 **Poster Session**

Personalized neoantigen DNA vaccines expand tumor-specific T cells in the periphery which infiltrate the tumor in hepatocellular carcinoma. *First Author: Renzo Perales, Geneos Therapeutics, Plymouth Meeting, PA*

Background: Tumor neoantigens are epitopes derived from tumor-specific mutations that can be incorporated in personalized vaccines to prime T cell responses. DNA vaccines delivered with electroporation have recently shown strong CD8 and CD4 T cell responses in clinical trials. In preclinical studies, DNA-encoded neoantigen vaccines have shown induction of CD8 T cells against 50% of predicted high affinity epitopes with the ability to impact tumor growth. **Methods:** Paired blood and tumor biopsy samples were collected from a patient with hepatocellular carcinoma before and after treatment with GNOS-PV02 (DNA neoantigen targeted vaccine) + plasmid IL-12 + pembrolizumab. Treatment resulted in a partial response with a decrease in tumor size of 44% by RECIST (168 mm to 94 mm). TCRbeta sequencing was performed on all 4 samples and single cell TCR and transcriptome sequencing was performed from T cells isolated from the post-treatment blood sample. Newly identified TCRs in blood and tumor after vaccination were inserted into an expression vector and used to generate engineered TCR T cells. Engineered TCR T cells were tested against the neoantigens included in the vaccine and their responses characterized by flow cytometry. **Results:** We identified 67,893 new clones in PBMC after vaccination, 3 of which comprised between 0.1 to 1% of the total T cell clones. Moreover, we identified 5126 new clones in the tumor post vaccination, out of these, 3878 (75.68%) were not found within the patient's pre vaccination PBMCs and 556 (10.86%) were identified within the pre vaccination PBMC pool. Importantly, of the newly identified T cells infiltrating the tumor post vaccination, we observed high frequency TCR clones of which 44 and 7 clones were above 0.1% and 1%, respectively. The majority of the newly identified T cell clones were CD8 T cells (68.75%) with an activated phenotype. Importantly, the 6 most expanded clones in blood were identified to be activated CD8+CD69+ T cells (81.82%). Engineered TCR T cells generated encoding the TCRs of these newly identified CD8 T cells showed activation when exposed to the tumor neoantigens encoded in the neoantigen DNA vaccine GNOS-PV02. **Conclusions:** GNOS-PV02, a neoantigen DNA vaccine, in combination with plasmid IL-12 and pembrolizumab resulted in expansion of newly identified T cells, primarily activated CD8, which trafficked to the tumor. These new tumor infiltrating T cells showed TCR specificity against tumor neoantigens encoded in GNOS-PV02 and may account for the observed objective decrease in tumor size. Research Sponsor: Geneos Therapeutics.

2639 **Poster Session**

Preliminary results from an early phase trial of in situ immunization of lymphoma with a virus likeparticle containing a TLR9 agonist combined with anti-PD1 therapy (NCT03983668). *First Author: Umar Farooq, University of Iowa Hospitals and Clinics, Holden Comprehensive Cancer Center, Iowa City, IA*

Background: *In situ* immunization involves intratumoral (IT) injection of immunostimulatory agents to modify the tumor microenvironment with the goal of inducing an anti-tumor T cell response. Here, we report preliminary results of a clinical trial exploring *in situ* immunization with a virus like particle (VLP) combined with systemic pembrolizumab (Pembro) in lymphoma. The VLP, known as CMP-001 or vidutolimod (Vidu), is composed of the bacteriophage Qb capsid encapsulating the TLR9 agonist G10. Preclinical studies demonstrated generation of antibodies against the Qb capsid (anti-Qb) is necessary for Vidu to induce an anti-tumor response. In other cancers, early phase clinical trials of *in situ* immunization with Vidu, with and without systemic anti-PD1 therapy, have revealed early promising results. **Methods:** This trial included patients with relapsed lymphoma that have failed at least 1 line of therapy. The first dose of Vidu is given subcutaneously to stimulate anti-Qb that opsonizes the VLP. This is followed by IT Vidu administered weekly for seven doses, then at 3-week intervals. Pembro (200 mg fixed dose) is given intravenously every 3 weeks. Subjects continue treatment if they do not experience unacceptable toxicities and in the investigator's opinion continued treatment is in the subject's best interest. Fine needle aspirates for flow cytometric analysis are obtained prior to therapy and 4-6 weeks following initiation of therapy. **Results:** Six patients have enrolled to date (1 CR, 2 PR, 1 SD, 2 PD). The first 3 patients received 5mg Vidu per dose and the second cohort 7.5 mg per dose. Common side effects included chills, rigors, mild headache, and fatigue. These typically resolved within 4 hours after receiving the injection. **Conclusions:** *In situ* immunization with Vidu plus systemic anti-PD1 is a promising therapy in lymphoma. The ability to generate anti-Qb that opsonizes the VLP appears to be necessary for Vidu to induce an immune and therapeutic response. Accrual and correlative studies are continuing with the modification that generation of functional-Qb after the first dose of Vidu is required before patients receive IT therapy. Clinical trial information: NCT03983668. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

Pt.	Diagnosis and key prior Rx	Clinical and correlative findings	Preliminary interpretation
1	DLBCL Post CAR-T	No benign B cells, toxicity, or anti-Qb generated - Progression	Anti-Qb is required for therapeutic response
2	FL < 1 yr post rituximab		
3	FL > 2 yrs post rituximab	Flare reaction on PET but achieved CR	Vidu can cause PET pseudo-progression
4	ALK + ALCL	- PR	T cell lymphomas can respond
5	FL ~ 1.5 yrs post obinutuzumab	Generated very low, but functional levels of anti-Qb, Low grade toxicity - SD	Low levels of anti-Qb are adequate for opsonization of VLP
6	FL > 2 yrs post rituximab	Regression of injected and contralateral (un-injected) nodes - PR	Anti-tumor effect is systemic

2640 **Poster Session**

First-in-human/phase I trial of PE0116 (4-1bb Ig G4 McAb) as single agent in patients with solid tumors progressed after lines of therapies in China. *First Author: Hui Zhao, Departments of Internal Oncology, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiaotong University, Shanghai, China*

Background: The 4-1BB co-stimulatory protein is an important modulator of the adaptive T Cell immune responses, and potentially a vital target for immunotherapies in oncology. HE0116 is a humanized agonist antibody to 4-1BB that promotes proliferation and activation of T cells. The FIH/phase Ia/Ib study was conducted to establish a maximum tolerated dose, identify dose-limiting toxicities (DLTs) and to assess safety, tolerability, and pharmacokinetics of HE0116 as single agent in patients with solid tumors who have progressed on standard of care (SoC) and experimental therapies. **Methods:** Patients (pts) with histologically confirmed solid tumors who progressed after prior SoC and experimental therapies were enrolled. A Fibonacci 3+3 design was employed for the phase 1a dose escalation of 9 dose levels. HE0116 was administered intravenously once in first 28-day cycle for PK analysis and DLT assessment. Pts continued HE0116 treatment every 3 weeks until experiencing an intolerable toxicity, disease progression or withdrawing consent. **Results:** As of January 25, 2022, 19 pts were enrolled in the dose-escalation phase). All pts had progressed on multiple lines of therapies, including but not limited to, chemotherapy, hormonal therapy, or/and immunotherapy. As defined in study protocol, pts received HE0116 intravenously at least once at six dose levels: 0.03 mg/kg (n = 1), 0.1 mg/kg (n = 3), 0.3 mg/kg (n = 3), 1 mg/kg (n = 4), 2 mg/kg (n = 3), and 3 mg/kg (n = 5). One DLT of Grade (g) 4 platelets decrease was reported at 3 mg/kg, thus 3 new pts were added at this dose. The grade1 and grade2 HE0116 related adverse events (AEs) per CTCAE v5 that occurred (< 10% frequency) were ALT and AST increase, platelet decrease, WBC decrease, anemia, hypokalemia, hyponatremia, hypoalbuminemia, hypothyroidism, or bone pain. Three SAE were reported: 1 g2 ascites, 1 g4 dyspnea, 1 g2 fever. To date there was one iPR at 1 mg/kg for a pt with advanced ovarian cancer with liver met after 6 cycles of treatment, and 4 iSD (1 in 2 mg/kg, 3 in 3 mg/kg) were recorded. **Conclusions:** HE0116 administrated intravenously every 3 weeks is well tolerated with minimal toxicities. Preliminary data are very encouraging as single agent HE0116 showed durable responses with 1 iPR, 4 iSD in several difficult to treat late-stage cancer pts. Dose escalation is ongoing as per study protocol. Phase II in select patient populations, and clinical investigation of the combination of HE0116 with CTLA-4 or PD-1 are warranted. Clinical trial information: CTR20201794. Research Sponsor: HyaMab Biotech.

2641 **Poster Session**

A phase I dose-escalation and expansion study of HBM4003, an anti-CTLA-4 heavy chain only monoclonal antibody, in patients with advanced solid tumors. *First Author: Shanzhi Gu, Department of Interventional Radiology, Hunan Cancer Hospital, Changsha, China*

Background: HBM4003 is a fully human heavy chain only monoclonal antibody (HCAb) to CTLA-4, which has been engineered to deplete Treg cells by enhanced antibody-dependent cellular cytotoxicity (ADCC) activity. In the Phase 1 dose escalation part, HBM4003 showed favorable safety and efficacy profile in patients (pts) with advanced solid tumors. Here, we present the updated data from the dose escalation part and most recent safety and clinical activity data from three expansion cohorts of pts with advanced hepatocellular carcinoma (HCC), melanoma, and renal cell carcinoma (RCC). **Methods:** In the dose-escalation part, pts were enrolled into 3 dose levels (DL): 0.3mg/kg QW (28-day cycle), 0.45mg/kg Q3W (21-day cycle), and 0.6mg/kg Q3W (21-day cycle). In the dose-expansion part, pts with advanced HCC, melanoma, and RCC received 0.45 mg/kg Q3W (21-day cycle). Tumor measurements were performed every 6 weeks for up to 12 months and subsequently every 12 weeks per RECIST v1.1. **Results:** In total 60 pts were included for this analysis, including 24 pts with advanced solid tumors in the dose escalation part and 36 pts in the dose expansion part: 18 pts with HCC, 4 pts with melanoma, and 14 pts with RCC, from 12 sites in mainland China, 5 sites in Australia, and 1 site in Hong Kong. 46 pts (77%) received ≥ 2 lines of previous systemic therapies and 37 pts (62%) received previous PD-1/PD-L1 treatment. For the HCC cohort, 19 pts were treated in dose-escalation (1 pt, 0.45 mg/kg Q3W) and dose-expansion parts. All 19 pts received previous PD-1/PD-L1 therapy. 12 pts were evaluable for efficacy. Two had stable disease (SD), 2 pts had partial response (PR) as best response. For 12 evaluable pts, ORR was 16.7% and disease control rate (DCR) was 33.3%. For the RCC cohort, 19 pts were treated in dose-escalation and dose-expansion parts; 18 pts were evaluable for efficacy. Eight had SD as best response; the DCR was 44.4%. Overall, the most common treatment-related adverse event (TRAE) (incidence ≥ 10%) of all grades was rash (16 [26.7%] pts). At the 0.45 mg/kg Q3W DL, the most common TRAE of all grades was hepatic function abnormalities (12 [27.9%] pts) and rash (12 [27.9%] pts). 30 (69.8%) pts reported Gr 1 or 2 TRAEs. Gr ≥3 TRAEs occurred in 4 (9.3%) pts. 1 pt reported Gr 4 TRAE: blood creatine phosphokinase increased. No Gr 5 TRAE was reported. TRAE leading to discontinuation occurred in 4 pts. In mouse model, only tumor infiltrating lymphocytes Treg was depleted upon HBM4003 treatment while no Treg change in blood and spleen. In pts, Treg depletion was observed only in tumor tissue on day 21 post dosing. Overall, HBM4003 demonstrated dose proportional pharmacokinetics and low immunogenicity. **Conclusions:** HBM4003 showed a favorable safety profile, promising antitumor activity and intratumoral Treg depletion in pts with advanced solid tumors at the 0.45 mg/kg Q3W DL. Clinical trial information: NCT04135261. Research Sponsor: Harbour BioMed US, Inc.

2643 **Poster Session**

Phase Ia dose-escalation study of the anti-BTLA antibody icatolimab as a monotherapy in patients with advanced solid tumor. *First Author: Russell J. Schilder, Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA*

Background: The B- and T-lymphocyte attenuator (BTLA) is an inhibitory receptor expressed on B, T and NK cells. Icatolimab (TAB004 or JS004) is a humanized IgG4 monoclonal antibody (mAb) with a hinge mutation (S228P) that binds BTLA and blocks its interaction with its ligand HVEM. In preclinical studies, icatolimab monotherapy suppressed tumor growth in murine tumor models using human BTLA knock-in mice. In this first-in-human dose-escalation study, we report the preliminary safety and efficacy of icatolimab as a single agent in patients with advanced solid tumors. **Methods:** Eligible patients with advance solid tumors refractory to standard therapies were enrolled in this study. Icatolimab was administered at escalating doses of 0.3, 1, 3 and 10 mg/kg intravenously Q3W and followed by dose expansion in 3 and 10 mg/kg cohorts until disease progression or intolerable toxicity. Dose-limiting toxicity (DLT) was evaluated by a safety monitoring committee. Study objectives included safety, pharmacokinetics, pharmacodynamics, and anti-tumor activity. **Results:** A total of 25 patients with solid tumor were enrolled in the Part A of this phase I study (NCT04137900). The median age was 62 (range 32-85) years with 16 (64%) male patients. Patients were heavily pretreated with a median of 4 prior lines of therapy. Fifteen (60%) patients received and progressed upon prior anti-PD-1/L1 therapy. By the data cutoff date of December 31, 2021, the median follow-up was 32 weeks. No DLT was observed. 24 (96%) patients experienced treatment emergent adverse event (TEAEs), with 7 (28%) experienced grade 3 TEAEs. No grade 4 or 5 TEAE occurred. The incidence or severity of AE was not associated with the dose. The most common TEAEs were fatigue (32%), abdominal pain (20%), diarrhea (16%), arthralgia (16%), aspartate aminotransferase increased (16%), constipation (16%), and contusion (16%). One (4%) TEAE led to discontinuation of study drug. Four (16%) patients experienced immune related AE. Among 19 evaluable patients by the cutoff date, 1 confirmed PR (melanoma) and 6 SD were observed as assessed by the investigator per RECIST v1.1. The response was still ongoing over 12 months in the melanoma patient who had progressed upon prior nivolumab and BRAF/MEK inhibitors treatments. BTLA receptor was fully occupied in the 3 and 10 mg/kg cohorts. The mean elimination half-life of icatolimab was 7.5 to 19.2 days in four dose cohorts. Biomarker analysis indicated co-expression of HVEM and CD8 was associated with favorable response. **Conclusions:** Icatolimab monotherapy were well tolerated in all doses evaluated and showed preliminary clinical efficacy as a monotherapy. Icatolimab in combination with toripalimab (anti-PD-1) for the treatment of patients with advanced solid tumors is currently ongoing. Clinical trial information: NCT04137900. Research Sponsor: Shanghai Junshi Biosciences and TopAlliance Biosciences.

2644 **Poster Session**

Preliminary analysis of a phase I study of SNK01 (Autologous Non-genetically Modified Natural Killer Cells With Enhanced Cytotoxicity) monotherapy in patients with advanced solid tumors. *First Author: Victoria S. Chua, Sarcoma Oncology Research Center, Santa Monica, CA*

Background: Natural killer (NK) cells play a key role as the main effector cells toward cancer in innate immunity. Thus, a leading approach is to boost NK-cell mediated anti-tumor activity using adoptive transfer of ex vivo activated NK cells. NK cells have always been challenging to grow ex vivo especially when derived from heavily pretreated donors, thus most have focused on universal allogenic donor derived products. SNK01 is a first-in-kind, autologous non-genetically modified NK cell product with significant anti-tumor cytotoxicity and over 90% expression of CD16, NKG2D, NKp46, and DNAM-1, that can be consistently produced even from heavily pre-treated cancer patients (pts). While most if not all NK cell therapy has focused on liquid malignancies, SNK01 has been found to have strong activity against both liquid and solid tumors preclinically. We hypothesized that SNK01 would be safe without need for lymphodepletion and may demonstrate activity against heavily pre-treated solid tumors. **Methods:** In this Phase 1 dose escalation study (NCT03941262), SNK01 was administered intravenously (IV) weekly for 5 consecutive weeks using a 3+3 design in pts with advanced solid tumors. The starting dose was 1 x 10^9SNK01 cells and the highest dose was 4 x 10^9 SNK01 cells. Primary endpoint was safety based on AEs, vitals, laboratory tests, and PEs. Individual NK cell expansion was characterized for increases in cytotoxicity and changes in activating receptor expression. **Results:** As of Feb 1, 2022, 10 pts with advanced refractory solid tumors have been enrolled. Median age is 50 (range 32 – 75) and 6 were male. Pts had a median 5.5 lines of prior therapy (range 2-10). The subtypes were 4 leiomyosarcoma, 1 chondrosarcoma, 1 NSCLC, 1 small round cell tumor, 1 colorectal, 1 synovial cell sarcoma, 1 angiosarcoma. NK cells were successfully activated and expanded, even from heavily pre-treated pts. Average cytotoxicity was increased over 400% and average activating receptor expression was greater than 90%. There were only two Grade 1 adverse events reported in the 50 total doses given. Best objective response of SD was demonstrated in 7 pts. Of patients who progressed in the dose escalation cohorts, several reported an overall improvement in their QOL. Based on this improvement, patients then became eligible to be treated with additional salvage chemotherapy to which some then showed additional response. **Conclusions:** SNK01 with high cytotoxicity and activating receptor expression can be consistently produced from heavily pretreated patients. SNK01 was very safe and appears to have some clinical activity against heavily pretreated solid tumors and may even sensitize tumors to additional chemotherapy. SNK01 will be studied further as monotherapy and in various combination regimens. Clinical trial information: NCT03941262. Research Sponsor: NKGen Biotech.

2645 **Poster Session**

Promising clinical benefit rates in advanced cancers alongside potential biomarker correlation in a phase I/II trial investigating bexmarilimab, a novel macrophage-guided immunotherapy. *First Author: Petri Bono, Terveystalo Hospital and University of Helsinki, Helsinki, Finland*

Background: Clever-1 is an immunosuppressive scavenger receptor expressed on tumor associated macrophages. High levels of Clever-1 are associated with poor survival and immunotherapy resistance. Bexmarilimab (FP-1305) is a novel humanized anti-CLEVER-1 IgG4-antibody capable of inducing a phenotypic M2 to M1 immune switch of tumor-associated macrophages. **Methods:** MATINS (Macrophage Antibody To INhibit immune Suppression) trial is a first-in-human phase I/II study (NCT03733990) to assess safety and preliminary efficacy of Bexmarilimab in patients with refractory advanced solid tumours. Part I has been completed with initial good safety profile of the IMP, preliminary signs of efficiency, and recommended dose of 1mg/kg Q3W for part II (ESMO 2020). In Part II (ESMO 2021), 10 distinct solid tumour types were enrolled to assess preliminary efficacy (overall survival (OS), progression free survival (PFS), and clinical benefit rate (CBR). Clever-1 IHC in pre-treatment biopsies with Ventana platform using a primary antibody 4G9 (Santa Cruz) was scored by % of positive cells compared to the viable tumor cells. **Results:** At the Jan 2022, a total of 193 patients have been enrolled to the study. In the completed cohorts, 138 patients have received 1-21 doses (median 3) of Bexmarilimab Q3W. Bexmarilimab was well tolerated, and no new safety signals were detected. Part I and Part II fully enrolled 11 cancer cohorts, the median PFS was 2.0 months (95% CI 1.9 – 2.0) and the median OS was 5.2 months (95% CI 4.3 – 6.4). CBR for Part II was 17.3% (19/110) at cycle 4 of treatment (by RECIST v.1.1). Notably, 30-40% CBR at cycle 4 was seen in cutaneous melanoma (30%), gastric cancer (30%), cholangiocarcinoma (30%), hepatocellular cancer (40%), and ER+ breast cancer (40%). Six-month survival rates (landmark analysis) were 70.1% for CBR compared to 34.7% for non-CBR patients, with a similar duration of prior therapy in both groups. Preliminary biomarker analysis (n = 77) demonstrated positive trend (p = 0.038) between CBR and higher intratumoral Clever-1 positivity (median of 15% positivity (range 0-25) in CBR and 3% (range 0-85) in non-CBR patients) **Conclusions:** Bexmarilimab continues to demonstrate promising anti-tumour activity as a monotherapy in several refractory solid tumours. Furthermore, preliminary biomarker analysis suggests a possibility for patient selection based on tumour Clever-1 expression. Further expansion of the study will investigate optimal dosing and biomarkers of efficacy. Clinical trial information: NCT03733990. Research Sponsor: Faron Pharmaceuticals.

2646 **Poster Session**

Phase I study of the efficacy and safety of IBI319 in patients with advanced malignant tumors. *First Author: Yi-Long Wu, Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital & Guangdong Academy of Medical Sciences, Guangzhou, China*

Background: IBI319 is a recombinant fully human anti-CD137/PD-1 bispecific antibody. In preclinical studies, IBI319 demonstrated a better anti-tumor efficacy and safety. Here we report the initial results from the first-in-human study of IBI319 in patients with advanced malignancies. **Methods:** Enrolled patients (pts), ECOG PS ≤ 1, had advanced solid tumors or hematological malignancies and failed standard treatment. This phase 1 monotherapy dose-escalation includes accelerated titration (0.03 and 0.1mg/kg) and conventional 3+3 dose escalation (0.3, 1.0, 3.0, 6.0 and 10.0 mg/kg). IBI319 is administered intravenously every 14 days after dose-limiting toxicity (DLT) evaluation. Objectives include evaluation of safety, DLT, pharmacokinetic (PK) and antitumor activity. Adverse events (AEs) were reported per CTCAE v5.0 and DLTs evaluated within a 28-day window. **Results:** At cutoff date of February 10, 2022, 21 pts were enrolled (median age 55 years; 81.0% male; 19.1% ECOG PS 1; 52.4% advanced solid tumors). The following dose levels have been evaluated; 0.03 mg; 0.1 mg; 0.3 mg; 1 mg; 3 mg and 6 mg. Dose escalation is ongoing. The maximum tolerated dose has not been reached. Treatment-emergent adverse events (TEAEs) was reported in 15 out of 21 (71.4%) pts, among which 1 pts had back pain and nausea of grade 3. The most common TEAEs (> 10%) were interleukin level increased (6 pts, 28.6%) and C-reactive protein increased (3 pts, 14.3%). Eleven pts (52.4%) experienced treatment-related AEs; none were grade 3 or higher. The most common TRAEs (> 10%) were interleukin level increased (6 pts, 28.6%) and C-reactive protein increased (3 pts, 14.3%). Importantly, no drug-related elevations in transaminases (ALT, AST) or bilirubin have been seen. No DLT was observed. PK analysis of IBI319 demonstrated consistent exposure with linear PK. For 14 evaluable pts, 1 classical Hodgkin lymphoma patient achieved PR as best response. **Conclusions:** IBI319 demonstrates good tolerability in patients with advanced solid tumors or hematological malignancies, with a safety profile characterized by a lack of hepatotoxicity frequently observed with CD137-targeting antibodies. Clinical trial information: NCT04708210. Research Sponsor: Innovent Biologics Inc.

2647 **Poster Session**

Phase 1 dose escalation study of DSP107, a first-in-class CD47 and 4-1BB targeting multifunctional immune-recruitment protein, in patients with advanced solid tumors. *First Author: Jason J. Luke, University of Pittsburgh, Pittsburgh, PA*

Background: DSP107 is a bi-functional, trimeric, fusion protein composed of sequences from the extracellular domain of SIRPα and 4-1BBL. The SIRPα arm targets CD47 overexpressed on tumor cells, blocking the "don't eat me" checkpoint and triggering tumor cell phagocytosis. The trimeric 4-1BBL arm, once cross-presented and immobilized by SIRPα binding to CD47, interacts with 4-1BB expressed on activated immune cells, mainly T- and NK cells in the tumor microenvironment, and stimulates their proliferation and activation. Thereby, DSP107 triggers both an innate and an adaptive immune response. Here we describe data from the completed DSP107 monotherapy dose escalation portion of study NCT04440735. **Methods:** Adult patients with advanced solid tumors were treated with weekly intravenous DSP107 infusions (0.01 - 10 mg/kg) during 3-week treatment cycles. An accelerated dose escalation in single patient cohorts (dose levels 1-3) was followed by a standard 3 + 3 design. The primary objective was to determine safety, tolerability and pharmacokinetic (PK) parameters. Paired biopsies were obtained from 8 patients (screening, after cycle 2). Restaging imaging was performed every two months and evaluated by RECIST criteria. **Results:** In 23 patients, DSP107 demonstrated no treatment related hematologic or hepatic adverse events (AEs) and no dose limiting toxicities. Grade 1-2 treatment related AEs were observed in 70% of patients (16/23). The most frequent AEs included infusion related reaction (IRR; 26%), diarrhea (17%), fatigue (17%), nausea (13%) and constipation (9%). IRRs were managed during subsequent infusions by reducing the infusion rate and administering IV fluids. No significant systemic cytokine release was measured at any dose level using a 10-plex, pro-inflammatory panel. PK analysis revealed 100% CD47 receptor engagement on peripheral T and NK cells at doses of 3 mg/kg and above. DSP107 did not bind CD47 on red blood cells at any dose. Preliminary histologic assessment of paired biopsies by an independent, blinded pathologist demonstrated increased tumor necrosis compared to screening in 3 out of 4 patients associated with immune cell infiltration. Immuno-profiling of tumor by immunofluorescence is on-going. Stable disease as best response was observed in 11/22 patients with treatment duration up to 26 weeks. **Conclusions:** DSP107 is a novel, CD47 and 4-1BB targeting fusion protein with a differentiated safety, binding and pharmacodynamic profile compared to other CD47 and 4-1BB targeting agents. Clinical trial information: NCT04440735. Research Sponsor: KAHR Medical Ltd.

2648 **Poster Session**

A phase 1a dose-escalation study of PY314, a TREM2 (Triggering Receptor Expressed on Macrophages 2) targeting monoclonal antibody. *First Author: Amita Patnaik, START San Antonio, San Antonio, TX*

Background: To characterize the safety and tolerability of PY314, an immunosuppressive macrophage depleting antibody, as a single agent and in combination with pembrolizumab in subjects with advanced refractory solid tumors including subject's refractory to checkpoint inhibitors if approved for that indication. **Methods:** Two were evaluated in subjects with advanced solid tumors, single agent PY314 and PY314 in combination with 200 mg of pembrolizumab using a 3+3 dose escalation study design. Dosing was intravenous and administered once every 3-weeks, a defined cycle. Disease assessment by RECIST 1.1 was performed every 6 weeks. Each stratum included 4 dose levels of PY314 (1, 3, 10, and 20 mg/kg). Pharmacokinetics were evaluated at specified time points. Archival tumor tissue was analyzed for TREM2 expression by immunohistochemistry. Based on preclinical evaluation of TREM2 expression, HR+ HER2- and triple negative breast cancer, colorectal cancer, renal cell cancer, non-small cell lung cancer and gynecologic cancers were studied. **Results:** 28 subjects (median age 60 years [range 26-76], 22 females and 6) with an ECOG PS <2 were enrolled and all, but one was (1 subject withdrew consent after dosing). 15 subjects were treated with single agent PY314 and 13 were treated with the combination. No infusion-related reactions, dose limiting toxicities, suspected unexpected serious adverse reactions or high-grade treatment related adverse events (TRAEs) that resulted in treatment discontinuance was seen. 12 subjects experienced at least one TRAE, and in all but one subject, these were low grade. One subject experienced a treatment-related immune system disorder. serious adverse events, all unrelated to treatment. TREM2 expression in archival tumor ranged from 0.0-20%. PY314 pharmacokinetics were linear, dose proportional, unaffected by concomitant pembrolizumab and with a half-life of 8-9 days. Best radiographic response was stable disease seen in 11 subjects (39.3%) ranging in duration from 9-42 weeks. 6 subjects with stable disease have progressed and 5 remain on treatment. **Conclusions:** PY314 was well tolerated and has an excellent safety profile both as a single agent and in combination with pembrolizumab. A recommended dose for expansion was derived and enrollment in five prespecified cancers is ongoing. Clinical trial information: 04691375. Research Sponsor: Pionyr Immunotherapeutics.

2649 **Poster Session**

Pan-cancer (ca) analysis of the safety and efficacy of immune checkpoint inhibitors (ICI) in patients (pts) living with HIV (PLWH): Results from the international CATCH-IT consortium. *First Author: Talal El Zarif, Dana Farber Cancer Institute, Boston, MA*

Background: PLWH and ca are inadequately represented in clinical trials evaluating ICI especially in the setting of low CD4 counts (ct) and elevated HIV viral loads (VL). We assembled an international cohort of PLWH and ca treated with ICI to evaluate toxicity profiles and clinical outcomes. **Methods:** We retrospectively collected data on 204 PLWH and ca receiving ≥ 1 cycle of ICI between 2015-2021 at 14 academic medical centers in the US and Europe. Immune-related adverse events (irAEs) were graded per the Common Terminology Criteria for Adverse Events (CTCAE) V5.0. Baseline CD4 ct, CD8 ct and HIV VL were collected within 3 months (mo) of ICI initiation when available. Fisher's exact test was performed to compare categorical variables. Median (med) Overall Survival (OS) and Objective Response Rate (ORR) were calculated for 186 pts treated in the metastatic (met) setting. **Results:** Among 204 PLWH treated with ICI, 174 (85%) were cis-gender males. 61 (31%) were Black and 34 (18%) were Hispanic/Latinx. Pts were treated with pembrolizumab (n=93), nivolumab (n=71), atezolizumab (n=20), nivolumab and ipilimumab (n=13), durvalumab (n=6), or avelumab (n=1). Med number of prior lines of systemic therapy was 1 (range: 0-5). Among pts with available baseline data, 36/133 (27%) had CD4 ct <200 cells/μL while 12/136 (9%) had VL ≥400 copies/mL. irAEs of any grade occurred in 43 (21%) pts and 13 (7%) were grade ≥3 while 19 (9%) required steroids. Pts with CD4 ct <200 cells/μL experienced fewer irAEs than pts with CD4 ct ≥200 cells/μL (2/36 vs 26/97; p<0.01). The incidence of any grade irAEs was similar between pts with CD4/CD8 ratio <0.4 vs ≥0.4 (8/54 vs 18/72; p=0.16) and between pts with HIV VL ≥400 vs <400 copies/mL (1/12 vs 28/124; p=0.46). Clinical outcomes are shown in the table below. Among 29 pts with met non-small cell lung ca (NSCLC) with available CD4 ct, the ORR of pts with CD4 ct <200 cells/μL was 13% (95% CI:0-53) vs 38% (95% CI:18-62) in pts with CD4 ct ≥ 200 cells/μL (1/8 vs 8/21; p=0.38). **Conclusions:** In the largest dataset to our knowledge, we demonstrate tolerability and activity of ICI among PLWH regardless of CD4 ct and HIV VL levels. CD4 ct <200 cells/μL may be associated with a lower incidence of irAEs. An analysis of a larger cohort is underway. Research Sponsor: None.

Ca Type	N total (%) (N=204)	Grade 3+ irAEs N (%)	Med baseline CD4 ct, cells/μL (range)	N met (%) (N=186)	Med OS (95% CI), mo	ORR (95% CI), %
NSCLC	50 (25)	2 (4)	314 (6-1721)	46 (25)	10.6 (7.4-NR)	23 (11-38)
Hepatocellular ca	19 (9)	1 (5)	375 (234-1034)	17 (9)	14.9 (4.2-NR)	0 (0-22)
Anal ca	17 (8)	2 (12)	190 (110-494)	16 (9)	7.5 (1.3-11.6)	19 (4-46)
Kaposi sarcoma	17 (8)	1 (5)	251 (10-1210)	16 (9)	6.5 (2.1-30.3)	67 (38-88)
SCLC	16 (8)	2 (13)	662 (236-844)	15 (8)	9.6 (4.3-14.5)	8 (0-38)
Head and neck ca	15 (7)	2 (13)	270 (115-385)	15 (8)	5.8 (0.9-NR)	7 (3-34)
Others	70 (34)	3 (4)	281 (20-1154)	61 (33)	NA	NA

NR: Not Reached; NA: Not Applicable

2650 **Poster Session**

IBI110 (anti-LAG-3 mAb) as a single agent or in combination with sintilimab (anti-PD-1 mAb) in patients with advanced solid tumors: Updated results from the phase Ia/Ib dose-escalation study. *First Author: Nong Xu, The First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China*

Background: Lymphocyte-activation gene 3 (LAG-3) is an immune checkpoint receptor protein that functions to control T cell response, activation and growth. Dual inhibition of PD-1 and LAG-3 may improve anti-tumor effect synergistically. A phase Ia/Ib dose-escalation study evaluated IBI110 ± sintilimab in patient with advanced solid tumors; initial efficacy and safety data were previously presented (C Zhou et al. ASCO 2021; NCT04085185). Here, we reported the updated results. **Methods:** Eligible patients were ECOG PS 0-1 and had locally advanced, recurrent or metastatic solid tumors for whom standard therapy had failed. Patients received escalating doses of IBI110 (0.01/0.1/0.3/1/3/10/20mg/kg) IV Q3W in phase Ia and escalating doses of IBI110 (0.3/0.7/1.5/3/5/8/10 mg/kg) in combination with sintilimab 200 mg IV Q3W in phase Ib. Crossover from monotherapy to combination therapy was allowed at progression. The primary objectives were safety, tolerability, and anti-tumor activity of IBI110 alone or IBI110+sintilimab (per RECIST v1.1). **Results:** Phase Ia: 28 patients (median age of 60.5 years [range 35-72], ECOG PS of 0 [n = 14] and 1 [n = 14]) were enrolled. Dose escalation was completed and no dose-limiting toxicity (DLT) was observed in all dose cohorts. The safety profile was generally consistent with the initial. By investigator-assessment, best response was 1 confirmed partial response (PR) and 6 stable diseases (SD) with monotherapy. After crossing to combination therapy at progression, 8 patients who failed prior anti-PD-(L)1 mAb therapy achieved SD. Phase Ib: Overall, 45 patients (median age: 60.0 yr [range 33-74]; ECOG PS: 0 [n = 14], 1 [n = 31]) were enrolled in all dose levels. Dose escalation was completed and no DLT was observed. The most common treatment-related adverse events (TRAEs) were aspartate aminotransferase increased (28.9%), anaemia (24.4%), and alanine aminotransferase increased (22.2%). TRAEs ≥ grade 3 occurred in 10 (22.2%) patients. Immune-related AE (irAE) incidence was 31.1%, and the most common irAE was hypothyroidism (15.6%). In 43 patients who had undergone at least 1 post-baseline tumor assessment, the investigator-assessed best response included 6 PRs (1 endometrial cancer, 4 NSCLC, and 1 SCLC patients) and 23 SDs. Three patients showed a progression-free survival > 1 year and continued treatment. **Conclusions:** IBI110 alone or plus sintilimab demonstrated acceptable safety profile and promising antitumor activity in patients with advanced solid tumors. Clinical trial information: NCT04085185. Research Sponsor: Innovent Biologics, Inc., China.

2651 **Poster Session**

Safety and efficacy of etigilimab in combination with nivolumab in select recurrent/advanced solid tumors. *First Author: Meredith McKean, Sarah Cannon Research Institute, Tennessee Oncology, PLLC, Nashville, TN*

Background: Etigilimab (etig), a humanized IgG1 monoclonal antibody, blocks TIGIT interaction with PVR (poliovirus receptor) and inhibits downstream signalling with target cell killing. Etig +/- nivolumab (nivo) showed acceptable safety and preliminary activity in a FIH Phase 1a/b study in solid tumors. ACTIVATE, an open-label Phase 1b/2 basket study is evaluating further efficacy, safety, tolerability and PK/PD of etig+nivo. This is a preliminary efficacy and safety analysis from ACTIVATE. **Methods:** Subjects with advanced/metastatic solid tumors without curative/standard of care therapies are given IV etig+nivo Q2W until disease progression or intolerable toxicity. Six open cohorts are enrolling in parallel: endometrial cancer (post-front-line platinum), endometrial cancer (2-3 prior lines), PD-L1+ checkpoint-inhibitor-naïve (CPI-n) cervical cancer, rare cancers (germ cell tumor (GCT), sarcoma, uveal melanoma), ovarian cancer (post-front-line platinum) and TMB-h/MSS, (TMB >10mut/mb) tumors. Tumor assessments are done every 8 weeks following baseline scan. Primary endpoint is investigator-assessed ORR by RECIST 1.1. Secondary endpoints include duration of response and safety. **Results:** Of 27 efficacy-evaluable subjects enrolled in the 6 open cohorts with minimum 1 staging scan or radiological/clinical progression at data cut-off of 02/10/22, 12 had clinical benefit with 1 complete response (CR), 2 partial responses (PRs) and 9 stable diseases (SDs) and 15 had radiological/clinical progressive disease (PD), with an overall response rate (ORR) of 11% and disease control rate (DCR) of 44%. **Conclusions:** Etig+nivo is safe and well tolerated with no new safety signals. Early efficacy was noted in cervical cancer (1CR, 1PR and 1SD) and uveal melanoma (3 SDs >20 weeks). Encouraging activity was also noted in ovarian cancer and post-CPI treated TMB-H/MSS NSCLC. These early data support continued evaluation of the combination of etig+nivo. Clinical activity was notable as below. Clinical trial information: NCT04761198. Research Sponsor: Mereo BioPharma 5 Inc.

	Best Observed Response (BOR)[1] (n), CR/PR/SD Duration on study			
COHORTS	**CR**	**PR**	**SD**	**PD**
CPI-n CPS>1% Cervical Cancer (n=3)	1[2] 63 days^	1 72 days*	1[3] 174 days^	**0**
CPI-n Uveal Melanoma(n=6)	-	-	3 175 days^; 178 days*; 143 days*)	3
Ovarian cancer (n=8)	-	1 112 days^	3 80 days^; 58 days*; 51 days*	4
TMB-H/MSS (n=4)	-	-	1[4] 100 days*	3
Rare: Sarcoma (n=3)	-	-	1 63 days*	2
Rare: GCT (n=3)	-	-	-	3
Total (n=27)	1	2	9	15

[1]BOR at data cut-off,*On-study, ^Off-study. [2]Off study, withdrew consent with ongoing CR. [3]Unrelated death with ongoing SD. [4]NSCLC, CPS <1%. Treatment-related adverse event (TRAE) rate was 25% (safety analysis set n=41, ≥ 1 dose of etig+/-nivo). Two G3 TRAEs (immune-related diabetes mellitus and maculopapular rash), and 3 G2 infusion-related AEs occurred. There were no >G3 TRAEs and no treatment-related SAEs/discontinuations. Most common TRAEs were G1-2 skin rashes (36% of TRAEs); 1 G3 rash AE required systemic steroids for resolution.

2652 **Poster Session**

Enhanced tumor control with a combination of APG-157 and immune checkpoint inhibitors for head and neck cancer. *First Author: Daniel Sanghoon Shin, University of California Los Angeles Medical Center/Veterans Affairs, Los Angeles, CA*

Background: Natural botanical drugs containing flavonoids are under clinical investigation for the treatment of malignancies. A phase I clinical study for patients with locally advanced head and neck cancer with a new class of botanical drug APG-157 showed excellent tolerability, systemic absorption via sublingual administration, and enhanced immune cell infiltration into the tumor microenvironment and suppression of T cell inhibitory inflammatory cytokine production. We sought to evaluate the efficacy of tumor control for the combination of APG-157 and checkpoint blockade immunotherapy using a head and neck cancer mouse model. **Methods:** SCCVII (HPV-) and MEER (HPV+) head and neck cancer murine cell line models were utilized in *in vivo* tumor growth study. After optimization for route and cell number, we measured tumor growth after treating mice with following groups: i) control, ii) APG-157, iii) anti-PD-1, iv) anti-CTLA-4, v) APG-157 + anti-PD-1, vi) APG-157 + anti-CTLA-4, vii) anti-PD-1 and anti-CTLA-4 , viii) APG-157 + anti-PD-1 + anti-CTLA-4. Tumors were collected after 2 injections of immune checkpoint inhibitors and characterized for immunophenotype by multi-color flow cytometry, immunohistochemistry, and RNA-sequence analysis. Fecal microbiome was analyzed by 16S rRNA sequence for SCCVII model to assess the impact of APG-157 on the microbiome as we observed the shift of oral microbiome species in the human trial. **Results:** We confirmed by serum concentration of APG-157 metabolites that the best route of administration is via oral route by mixing with APG-157 with mouse chow. Tumor growth optimization experiments determined that 100,000 cells of SCCVII is the ideal number of cells to inject and day 5-6 is the time to initiate treatment. Among 8 treatment groups, APG-157 + anti-CTLA-4 demonstrated best tumor control (p = 0.0065 compared to control), followed by anti-PD-1 + anti-CTLA-4 treatment group (p = 0.48 compared to control). The immunophenotype assessment by flow cytometry showed over 30% of CD8+ T cell in APG-157 + anti-CTLA-4 group compared to 4-5% of CD8+ T cell for the control group. GSEA analysis from the SCCVII tumors revealed that APG-157 + anti-CTLA-4 group showed an enriched set of genes for inflammatory response, apoptotic signaling pathways. The fecal microbiome analysis showed a substantial difference of lactobacillus genus among groups, highest in the group of APG-157 + anti-CTLA-4 treatment group. The MEER model (HPV positive) tested with same immunotherapy as single or in combination with APG-157 did not grow the tumor, thus we were unable to collect the tumor for immunophenotyping and other studies. **Conclusions:** These study results indicate that APG-157 is able to modulate the immune system and fecal microbial species that could potentially lead to improved anti-tumor immunity and warrants further studies to define mechanism and the potential for human clinical trial. Research Sponsor: Institutional Start Up fund and pharmaceutical company (AvetaBiomics).

2653 **Poster Session**

Immune checkpoint inhibitor-related endocrinopathies: A nationwide population-based study. *First Author: Dina Elantably, Metrohealth Medical Center Case Western Reserve University, Cleveland, OH*

Background: Immune checkpoint inhibitors (ICIs) have revolutionized cancer therapy. However, unleashing the body's immune system against cancer is not without consequences and may trigger immune-related adverse events (irAEs), such as endocrinopathies. Real-world data of these endocrinopathies is lacking. This study aims to obtain the prevalence of endocrine irAEs and identify possible underlying demographic risk factors or disparities. **Methods:** A cross-sectional study was performed using a US-based population database (Explorys) that aggregates records from 26 healthcare systems and includes over 79 million patients. Our sample included all patients on an ICI, and we further identified patients who developed endocrinopathies while on different ICI regimens. The demographic data extracted was categorical, hence presented as counts and percentages. The odds ratio (OR), standard error, and 95% confidence interval were calculated with the use of SPSS software version 28.0 (IBM). **Results:** There were 20,950 patients on an ICI; 58% males, 83% Caucasians, 10% African-Americans (AA), 38% aged between 18-65, and 63% were over 65 years. The prevalence of the studied endocrinopathies is listed in the table. The most prevalent ICI-induced endocrinopathy was hypothyroidism (7.9-13%). Combination therapy with ipilimumab and nivolumab showed the highest prevalence of ICI-induced endocrinopathies, followed by durvalumab. The odds of developing ICI-induced endocrinopathy were significantly higher with combination therapy than nivolumab monotherapy (OR 1.6; 95% CI 1.4-1.9). There was no statistically significant difference in endocrinopathy prevalence when comparing Caucasians to AA and adults18-65 years to seniors over 65 years. **Conclusions:** This is the largest epidemiological study of ICI-related endocrinopathies. We find an intriguing divergence from endocrinopathy prevalence reported in the literature and real-world data we are presenting here. Over diagnosis of overt hypothyroidism, as opposed to subclinical hypothyroidism, is concerning as the former necessitates levothyroxine therapy. More alarming is the under diagnosis of hypopituitarism and PAI, in which delay in treatment can be fatal. The diagnosis of these conditions can be challenging. Raising awareness, setting protocols for testing, and involving endocrinologists are crucial. Further studies are needed to clarify our findings. Research Sponsor: None.

Prevalence of immune checkpoint related endocrinopathies.

ICI (Total patients on ICI)	ICI-induced endocrinopathy	Acquired hypothyroidism	Subclinical hypothyroidism	Hyperthyroidism	Hypopituitarism	PAI	Type 1 DM
Nivolumab (6700)	10.4%	8.2%	1%	2.2%	0.3%	0.07%	1.19%
Pembrolizumab (9580)	11%	8.9%	2%	2.5%	0.4%	0.3%	1.04%
Atezolizumab (2020)	10.4%	7.9%	0.2%	2.97%	0.24%	0.24%	1.48%
Durvalumab (940)	17%	13.8%	0.5%	6.38%	0.5%	0.5%	0 %
Ipilimumab & nivolumab (1760)	17.6%	13%	0.3%	3.4%	1.13%	1.7%	1.7%

2654 **Poster Session**

Immune-related adverse events and immunotherapy efficacy in patients with cancer: A retrospective study. *First Author: Lyndsey L. Prather, Baylor College of Medicine, Houston, TX*

Background: Immune checkpoint inhibitors are revolutionizing cancer care and providing new treatment options with promising outcomes for many cancers. However, immune-related adverse events (irAEs) are not infrequent and can be severe. An intriguing relationship between the presence of irAEs and treatment efficacy has been described but lacks thorough characterization. We aimed to further elucidate a relationship between immune checkpoint inhibitor (ICI) irAEs and efficacy. **Methods:** We identified cancer patients treated with ICI from 2015-2021 across two institutions: Michael E DeBakey Veterans Affairs Medical Center (MEDVAMC) and Baylor St. Luke's Medical Center (BSLMC). Clinical data including cancer type, irAEs type and grade, ICI response, progression free survival (PFS) and overall survival (OS) was collected. Using the Kaplan Meier method, survival curves were generated and comparisons were made amongst groups using the log-rank test. Fisher's exact test was used to compare progression of disease between groups. To determine if variables were associated with survival, multivariable Cox regression analysis was used. **Results:** Of the 456 patients treated with ICI, irAEs were seen in 165 (36%) patients. Of these, 81 (49%) patients had grade 1 toxicities, most commonly arthritis, diarrhea, and dermatitis. 47 (28%) patients had grade 2 toxicities (colitis, hypothyroidism, adrenal insufficiency). 34 (21%) patients had grade 3 toxicities (pneumonitis, pancreatitis, hepatitis). 3 patients had grade 4 toxicities (pneumonitis, DRESS syndrome, and hepatorenal syndrome). 1 patient expired and 24 (15%) patients discontinued ICI due to irAEs. 55 (33%) of patients with irAEs were treated with steroids. For patients assessed for efficacy, objective response rate (ORR) to ICI was higher in patients with irAEs [47% (12% CR) vs 33% (11% CR)]. In fact, the presence of any irAEs was significantly likely to predict response to ICI (OR 1.90, 95% CI 1.25 - 2.86, p = 0.0026). In a subset of patients evaluable for survival (n = 375), patients with any irAEs had a significantly improved median PFS compared to those without irAEs (9.0 vs. 4.8 months, p = 0.0018). Multivariable analysis demonstrated that the development of any irAEs was related to a significantly improved OS (HR 0.63, 95% CI 0.43-0.89, p = 0.01). **Conclusions:** The development of irAEs in cancer patients treated with immunotherapy may predict better treatment efficacy and overall survival. Further prospective studies are needed to confirm these associations and mechanism of action. Research Sponsor: None.

2655 **Poster Session**

Comparison of the checkpoint inhibitor pneumonitis incidence between immunotherapy alone or in combination with chemotherapy for lung cancer: An observational, retrospective pharmacovigilance study. *First Author: Pei-Hang Xu, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China*

Background: Clinical trials lack direct cross-comparison in safety between immune checkpoint inhibitor (ICI) as monotherapy and in combination with chemotherapy. The adverse event of checkpoint inhibitor pneumonitis (CIP) is an important factor influencing the treatment decision making. We performed a real-world pharmacovigilance study in the US Food and Drug Administration Adverse Event Reporting System (FAERS) to determine if ICI combination therapy is superior to monotherapy for lung cancer patients in terms of CIP incidence. **Methods:** The database of lung cancer patients receiving ICI between 2015 and 2020 was extracted for this study. The strategy-specific durations of the pneumonitis event were compared using the Kaplan-Meier method. Reporting odds ratio (ROR), a surrogate measure in disproportionality analysis, was used to assess the signal of CIP between ICI treatment strategies. **Results:** A total of 27,882 lung cancer patients with reported adverse events were involved. Among them, 1763 (6.3%) CIP after ICIs therapy were identified. In general, ICI usage was associated with over-reporting frequencies of CIP, but this association was no longer significant after adjustment (ROR: 1.14, 95%CI 0.86-1.49). The median times to CIP occurred early after therapy onset, either in ICI monotherapy or in combination with chemotherapy (41 days and 37 days, log-rank $p>0.05$). Different reporting frequencies emerged when we further compared different ICI strategies. Combination therapy with anti-PD-1 and chemotherapy was associated with a higher CIP incidence compared with anti-PD-1 monotherapy (ROR: 1.86, 95%CI 1.37-2.51), whereas anti-PD-L1/ CTLA-4 medications had lower risks in combination with chemotherapy (ROR: 0.31, 95%CI 0.16-0.56 and ROR: 0.41, 95%CI 0.09-1.22). Subgroup analyses on those with recorded therapy duration also indicated that reports of CIP were significantly lower with combination therapy of PD-L1 and CTLA-4 (ROR: 0.52, 95%CI 0.36-0.74 and ROR: 0.22, 95%CI 0.09-0.51 respectively). **Conclusions:** Compared with ICI monotherapy, the combination with chemotherapy might have an acceptable risk of CIP. Anti-PD-1 medications with additional chemotherapy could increase the risk of pneumonitis, whereas the risk was lower in the combination strategy with anti-PD-L1/CTLA-4. The combination might be a better therapeutic strategy than ICI monotherapy in treating lung cancer, regarding the CIP incidence. Research Sponsor: Guangzhou Science and Technology Planning Program (202002030023).

Disproportionality of checkpoint inhibitor pneumonitis in those treated with ICI combination therapy versus monotherapy.

	Crude ROR (95%CI)		Adjusted ROR (95%CI)	
All ICIs	0.91	(0.78-1.05)	1.14	(0.86-1.49)
Anti-PD-1	1.21	(1.02-1.44)	1.86	(1.37-2.51)
Anti-PD-L1	0.41	(0.31-0.54)	0.31	(0.16-0.56)
Anti-CTLA-4	0.28	(0.13-0.54)	0.41	(0.09-1.22)

2656 **Poster Session**

Comparing rate of immunotherapy treatment change due to toxicity by gender. *First Author: Kevin Joseph Chua, Section of Urologic Oncology, Rutgers Cancer Institute of New Jersey and Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ*

Background: Immunotherapy (IO) is associated with a variety of treatment related toxicities. However, the impact of toxicity on the treatment discontinuation rate between males and females is unknown. We hypothesized that immune related adverse events would lead to more frequent treatment changes in females since autoimmune diseases occur more frequently in females **Methods:** The Oncology Research Information Exchange Network (ORIEN) Avatar Database collects clinical data from ten different United States cancer centers, where patients receive IO. Of 1,035 patients receiving IO, 447 patients were analyzed, excluding those (N = 573) who did not have documentation noting if a patient changed treatment. 15 additional patients with an unknown or gender-specific cancer were excluded. All cancer types and stages were included. Primary endpoint was documented treatment change due to toxicity. Significance was calculated with logistic regression, linear regression, chi-squared test for categorical variables and Mann-Whitney U test for continuous nonparametric variables. **Results:** 447 patients (281 males and 166 females) received IO treatment for cancer. The most common cancers treated were kidney, skin, and lung for 99, 84, and 54 patients, respectively. Females had a shorter IO course compared to males on Mann-Whitney U test (median 3.7 vs 5.1 months, respectively, p=0.02) and multivariable linear regression (Beta -3.87, 95% CI -6.591, -1.149, p=0.005). 54 patients changed IO treatment due to toxicity. There was no significant difference in the rate of treatment change due to toxicity between females and males on chi-square test (11.4% vs. 12.5%, respectively, p = 0.75) and logistic regression (Table). Pembrolizumab, Nivolumab, Ipilimumab/Nivolumab, Ipilimumab, Durvalumab, Avelumab, and Atezolizumab were given to 16, 14, 9, 9, 3, 2 and 1 patients who changed treatment due to toxicity, respectively. The median length of time for IO treatment prior to change for toxicity was 3 months (IQR 1.4 – 5.9 months). Significantly more patients with COPD changed treatment due to toxicity (Table). **Conclusions:** Females received a shorter course of IO than males. However, there was no significant difference in the treatment discontinuation rate due to toxicity between males and females receiving IO. Toxicity related treatment change was associated with COPD. Studies with larger sample sizes with more granular data (i.e., type of adverse effects) are needed to truly characterize if a difference between genders and IO toxicity exists. Research Sponsor: U.S. National Institutes of Health.

Analysis of risk factors associated with changing IO due to toxicity.

	Univariable			Multivariable		
	OR	95% CI	p-value	OR	95% CI	p-value
Female	0.908	0.501-1.647	0.752	0.924	0.453-1.885	0.827
Age ≥ 60	1.241	0.688-2.240	0.473	1.409	0.699-2.842	0.338
BMI ≥ 25	0.838	0.426-1.648	0.608	0.760	0.374-1.544	0.448
COPD	2.335	1.045-5.220	0.039	2.491	1.025-6.054	0.044
Combo IO	1.719	0.853-3.466	0.130	2.122	0.951-4.738	0.066

2657 **Poster Session**

Inpatient complications of immunotherapy-associated colitis in solid malignancies: Real-world data analysis. *First Author: Rayli Pichardo, Henry Ford Hospital, Detroit, MI*

Background: Immune checkpoint inhibitors (ICPis) and their containing regimens have been proven beneficial for the treatment of multiple malignancies, while immune-related adverse events (IrAEs) have become constant safety challenges in their clinical management through all ICPi therapies. Diarrhea resulted from immune-mediated colitis has been one of the most common IrAEs. The Aim of this study is to evaluate the real-world incidence and factors that contributed to colitis among patients hospitalized for anti-neoplastic immunotherapy using a large nation-wide database. **Methods:** We performed a retrospective analysis with the National Inpatient Sample (NIS) using ICD10-CM and PCS codes to identify patients with solid tumors hospitalized for immunotherapy between October 2015 and 2018. A comparison analysis was made between patients who developed diarrhea (or colitis) or not during their hospitalizations. Patient characteristics included past medical history, location, charges, length of stay (LOS) and inpatient complications variables, data were compared between the two groups. **Results:** The data from 5,795 admissions for immunotherapy were included, of which 615 (10.61%) inpatient events were complicated by diarrhea (colitis). Patients with diarrhea tended to be males (60%), slightly older at age 57 years, higher percentage of white patients (78%) though not statistically significant from those who did not have colitis. On the other hand, the length of inpatient stay was statistically longer (7 vs 5 days, $p < 0.05$), and associated with higher expenses ($214,612 vs $ 134,195, $p < 0.05$). In addition, inpatient admissions with colitis were more towards larger academic hospitals (80% vs 67%, p = 0.01). ICPi-treated patients with genitourinary (GU) cancers were observed more with colitis among these admissions (27% vs 15%, $p < 0.05$). Though no difference from mortalities observed, serious complications, such as acute kidney injury (AKI) (44% vs 20%, $p < 0.05$) and non-septic shock rates were higher (7% vs 2%, p = 0.01) among colitis admissions. **Conclusions:** This real-world data analysis of inpatient admissions from ICPi-treated cancer patients demonstrated colitis with diarrhea as a common safety concern over ICPi-therapies, a higher risk among patients of GU primaries, higher risk with serious medical complications: acute renal dysfunction and non-septic shock, led to increased length of stays (LOS) and financial burden. Special attention and further study may be placed among ICPi-treated GU cancer patients. Research Sponsor: Henry Ford Cancer Institute.

	No Diarrhea	Diarrhea	p value
Male	62%	60%	0.71
Age	56	57	0.28
LOS	5.14	7.24	**0**
Total Charges	$134,195	$214,612	**0**
Race (White)	66%	78%	0.08
Large Academic Hospital	67%	80%	**0.01**
Cancer type			**0**
Other	66%	41%	
Lung Ca	15%	20%	
GU ca	15%	27%	
Melanoma	4%	13%	
Inpatient complications			
AKI	20%	44%	**0**
Non-Septic Shock	2%	7%	**0.01**
Death	0.48%	0.00%	0.45

2658 **Poster Session**

Association between germ-line HLA and immune-related adverse events. *First Author: Ning Jiang, Department of Radiation Oncology, The Affiliated Cancer Hospital of Nanjing Medical University, Jiangsu Cancer Hospital, Jiangsu Institute of Cancer Research, Nanjing, NC, China*

Background: In recent years, great progress has been made in immune checkpoint inhibitors (ICIs), opening a new chapter for cancer treatment. However, accompanied by remarkable efficacy, immune-related adverse events (irAEs) also arose. Though some pilot studies have explored the possible factors that may influence the development of irAEs, the mechanism of irAEs remains unclear. Previous studies indicated a positive association between certain HLA types and irAEs. To uncover the relationship between irAEs and divergent HLA types, we initiated a large cohort study. **Methods:** We screened 626 patients who have been treated in the clinical research ward, Cancer Hospital of Chinese Academy of Medical Sciences. All participants included should be diagnosed with malignant tumors and have received at least 2 cycles of ICIs with complete security follow-up data in the original electronic medical records. The blood samples were collected before the first cycle of treatment. Sequencing libraries were generated using a customized panel. Six digit formatted HLA alleles were extracted from HLA-HD (v1.4.0) results for further analysis. Fisher-exact test was used to perform association analysis between HLA and different irAEs. To control the type I error, we introduce two external reference groups as well as the non-irAE control group. In addition, false discovery rate (FDR) correction was performed with the resulting p-values when comparing the HLA allele frequency between patients with irAEs and the MHC-han Chinese reference cohort. We also explored the relationship between zygosity of HLA genes, evolutionary divergence of HLA class I genotype (HED) and irAEs. **Results:** Of the 626 participants, 530 received at least 2 doses of ICIs. The median follow-up time was 10.3 months. 97% patients received anti-PD-1/PD-L1 treatment. Of all participants, 78% reported irAEs of any grade, with 10.2% reporting grade 3 and above irAEs. The occurrence of overall irAEs showed no significant difference between homozygous group and heterozygous group. We did not find any significant association between irAEs and HED. We found that some HLA types are associated with irAEs of different organs, including the significant association between HLA-DRB3*01:01 and thrombocytopenia (OR 3.48 (1.19,9.42), p = 0.011), HLA-DPB1*04:02 and hypokalemia/ hyponatremia (OR 3.44 (1.24,9.1), p = 0.009), leukopenia (OR 2.1 (0.92,4.8) , p = 0.037) as well as anemia (OR 2.33 (1.0,5.41) , p = 0.026), HLA-A*26:01 and bilirubin elevation (OR 2.67 (0.92,8.31) , p = 0.037). **Conclusions:** IrAEs in specific organs and tissues may be associated with certain HLA types, while HLA heterogeneity have no significant influence on the happening of irAEs. More research is needed to explore the role of germline genetic changes in the risk assessment of irAEs, and potential therapies targeting irAE-inducing HLA types without influencing the anticancer effect may be considered to benefit the patients. Research Sponsor: None.

2659 **Poster Session**

Dysthyroidism during immune checkpoint inhibitors is associated with improved overall survival in solid tumors: Data-mining of 1,382 electronic patient records. *First Author: Mathilde Beaufils, Institut Paoli-Calmettes, Marseille, France*

Background: Medical treatment of solid tumors cancer has irreversibly changed since the development of immune checkpoint inhibitors (ICI). However, immune-related adverse events (irAE) are challenging in routine practice. Dysthyroidism is the most common endocrine irAE and small series suggest that dysthyroidism might be associated with ICI efficacy. This led us to explore the association between ICI-induced dysthyroidism and overall survival (OS) in a large cohort of solid tumor patients (pts) using data mining of electronic patient records (EPR). **Methods:** ConSoRe is a new generation data analytics solution using natural language processing to search aggregated data and perform advanced data mining. It was used for data extraction from EPR of pts treated with ICI for solid tumors in Institut Paoli-Calmettes (Marseille Cancer Center, France), with validation using manual screening of 28.8% EPR. All dysthyroidism were verified and only dysthyroidism ICI-induced were retained. Survival analyses were performed by Kaplan-Meier method and compared using the log-rank test (survminer R package). In the uni/multivariate analysis, the Cox proportional-hazards model was used to estimate the variables associated with OS, using hazard ratio (HR) and its associated 95% confidence interval. **Results:** Data extraction identified 1,385 pts treated with ICI in 2011-2021. Dysthyroidism was observed in 90 pts (6.5%), including 22 hyperthyroidism (24%), 36 hypothyroidism (40%) and 32 hyperthyroidism and hypothyroidism (36%). In this cohort, 81 % of the dysthyroidism were related to PD(L)-1 inhibitors and 19 % to CTLA-4/ PD(L)-1 inhibitors combination. No statistical difference was observed in term of tumor location between patients with or without dysthyroidism. Dysthyroidism was associated with improved OS (HR=0.46, 95%CI 0.29-0.70, p=0.0005) with a median OS of 65 months (mo) *vs.* 30 mo in patients without dysthyroidism. Survival impact of dysthyroidism was consistent using a 2-mo landmark analysis, fixed on median time to dysthyroidism. In multivariate analysis including sex, age, tumor localization, line numbers and type of ICI, dysthyroidism was independently associated with an improved OS (HR=0.49, 95%CI 0.32-0.75, p=0.001), as presented in the Table. **Conclusions:** Data mining identified a large number ICI-induced dysthyroidism, associated with an improved OS. The onset of dysthyroidism might help oncologist detecting patients more likely to benefit from ICI. Research Sponsor: None.

Characteristic	HR	95% CI	p
Age: >65 vs <65	1.18	0.99, 1.41	0.071
Sex: Female vs Male	0.83	0.68, 1.00	0.051
Dysthyroidism (yes vs no)	**0.49**	**0.32, 0.75**	**0.001**
Tumor localization (ref : lung):			
melanoma	0.87	0.51, 1.50	0.6
bladder	1.21	0.86, 1.70	0.3
kidney	1.00	0.78, 1.29	>0.9
ICI group (ref : anti-PD(L)1)			
anti-CTLA4	1.00	0.58, 1.73	>0.9
ipilimumab/nivolumab	0.65	0.41, 1.04	0.071

2660 **Poster Session**

The impact of pembrolizumab on patients with pre-existing autoimmune diseases. *First Author: Noor Bazerbashi, Houston Methodist Hospital, Houston, TX*

Background: Immune checkpoint inhibitors (ICI) have changed the therapeutic landscape across a range of solid and hematologic malignancies. With the mechanistic activation of the adaptive immune response and known unique development of immune-related adverse effects (irAE), there is a theoretical risk of causing detrimental effects on patients with pre-existing autoimmune diseases (AID). However, this patient population was excluded from many clinical trials, and there is limited and conflicting retrospective data speculating upon the impacts of using ICI therapy in patients with AID. This study aims to report the impact of pembrolizumab in patients with AID. **Methods:** Patients who received pembrolizumab for treatment of any type of cancer between 1/1/2017-8/1/2021 were retrospectively reviewed, and patients with AID (rheumatologic or non-rheumatologic) were identified. Data including age, gender, race, ECOG, and primary cancer diagnosis were collected. AID was characterized by type, activity (symptomatic vs. asymptomatic at ICI initiation), and immunosuppressive treatment (IST) use. Outcomes included flare of AID, irAE, and ICI discontinuation. **Results:** Out of 810 patients, 12 with pre-existing AID were found and being treated for non-small cell lung cancer (NSCLC) (58% N=7), renal cell carcinoma (RCC) (16.6% N=2), colorectal cancer (CRC) (8% N=1), head and neck cancer (8% N=1), and cervical cancer (8% N=1). Around 67% of these patients were females with a median age of 65 years (50-77). Median ECOG was 1 (0-2). 9 patients (75%) had rheumatologic disease (5 rheumatoid arthritis (RA), 1 systemic lupus erythematosus (SLE), 2 psoriatic arthritis, and 1 systemic sclerosis (SS)). 3 patients (25%) had non-rheumatologic AID (1 multiple sclerosis (MS), 1 autoimmune hepatitis, and 1 Evan's syndrome). All patients were asymptomatic prior to initiation of therapy. At the time of ICI initiation, 11 patients (92%) were on therapy, including steroids, methotrexate, and other IST. Due to concern for severe flare, pembrolizumab was discontinued in 3 (25%) MS, RA, and SS patients treated for RCC, CRC, and NSCLC, respectively. 3 patients (25%) developed irAE unrelated to their AID (pneumonitis, dermatitis, arthritis, gastritis) and received steroids. 4 patients (33.3%) had documented flares while on pembrolizumab requiring escalation of their ongoing therapy, and 1 NSCLC patient had a severe exacerbation of SS requiring cyclophosphamide and rituximab infusions. **Conclusions:** This analysis adds to the limited available literature that patients with an AID and on IST appear to have minimal AID-associated flares requiring intervention and tolerate pembrolizumab with a similar rate of irAE compared to patients without AID. Additional larger studies are needed to assess the efficacy of treatment in this population. Research Sponsor: None.

2661 **Poster Session**

Immune-related adverse effects of long-term PD-1/PD-L1 inhibtor treatment. *First Author: Sarah Kim, Stanford Health Care, Stanford, CA*

Background: Immune-related adverse effects (irAE) are autoimmune-like toxicities caused by immune checkpoint inhibitor (ICI) treatment and often necessitate interventions such as corticosteroids, treatment interruptions/discontinuation, or hospital admission. Although ICI related irAEs are well described in literature, data on the toxicity profile associated with long-term ICI use remains limited. Since the optimal duration of therapy with ICI agents is currently unknown, it is crucial to assess the risks of long-term ICI use. **Methods:** This was a retrospective, observational, single-center study of adult oncology patients who received at least 1 year of programed death 1 (PD-1) inhibitor or programmed death ligand-1 (PD-L1) inhibitor treatment. The objective of this study was to characterize late-onset irAEs defined as greater than 1 year with long-term ICI treatment. Clinically significant irAEs were defined as those requiring corticosteroid treatment, hospital admission, treatment interruption or treatment discontinuation. This study included patients who received at least 1 year of nivolumab, pembrolizumab, atezolizumab or durvalumab between January 2016 and September 2021. Disease states included head and neck cancer, renal cell carcinoma, non-small cell lung cancer, and melanoma. Patients with concurrent exposure to other treatment such as chemotherapy, radiation, surgery, tyrosine kinase inhibitors and monoclonal antibodies while on ICI treatment were included in the study. Exclusion criteria included patients with treatment breaks of greater than 6 months, two malignancies undergoing active treatment, and treatment administration outside of the study center. **Results:** Of 282 patients assessed, 143 met study inclusion criteria. The median ICI treatment duration was 19 months (IQR 14-27). There was a 30% incidence of late-onset irAEs, of which 22% were clinically significant. Most late-onset irAEs were low in severity, as 45 (90%) were grade 1-2 and 5 (10%) were grade 3. The most common late-onset irAEs were pulmonary (8%) and gastrointestinal (7%). Univariate analysis suggests risk factors potentially associated with late-onset irAEs include concurrent exposure to additional therapies during ICI treatment and past medical history of rheumatologic disease. **Conclusions:** Although the optimal duration of ICI therapy is unknown, this study suggests that long-term ICI use was associated with a low but notable incidence of toxicities, of which most were low in severity. Research Sponsor: None.

Characterization of late-onset irAEs.

irAE	Incidence N=143 (%)	Median time to onset (months)
Dermatologic	7 (5)	15
Endocrine	7 (5)	17
Gastrointestinal	10 (7)	15
Hematologic	1 (1)	17
Hepatic	6 (4)	22
Ocular	2 (1)	19
Pulmonary	12 (8)	18
Rheumatologic	5 (4)	19

There were no incidences of late-onset cardiovascular, renal, neurologic, or pancreatic irAEs. Seven patients experienced multiple irAEs.

2662 **Poster Session**

Density patterns of tumor-infiltrating lymphocytes and association with objective response to nivolumab in patients with lung adenocarcinoma from CheckMate 057. *First Author: Germán Corredor, Case Western Reserve University, Cleveland, OH*

Background: Immune checkpoint inhibitors (ICIs) are currently approved for use as therapy in advanced stage lung adenocarcinoma (LUAD). ICIs can decrease risk of progression by up to 60% when compared to chemotherapy, but only about 20% of patients (pts) show response. Given that high levels of tumor-infiltrating lymphocytes (TILs) have been shown to be associated with better prognosis, here, we assess whether computationally derived TIL density measures on digitized H&E images can predict RECIST derived response to nivolumab in LUAD in Checkmate 057 (CM057). CM057 is a clinical trial designed to compare the overall survival of metastatic non-squamous non-small cell lung cancer subjects treated with either nivolumab or docetaxel after failing platinum-based chemotherapy. **Methods:** H&E-stained samples of 683 LUAD pts were collected from TCGA (n = 421), University of Bern (UBern) (n = 100), and CM057 (n = 162). Tumor response was assessed using RECIST v1.1. Samples were digitized as whole slide images. 294 pts randomly selected from TCGA formed the training set. The remaining 389 pts were used for validation in response to nivolumab in CM057 and prognosticating overall survival (OS) in UBern and TCGA. Computerized algorithms automatically identified TILs and extracted features related to quantity and compactness of TILs with respect to other surrounding nuclei. The top 6 features, determined by least absolute shrinkage and selection operator, were used to train Cox regression models that assign a death risk score to each patient. Pts with risk scores higher than the training median score were considered "high risk" or "non-responders" while pts with lower scores were considered "low risk" or "responders". **Results:** The classifier predicted objective response in CM057 with an AUC = 0.61. Additionally, survival analysis showed that the model was prognostic for OS with hazard ratios of 2.38 (confidence interval (CI): 1.32-4.29, p = 0.01, n = 127) in TCGA and 2.37 (CI: 1.32-4.25, p < 0.01, n = 100) in UBern. **Conclusions:** A computerized image analysis model based on measurements of TIL density showed association with response to treatment in LUAD pts who received nivolumab and was prognostic of OS. Although the AUC was not high, the results suggest analysis of TILs has potential to identify pts who will respond to treatment. Future work will include training a classifier using response to treatment as endpoint and combining the TIL measures with other biomarkers like TMB or PD-L1. Research Sponsor: U.S. National Institutes of Health, Other Foundation, Other Government Agency.

2663 **Poster Session**

Tumor-infiltrating lymphocyte enrichment predicted by CT radiomic analysis is associated with clinical outcomes of immune checkpoint inhibitor in non–small cell lung cancer. *First Author: Changhee Park, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea*

Background: Enrichment of tumor-infiltrating lymphocytes (TIL) in the tumor microenvironment (TME) is a reliable biomarker of immune checkpoint inhibitors (ICI) in non-small cell lung cancer (NSCLC). Phenotyping through CT radiomics has the overcome the limitations of tissue-based assessment, including for TIL analysis. Here, we objectively assess TIL enrichment using an artificial intelligence-powered H&E analyzer, Lunit SCOPE IO, and analyze its association with advanced quantitative imaging features extracted via radiomic analysis. Clinical significance of the selected radiomic features (RFs) is then validated in independent NSCLC patients who received ICI. **Methods:** In the training cohort, which included 235 NSCLC patients with both tumor tissue and corresponding CT images obtained within 1 month, we extracted 86 RFs from the CT images. From tissue, a patient's TIL enrichment score (TILes) was defined as the fraction of tissue area with high intra-tumoral or stromal TIL density, divided by the whole TME area, as measured on an H&E slide. From the corresponding CT images, the least absolute shrinkage and selection operator model was then developed using features that were significantly associated with TIL enrichment. The CT model was then applied to CT images from the validation cohort, which included 242 NSCLC patients who received ICI as ≥ second line. **Results:** Among the extracted RFs, 22 features were significantly associated with TILes ($p < 0.005$). After excluding features of multicollinearity and/or zero-coefficient, two features, gray level variance (coefficient 1.71×10^{-3}) and low gray level emphasis (coefficient -2.48×10^{-5}), were finally included in the model. The two features were both computed from the size-zone matrix (SZM), the idea of which is to break down a given tumor volume into smaller spatially contiguous compartments of different sizes. In the validation cohort, the patients with high predicted TILes (≥ median) had significantly prolonged progression-free survival compared with those with low predicted TILes (median 3.81 months [95% CI 2.14 – 5.69] versus 1.94 months [95% CI 1.58 – 2.93], hazard ratio 0.69 [95% CI 0.53 – 0.90], p = 0.007). **Conclusions:** This CT radiomics model is able to assess TIL enrichment in TME, which is significantly associated with favorable ICI outcomes in NSCLC. Analyzing the TME through radiomics may overcome limitations of tissue-based analysis and inform clinical decisions, particularly related to use of ICI. Research Sponsor: None.

2664 **Poster Session**

Increased incidence of immune-mediated myocarditis in advanced skin malignancies treated with immune checkpoint inhibitors in the COVID-19 era. *First Author: Allison Gradone, University of Michigan, Department of Internal Medicine, Ann Arbor, MI*

Background: Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of advanced stage skin malignancies. Immunotherapy related adverse events (irAE) are toxicities associated with ICI therapy. Myocarditis is a rare life-threatening irAE. We attempt to characterize cases of myocarditis related to ICI therapy that have occurred since the start of the COVID-19 pandemic. **Methods:** We performed a single-center, retrospective cohort analysis of patients with advanced stage skin cancers who were treated with ICIs and identified cases of ICI-mediated myocarditis. ICI-mediated myocarditis was defined as evidence of myocardial injury in the setting of irAEs and exclusion of cardiovascular causes. Clinicopathologic variables and clinical outcomes were assessed in these patients. **Results:**A review of 361 patients that received ICI from 9/2014 – 10/2019 found 0 cases of ICI-mediated myocarditis. From 11/2019 – 12/2021, an additional 425 patients were identified of whom 11 (2.6%) developed ICI-mediated myocarditis. 10 patients had melanoma and 1 patient had Merkel cell carcinoma. 10/11 patients were male. 9/11 were treated with anti-PD-1 monotherapy and 2/11 were treated with ipilimumab with nivolumab. All patients had elevated high sensitivity troponin (median 361 pg/mL on presentation, reference range 0-19 pg/mL). 11/11 patients presented with elevated CPK (median 1734 IU/L, reference range 38-240 IU/L) and 8/11 presented with elevated AST:ALT ratio (median 1.58:1) on routine screening which prompted further investigation. 1 patient tested positive for COVID-19 13 days after initial biochemical concern for myocarditis, and 5 patients had received COVID-19 vaccines between 2.5-11 months prior to myocarditis onset. All patients were treated with high dose steroids, and 4 were treated with abatacept. 2 patients died within 30 days after diagnosis of myocarditis and 2 patients later died from malignancy progression. 2 patients developed progressive disease and 1 was successfully rechallenged with ICI with no myocarditis recurrence. 2 patients remain on active surveillance, 2 continue on a steroid taper, and 1 was lost to follow up. All patients with at least 5 months of follow up from myocarditis onset (n = 5) had persistently elevated HS-troponin despite normalization of CPK levels. **Conclusions:** In this single center study, we noted an increase in the frequency of ICI-mediated myocarditis in patients with advanced skin cancers during the pandemic era (2.6% vs 0% pre-pandemic) which is higher than reported in the literature (0.04-1.14%). The impact of COVID-19 during this time is suspicious and warrants further investigation. Therefore, we suggest heightened awareness in the COVID-19 era that elevated CPK levels and AST:ALT ratios merits further diagnostic investigation of ICI-mediated myocarditis. Research Sponsor: None.

2665 **Poster Session**

Management of infliximab-refractory immune checkpoint inhibitor gastrointestinal toxicity: A multicenter case series. *First Author: Catriona Harvey, Royal North Shore Hospital, Sydney, Australia*

Background: Immune checkpoint inhibitor (ICI) GI tox (gastritis, enteritis, colitis) is a major cause of morbidity and treatment-related death. Guidelines agree steroid-refractory cases warrant infliximab (IFx); however not all pts respond and best management of IFx-Refractory ICI GI toxicity (IRIGItox) is not clear. **Methods:** We conducted an international multi-centre retrospective case series. IRIGItox was defined as failure of symptom resolution ≤ Gr 1 (CTCAE v5.0) following ≥ 2 IFx doses *or* failure of symptom resolution ≤ Gr 2 after 1 dose. Data were extracted regarding demographics, steroid use, response and survival. Tox was graded at symptom onset and time of IFx failure. Efficacy of IFx refractory therapy was assessed by symptom resolution, time to resolution and steroid wean. **Results:** 78 pts were identified; med age 60 yrs (95% CI 56-65), 56% male. 70 (90%) had melanoma, 55 (71%) had advanced-stage, 60 (77%) received anti-CTLA-4 (with anti-PD1 50, single agent 10). Most had colitis (N=75, 96%) and ≥ Gr 3 tox (N=74, 95%) at symptom onset. Pre-IFx investigation varied: imaging 37%; faecal calprotectin 29%; endoscopy 59%. All pts received Med time to steroid initiation was 3 days (95% CI 2-4). 46 (59%) had primary steroid refractory disease, . Med time from symptom onset to IFx was 18 days (95% CI 12-23), a med 2 (range 1-6) doses of IFx were given, 69 (88%) pts received > 1 IFx dose. Across 78 pts, 105 post IFx treatments were given: calcineurin inhibitors (ciclosporin, tacrolimus, 32); antimetabolites (mycophenolate, azathioprine, 26); non-TNF-α MABs (vedolizumab, ustekinumab, 20); non-targeted anti-inflammatory (mesalazine, 16); non-pharmacological (colectomy 5, faecal transplant 1, photophoresis 1). 4 pts did not receive therapy for IRIGItox. Of these, 2 died of melanoma prior to resolution of tox; 1 had resolution after 4 doses IFx, 1 had recurrent melanoma and flare of tox on PD1 re-challenge. IRIGItox outcomes by post IFx treatment are shown in Table. **Conclusions:** This retrospective case series confirms heterogeneous management of IRIGItox. Non-pharmacological interventions and calcineurin inhibitors appear most likely to result in tox resolution. Calcineurin inhibitors have the shortest time to resolution in responders. Further details on post-IFx management and oncological outcomes will be examined. Research Sponsor: None.

Post IFx treatment (n)	Tox resolution n (%)	If resolved, time to resolution (med (95% CI), days)	If resolved, time to physiological steroid (med (95% CI), days)
All (105)	55 (52)	28 (16-44)	54 (49-67)
Calcineurin inhibitor (32)	22 (67)	14 (8-30)	51 (38-74)
Antimetabolite (26)	12 (46)	18 (10-68)	54 (43-225)
Non TNF-α MAB (20)	8 (40)	66 (50-217)	126 (72-293)
non-targeted anti-inflammatory (16)	7 (44)	41 (10-64)	7 (0-64)
non-pharmacological (7)	5 (71)	28 (22-369)	53 (42-61)
Nil (4)	1 (25)	55*	55*

*Calculated from last dose IFx

2666 **Poster Session**

Evaluating survival following severe immune-related adverse events requiring hospitalization. *First Author: Francis Wright, University of California San Francisco, School of Medicine, San Francisco, CA*

Background: As immune checkpoint inhibitors (CPI) are increasingly approved for the treatment of multiple cancer types, hospitalizations related to severe immune-related adverse events (irAE) will increase in tandem. Here, we identify patients hospitalized due to irAEs and describe survival outcomes across irAE, CPI, and cancer type. **Methods:** We identified patients exposed to CPIs who were hospitalized from 1/2012 to 12/2020 at our tertiary care hospital by computationally extracting data from the electronic health record. We then performed manual chart review to include only confirmed irAE-related hospitalizations. Survival outcomes were analyzed using Kaplan-Meyer survival curves with log-rank tests. **Results:** Of 3137 patients treated with CPIs, 117 were hospitalized for irAEs (cumulative incidence 4%). Of these, 36% had melanoma, 15% had lung cancer, 9% had renal cell carcinoma (RCC), and the rest were distributed across other cancers. The average number of irAE-related hospitalizations per patient was 1.25 (ranging from 1-3). Among 153 irAEs requiring hospitalization, 39% were gastrointestinal (GI) (including hepatitis), 12% endocrine, 12% pulmonary, 12% neurologic, 12% musculoskeletal, 7% cardiovascular, 6% dermatologic, and the rest affected other organs. Across all patients hospitalized for irAEs, median survival following hospitalization was 980 days. Patients with GI and endocrine irAEs had longer median survival (1474 days and median not reached [NR], respectively), while patients with pulmonary irAEs had shorter median survival (64 days) [p=0.002]. Patients with melanoma and RCC had longer median survival (2796 days and NR, respectively), while patients with lung cancer had shorter median survival (165 days) [p=<0.001]. Survival was not significantly different across CPI type [p=0.20]. **Conclusions:** Although hospitalization for severe irAE was rare, these findings suggest that among these patients, survival differs by irAE and cancer type. This real world data can contribute to clinical models that predict the risk of hospitalization and the risk of death due to severe irAEs, which may inform patient counseling and treatment decision-making. Research Sponsor: U.S. National Institutes of Health.

Frequency, survival, and follow up across irAE, cancer, and CPI type for sample sizes greater than ten.

irAE, Cancer & CPI type	Frequency (n)	%	Median Survival (days)	Time at Risk (days)	Survival IQR (days)	Median follow up (days)	Median follow up range (days)
GI irAE	46	39	1,474	38,213	172 - NR	469	3 - 3,304
Endocrine irAE	15	13	NR	10,876	552 - NR	861	60 - 1,699
Pulmonary irAE	14	12	64	3,789	21 - 604	83	10 - 859
Multiple irAEs	24	21	1,958	14,718	85 - NR	420	7 - 2,309
Melanoma	42	36	2,796	47,128	604 - NR	778	2 - 3,304
Lung Cancer	17	13	165	3,432	105 - NR	160	15 - 787
RCC	11	9	NR	7,535	552 - NR	513	85 - 1,787
PD-1 Inhibitor	65	56	789	36,746	113 - NR	430	2 - 2,192
Combination PD-1/ CTLA-4 Inhibitors	40	34	1,476	29,341	181 - NR	558	30 - 2,309

2667 **Poster Session**

Landscape of tumor mutation burden and correlation to clinical outcomes in 1,744 solid cancers. *First Author: Jaeyun Jung, Samsung Medical Center, Seoul, South Korea*

Background: Tumor mutation burden (TMB) has proven clinical utility and efficacy related to immune checkpoint inhibitor (ICI) treatment in different tumor types. However, limited data were available to understand the landscape and matched clinical outcomes to a pan-cancer extent. **Methods:** Target sequencing results, using TruSight Oncology 500, from 1,744 solid cancer between 2019 and 2021 as a part of real-world clinical practice were collected. Matched clinical and histological outcomes, including PD-L1 expression (n= 798) and immunotherapy treatment (n= 400), were analyzed. **Results:** Among the 33 different cancer types, high TMB was observed in 257 patients (14.7%) with a significantly higher incidence observed in carcinoma of unknown origin (33.3%), bladder cancer (32.3%), and small bowel cancer (30.0%). TMB was positively correlated with the degree of mutation in homologous recombination genes (HRD, 0.76) and microsatellite instability (MSI, 0.51). The predictive value of high TMB to ICI treatment seemed to be enhanced when it was combined with PD-L1 expression, showing higher response rates in the PD-L1 high group (63.3%) than in the low group (22.2%). In the patients with high TMB, both longer overall survival (p = 0.015) and progression-free survival (p = 0.020) were observed compared to the patients with low TMB. **Conclusions:** We examined the landscape of TMB in a different type of cancer using clinical-level target sequencing outcomes. High TMB seems to be a promising predictive biomarker of ICI, showing a positive correlation with alteration in other DNA damage response and repair-related genes and additive value to PD-L1, which needs to be validated through further prospective trials. Research Sponsor: None.

2668 **Poster Session**

Immune checkpoint inhibitor–induced diabetes mellitus across NCI trials. *First Author: Zoe E. Quandt, University of California-San Francisco, Division of Endocrinology, San Francisco, CA*

Background: Immune checkpoint inhibitors (CPI) are known to rarely cause new onset diabetes (CPI DM). While rare, this adverse event is quite challenging for patients and clinicians to manage. Therefore, it is important to identify risk factors and clinical characteristics. This is the first comprehensive, multi-institutional study of CPI-DM across multiple agents and cancer types. **Methods:** The NCI Cancer Therapy Program (CTEP) database of adverse events (AEs) was queried for AEs related to diabetes (Grade 3 or 4 hyperglycemia, Acidosis including Diabetic Ketoacidosis (DKA), glucose intolerance and diabetes mellitus) among 6,925 patients who had been treated with a PD-(L)1 inhibitor alone or in combination from 6/2015 to 12/2019. Each AE report was reviewed and classified as due to CPI DM, new onset type 2 diabetes mellitus (T2DM), T2DM exacerbation without medication non-compliance, existing DM with medication non-compliance, or association with steroids (SDM). CPI DM was diagnosed based on: evidence of insulin deficiency either through presentation in DKA or low c-peptide with need for long term basal bolus insulin to maintain euglycemia and/or positive islet autoantibodies. **Results:** In total, there were 82 cases with at least one of these AEs; 41 had CPI-DM, 22 had SDM, 1 had new T2DM, 4 had T2DM exacerbation, 3 had medication noncompliance and 11 had acidosis not attributable to diabetes or had insufficient data. After excluding non-hyperglycemic acidosis, 57.8% had CPI-DM. Furthermore, if not on steroids and in good compliance with diabetes medications, 89.1% had CPI-DM. The incidence of CPI-DM was 0.59%; it was most common on combination PD-1/CTLA-4 inhibitor therapy (0.85%, 15/1767), followed by PD-(L)1 inhibitor monotherapy (0.54%, 18/3354), followed by CPIs combined with additional agents including chemotherapy and targeted agents (0.44%, 8/1804)(p = 0.25). Hospitalization was required for 87.5% of CPI-DM cases with 74.3% of those requiring an inpatient endocrine consult. All but one CPI-DM case had an endocrine consult at as either an inpatient or outpatient. **Conclusions:** While rare, this cohort shows the large health care burden of CPI-DM and that any hyperglycemia, and especially marked hyperglycemia, should be treated as CPI-DM until proven otherwise. Research Sponsor: American Diabetes Association.

	Total (n 41)		PD-(L)1 inhibitor (n 18)		Combination PD-1/ CTLA-4 Inhibitor (n 15)		CPI & non-CPI Agent (n 8)	
	n or Median	% or range	n or Mean	% or range	n or Mean	% or range	n or Mean	% or range
Melanoma	14	34.1	6	33.3	8	53.3	0	0
Lung Cancer (NSCLC & SCLC)	5	12.2	1	5.6	1	6.7	3	37.5
GU Cancer (Renal/ Urothelial/Bladder)	6	14.6	4	22.2	1	6.7	1	12.5
Other Cancer	16	39.0	7	38.9	5	33.3	4	50.0
Any Islet Autoantibody Positive	12	29.3	7 (9 tested)	77.8	5 (9 tested)	55.6	4 (8 tested)	50.0
Prior Thyroid irAE or Pre-CPI hypothyroidism	17	41.5	8	44.4	4	26.7	5	62.5
ICU and/ or insulin drip	29	70.7	12	66.7	11	73.3	6	75.0
Glucose at CPI-DM diagnosis (mg/dL)	650	279-1193	615	279-1037	652	367-1044	733	359-1193

2669 **Poster Session**

A systematic review and meta-analysis of early death (ED) upon immune checkpoint inhibitors (ICI) alone or combined with other non-ICIs treatments as first-line treatment of advanced solid tumors. *First Author: Giuseppe Viscardi, Medical Oncology, Precision Medicine Department, Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy*

Background: An early crossing of the Kaplan-Meier overall survival curves in randomized clinical trials (RCTs) comparing ICI alone to standard treatments has been observed across different cancer types, suggesting the existence of an excess of mortality upon ICI. Whether ED reflects the natural history of the disease or it is a treatment specific phenomenon remains unclear. Therefore, we conducted a metanalysis of RCTs to analyze the association of ICI treatment with ED. **Methods:** PubMed, Embase and Cochrane were searched (until 12/2021) for RCTs comparing 1st-line PD-1/PD-L1 inhibitors +/- CTLA-4 inhibitors (ICI-only group) or the same drugs in combination with other non-ICI therapies (ICI+OT group) (experimental arms) vs non-ICI treatments (control arm) in patients (pts) with advanced solid cancers. ED was defined as death within the first 3 months of treatment. RCTs providing the number of pts in the intention-to-treat (ITT) population who were alive within 0-3 months from randomization were considered eligible. Primary outcome was ED rate both in the ICI-only and in the ICI+OT groups vs control arm. Secondary outcome was to compare ED risk between ICI-only group and ICI+OT group. Further analysis according to PD-L1 level were performed. The ED rates were estimated by risk-ratio (RR) with 95% confidence intervals (CI) and pooled by random effect model. Heterogeneity was assessed by I^2 statistics. **Results:** 56 RCTs (n = 38697 pts) were eligible, 48.2% included pts with thoracic malignancies. In the ICI-only group (18 RCTs, n = 6638 pts) 50.5% of pts received anti-PD-1/PD-L1 monotherapy and 43.4% anti-PD-1/PD-L1 + anti-CTLA-4 agents. In the ICI+OT group (43 RCTs, n = 15421 pts) 80.1% of pts received ICI + chemotherapy. Compared to control arm, risk of ED was significantly higher for pts who received ICI-only therapies (RR 1.27, 95% CI 1.04-155, p = 0.02, I^2: 73%), but significantly lower in ICI+OT group (RR 0.80, 95% CI 0.71-0.89, p < 0.00001, I^2: 36%). Risk of ED was also significantly higher with ICI-only compared to ICI-OT (RR 1.59, 95% CI 1.26-2.00). ED risk was higher upon ICI-only also in pts with high PD-L1 expression (TPS ≥50%, TC or IC 3, CPS ≥10) and, after excluding Keynote-024, this result became statistically significant (7 RCTs, RR 1.54, 95% CI 1.13-2.10, p = 0.007) with I^2 reducing from 63 to 46%. **Conclusions:** Across cancer types ED is a treatment specific phenomenon, increasing with first-line anti-PD-1/PD-L1 +/- CTLA-4 inhibitors and occurring also in pts with high PD-L1 expression, whereas it can be prevented by combining ICI with other non-ICI treatments. Research Sponsor: None.

TPS2670 **Poster Session**

Phase I study of HFB200301, a first-in-class TNFR2 agonist monoclonal antibody in patients with solid tumors selected via Drug Intelligent Science (DIS). *First Author: Alexander I. Spira, Virginia Health Specialists, Fairfax, VA*

Background: Tumor necrosis factor receptor-2 (TNFR2) is expressed on effector CD8+ T cells, CD4+ T cells, T regulatory cells, natural killer cells, and myeloid cells. Targeting TNFR2 is anticipated to yield effective anti-tumor immunity by stimulating T-cell and NK-cell activation and proliferation in the tumor microenvironment. HFB200301 is a first-in-class anti-TNFR2 agonistic monoclonal antibody that triggers both innate and adaptive immune stimulation by binding to a specific epitope on TNFR2. HFB200301 has demonstrated dose-dependent anti-tumor activity in human TNFR2 knock-in mice bearing MC38 and Hepa1-6 syngeneic tumors. **Methods:** HFB200301 is being evaluated in a first-in-human, open-label, multi-center, dose escalation and expansion study in adult patients with advanced solid tumors. A single-cell immune profiling platform, DIS, was deployed to identify unique tumor-infiltrating T cell signatures that could help optimize patient selection for HFB200301 treatment. It is hypothesized that the presence of an effector T cell subpopulation that express both TNFR2 and CD8A in solid tumors may represent a tumor microenvironment favorable to TNFR2 agonism. The following cancer indications have been identified based on the prevalence of a TNFR2 high/CD8 high signature: Epstein-Barr Virus positive (EBV+) gastric cancer, clear cell renal cell carcinoma (ccRCC), cutaneous melanoma, testicular germ cell tumor (TGCT), soft tissue sarcoma (STS), and PD-L1+ cancers: cervical cancer, pleural mesothelioma, lung adenocarcinoma, and head and neck squamous cell carcinoma (HNSCC). The escalation portion of the study explores increasing doses in cohorts of up to six patients, utilizing mTPI-2 design to determine recommended dose(s) for expansion (RDE(s)). Based on pharmacokinetic modeling to maximize HFB200301 activity, 60-minute intravenous infusions of HFB200301 are administered every 4 weeks. Once RDE(s) is determined, expansion into three indication-specific cohorts is planned to determine the recommended phase 2 dose (RP2D). Key eligibility criteria include histologically documented advanced or metastatic solid tumors in the above listed indications. Patient enrollment opened in February 2022 in the USA, with plans for additional clinical sites in Spain and China. The primary objective is to identify the RDE, characterize safety and tolerability of HFB200301, and determine RP2D. Secondary objectives include pharmacokinetic parameters, preliminary evidence of anti-tumor efficacy (e.g., ORR, DCR, DOR) and pharmacodynamic evaluation (e.g., T cell subsets) in the blood and in the tumor. Furthermore, a potential predictive biomarker signature derived based on the DIS single-cell immune profiling approach will be investigated retrospectively. Clinical trial information: NCT05238883. Research Sponsor: HiFiBiO Inc.

TPS2671 **Poster Session**

Trial in progress: A phase 1-2, first-in-human, open label, dose escalation and expansion study of AU-007, a monoclonal antibody that binds to IL-2 and inhibits IL-2Rα binding, in patients with advanced solid tumors. *First Author: James Robert Vasselli, Aulos Bioscience, Larkspur, CA*

Background: AU-007 is a computationally designed, monoclonal antibody that binds to IL-2 on its CD25 binding epitope. AU-007 bound IL-2 (A/IL-2) cannot bind to high affinity trimeric IL-2 receptors (IL-2R) consisting of CD25, CD122, and CD132 expressed on Tregs and vascular endothelium, but its binding to low affinity dimeric IL-2Rs (CD122 and CD132) expressed on T effector and NK cells is unhindered. Thus, AU-007 redirects endogenously produced or exogenous IL-2 (aldesleukin) towards activation of immune stimulating T effector and NK cells, while diminishing Treg activation and expansion. AU-007 will also bind and redirect newly secreted endogenous IL-2 resulting from A/IL-2 driven T cell expansion in the tumor, converting a Treg mediated autoinhibitory loop into an immune stimulating loop. AU-007 is unique in the IL-2 therapeutic field as engineered exogenous, recombinant "non-CD25" IL-2s in development cannot address the autoinhibitory effect of endogenous IL-2. Preclinically, AU-007 has been demonstrated to capture endogenous human IL-2 *in vivo*. AU-007 with a single low dose of IL-2 has demonstrated efficacy in multiple cancer models and has an excellent safety profile in non-human primates. **Methods:** This first-in-human, multicenter, open label Phase 1- 2 study evaluates the safety, tolerability, and initial efficacy of AU-007 +/- aldesleukin in patients with advanced solid tumors (CT-2021-CTN-03938-1). Phase 1 consists of 3 escalation arms each starting with a single 1+2 escalation cohort followed by 3+3 escalation cohorts to define the recommended Phase 2 dose (RP2D) or maximum tolerated dose (MTD). Patients with melanoma, renal cell carcinoma (RCC) and 17 selected solid tumors are eligible. Prior treatment with check point inhibitors is allowed. In Arm A, escalating doses of Q2w AU-007 are evaluated in sequential escalation cohorts. In Arm B, a single dose of aldesleukin is given with the initial AU-007 dose. AU-007 is given at a fixed dose Q2w with an escalating single aldesleukin dose in sequential escalation cohorts. In Arm C, AU-007 is evaluated in combination with aldesleukin, both given Q2w. AU-007 is administered at a fixed dose with an escalating dose of aldesleukin in sequential cohorts. The Phase 2 cohort expansion portion of the study evaluates the initial efficacy at the RP2D defined in escalation cohorts A, B, and C in 3 matching expansion cohorts of up to 20 patients each. Patients with advanced melanoma, RCC and other tumors including, but not limited to, Merkel Cell Carcinoma, NSCLC, and urothelial cancer are eligible. Enrolment to the study commences in Australia, with US sites planned to open later in 2022. Clinical trial information: CT-2021-CTN-03938-1. Research Sponsor: Aulos Bioscience.

TPS2672 **Poster Session**

A phase 1/2a open label, multicenter study to assess the safety, tolerability, pharmacokinetics, and efficacy of AFM24 in patients with advanced solid cancers: Study design and rationale. *First Author: Omar Saavedra Santa Gadea, Vall d'Hebron University Hospital and Institute of Oncology (VHIO), Barcelona, Spain*

Background: AFM24 is a first-in-class, tetravalent, bispecific, fragment crystallizable-silenced antibody that targets epidermal growth factor receptor-expressing (EGFR+) solid tumors. Of its 4 binding sites, 2 are specific for EGFR, and 2 are specific for CD16A, the Fcγ receptor expressed by natural killer (NK) cells and macrophages. The primary mode of action of AFM24 is not to inhibit EGFR signaling, but to redirect NK cells and macrophages to EGFR+ tumor cells to induce antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP), respectively. Preclinical studies showed AFM24 induced killing of EGFR+ tumor cell lines, and the activity was independent of EGFR cell surface expression level. A favorable safety profile was also demonstrated in cynomolgus monkeys. Therefore, AFM24 may utilize the patients' innate immunity to redirect and activate immune cells, overcoming resistance to current therapies and offering a favorable safety profile. An ongoing Phase 1/2a, first-in-human study (NCT04259450) is evaluating AFM24 in patients with locally advanced or metastatic, treatment refractory solid tumors that are known to express EGFR. The Phase 1 dose escalation study was designed to establish the maximum tolerated dose and/or the recommended Phase 2 dose (RP2D) of AFM24 and evaluated the safety, efficacy, immunogenicity, pharmacokinetic (PK) and pharmacodynamic (PD) responses. AFM24 was administered intravenously once weekly until disease progression, intolerable toxicity, patient withdrawal, or termination at the investigator's discretion. AFM24 had a well-managed safety profile and the RP2D was established. **Methods:** In parallel to the continuing dose escalation phase, the Phase 2a dose expansion study was initiated, and the first patient was enrolled in January 2022. This study will assess AFM24 at the RP2D of 480 mg in patients with different EGFR-expressing tumors and will follow a Simon's two-stage design; the trial will progress to the second stage unless the null hypothesis, that the true tumor response rate is below a specified value, is confirmed at the end of stage one. Eligible patients must have positive histological or cytological staining of EGFR in > 1% of tumor cells. The primary endpoint is to establish the overall response rate (assessed by the investigator per RECIST v1.1) in three disease-specific cohorts. These comprise patients with clear cell renal cell carcinoma (ccRCC), KRAS wild-type colorectal cancer (KRASwt CRC), and EGFR-mutant non-small cell lung cancer (EGFRmut NSCLC). Secondary endpoints include treatment-emergent adverse events, serious adverse events, PK, PD, and immunogenicity. Clinical trial information: NCT04259450. Research Sponsor: Affimed GmbH.

TPS2673 **Poster Session**

AFM24 in combination with atezolizumab in patients with advanced EGFR-expressing solid tumors: Phase 1/2a study design and rationale. *First Author: Omar Saavedra Santa Gadea, Vall d'Hebron University Hospital and Institute of Oncology (VHIO), Barcelona, Spain*

Background: Innate Cell Engagers (ICE) are bispecific molecules that bind both a tumor cell-surface antigen and to CD16A expressed on natural killer (NK) cells and macrophages, inducing antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP), respectively. As epidermal growth factor receptor (EGFR) is often overexpressed in several types of solid tumors, this provides an ideal tumor-cell surface antigen which may be targeted using ICE molecules. AFM24 is a first in class, tetravalent, bispecific, novel ICE targeting EGFR. By binding to EGFR on tumor cells and CD16A on innate immune cells, AFM24 may utilize a patient's innate immunity to induce ADCC/ADCP towards tumor cells. Anti-programmed death-ligand 1 (PD-L1) immune checkpoint inhibitors, which enhance the anti-tumor activity of a patient's adaptive immunity, have also demonstrated efficacy as monotherapy and are playing an increasingly prominent role in treatments. The combination of AFM24 and the PD-L1 inhibitor, atezolizumab, may therefore represent a rational new treatment modality, enhancing both the innate and adaptive immune responses to target EGFR+ tumor cells. **Methods:** An ongoing Phase 1/2a open-label, non-randomized, multicenter, dose escalation (Phase 1) and dose expansion (Phase 2a) study was initiated in November 2021 (NCT05109442) to evaluate the safety, tolerability and efficacy of AFM24 in combination with atezolizumab. The primary aim of the Phase 1 study is to determine the maximum tolerated dose and the recommended Phase 2 dose (RP2D) of AFM24. Eligible patients must have advanced histologically confirmed EGFR+ disease and confirmed disease progression after treatment with ≥1 prior therapy. Patients undergo a safety lead-in phase with AFM24 as a single agent 7 days before receiving the combination therapy. A standard 3+3 design will be used to determine the RP2D. Escalating doses of AFM24 will be given to each cohort as weekly intravenous (IV) infusions; the starting dose and at least two planned dose escalations are based on results from the ongoing AFM24 monotherapy trial (NCT04259450). Atezolizumab will be given at a fixed dose of 840 mg as a biweekly IV infusion. Patients will receive AFM24 and atezolizumab treatment until disease progression, intolerable toxicity, patient withdrawal, or termination at the investigator's discretion. The Phase 2a study will then establish the overall response rate (as per RECIST v1.1) and safety of combination therapy in patients with advanced/ metastatic, or treatment refractory gastric, esophagogastric, hepatocellular, hepatobiliary, pancreatic, or non-small cell lung cancer. For both phases, secondary endpoints include treatment-emergent adverse events, serious adverse events, pharmacokinetics, pharmacodynamics, and immunogenicity. Clinical trial information: NCT05109442. Research Sponsor: Affimed GmbH.

TPS2674 **Poster Session**

A non-inferiority randomized phase III trial of standard immunotherapy versus reduced dose intensity in responding patients with metastatic cancer: MOIO study. *First Author: Gwenaelle Gravis, Department of Medical Oncology, Institut Paoli-Calmettes, Aix-Marseille Universite, CRCM, Marseille, France*

Background: Immunotherapy (IO) is increasingly used for treating various metastatic cancers. With respect to the pharmacologically-active levels of IO drugs and their pharmacokinetics features, standard scheduling lead to plasma exposures largely exceeding the thresholds associated with target engagement. Indeed, phase I studies have shown that saturation of the target can persist far beyond the serum IO drugs half-life. *In silico* modeling has suggested that alternate scheduling (i.e. 3-monthly dosing) could be performed without compromising efficacy. Indeed, prolonged IO half-lives, time-varying clearance plus plasma concentrations far above the threshold associated with maximal target-engagement, suggest that the rhythm of IO administration could be slowed down. A phase II showed that extending IO dosing intervals did not compromise efficacy, while reducing toxicity in metastatic renal cell cancer. **Methods:** This non-inferiority, randomized, French national multicenter (36 centers involved) phase III study (NCT05078047) aims to compare the standard scheduling of a variety of IO drugs VS. 3-monthly scheduling in adult patients with metastatic cancer in partial (PR) or complete response (CR) after 6 months of standard IO dosing (except melanoma in CR). The main objective is to demonstrate the non-inferiority in Progression-Free Survival (PFS) of the reduced intensity group compared to the standard regimen. Secondary objectives are cost-effectiveness, quality of life, anxiety and fear of relapse, response rate, overall survival, and toxicity. A 1:1 randomization by minimization will be conducted on the following stratification factors: therapy line (first line vs others), tumor type, IO type (anti-PD-1 vs anti-PD-L1) and response status (PR, CR). A total of 646 pts will be randomized to get the 498 events necessary to prove non-inferiority between groups. The main analysis will conclude that reduced dose intensity is non-inferior to standard scheduling if the hazard ratio for PFS, estimated by a Cox model after adjustment for stratification factors, is significantly lower than the predefined 1.30 non-inferiority margin. In order to minimize the number of patients exposed to suboptimal treatment, an independent data monitoring committee will specifically review the efficacy data and recommend the early termination of the trial if lack of efficacy is evidenced. Ancillary studies of pharmacokinetics and immune-monitoring will be conducted to provide mechanistic insights supporting the clinical outcomes observed in both groups. **Conclusion** Should the hypothesis of non-inferiority with an IO reduced dose intensity be validated, alternate scheduling could preserve efficacy while being cost-effective and allowing a reduction of the toxicity, with an increase in patient's quality of life. Clinical trial information: NCT05078047. Research Sponsor: Institut National du Cancer France.

TPS2675 **Poster Session**

The combination of CD16A/EGFR innate cell engager, AFM24, with SNK01 autologous natural killer cells in patients with advanced solid tumors. *First Author: Anthony B. El-Khoueiry, University of Southern California, Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: Natural killer (NK) cells are a critical component of the innate immune system involved in the eradication of transformed cells via antibody-dependent cellular cytotoxicity (ADCC). For treatment of solid tumors autologous NK cell transfer represents a promising treatment strategy, with *ex vivo* expansion and activation enhancing the specificity and anti-tumor activity of NK cells. The efficacy of this approach may be enhanced through the addition of tumor-targeting antibodies, augmenting NK cell-mediated ADCC. Innate Cell Engagers (ICE) are bispecific antibodies that target a tumor cell-surface antigen and bind to CD16A expressed on NK cells. AFM24 is a novel ICE that targets epidermal growth factor receptor (EGFR), which is often overexpressed in solid tumors. The Phase 1 study of AFM24 monotherapy showed patients had a manageable safety profile, and SNK01 monotherapy has also shown to be well-tolerated in patients with rapidly progressive solid tumors. This study seeks to investigate AFM24 in combination with SNK01 autologous NK cells in patients with advanced EGFR+ solid tumors. **Methods:** An ongoing Phase 1/2a open-label, non-randomized, multicenter, dose escalation (Phase 1) and dose expansion (Phase 2a) study was initiated in November 2021 (NCT05099549) to evaluate the safety, tolerability and efficacy of AFM24 in combination with SNK01 NK cells in EGFR+ solid tumors. The primary aim of the Phase 1 study is to determine the maximum tolerated dose and/or recommended Phase 2 dose (RP2D) of AFM24 in combination with SNK01 at a fixed dose NK cells using a standard 3+3 design. Eligible patients must have advanced or metastatic disease with positive immunohistochemical staining for EGFR in >1% of tumor cells and be refractory to standard-of-care treatment. Treatment begins with a safety lead-in phase with a single dose of AFM24 7 days prior to combination therapy. AFM24 will be administered at an escalating dose as weekly intravenous (IV) infusions; the starting dose (160 mg) and dose escalations for each cohort are based on results from the ongoing AFM24 monotherapy trial (NCT04259450). SNK01 NK cells will be given at a fixed dose (4.0 x10^9 cells) as a weekly IV infusion concomitantly with AFM24. Patients will receive combination therapy until disease progression, intolerable toxicity, patient withdrawal or termination at the investigator's discretion. Phase 2 will then establish the overall response rate (as per RECIST v1.1) of combination therapy in patients with treatment refractory, advanced or metastatic squamous cell carcinoma of the head and neck, non-small cell lung cancer, or colorectal cancer as the primary endpoint. Efficacy will also be assessed by assessing progression-free and overall survival. Secondary endpoints for both phases include treatment-emergent adverse events, serious adverse events, pharmacokinetics and immunogenicity. Clinical trial information: NCT05099549. Research Sponsor: Affimed GmbH and NKGen Biotech, Inc.

TPS2676 **Poster Session**

BASECAMP-1: Leveraging human leukocyte antigen (HLA) loss of heterozygosity (LOH) in solid tumors by next-generation sequencing (NGS) to identify patients with relapsed solid tumor for future logic-gated Tmod CAR T-cell therapy. *First Author: Diane M. Simeone, Department of Surgery, New York University Langone Health, New York, NY*

Background: Solid tumors comprise > 90% of cancers. Metastatic colorectal cancer, non-small cell lung cancer, and pancreatic cancer are among the leading causes of cancer-related mortality (5-year overall survival: 14%, 6%, and 3%, respectively) (ACS. 2021). Chimeric antigen receptor (CAR) T-cell therapy has demonstrated clinical efficacy in hematologic malignancies (Neelapu S. et al. *N Engl J Med*. 2017). Translating engineered T-cell therapies to solid tumors has proven to be challenging due to a lack of tumor-specific targets that can discriminate cancer cells from normal cells. Previous studies using carcinoembryonic antigen (CEA) T-cell receptors and mesothelin (MSLN) CARs resulted in dose-limiting on-target, off-tumor toxicities (Parkhurst M, et al. *Mol Ther*. 2011; Tanyi J. Cellicon Valley '21). To create a therapeutic safety window, Tmod CAR T-cell therapy utilizes dual-signaling receptors to create a robust NOT logic gate capable of killing tumor cells, while leaving healthy cells intact (Hamburger A, et al. *Mol Immunol*. 2020). The 2 receptors in Tmod CAR T-cell therapy comprise an activator that recognizes an antigen on the surface of tumor cells that may also be present on normal cells, such as CEA and MSLN, and a blocker that recognizes a second surface antigen from an allele lost only in tumor cells. The frequency of HLA LOH among advanced GI solid tumor cancers in the Tempus real-world dataset is 16.3% with a range of 15.6%-20.8% between colorectal, pancreatic, and gastroesophageal tumors (Hecht R. et al. ASCO-GI 2022. Abstract #190). As such, HLA LOH offers a definitive tumor versus normal discriminator target for CAR T-cell therapy. Different activator/blocker combinations can be engineered with the Tmod platform technology and may be applied to T cells and natural killer cells in autologous and allogeneic settings. BASECAMP-1 is a currently enrolling observational study with key objectives of 1) To identify patients with somatic HLA LOH eligible for Tmod CAR T-cell therapy, and 2) To obtain leukapheresis and feasibility for the future EVEREST Tmod CAR T-cell trial. **Methods**: BASECAMP-1 (NCT04981119) patient eligibility has 2 parts: 1) Patients will be initially screened to identify germline HLA-A*02 heterozygosity by central NGS. If HLA-A*02 heterozygosity is confirmed, primary archival tumor tissue will be analyzed for somatic mutations by xT-Onco NGS testing. 2) If the tumor demonstrates HLA-A*02 LOH and the patient is eligible after screening, the patient will undergo leukapheresis. Banked T cells will be available for the autologous EVEREST Tmod CAR T-cell therapy interventional study to reduce waiting time at relapse. Clinical trial information: NCT04981119. Research Sponsor: A2 Biotherapeutics.

TPS2677 **Poster Session**

A phase 1, first-in-human (FIH) study of adenovirally transduced autologous macrophages engineered to contain an anti-HER2 chimeric antigen receptor (CAR) in participants with HER2 overexpressing solid tumors. *First Author: Kim Anna Reiss, University of Pennsylvania Abramson Cancer Center, Philadelphia, PA*

Background: Adoptive T cell therapies have led to remarkable advances among patients with hematologic malignancies, but have had less success in those with solid tumors. Macrophages are actively recruited and abundantly present in the solid tumor microenvironment (sTME). Tumor associated macrophages are predominantly immunosuppressive and support tumor growth (M2), while a subset of proinflammatory macrophages enhance anti-tumor immunogenicity (M1). M1 macrophage function can be augmented by CAR expression to selectively recognize and phagocytose antigen overexpressing cancer cells. Moreover, CAR macrophages can reprogram the sTME and present neoantigens to T cells, leading to epitope spreading and anti-tumor immune memory. Human Epidermal Growth Factor Receptor 2 (HER2) overexpression promotes tumorigenesis in many solid tumors (Table). CT-0508 is a cell product comprised of autologous monocyte-derived proinflammatory macrophages expressing an anti-HER2 CAR. Pre-clinical studies have shown that CT-0508 induced targeted cancer cell phagocytosis while sparing normal cells, decreased tumor burden, prolonged survival, and were safe and effective in a semi-immunocompetent mouse model of human HER2 overexpressing ovarian cancer. **Methods:** This Phase 1, FIH study is evaluating safety, tolerability, cell manufacturing feasibility, trafficking, and preliminary evidence of efficacy of investigational product CT-0508 in 18 participants (pt) with locally advanced (unresectable) or metastatic solid tumors overexpressing HER2. Pt previously treated with available therapies, including anti-HER2 therapies, as indicated, and subsequent progression are permitted. Filgrastim is used to mobilize autologous hematopoietic progenitor cells for monocyte collection by apheresis. CT-0508 is manufactured, prepared, and cryopreserved from mobilized peripheral blood monocytes. Group 1 pt (n=9) receive CT-0508 infusion split over D1, 3, and 5. A Safety Review Committee will review dose limiting toxicities. Group 2 pt (n=9) will receive the full CT-0508 infusion on D1. Pre- and post-treatment biopsies and blood samples will be collected to investigate correlates of safety (immunogenicity), trafficking (RNA scope), CT-0508 persistence in blood and in the tumor, target antigen engagement, TME modulation (single cell RNA sequencing), immune response (TCR sequencing) and others. Radiographic imaging is also being conducted to assess preliminary tumor activity. Clinical trial information: NCT04660929. Research Sponsor: Carisma Therapeutics.

HER2 overexpression across tumor types.

Tumor	HER2 Overexpression (%)
Bladder	8 - 70
Salivary duct / mucoepidermoid	30 – 40 / 17.6
Gastric	7 - 34
Ovarian / Cervical / Uterine	26 / 2.8 – 3.9 / 3
Breast	11 - 25
Esophageal	12 - 14
Gallbladder / Cholangiocarcinoma	9.8 – 12.8 / 6.3 - 9
Colorectal	1.6 - 5
Testicular	2.4

TPS2678 **Poster Session**

A phase I trial of T-cell receptor gene therapy targeting KK-LC-1 for gastric, breast, cervical, lung and other KK-LC-1 positive epithelial cancers. *First Author: Scott Norberg, National Cancer Institute, Bethesda, MD*

Background: T cell receptor (TCR)-T cell therapy is an emerging cancer treatment strategy. Thus far, demonstration of clinical activity has been limited to a subset of solid tumors including melanoma, synovial cell sarcoma and HPV-associated cancer. It is estimated that metastatic epithelial cancers are responsible for approximately 90% of cancer deaths in the United States. The estimated 600,000 cancer deaths each year is driven largely by lung adeno- and squamous cell carcinoma and invasive breast cancer, which account for approximately 30% of all cancer-related deaths. Kita-Kyushu Lung Cancer Antigen 1 (KK-LC-1) is a cancer germline antigen with expression restricted to germ cells in adults and certain epithelial cancers including lung, breast, gastric and cervical. We identified a KK-LC-1 TCR from the tumor-infiltrating lymphocytes (TIL) of a patient with cervical cancer who had a complete tumor response to TIL therapy. The KK-LC-1 TCR was the most dominate clonotype in the infused TIL product and persisted in the peripheral blood following infusion, suggesting that it may have contributed to cancer regression in this patient. **Methods:** We are conducting a phase I cell dose escalation trial to test the safety and efficacy of KK-LC-1 TCR-T cell therapy in patients with metastatic KK-LC-1 positive epithelial cancer. Patients receive a lymphocyte depleting conditioning regimen followed by a one-time infusion of genetically engineered T cells expressing the KK-LC-1 TCR (KK-LC-1 TCR-T cells) and high-dose systemic aldesleukin. KK-LC-1 positivity is determined by RNAscope assay measuring the percentage of cancer cells expressing CT83 (gene encoding KK-LC-1) with a percentage of 25 or greater considered positive. Main inclusion criteria include HLA-A*01:01 allele, prior first-line therapy, ECOG of 0 or 1 and adequate organ and hematologic function. Main exclusion criteria include active major medical illness of the cardiovascular, respiratory or immune system, primary or secondary immunodeficiency and autoimmune disease. Participants will be entered in sequential dose levels and receive escalating doses of cells beginning at $1x10^8$ and ending with $6x10^{10}$. Dose-limiting toxicities will be assessed during the first 30 days of cell infusion. The primary objective is to determine the maximally tolerated dose of KK-LC-1 TCR-T cells. Exploratory objectives include assessing the safety and efficacy of KK-LC-1 TCR-T cells and to conduct immunologic studies to understand and improve the administered treatment. Clinical trial information: NCT05035407. Research Sponsor: U.S. National Institutes of Health.

TPS2679 **Poster Session**

First-in-human phase 1/2 study of autologous T cells engineered using the Sleeping Beauty System transposon/transposase to express T-cell receptors (TCRs) reactive against cancer-specific mutations in patients with advanced solid tumors. *First Author: Marcelo Vailati Negrao, Department of Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: In 2022 approximately 1.7 million Americans will die from solid cancers. Recently there have been significant advances in the genetic engineering of T lymphocytes to recognize neoantigens on tumors in vivo, resulting in remarkable cases of tumor regression and remission. Cancer cells frequently harbor *KRAS, TP53,* and *EGFR* somatic hotspot mutations that can be processed and presented by tumor HLA as neoantigens to T cells through their T-cell receptor (TCR). These neoantigens are not present in the normal tissues; thus, they are attractive targets for adoptive T cell therapy. Given the number and complexity of different neoantigen/HLA combinations on solid tumors, a TCR library approach is warranted. Therefore, we have developed a library of TCR-T cell therapies including those targeting shared *KRAS, TP53* and *EGFR* mutations. **Methods:** Patients for whom a TCR matching the subject's somatic mutation(s) and HLA type is available in our TCR library, and have progressive or recurrent disease following standard therapy are eligible for enrollment on this protocol. Patients with the following tumor types will be enrolled: ovarian, endometrial, colorectal, pancreatic, cholangiocarcinoma, and non-small cell lung cancer. This first-in-human study includes Screening, Pre-Treatment, Treatment and Follow-up Periods. During the Pre-Treatment Period, subjects will undergo apheresis for PBMCs isolation. The PBMCs will be transposed using the *Sleeping Beauty* system to express the subject's mutation specific TCR. Bridging therapy after apheresis is allowed once the apheresis product has been accepted. During the Treatment Period, patients will undergo lymphodepletion with cyclophosphamide and fludarabine. After which, the TCR-T cell drug product will be administered to the subject by infusion at the assigned dose level. The starting dose level of Arm A (monotherapy) will be DL1 ($5 x10^9$ TCR+ Cells) administered on Day 0. Dose escalation will continue utilizing the accelerated BOIN design (planned escalation dose levels: $5 x10^9$, $4 x10^{10}$ and $1 x10^{11}$ TCR+ Cells). In Arm B, if initiated by protocol, subjects will also receive aldesleukin (interleukin-2) infusion starting on Day 0 (within 24 hours of TCR-T cell product infusion) at 720K IU/kg, every eight hours for up to 4 days. The Follow-up Period will begin after the subject completes their Day 28 visit. Clinical and radiologic response will be assessed at 6 and 12 weeks after TCR-T cell drug product infusion and every 12 weeks thereafter until up to 2 years or study discontinuation (e.g., disease progression, initiation of new anti-cancer therapy, consent withdrawn), whichever occurs first. All subjects will continue to be followed in the Long-Term Follow-up Protocol for up to 15 years post-TCR-T cell drug product infusion. Clinical trial information: NCT05194735. Research Sponsor: Alaunos Therapeutics.

TPS2680 **Poster Session**

A phase 1/2 study of RTX-224, an engineered red blood cell expressing 4-1BB ligand and membrane-bound IL-12, for the treatment of patients with select advanced solid tumors. *First Author: Alexander I. Spira, NEXT Oncology - Virginia Cancer Specialists, Fairfax, VA*

Background: RTX-224 is a genetically engineered off-the-shelf, allogeneic red blood cell that expresses the costimulatory molecule 4-1BB ligand (4-1BBL) and cytokine interleukin-12 (IL-12) on the cell surface. The use of 4-1BB and IL-12 agonists for cancer immunotherapy has been limited due to systemic toxicities. Unlike agonist antibodies and recombinant cytokines, which are distributed systemically, Red Cell Therapeutics, such as RTX-224, are restricted to the vasculature and spleen, which may limit toxicities previously observed with agonist 4-1BB monoclonal antibodies and recombinant IL-12. RTX-224 is designed to be a broad immune agonist of both adaptive and innate responses that activates and expands effector and memory CD8+ and CD4+ T cells, cytotoxic natural killer (NK) cells and produces inflammatory cytokines and chemokines, leading to enhanced antigen presentation. In preclinical studies, the combined activation of both adaptive and innate immune responses by the murine surrogate of RTX-224 led to antitumor activity while the restricted biodistribution improved the safety profile. **Methods:** The RTX-224-01 study is a Phase 1/2, first-in-human, multi-center, dose-escalation and expansion study of RTX-224 in patients with relapsed or refractory urothelial cancer, squamous cell carcinoma of the head and neck, non-small cell lung cancer, triple negative breast cancer and cutaneous melanoma. Safety, tolerability, pharmacokinetics and pharmacodynamics and anti-tumor activity of RTX-224 will be assessed. Approximately 28 patients will be enrolled across dose level cohorts to identify the recommended Phase 2 dose (RP2D). The starting dose is 100 million ($1x10^8$) cells administered intravenously every 3 weeks (Q3W) and the dose will be escalated by half-log increments following a Bayesian logarithmic regression model (BLRM) with overdose control. Following RP2D selection, each of the 5 expansion cohorts will enroll approximately 20 patients. Pharmacodynamic and exploratory biomarker studies correlative to clinical response will be evaluated on peripheral blood and paired tumor biopsies. Multiple technologies will be employed to profile the innate and adaptive responses following RTX-224 treatment. The study is open and enrolling patients in Phase 1. Clinical trial information: NCT05219578. Research Sponsor: Rubius Therapeutics, Inc.

TPS2681 **Poster Session**

ZENYTH-ESO: Master protocol to assess the safety and recommended phase II dose of next generation NY-ESO-1-specific TCR T-cells in HLA-A*02 patients with synovial sarcoma and myxoid/round cell liposarcoma [Substudy 3, GSK4427296]. *First Author: Dejka M. Araujo, University of Texas MD Anderson Cancer Center, Department of Sarcoma Medical Oncology, Houston, TX*

Background: Letetresgene autoleucel (lete-cel; GSK3377794) is an autologous T-cell therapy expressing an affinity-enhanced T-cell receptor (TCR) to improve recognition of cancer cells expressing NY-ESO-1 and/or LAGE-1a. Next generation NY-ESO-1 TCR T-cell therapy, GSK4427296, utilizes the same TCR as lete-cel, as well as an epigenetic reprogramming process (Epi-R) developed by Lyell Immunopharma to alter the phenotypic T-cell profile of the manufactured product, and is intended to increase the proportion of cells with properties of durable stemness. T cells with properties of durable stemness are able to proliferate, persist, and self-renew with anti-tumor functionality. A first-time-in-human master protocol (NCT04526509) is underway to evaluate the safety, tolerability, and recommended phase II dose (RP2D) of next generation NY-ESO-1 TCR T-cell therapies. Substudy 3 is added to this master protocol to assess GSK4427296 in patients with advanced synovial sarcoma (SS) or myxoid/round cell liposarcoma (MRCLS). **Methods:** This substudy includes a dose confirmation stage to assess RP2D and a dose expansion stage, aiming to dose 10 participants at the RP2D. Key inclusion criteria: age ≥18 years; measurable disease per RECIST v1.1; HLA-A*02:01, A*02:05, or A*02:06 positivity; NY-ESO-1/LAGE-1a tumor expression; advanced (metastatic/unresectable) SS with t(X;18) translocation or MRCLS with a translocation involving *DDIT3* and/or *FUS* and/or *EWSR1* genes; and anthracycline-based therapy receipt/completion/intolerance. Key exclusion criteria: prior malignancy that is not in complete remission or clinically significant systemic illness; prior receipt of gene or allogenic stem cell/solid organ transplant; and central nervous system metastases. Primary endpoints: safety (adverse events) and tolerability (dose-limiting toxicities). Secondary endpoints: investigator-assessed overall response rate, duration of response, maximum transgene expansion (C_{max}), T_{max}, and $AUC_{(0\text{-}t)}$. Analyses will be descriptive. The master protocol is open for recruitment. Clinical trial information: NCT04526509. Research Sponsor: GlaxoSmithKline; GSK4427296 produced by and used in collaboration with Lyell Immunopharma.

TPS2682 **Poster Session**

NEBULA: A multicenter phase 1a/b study of a tumor-selective transgene-expressing adenoviral vector, NG-641, and nivolumab in patients with metastatic or advanced epithelial tumors. *First Author: Thomas Lillie, PsiOxus Therapeutics Ltd, Abingdon, United Kingdom*

Background: Tumor-Specific Immuno Gene Therapy (T-SIGn) vectors are next-generation transgene-armed variants of the adenoviral vector enadenotucirev that selectively replicate in epithelial tumor cells. T-SIGn vectors are blood-stable, allowing IV delivery to be coupled with local transgene expression in the tumor microenvironment (TME), thereby targeting all lesions while limiting systemic exposure. The T-SIGn vector NG-641 encodes four immunostimulatory transgenes: fibroblast activation protein-directed bi-specific T-cell activator antibody to target cancer-associated fibroblasts (CAFs), IFNα2 to promote innate and adaptive immune responses, and CXCL9/10 to induce T-cell infiltration. Through this novel multimodal combination of immunostimulatory effects NG-641 is designed to re-program the TME to allow functional anti-cancer immune responses. In the ongoing STAR study (NCT04053283), NG-641 has been successfully dose-escalated to 1×10^{12} viral particles (vp) on Day 1 and 3×10^{12} vp on Days 3 and 5, with promising preliminary safety/tolerability and pharmacodynamic results. Based on these encouraging preliminary data with NG-641 monotherapy, we designed a new study to assess NG-641 + nivolumab. **Methods:** NEBULA (NCT05043714) is an open-label, dose-escalating, phase 1a/b study of NG-641 + nivolumab in patients (pts) with advanced/metastatic epithelial tumors that have progressed after ≥1 line of systemic therapy and are incurable by local therapy. Pts are eligible for phase 1a if they have received prior PD-1/PD-L1 inhibition as part of any line of therapy. During phase 1a, up to 30 pts will receive escalating doses of IV NG-641 to a maximum dose of 1×10^{12} viral particles (vp) on Day 1 and 1×10^{13} vp on Days 3 and 5 (1 cycle; Bayesian Optimal Interval design). Pts will receive a fixed-dose of nivolumab (480 mg IV) on Day 15 and then every 4 weeks thereafter for up to 8 cycles. In phase 1b, the recommended dose regimen will be further studied in patients with primary resistance to PD-1/PD-L1 inhibition; patients will be enrolled in up to 3 tumor-specific cohorts (Cohorts A-C; Simon 2-stage design). Co-primary objectives are to characterize the safety and tolerability of NG-641 + nivolumab and to identify a recommended dose. Preliminary efficacy and immunogenicity are secondary endpoints. Pharmacodynamic outcomes will also be assessed. Viral replication, transgene expression, immune/inflammatory responses and effects on CAFs by IHC and gene expression analysis will be analyzed using tumor tissue from serial biopsies (taken at baseline and Day 15 of cycles 1-3 [cycles 1-2 only in Phase 1b]). Serial blood samples will be analyzed to study cytokine production and changes in peripheral immune cell subsets. Enrollment to the first dose-escalation cohort is ongoing. Clinical trial information: NCT05043714. Research Sponsor: Funded by PsiOxus Therapeutics Ltd, in collaboration with Bristol Myers Squibb.

TPS2683 **Poster Session**

Davoceticept (ALPN-202), a PD-L1-dependent CD28 costimulator and dual checkpoint inhibitor, in combination with pembrolizumab in patients with advanced malignancies (NEON-2). *First Author: Amita Patnaik, START, San Antonio, TX*

Background: Despite successes with checkpoint inhibition (CPI) in a wide range of tumors, most demonstrate primary or acquired resistance, warranting better therapeutic strategies. PD-1 is now recognized to effect much of its benefit by disinhibiting CD28 signaling – a mechanism expected to require intra-tumoral engagement of CD28 by its ligands CD80/CD86. Davoceticept (ALPN-202), a variant CD80 vIgD-Fc fusion protein, was engineered to provide tumor localizing PD-L1-dependent CD28 agonism, while inhibiting PD-L1 and CTLA-4. Davoceticept has demonstrated superiority to CPI-only therapies in both in vitro and in vivo tumor models, while also demonstrating additional benefit in combination with targeted PD-1 axis blockade (Lewis et al. (2019) J Immunother Cancer 7(S1): P467). The benefit appeared at least additive in models of poorly immunogenic tumors, suggesting the possibility of meaningful clinical benefit where CPI therapeutic efficacy is limited, such as noninflamed tumors. Single agent safety and tolerability of davoceticept has been demonstrated along with pharmacodynamic evidence of CD28 engagement with immune checkpoint inhibition (Moser et al. (2021) J Clin Oncol 39(s15): 2547). **Methods:** NEON-2 is an open-label dose escalation and expansion study of davoceticept combined with pembrolizumab in adults with advanced solid tumors or lymphoma that was initiated in June 2021 (NCT04920383). Eligibility includes tumors where single agent PD-(L)1 antagonists are SOC, are refractory or resistant to standard therapies (including approved CPIs), or have no standard or curative therapy. The study employs a standard 3+3 dose escalation design with two schedules, Q1W and Q3W of davoceticept. Pembrolizumab is given per label at 400 mg IV Q6W. Objectives include evaluation of safety and tolerability, identification of the recommended phase 2 dose(s) (RP2D), PK, PD, exploratory predictive biomarker analysis (i.e., PD-L1, CD28, CD80 and CD86 expression, as well as immunophenotyping of immune cell populations on treatment) and preliminary anticancer activity of davoceticept in combination with pembrolizumab. Disease assessments are evaluated by RECIST v1.1 for solid tumors or by Lugano Classification for lymphoma. Efficacy endpoints include ORR, duration of response and disease control rate. Once the RP2D combination is identified, tumor-specific expansion cohorts of ~ 30- 35 patients will be performed, including histologies that have not been demonstrated to be CPI responsive, as well as those where CPIs are approved SOC. The 0.1 mg/kg cohorts have been completed without DLT. Enrollment to the 0.3 mg/kg cohorts began in September 2021. Clinical trial information: NCT04920383. Research Sponsor: Alpine Immune Sciences.

TPS2684 **Poster Session**

ARTISTRY-3: Effect of nemvaleukin alfa with a less frequent IV dosing schedule as monotherapy and in combination with pembrolizumab and impact on the tumor microenvironment (TME) in patients (pts) with advanced solid tumors. *First Author: Sarina Anne Piha-Paul, Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Nemvaleukin alfa (nemvaleukin, ALKS 4230) is a novel engineered cytokine that selectively binds the intermediate-affinity interleukin-2 (IL-2) receptor, preferentially activating and expanding antitumor $CD8^+$ T cells and NK effector cells, with minimal effect on regulatory T cells. Nemvaleukin was designed to leverage antitumor effects of the IL-2 pathway while limiting typical IL-2–associated toxicity. In ARTISTRY-1, the recommended phase 2 dose (RP2D) for nemvaleukin monotherapy of 6 μg/kg IV on days 1 to 5 of a 21-day cycle elicited durable and deep responses in pts with advanced melanoma and renal cell carcinoma (Boni et al. ASCO 2021:abstr 2513). Responses with nemvaleukin plus pembrolizumab were also observed in platinum-resistant ovarian, breast, cervical, gastrointestinal, and genitourinary cancers. ARTISTRY-3 will investigate the effects of nemvaleukin as monotherapy and in combination with pembrolizumab on the TME in pts with advanced solid tumors, and in an additional cohort (Cohort 2), to further assess a less frequent IV dosing schedule for nemvaleukin. **Methods:** The phase 1/2, open-label ARTISTRY-3 (NCT04592653) study will enroll adults (≥18 years) with select advanced solid tumors, ≥1 accessible lesion for biopsy, ≥1 target lesion (per RECIST v1.1), ECOG PS of 0 or 1, estimated life expectancy of ≥3 months, adequate hematologic reserve, and adequate hepatic and renal function. Primary objectives: to evaluate effects of nemvaleukin monotherapy on the TME (Cohort 1) and to determine RP2D for less frequent dosing schedule (Cohort 2). Additional objectives are to evaluate: efficacy, safety, immunogenicity, and pharmacokinetics of nemvaleukin monotherapy; effects of nemvaleukin plus pembrolizumab on the TME; and correlative biomarkers of nemvaleukin as monotherapy and combination. Following the protocol amendment, additional pts enrolled in Cohort 1 will receive lead-in monotherapy at a dose selected based on results from Cohort 2, and pre- and on-treatment biopsies will be collected for TME assessments. Subsequent cycles will be administered in combination with pembrolizumab, and a biopsy may be collected at cycle 4 or 5. Tumor types eligible for Cohort 2 are selected based on activity observed in the ARTISTRY-1 study. A quantitative system pharmacology model was applied to identify a less frequent schedule for nemvaleukin monotherapy and combination. Cohort 2 will initially assess safety and tolerability of nemvaleukin at 1 dose per 21-day cycle. Two doses per 21-day cycle may be implemented to achieve optimal PK/PD parameters. Bayesian optimal interval design methodology with open enrollment will be applied to facilitate dose escalation decisions. Clinical trial information: NCT04592653. Research Sponsor: Alkermes, Inc.

TPS2685 **Poster Session**

BMC128: A rationally designed live bacterial consortium for the potentiation of immune checkpoint therapy in solid tumors. *First Author: Corinne Maurice-Dror, BC Cancer, Vancouver, BC, Canada*

Background: Immune-Checkpoint inhibitors (ICI) have transformed the treatment of solid tumors, specifically in cutaneous melanoma, clear cell renal cell carcinoma (ccRCC) and non-small cell lung cancer (NSCLC). Despite these advances, a significant proportion of patients do not respond to ICI and only a fraction of responding patients will experience durable responses. Recent reports have found that patients showing poor response to ICI are characterized by a reduced gut microbiome diversity, suggesting that the gut microbiome might affect immune activation by ICI. BMC128 is a live bacterial consortium of 4 bacterial strains predicted to induce anti-tumor immune function when given in conjunction with ICI. These strains were identified by analyzing data obtained from NSCLC and ccRCC patients presenting varied responses to ICI, using a proprietary computational discovery platform enabling high-resolution functional microbiome analysis. In pre-clinical studies, treatment with BMC128 potentiated the efficacy of ICI in breast cancer and melanoma mouse models, reducing tumor volume, increasing the number of responders, and demonstrating an increase in infiltrating immunocytes: CD4, CD8 and NK cells. **Methods:** In this phase I, first-in-human trial, patients with ccRCC, cutaneous melanoma and NSCLC-adenocarcinoma (EGFR/ALK wild-type), who previously progressed on PD1/PDL-1 inhibitors will be treated with BMC128 $8*10^8$ CFU BID in combination with Nivolumab at a fixed-dose of 480mg q4weeks in a 3+3 design, followed by a 9 patient expansion phase. No dose escalation is planned. The primary objective is to investigate the safety and tolerability of BMC128 in combination with Nivolumab. Enrollment is intended to start in Feb, 2022. Clinical trial information: 202122207. Research Sponsor: Biomica Ltd.

Overall study design.

	Period		Duration (days)
1	Screening	Screening	
2	DLT period	Native microbiota depletion	1
3		Induction (BMC128 monotherapy)	14
4		Combination treatment, cycle 1: BMC128+Nivolumab	28
5	Cycles 2-4	Combination treatment, BMC128+Nivolumab	84
6	Cycles 5-26	Nivolumab monotherapy	~590
7	Follow up	Follow up	30

TPS2688 **Poster Session**

A phase 1 dose-escalation study to investigate the safety, efficacy, pharmacokinetics, and pharmacodynamic activity of CLN-619 (anti-MICA/MICB antibody) alone and in combination with pembrolizumab in patients with advanced solid tumors. *First Author: John D. Powderly, Carolina BioOncology Institute, Huntersville, NC*

Background: The major histocompatibility complex (MHC) class I-related proteins MICA and MICB are stress-inducible, surface glycoproteins that are up-regulated on human tumors. MICA/MICB are ligands for the activating receptor, Natural Killer Group 2 member D (NKG2D) expressed on Natural Killer (NK) cells, CD8+ T cells, $\gamma\delta$ T cells and iNKT cells. Proteases in the tumor microenvironment cleave MICA/MICB from the cell surface which enables tumor cells to evade immune cell recognition and destruction by NKG2D-expressing cells. Increased concentrations of shed MICA have been observed in serum from patients across multiple tumor types and correlate with poor survival. CLN-619 is a humanized, clinical-stage, MICA/MICB-specific IgG1 monoclonal antibody that prevents the proteolytic release of MICA/MICB thereby exposing tumor cells for immune destruction through both NKG2D-mediated and antibody-dependent cell-mediated cytotoxicity (ADCC). The antibody has been shown to restore the MICA/MICB-NKG2D axis to promote NK-mediated tumor cell lysis (AACR Annual Meeting abstract 3506, April 2022). In mice bearing MICA/MICB-expressing human tumor xenografts, CLN-619 treatment yielded robust anti-tumor activity at low doses. MICA/MICB is expressed in a wide range of solid tumors. Therefore, CLN-619 is expected to have broad anti-tumor activity. **Methods:** CLN-619 is being evaluated in an open-label, non-randomized, dose-escalation (phase 1) study as monotherapy, and in combination with pembrolizumab, in patients with advanced solid tumors. Cohort expansion in patients with specific indications as monotherapy and in combination with pembrolizumab will be conducted. The phase 1 study explores ascending intravenous doses of CLN-619 as monotherapy (0.1, 0.3, 1.0, 3.0, 6.0 and 10.0 mg/kg) and in combination with pembrolizumab (200 mg) in 21-day cycles to identify the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D). Key eligibility criteria include 1) histological or cytological diagnosis of cancer and 2) refractory metastatic disease, or locally advanced disease not amenable to local therapy. At the RP2D, CLN-619 monotherapy will be evaluated in non-small cell lung and cervical cancer. In parallel, a cohort of patients will be administered CLN-619 in combination with pembrolizumab. Serum levels of soluble MICA/MICB, identity of MICA/MICB alleles, phenotypes of peripheral blood mononuclear cells, cytokines and tumor biopsies will be investigated for correlative pharmacodynamic and predictive biomarkers. This clinical trial is in progress (NCT05117476) and has completed accrual of three participants at the first dose level. Clinical trial information: NCT05117476. Research Sponsor: Cullinan Oncology, LLC.

TPS2689 **Poster Session**

A combined phase I/II study of a novel bicycle tumor-targeted immune cell agonist BT7480 in patients with nectin-4 associated advanced malignancies. *First Author: Kyriakos P. Papadopoulos, START San Antonio, San Antonio, TX*

Background: BT7480 is a novel, first-in-class, Nectin-4/CD137 *Bicycle* tumor-targeted immune cell agonist (*Bicycle* TICA) that co-ligates cluster of differentiation (CD)137 (on immune cells) and Nectin-4 (on tumor cells). BT7480 comprises 3 bicyclic peptides (*Bicycles*), 1 that binds to Nectin-4 and 2 that bind to CD137. The *Bicycles* are conjugated via a branched trimeric polyethylene glycol linker. Co-ligation of Nectin-4 and CD137 by BT7480 is hypothesized to induce oligomerization and activation of CD137 resulting in a tumor-localized costimulatory signal that leads to an antitumor response in preclinical studies. Nectin-4 is reported to be highly expressed in numerous tumors with unmet medical need including bladder, pancreas, breast, ovary, esophagus, head and neck, stomach, and lung cancers. Many of these tumor types also contain CD137 expressing cells. BT7480 exhibited a favorable preclinical profile supporting initiation of a first-in-human study to investigate safety and efficacy in indications with evidence of Nectin-4 expression. **Methods:** BT7480-100 (NCT05163041) is a PhI/II study to evaluate safety and tolerability of BT7480 administered as an intravenous infusion QW in a 28-day cycle, and to determine a recommended Phase 2 dose to further explore efficacy and safety. Patients will be recruited with advanced solid tumors associated with Nectin-4 expression including urothelial; head and neck squamous cell; non-small cell lung; ovarian, breast, gastric or esophageal carcinoma after exhausting standard of care options. Patients must have available tumor tissue, acceptable hematologic and other critical organ function. Exclusion criteria include uncontrolled brain metastases, uncontrolled hypertension, significant history of autoimmune disease and prior CD137 targeted therapy. Pharmacokinetic and pharmacodynamic analyses will be performed to support dose escalation decisions and increase the understanding of safety and clinical activity signals observed during the study. Tumor response will be assessed per RECIST every 8 weeks. Cohorts 1 and 2 have been completed without DLT. Enrollment in cohort 3 began in January 2022. Clinical trial information: NCT05163041. Research Sponsor: BicycleTx Limited.

TPS2690 **Poster Session**

Phase 1a/1b study design of the novel STING agonist, immune-stimulating antibody-conjugate (ISAC) TAK-500, with or without pembrolizumab in patients with advanced solid tumors. *First Author: Jennifer Robinson Diamond, University of Colorado Anschutz Medical Campus, Aurora, CO*

Background: Tumor resistance to immune checkpoint inhibitors (CPIs), including pembrolizumab, is common. Suggested mechanisms of resistance include reduced interferon (IFN) signaling, immune escape, and immunosuppressive tumor phenotypes. Innate immune cell stimulation in the tumor microenvironment may be a potential pathway to overcome this resistance. Stimulator of interferon genes (STING) is a cytosolic protein critical for initiation of type-1 IFN-dependent innate immunity. TAK-500 is a novel ISAC comprising a STING agonist (based on TAK-676, which is currently in phase 1 clinical trials [NCT04420884, NCT04879849]), an IgG1 anti-cysteine-cysteine chemokine receptor 2 (CCR2) antibody, and a self-immolating maleimide-containing protease-cleavable peptide linker. CCR2-expressing myeloid cells, including tumor associated macrophages (TAMs), promote immune evasion in part by reducing infiltration of CD8+ T cells into the tumor microenvironment. As such, TAK-500 has the potential to mitigate CPI resistance in solid tumors via targeted STING activation of tumor-infiltrating CCR2-expressing myeloid cells, thus leading to stimulation of innate and adaptive immunity within the tumor microenvironment through three potential mechanisms of action: activation of IFN signaling, reprogramming of CCR2-expressing myeloid cells to an inflammatory phenotype, and blockade of suppressive TAM recruitment. **Methods:** Adult patients with a diagnosis of locally advanced or metastatic gastroesophageal adenocarcinoma, pancreatic adenocarcinoma, hepatocellular carcinoma, non-squamous non-small cell lung cancer, squamous cell carcinoma of the head and neck, mesothelioma or triple-negative breast cancer are eligible. All patients must have progressive disease while on, or be intolerant to, all current standard therapies. Approximately 106 patients in total will be enrolled to the dose escalation and expansion cohorts. In the dose escalation phase, intravenous (IV) TAK-500 will be administered over the range 8–480 μg/kg on day 1 of every 21-day cycle (Q3W) to establish the pharmacologically active dose (PAD) range. An additional escalation cohort of patients will receive TAK-500 + IV pembrolizumab 200 mg Q3W, starting at a dose of TAK-500 that is 1–2 dose levels below the lowest PAD range established in the single agent cohort. Dose escalation in both cohorts will be guided by Bayesian Optimal Interval design. In the dose expansion phase, only the combination of TAK-500 + pembrolizumab will be evaluated. Primary objectives of this study are safety and tolerability; secondary objectives include determination of the PAD range, the recommended phase 2 dose, pharmacokinetics, pharmacodynamics, and antitumor activity of TAK-500 as a single agent and in combination with pembrolizumab. Clinical trial information: NCT05070247. Research Sponsor: Takeda Development Center Americas, Inc. (TDCA).

TPS2691 **Poster Session**

A first-in-human phase 1 trial of nx-1607, a first-in-class oral CBL-B inhibitor, in patients with advanced solid tumor malignancies. *First Author: Adam Sharp, The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom*

Background: Casitas B-lineage lymphoma proto-oncogene B (CBL-B) is an E3 ubiquitin ligase expressed in multiple immune cell lineages, which in contrast to cell surface immune checkpoints, acts as a regulator of both T and NK cell activation. Inhibition of CBL-B enhances T-cell response, increases response to suboptimal priming, and restores response in exhausted T cells. Thus CBL-B is a promising immune-oncology target and may overcome challenges seen with other T-cell directed therapies. NX-1607 is an oral small molecule inhibitor of CBL-B that has demonstrated anti-tumor activity and long-term survival in murine models as both a single agent and in combination with programmed cell death protein-1 (PD-1) antibodies. Further, NX-1607 elicits dose-dependent increases in cytokine secretion and proliferation in T-cell receptor-stimulated primary human T cells with enhanced tumor antigen-specific T-cell and NK cell anti-tumor responses. Thus, NX-1607 may be effective as a single agent or it may significantly enhance efficacy of other anti-tumor agents. **Methods:** NX-1607-101 is a first-in-human, multicenter, open-label, Phase 1 dose escalation and expansion trial evaluating NX-1607 in a variety of indications including platinum-resistant epithelial ovarian cancer (EOC), gastric cancer, squamous cell carcinoma of the head and neck (HNSCC), metastatic melanoma, non-small cell lung cancer (NSCLC), metastatic castration-resistant prostate cancer (mCRPC), malignant pleural mesothelioma (MPM), triple-negative breast cancer (TNBC), locally advanced or metastatic urothelial cancer, cervical cancer, microsatellite stable colorectal cancer (MSS CRC), and diffuse large B-cell lymphoma with Richter transformation (DLBCL-RT). The main objective is to establish the safety and tolerability of NX-1607, characterize PK/PD, and determine the recommended Phase 1b dose. NX-1607 will be given orally once daily at doses ranging from 5 to 100 mg in up to 6 dose levels. Dose escalation will proceed using an accelerated modified Fibonacci dose escalation design that transitions to a standard 3 + 3 design based on protocol-specific criteria. Up to 8 expansion cohorts in Phase 1b will be composed of patients with subsets of advanced cancers. Key eligibility criteria include patients with metastatic or unresectable disease that have progressed after prior therapy and for whom standard therapy with proven clinical benefit does not exist, is no longer effective, or is not appropriate. Prior treatment with immune checkpoint inhibitors or CAR-T cells with washout is allowed, but a history of active autoimmune disease is not. Up to 336 patients (60 in Phase 1a, 276 in Phase 1b using a Simon 2-stage design) will be enrolled at approximately 20 sites in the UK and US and treated until disease progression or unacceptable toxicity. Dose escalation is ongoing. Clinical trial information: NCT05107674. Research Sponsor: Nurix Therapeutics, Inc.

TPS2693 **Poster Session**

A phase 1/2 dose escalation/expansion study of OR2805 alone or in combination in subjects with advanced solid tumors. *First Author: Anthony W. Tolcher, NEXT Oncology and Texas Oncology, San Antonio, TX*

Background: M2-like macrophages are thought to promote an immunoinhibitory environment and prevent activation and proliferation of T cells, leading to resistance to checkpoint inhibitor (CPI) therapy. OR2805 is a fully human monoclonal antibody identified in a patient who had an exceptional response to CPI. OR2805 recognizes CD163, an immunosuppressive scavenger receptor highly expressed on M2 tumor-associated macrophages (TAMs). OR2805 treatment reprograms M2 macrophages to take on an immunostimulatory, M1-like phenotype. In macrophage/T cell coculture assays, OR2805 treatment relieved the suppressive effect of M2c macrophages as demonstrated by increased T-cell proliferation and stimulation of IFN-γ and perforin release. OR2805 restored the IFN-γ production of exhausted T cells and showed a synergistic effect on cocultures treated in combination with CPI. OR2805 monotherapy demonstrated significant anti-tumor activity in lung cancer xenograft models in NSG-SGM3 mice. Relieving the immune suppression of CD163-expressing TAMs by OR2805 to improve anti-tumor T-cell responses will be evaluated alone and in combination with CPI therapy. **Methods:** This phase 1/2, open-label, multicenter, dose-escalation/expansion study is assessing the safety, tolerability and preliminary activity of OR2805 alone and in combination with anti-PD-1 or chemotherapy in up to 325 adults (≥18 years) with histologically or cytologically confirmed metastatic or locally advanced solid tumors. The study is divided into 3 parts. Part A will enroll subjects with advanced solid tumors of any histology to describe the preliminary safety profile of OR2805 and determine the recommended phase 2 dose (RP2D) of OR2805 alone and in combination with an anti-PD-1 monoclonal antibody. Part B will further characterize the safety and preliminary antitumor activity of OR2805 either alone or in combination with an anti-PD-1 or chemotherapy in previously treated non-small cell lung cancer (NSCLC), melanoma and liposarcoma, as well as in previously untreated NSCLC in combination with an anti-PD-1 antibody. Part C will evaluate OR2805 monotherapy in relapsed squamous cell carcinoma of the head and neck and other tumor types with an emphasis on correlative biomarker analysis. OR2805 will be infused on Day 1 of 21-day cycles. Primary endpoints are adverse events, laboratory abnormalities, dose-limiting toxicities, and dose-level safety and activity. Secondary endpoints are objective response rates, duration of response, complete response, progression-free survival, overall survival, PK, and antidrug antibodies. Exploratory biomarkers of OR2805-mediated pharmacodynamic effects and immune stimulation will be explored. The study was opened September 2021 and is enrolling at sites in the United States with planned expansion within the US and to Europe. Clinical trial information: Clinical trial information: NCT05094804. Research Sponsor: Oncoresponse, Inc.

TPS2694 **Poster Session**

An open-label, non-randomized, multi-center phase I study evaluating the safety, tolerability, pharmacokinetics and preliminary efficacy of bi-ligand-drug conjugate CBP-1018 in patients with advanced solid tumors. *First Author: Kaiwen Li, Department of Urology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China*

Background: Folate-receptor 1 (FOLR1) and prostate specific membrane antigen (PSMA) are overexpressed on tumor and angiogenic endothelial cells in solid tumors, including prostate cancer, renal cell cancer and lung cancer. CBP-1018 is a first-in-class bi-ligand drug conjugate targeting to both FOLR1 and PSMA, with a tubulin inhibitor payload, monomethyl auristatin E (MMAE). We herein introduce its first-in-human study which is designed based on the significant anti-tumor potency and acceptable safety profile in nonclinical studies. **Methods:** This study is a phase Ia/Ib, multicenter, open-label study enrolling patients with advanced solid tumor relapsed after previous standard therapies. The primary objective is to assess CBP-1018 safety, tolerability, dose limiting toxicity and maximum tolerated dose. Preliminary efficacy including objective response rate, duration of response and progression-free survival will be observed. Pharmacokinetics, immunogenicity and biomarkers will be also evaluated. This study includes 2 parts: Ia (Dose Escalation) and Ib (Dose Expansion). CBP-1018 is administrated iv Q2W (4 weeks/cycle) in Ia, with accelerated titration at lower doses (0.03 mg/kg and 0.06 mg/kg) and an i3+3 design at following doses (0.08 mg/kg, 0.10 mg/kg, 0.12 mg/kg and 0.14mg/kg, etc.). Subjects will be enrolled in 4 cohorts in Ib: metastatic castration resistant prostate cancer, advanced renal cell cancer, advanced lung squamous cell cancer, and other advanced solid tumors. Efficacy will be assessed every 8 weeks (±7days) according to RECIST 1.1, PCWG3 and PSA assessment (only for prostate cancer). Treatment will be continued untill disease progression or intolerable toxicity. Enrollment has been started in Nov. 2021 and is ongoing. Clinical trial information: NCT04928612. Research Sponsor: Coherent Biopharma (Suzhou) Co., Ltd.

TPS2695 **Poster Session**

IL believe: A phase 1/2, open-label, dose escalation and dose expansion study of TransCon IL-2 β/γ alone or in combination with pembrolizumab or standard-of-care chemotherapy in patients with locally advanced or metastatic solid tumors. *First Author: Alexander Starodub, The Christ Hospital, Cincinnati, OH*

Background: Advances in immunotherapy have led to significantly improved survival and quality of life in some cancer patients, but many with less immunogenic tumor types derive suboptimal clinical benefit. Recombinant human interleukin-2 (IL-2, aldesleukin) can induce a response rate of ~15% in metastatic renal cell carcinoma and metastatic melanoma, yet toxicities (vascular leak syndrome, cytokine storm) have limited its use. TransCon IL-2 β/γ, a novel prodrug with sustained release of a receptor-selective IL-2 (IL-2 β/γ), was designed to optimally address drawbacks of aldesleukin: potent activation of undesired IL-2Rα^+ cell types and high C_{max} with rapid clearance. TransCon IL-2 β/γ comprises 3 main components: IL-2 β/γ, a methoxy polyethylene glycol (mPEG) carrier molecule, and a linker connecting the two. Under physiological conditions, TransCon IL-2 β/γ releases active IL-2 β/γ from the mPEG carrier through cleavage of the TransCon Linker. This results in a lower C_{max} and much longer effective $t_{1/2}$ of free IL-2 β/γ compared to aldesleukin. PD-1 expression at the cell surface of activated cytotoxic T cells and natural killer cells provides a clear rationale to study TransCon IL-2 β/γ alone or in combination with pembrolizumab. **Methods:** IL Believe is a multicenter, first-in-human, Phase 1/2 study in 3 parts in adult patients with locally advanced or metastatic solid tumors. All patients need ≥1 measurable lesion per RECIST 1.1 and an ECOG score of ≤ 2. The primary objectives are to evaluate safety and tolerability, and to define the maximum tolerated dose and recommended Phase 2 dose (RP2D) of TransCon IL-2 β/γ alone or in combination with pembrolizumab. Parts 1 and 2 Dose Escalation (Phase 1) use a standard 3+3 design with increasing doses of intravenous (IV) TransCon IL-2 b/g alone (Part 1) or with 200 mg IV pembrolizumab in solid tumors where pembrolizumab monotherapy may have clinical activity (Part 2). Each part will enroll ~15 patients. Part 3, Combination Dose Expansion (Phase 2) will evaluate preliminary clinical efficacy of TransCon IL-2 β/γ at the RP2D determined in Part 2, combined with chemotherapy. Platinum Resistant Ovarian Cancer is currently planned for dose expansion with other indication specific cohorts to be included in a subsequent amendment. Each cohort will be analyzed using a Simon 2-stage design and will enroll ~56 patients. Other key objectives include the evaluation of pharmacokinetics, pharmacodynamic biomarkers, and antitumor activity according to RECIST 1.1. Recruitment started in January 2022 and is ongoing (NCT05081609). Clinical trial information: NCT05081609. Research Sponsor: Ascendis Pharma.

TPS2696 **Poster Session**

A phase 1 study of TPST-1495 as a single agent and in combination with pembrolizumab in subjects with solid tumors. *First Author: Diwakar Davar, University of Pittsburgh Medical Center, Hillman Cancer Center, Pittsburgh, PA*

Background: Prostaglandin E2 (PGE2) is a bioactive lipid that promotes cancer through diverse mechanisms including stimulating tumor proliferation, enhancing angiogenesis and suppressing immune function in the tumor microenvironment. PGE2 produced by tumor cells through upregulation of cyclooxygenase-2 (COX-2) is also a key mediator of adaptive resistance to immune checkpoint inhibitor therapy. While PGE2 signaling is important in cancer, how best to inhibit PGE2 for cancer treatment is under investigation. Inhibition of COX enzymes (e.g., with NSAIDS) has shown promise in large observational studies, but inconsistent results in prospective studies. Importantly, COX inhibition alters multiple prostanoids beyond PGE2, resulting in toxicity that limits therapeutic dosing for cancer. PGE2 signals through four receptors, EP1-4, that are variably expressed and have distinct activities. The tumor promoting and immunosuppressive activities of PGE2 predominantly arise from signaling through the EP2 and EP4 receptors, while signaling through the EP1 and EP3 receptors generally is pro-inflammatory. TPST-1495 is designed to be an oral, highly specific, antagonist of the EP2 and EP4 receptors, sparing the EP1 and EP3 receptors and the COX enzymes. Preclinical studies suggest that blocking EP2 and EP4 with TPST-1495 inhibits tumor proliferation and stimulates anti-cancer immunity better than inhibiting all 4 receptors together, the EP2 or EP4 receptors singly, or the upstream COX-2 enzyme. **Methods:** TPST-1495-001 is a first-in-human Phase 1 study (NCT04344795). In the Dose and Schedule Optimization Stage, the primary objectives are to characterize the safety and tolerability (including dose limiting toxicities) and determine the recommended phase 2 dose (RP2D) of TPST-1495 as monotherapy and in combination with pembrolizumab in patients with advanced solid tumors. Additional objectives include characterization of PK, PD, and evaluation of potential biomarkers, including through paired (pre- and on-treatment) tumor biopsies. Monotherapy dose-finding employs a modified 3+3 design evaluating BID and QD TPST-1495 schedules along with continuous or intermittent (Days 1-5 every 7 days) dosing. For the pembrolizumab combination, the starting dose and schedule of TPST-1495 are determined by safety, PK and PD of monotherapy. Indication-specific Expansion Stage cohorts will evaluate TPST-1495 at the selected RP2D and schedule for both monotherapy and combination in endometrial cancer, squamous cell carcinoma of the head and neck, and microsatellite stable colorectal cancer (combination only), as well as in a biomarker-specific cohort enrolling patients with pathogenic tumor PIK3CA gene mutation. Dose and Schedule Optimization enrollment (monotherapy and combination) is ongoing at abstract submission while Expansion Stages are planned after identification of the RP2Ds. Clinical trial information: NCT04344795. Research Sponsor: Tempest Therapeutics.

TPS2697 **Poster Session**

A first-in-human, multicenter, phase 1/2, open-label study of XTX202, a masked and tumor-selective recombinant human interleukin-2 (IL-2) protein, in patients with advanced solid tumors. *First Author: Meredith McKean, Sarah Cannon Research Institute, Tennessee Oncology, PLLC, Nashville, TN*

Background: High-dose interleukin-2 (IL-2) has been approved in metastatic renal cell carcinoma (RCC) and metastatic melanoma, and can result in durable complete responses, including cures. Its use has been limited by life-threatening treatment-related multisystem toxicities, consisting mainly of vascular leak syndrome. XTX202 is a masked, tumor-selective IL-2 that is designed to be pharmacologically inactive in non-tumor tissue when circulating systemically and unmasked by matrix metalloproteases (MMPs) found preferentially in the tumor microenvironment (TME). XTX202 is expected, therefore, to achieve a wider therapeutic index resulting in increased efficacy and lower toxicity compared to existing non-tumor selective IL-2 based-therapies. The IL-2 domain of the XTX202 molecule is modified to reduce binding to the high-affinity IL-2 receptor while maintaining binding to the intermediate-affinity IL-2 receptor, thereby decreasing activation of regulatory T-cells relative to wild-type IL-2, while still activating effector T cells. A masking domain is designed to pharmacologically inactivate IL-2 until it is activated by MMPs that are enriched in the TME. Cleavage at a protease cleavage site in the XTX202 linker by MMPs results in an active IL-2 moiety when the masking domain is released. XTX202 is designed with the goal of producing a localized anti-tumor immune response and limiting exposure of the active form of XTX202 in non-tumor tissue. Preclinically, XTX202 exhibited tumor-selective activity in mice without peripheral toxicities in non-human primates [O'Neil et al. ASCO 2021]. **Methods:** XTX202-01 trial (NCT05052268) is a first-in-human Phase 1/2 study to determine a recommended Phase 2 dose of XTX202 (Phase 1) and to evaluate the efficacy of XTX202 monotherapy in patients with metastatic RCC and unresectable or metastatic melanoma (Phase 2). Patients with advanced solid tumors are eligible for Phase 1 and will receive XTX202 monotherapy administered every 21 days in an accelerated and standard 3+3 dose escalation design. Phase 2 will consist of 2 parts: Part 2a will enroll patients with metastatic RCC who have received a prior tyrosine kinase inhibitor therapy and have been treated and progressed on an anti-PD-1 therapy. Part 2b will enroll patients with unresectable or metastatic melanoma who have received immune-checkpoint therapy with an anti-PD-1 therapy and an anti-CTLA-4 therapy to determine the efficacy of XTX202 monotherapy in this population. Enrollment to the study began in January 2022. Clinical trial information: NCT05052268. Research Sponsor: Xilio Therapeutics.

TPS2698 **Poster Session**

TAK-676 in combination with pembrolizumab after radiation therapy in patients (pts) with advanced non–small cell lung cancer (NSCLC), triple-negative breast cancer (TNBC), or squamous-cell carcinoma of the head and neck (SCCHN): Phase 1 study design. *First Author: Benjamin T. Cooper, Perlmutter Cancer Center, New York University School of Medicine, New York, NY*

Background: The cyclic GMP-AMP Synthase (cGAS)–STimulator of INterferon Genes (STING) pathway is an important modulator of the innate immune system via induction of type I interferon (IFN-I). Cytosolic DNA generated as a result of tumor cell death following radiation therapy has been demonstrated to activate the cGAS-STING signaling axis resulting in antitumor immunogenicity. TAK-676 is a novel, synthetic STING agonist and it has been shown in preclinical studies to potently modulate the innate immune system and subsequently activate the adaptive immune system to produce antitumor responses. TAK-676 is designed for prolonged half-life in serum and enhanced tissue permeability compared with other STING agonists designed for intratumoral injection, allowing for systemic IV delivery with access to tumor sites and lymphatic tissue. IFN signaling impairment has been linked to checkpoint inhibitor (CPI) resistance in tumors. Treatment with TAK-676 after radiation therapy has the potential to stimulate T cell-mediated antitumor immunity via STING-mediated IFN-I release, particularly when used with anti-PD-1/PD-L1 therapies. Preclinical data support the addition of STING agonists to reverse resistance in tumors with prior exposure to CPIs. TAK-676 is being investigated (+/- pembrolizumab) in an ongoing first-in-human phase 1 study (NCT04420884). Here, we describe another phase 1 trial to investigate the safety and preliminary antitumor activity of TAK-676 plus pembrolizumab following radiation therapy in pts with advanced or metastatic NSCLC, TNBC, or SCCHN (NCT04879849). **Methods:** Adult pts with progressive disease (PD) following CPI treatment and who have ≥2 lesions, 1 of which can be targeted with radiation, are being enrolled. Pts receive 8 Gy x 3 fractions of image-guided radiation followed (after ≥40 hours) by IV pembrolizumab 200 mg on day 1 plus escalating doses of IV TAK-676 on days 1, 8, and 15 of a 21-day cycle. TAK-676 dose escalation is guided by the Bayesian optimal interval design. Pts receive TAK-676 plus pembrolizumab until PD, intolerance to treatment, or withdrawal. Pts enrolled at TAK-676 dose levels shown to have pharmacodynamic activity, and who have a safely accessible lesion outside the radiation field, will have paired biopsies collected at screening and between days 15 and 21 of cycle 1. The primary objective is to determine the safety and tolerability of TAK-676 plus pembrolizumab following radiation therapy; secondary objectives are to establish the recommended phase 2 dose of TAK-676 plus pembrolizumab following radiation therapy, and to assess preliminary antitumor activity both locally (within the radiation field) and systemically (non-radiated lesions). As of February 2022, we have enrolled ~10% of the planned pts. Clinical trial information: NCT04879849. Research Sponsor: Takeda Development Center Americas, Inc. (TDCA).

TPS2699 **Poster Session**

Phase 2 study of the IDO/PD-L1-targeted immune-modulatory vaccine, IO102-IO103, plus pembrolizumab as first-line treatment for metastatic non–small cell lung cancer (NSCLC), squamous cell carcinoma of the head and neck (SCCHN), or urothelial bladder cancer (UBC). *First Author: Jonathan W. Riess, University of California Davis Comprehensive Cancer Center, Sacramento, CA*

Background: Immunotherapy has transformed the treatment of NSCLC and other solid tumors, such as SCCHN and UBC. However, even with standard-of-care anti-PD-1/PD-L1 therapies, few patients achieve durable benefit even when PD-L1 is overexpressed. IO102-IO103 is a potentially first-in-class, dual-antigen, immune-modulatory therapy that stimulates T cells to target tumoral immune escape via key checkpoint molecules IDO and PD-L1. It is thought that activating IDO/PD-L1-specific T cells in cancer patients through vaccination may support anticancer immunity by restricting immunosuppressive signaling and restoring the tumor immune microenvironment to render the tumor more susceptible to anti-PD-1 blockade. Thus there is a rationale for combining IO102-IO103 with anti-PD-1 therapy in the first-line treatment of metastatic tumors, such as NSCLC, SCCHN, or UBC. Combined IO102-IO103 and anti-PD-1 therapy (nivolumab) has already shown a robust signal of clinical activity (overall response rate [ORR], 80%; complete response rate [CRR], 43%; median progression-free survival [PFS], 26 months) and was well tolerated with minimal added toxicity to nivolumab in a Phase 1/2 study of anti-PD1-naïve patients with metastatic melanoma (Kjeldsen, et al. Nat Med 2021). **Methods:** This is a Phase 2, international, multicenter (US and Europe), non-comparative, open-label, multi-arm (basket) trial (EudraCT No. 2021-003026-69; ClinicalTrials.gov No. NCT05077709). Patients with recurrent, unresectable or metastatic solid tumors in 3 indications and no prior treatments for metastatic disease are being enrolled: NSCLC with a PD-L1 Tumor Proportion Score (TPS) ≥50% (Arm A); SCCHN with PD-L1 Combined Positive Scores (CPS) ≥20 (Arm B); or UBC with PD-L1 CPS ≥10 and not eligible for platinum-containing chemotherapy (Arm C). All patients, ~30 in each arm, will receive 3-week cycles of IO102-IO103 (85-85 μg on Day [D] 1 and 8 of Cycle 1 and 2, and D1 thereafter) subcutaneously plus pembrolizumab (200 mg on D1) intravenously, for up to 2 years. Primary endpoints are ORR by RECIST v1.1 or 6-month PFS rate by investigator assessment (to be analyzed either 6 months after last patient started treatment or after target ORR is achieved, whichever is earliest). Secondary endpoints include PFS, duration of response, complete response rate, disease control rate, time to response, overall survival, and safety. Exploratory endpoints include biomarker and immune marker correlative studies, and PFS by iRECIST. The trial will assess the opportunity for a positive risk–benefit based on 2 efficacy boundaries for the ORR and 6-month PFS rate in each arm, with cohort expansion permitted if a clinically relevant efficacy signal is observed. Clinical trial information: EudraCT No. 2021-003026-69; ClinicalTrials.gov No. NCT05077709. Research Sponsor: IO Biotech ApS & Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

TPS2700 **Poster Session**

A first-in-human, phase I, open-label study of a novel cancer vaccine labvax 3(22)-23 and adjuvant GM-CSF in patients with advanced stage adenocarcinomas. *First Author: Weijie Ma, University of California Davis Comprehensive Cancer Center, Sacramento, CA*

Background: Adenocarcinoma is the most common histologic type of solid tumors and can arise from almost anywhere in the body. Labyrinthin is a novel tumor-specific protein expressed on the cell surface of the majority of adenocarcinomas of various cancer types. Several therapeutic strategies targeting labyrinthin are under development. We hypothesize that vaccination against labyrinthin can elicit strong immune responses against the labyrinthin-positive adenocarcinomas in cancer patients. LabVax 3(22)-23 is a novel anti-tumor vaccine that contains 4 synthetic labyrinthin-based peptides designed to elicit both B-cell and T-cell responses. Sargramostim, a recombinant granulocyte macrophage colony-stimulating factor (GM-CSF), is given as an immunostimulator with LabVax 3(22)-23 to boost the anti-tumor immune response. Preclinical studies showed that LabVax 3(22)-23 significantly inhibited tumor growth that was augmented by GM-CSF without any significant toxicity in C57/BL6 transgenic mice expressing human PD-1/PD-L1 implanted with the murine colon adenocarcinoma cell line MC-38-huPD-L1. This single institution, first-in-human, phase I trial (UCDCC#296) evaluates LabVax 3(22)-23 and adjuvant sargramostim in patients with labyrinthin-positive metastatic or recurrent adenocarcinoma of any primary tumor site after all standard-of-care therapies. **Methods:** The primary objective is to assess the toxicity of LabVax 3(22)-23 and adjuvant sargramostim according to NCI CTCAE V5.0. The primary endpoint is dose limiting toxicity (DLT), which is defined as grade ≥ 2 allergic and autoimmune reaction, grade ≥ 3 injection site reaction, any grade 3 toxicities lasting >1 week, or any grade ≥ 4 toxicities. With a sample size of 10 patients, there is 89-97% of chance to observe ≥1 DLT if the true event rate is 20-30%. A secondary endpoint is the preliminary assessment of tumor response rate by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Exploratory objectives measure the effect of LabVax 3(22)-23 on various immune responses (cytokines, anti-labyrinthin antibody production) and the correlation between the level of labyrinthin expression and the efficacy of LabVax 3(22)-23. Eligible patients are required to have labyrinthin expression on their tumor cells by immunohistochemistry and adequate organ function. Patients receive sargramostim subcutaneously and LabVax 3(22)-23 intradermally on weeks 1, 2, 4, 8, and 12 in the absence of disease progression or unacceptable toxicity. After completion of study treatment, patients are followed every 3 months for 1 year. Two patients are enrolled at the time of submission. Clinical trial information: NCT05101356. Research Sponsor: UC Davis Comprehensive Cancer Center, Pharmaceutical/Biotech Company.

TPS2701 **Poster Session**

First-in-human phase 1 trial of ELI-002 immunotherapy as treatment for subjects with Kirsten rat sarcoma (KRAS)-mutated pancreatic ductal adenocarcinoma and other solid tumors. *First Author: Shubham Pant, Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Mutations in KRAS and NRAS occur in one quarter of human solid tumors. The G12D allele is the most commonly occurring variant in pancreatic, colorectal, non-small cell lung, ovarian, biliary and gallbladder cancers. ELI-002 2P is an immunotherapeutic comprised of a lymph-node targeted amphiphile (AMP)-modified G12D and G12R mutant KRAS peptides together with an AMP-modified CpG oligonucleotide adjuvant. In preclinical models, ELI-002 demonstrated increased cytotoxic KRAS-specific T cells compared to non-lymph node targeted controls using the same peptide and adjuvant. Clinical evaluation of adoptively transferred KRAS-specific T cells demonstrated objective antitumor activity (Tran 2016). Circulating tumor (ctDNA) methodology permits identification of patients with minimal residual disease (MRD) following locoregional treatment. In MRD setting, immunotherapy is anticipated to succeed as the ratio of effector T cells to target tumor cells is maximized prior to bulk visible disease. The AMPLIFY-201 study (NCT04853017) is evaluating ELI-002 in patients with KRAS mutated solid tumors with MRD. **Methods:** AMPLIFY-201 is an open-label, dose-escalation and expansion phase I, first in human, trial evaluating ELI-002 2P in patients with KRAS mutated tumors with MRD following standard of care therapy. The initial phase I cohort enrolls patients with colorectal and pancreatic cancer to receive multiple doses of AMP-peptides 70mcg each (1.4 mg total) admixed with AMP-CpG 0.1 mg, administered once every two weeks. Subsequent phase I cohorts will enroll patients with RAS-mutated pancreatic, colorectal, non-small cell lung, ovarian, bile duct or gallbladder cancer, who will receive a fixed dose of AMP-peptides 70 mcg each, together with escalating doses of AMP-CpG. Safety and efficacy will be summarized with descriptive statistics. The maximum tolerated dose (if any) and the recommended phase II dose (RP2D) will be determined with the dose-response activity of ELI-002 2P in eliciting functional KRAS-specific T cells. Preliminary antitumor activity will be characterized using changes from baseline in ctDNA, serum biomarkers appropriate for tumor type, and progression free survival time. Eligibility includes patients who have received standard of care locoregional treatment according to NCCN guidelines and whom have MRD persistence or relapse (ctDNA positive). Patients with colon and pancreas cancer with Stage IV oligometastatic disease (< 3 lesions in one organ) rendered surgically free of disease and with MRD, are also eligible. The dose escalation portion of the study is currently enrolling. Clinical trial information: NCT04853017. Research Sponsor: Elicio Therapeutics.

TPS2702 **Poster Session**

A phase 1 dose-finding and dose-expansion study evaluating the safety, tolerability, pharmacokinetics, and efficacy of a highly selective WEE1 inhibitor (Debio 0123) in adult patients with advanced solid tumors. *First Author: Kyriakos P. Papadopoulos, START San Antonio, San Antonio, TX*

Background: Debio 0123 is an oral, highly selective inhibitor of the tyrosine kinase WEE1. WEE1 is a key regulator of cell cycle progression that modulates the activity of CDK1 (CDC2), influencing entry into mitosis. WEE1 inhibition results in G2 checkpoint abrogation, triggering mitosis with unrepaired DNA leading to cell death. *In vitro* and *in vivo* tumor models have shown Debio 0123 antitumor activity. Continuous exposure seems to be needed to maximize monotherapy efficacy in preclinical models. Preliminary data from an ongoing phase 1 study of intermittent Debio 0123 combined with carboplatin, showed a manageable safety profile, and signals of antitumor activity in patients (pts) with advanced solid tumors. We present the design of a phase 1 study (NCT05109975) of continuous Debio 0123 administered as a single agent in pts with advanced solid tumors. **Methods:** The study comprises a dose escalation part and a dose expansion part. The primary objective of the dose escalation part of the study is to determine the maximum tolerated dose (MTD) and/or the recommended phase 2 dose (RP2D) of continuous Debio 0123 monotherapy in adults with previously treated advanced solid tumors. Key secondary objectives include characterization of safety and tolerability, pharmacokinetics (PK), and preliminary antitumor activity (overall response rate [ORR]). Key inclusion criteria are histologically or cytologically confirmed locally advanced or metastatic solid tumors, and ECOG-PS 0 or 1. Key exclusion criteria are asymptomatic or unstable brain metastases, history of cardiac disorders, inability to swallow oral medication or abnormalities affecting drug absorption. Approximately 30 dose-limiting toxicity (DLT)-evaluable pts are anticipated to be enrolled based on an escalation with overdose control (EWOC) approach for 21-day treatment cycles. When the pts of each cohort become evaluable, a safety monitoring committee will review safety and tolerability and based on EWOC recommendations will decide the next dose level or will declare the MTD and/or RP2D. Pharmacodynamic biomarkers will be correlated with tumor response and/or PK. The dose-expansion part may start after MTD and/or RP2D determination. The primary objective of this part will be to characterize the safety and tolerability (e.g. percentage of pts with DLTs, serious adverse events or discontinuations) of Debio 0123 monotherapy at the MTD/RP2D, and to evaluate the anti-tumor activity (ORR) in pts with selected recurrent/progressive solid tumors. Key inclusion criteria are measurable disease per RECIST 1.1 and specific tumor types. Based on a Simon 2-stage design, up to 34 pts per tumor type cohort may be enrolled. Currently accrual to the dose escalation is ongoing in the United States and Switzerland. Clinical trial information: NCT05109975. Research Sponsor: Debiopharm International SA.

TPS2703 **Poster Session**

CAIRE: A basket multicenter open-label phase 2 study evaluating the EZH2 inhibitor tazemetostat in combination with durvalumab in patients with advanced solid tumors. *First Author: Antoine Italiano, Institut Bergonié, Bordeaux, France*

Background: Recent studies have shown shown that genetic depletion of EZH2 in Tregs (using FoxP3creEZH2fl/fl mice) and pharmacological inhibition of EZH2 elicits phenotypic and functional alterations of Tregs, leading to an effector-like T cell profile. Further, EZH2 inhibition enhances the cytotoxicity of human Teffs in vitro and the proportion of tumor-infiltrating cytotoxic T cells in vivo in murine models. It has been shown that immune checkpoint inhibition (ICI) increases EZH2 expression in human T cells across various tumor types and that increased EZH2 expression in T cells inversely correlate with clinical outcome. Upregulation of EZH2 mediated by immune checkpoint inhibition in T cells modulates T cell responses and diminishes the effectiveness of immunotherapy. Consistent with this mechanism, pharmacologic inhibition of EZH2 has been shown to increase effector-like T cell responses and enhances effectiveness of immune checkpoint therapy in tumor-bearing mice [16-17]. Our group also reported first clinical data from a participant with sarcoma showing strong T cell infiltration after treatment with tazemetostat (Italiano et al Lancet Oncol 2018). Altogether, these findings pave the way for clinical trials combining ICI with the specific EZH2 inhibitor, tazemetostat in solid tumors. **Methods:** CAIRE (NCT04705818) is a multi-cohort, four single-arm phase 2, multicenter, open-label study investigating tazemetostat combined with durvalumab in patients with advanced cancers: pancreatic adenocarcinoma (cohort A), microsatellite stable colorectal cancer (cohort B), solid tumors with presence of tertiary lymphoid structures (assessed centrally) (cohort C), soft-tissue sarcomas (cohort D). Cohort A will enroll ~32 patients and cohorts B, C and D ~47 patients respectively. Eligible patients must have no standard treatment options available or a contraindication to standard treatment options, and ECOG PS 0–1. Patients with prior exposure to EZH2 inhibitor and/or PD1/PDL1 monoclonal antibodies are excluded. Tazemetostat will be administered per-os, twice daily (800 mg x 2), continuously. Treatment by Tazemetostat will start on Day 1 (of cycle 1). Durvalumab will be administered by intravenous infusion (1120 mg) on day 1, every 3 weeks. Treatment by Durvalumab will start on Day 1 of cycle 2. The primary endpoints are disease control rate within 24 weeks of treatment as per RECIST 1.1 in cohort A and B; objective response rate within 24 weeks of treatment as per RECIST 1.1 in cohort C, and 6-months non progression rate for cohort D. Secondary endpoints include adverse events (AEs)/serious AEs, duration of response, and progression-free survival. Pharmacodynamic and other biomarkers will be explored. The first patient received study drug on July, 30, 2022 and 1 site across France are currently enrolling patients. Clinical trial information: NCT04705818. Research Sponsor: Astra Zeneca, Other Government Agency.

TPS2704 **Poster Session**

A phase 1 trial of RP2, a first-in-class, enhanced potency oncolytic HSV expressing an anti-CTLA-4 antibody as a single agent and combined with nivolumab in patients with advanced solid tumors. *First Author: Kevin Joseph Harrington, The Royal Marsden//The Institute of Cancer Research NIHR Biomedical Research Centre, London, United Kingdom*

Background: RP2 is a selective replication-competent herpes simplex virus 1 (HSV-1) that contains a codon-optimized sequence for human granulocyte-macrophage colony-stimulating factor (GM-CSF), the gibbon ape leukemia virus surface glycoprotein (GALV-GP) with the R- sequence deleted (R-), GM-CSF, and an anti–cytotoxic T lymphocyte antigen 4 (CTLA-4) antibody-like molecule. These modifications are intended to increase oncolytic potency, cell-to-cell spread, tumor antigen release, and systemic antitumor immune activation. RP2 has demonstrated antitumor activity in preclinical models using viruses similar to RP2 expressing murine versions of anti-CTLA-4 and GM-CSF, both alone and in combination with PD1-1 blockade. **Methods:** This is a Phase 1 multicenter, open-label, study evaluating RP2 ± nivolumab (NCT04336241). Part 1 evaluated escalating doses of monotherapy RP2 with a modified 3 + 3 design. Patients (pts) received intratumoral (IT) injections of up to 10 mL of RP2 into superficial or visceral tumors Q2W x5 across two dose levels (DL1: 10^5 plaque-forming units (PFU)/mL once, then followed by 10^6 PFU/mL x4; DL 2: 10^6 PFU/mL once, then followed by 10^7 PFU/mL x4). The recommended Phase 2 dose of RP2 was identified as 10^6 PFU/mL once, followed by subsequent doses of 1×10^7 PFU/mL. In Part 2, up to 60 evaluable pts will be enrolled, including 30 pts in Cohort 2a and 30 in Cohort 2b. Cohort 2a was designed to evaluate the safety and antitumor activity of the combination in pts with solid tumors, and is fully enrolled. Cohort 2b is open for enrollment of pts with advanced or metastatic uveal melanoma, NSCLC, breast cancer, head and neck cancer or GI cancers (NSCLC, breast or GI cancers must have at least one liver tumor suitable for injection). Pts in Part 2 receive intra-tumoral RP2 at the RP2D Q2W for up to 8 doses in combination with 240 mg nivolumab IV Q2W or 480 mg nivolumab IV Q4W for up to two years from the first RP2 dose. In Part 3 (not yet open for enrollment), up to 15 evaluable pts are able to be enrolled to evaluate RP2 monotherapy including at least 10 pts with NSCLC, breast or GI cancers with at least one liver tumor suitable for injection. Reinitiation of up to 8 additional RP2 doses is permitted if prespecified criteria are met. Pts are dosed with RP2 by direct visualization or ultrasound-guided injection into superficial, subcutaneous, or nodal tumors and by image-guided injection into deeper lesions, including visceral lesions. Key inclusion criteria include histologically confirmed advanced or metastatic non-neurological solid tumors, at least one measurable and injectable tumor of diameter ≥1 cm, ECOG ≤1, and adequate hematologic, hepatic, and renal function. Exclusion criteria include prior treatment with oncolytic viruses, acute or chronic hepatitis B or C infection, and HIV infections. Clinical trial information: NCT04336241. Research Sponsor: Replimune Group Inc.

TPS2705 **Poster Session**

An open-label, multicenter, phase 1 study of RP3 as a single agent and in combination with nivolumab in patients (pts) with solid tumors. *First Author: Kevin Joseph Harrington, The Royal Marsden//The Institute of Cancer Research NIHR Biomedical Research Centre, London, United Kingdom*

Background: RP3 is a genetically modified herpes simplex virus 1 (HSV-1) that contains insertions for the gibbon ape leukemia virus surface glycoprotein (GALV-GP) with the R- sequence deleted (R-), an anti–cytotoxic T lymphocyte antigen 4 (CTLA-4) antibody-like molecule, CD40 ligand, and 4-1BB ligand. Together, these insertions are expected to increase oncolytic potency, cell-to-cell spread, immunogenic cell death, and systemic immune activation. RP3 has demonstrated antitumor activity in preclinical models using viruses similar to RP3 expressing murine versions of anti-CTLA-4, CD40L, and 4-1BBL both alone and in combination with PD1-1 blockade. **Methods:** This is an open-label, multicenter, Phase 1 study evaluating RP3 as monotherapy or in combination with nivolumab (nivo) in patients (pts) with solid tumors (NCT04735978). Part 1 evaluated escalating doses of RP3. Pts in Part 1 received IT injections of up to 10 mL RP3 into superficial, nodal, or visceral lesions Q2W x 5 across two dose levels (DL1: 10^5 plaque-forming units (PFU)/mL once, then 10^6 PFU/mL x 4; DL2: 10^6 PFU/mL once, then 10^7 PFU/mL x4). The RP2D is 10^6 PFU/mL once, followed by 10^7 PFU/mL IT Q2W. In Part 2, pts are being enrolled into expansion cohorts of 45 patients with GI (including HCC), lung, breast, and squamous cell carcinoma of the head and neck treated with RP1 combined with nivo. Additional cohorts will enroll patients treated with RP3 followed by nivo, RP3 monotherapy to further explore biomarkers in injected and uninjected tumors, and with the potential to also open a cohort in melanoma. Pts in both Part 1 and Part 2 may receive up to 8 additional doses of RP3 if protocol-specified criteria are met. Key inclusion criteria: confirmed advanced or metastatic non-neurological solid tumors, at least one measurable tumor $\geq$ 1 cm and injectable tumors $\geq$ 1 cm in aggregate, ECOG $\leq$1, and adequate hematologic, hepatic, and renal function. In Cohorts 1, 2, and 4, approximately 50% of the pts with lung, breast, and GI cancer must have liver lesions intended for injection. Exclusion criteria include prior oncolytic virus treatment, need for immunosuppressive therapy, an autoimmune disease requiring systemic therapy, active significant herpetic infections or prior complications of HSV-1 infection, active or chronic HBV or HCV infection, known HIV infection, or prior active malignancy within 3 years. Clinical trial information: NCT04735978. Research Sponsor: Replimune.

3000 **Oral Abstract Session**

A phase Ia/Ib study of CBP-1008, a bispecific ligand drug conjugate, in patients with advanced solid tumors. *First Author: Lingying Wu, Cancer Hospital Chinese Academy of Medical Sciences, Beijing, China*

Background: Folate receptor α (FRα) and vanilloid subfamily member 6 of transient receptor potential channels (TRPV6) are overexpressed in many solid tumors hence could be promising therapeutic targets. CBP-1008 is a first-in-class bispecific ligand drug targeting FRα and TRPV6 carrying monomethyl auristatin E (MMAE) as payload. Here we report the first-in-human, multicenter, phase Ia/Ib study designed to explore the safety, pharmacokinetics and efficacy of CBP-1008 in advanced solid tumors. **Methods:** CBP-1008 was administered by intravenous infusion. Phase Ia study included a dose-escalation period initiated by accelerated titration (0.015, 0.03mg/kg d1,15; q28d) and then switched to 3+3 scheme (0.12, 0.15, 0.17, 0.18mg/kg d1,15; q28d) and a dose expansion period. Phase Ib clinical expansion study included 3 cohorts, platinum-resistant ovarian cancer (OC), metastatic triple negative breast cancer (TNBC) and other solid tumors. The primary objective was to assess the safety and preliminary efficacy. **Results:** As of January 13, 2022, 106 patients received at least one dose of study drug were enrolled (phase Ia: n = 30; phase Ib: n = 76) and received median 3 prior regimens. Included tumor species were OC (n = 52), TNBC (n = 20), ER+/Her2+ breast cancer (BC) (n = 16), lung cancer (n = 3), pancreatic cancer (n = 2) and others (n = 13). In phase Ia study, DLTs were observed in 3 patients (0.12, 0.15, 0.18mg/kg, n = 1 each), including grade 4 hypophosphatemia, neutropenia, febrile neutropenia, and grade 3 hyperglycemia, alanine aminotransferase (ALT). MTD was not yet reached. Majority of adverse events were mild to moderate. The most common grade 3/4 treatment-emerging adverse events (TEAEs) were neutropenia (37.7%), AST elevation (6.6%), ALT elevation (5.7%), hyperglycemia (2.8%), hypohemoglobinemia (2.8%) and nausea (1.9%). Drug-related death was not observed. A total of 69 patients at dose of 0.15mg/kg or above were evaluable for efficacy assessment. There were 11 patients achieved partial response (PR) (OC n = 8, ER+/Her2+ BC n = 2, TNBC n = 1) and 30 patients achieved stable disease (SD). In 32 advanced platinum-resistant OC patients with FRα and/or TRPV6-positive expression, 6 PR and 16 SD were observed. Moreover, 6/18 PR (33.3%) and 8/18 SD (44.4%) were observed in enriched OC patients who showed high score of FRα/TRPV6 receptor. **Conclusions:** The preliminary results showed that CBP-1008 has manageable safety profile. Antitumor activity was observed in patients with FRα/TRPV6 receptor expression, especially in platinum-resistant OC cohort with high score of the two receptors. Clinical trial information: NCT04740398. Research Sponsor: Coherent Biopharma (Suzhou) Co., Ltd.

3001 **Oral Abstract Session**

Phase 1a/1b study of FOR46, an antibody drug conjugate (ADC), targeting CD46 in metastatic castration-resistant prostate cancer (mCRPC). *First Author: Rahul Raj Aggarwal, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA*

Background: FOR46, a fully human antibody (ab) conjugated to monomethyl auristatin E (MMAE), targets a tumor selective epitope of CD46, which is highly expressed in mCRPC and treatment-emergent small cell neuroendocrine cancer (t-SCNC). CD46 is enriched in tumor cells upon treatment with androgen signaling inhibitors (ASI). Following dose escalation (Phase 1a), dose expansion was undertaken in 2 cohorts (Phase 1b): 1) Pts with *de novo* or t-SCNC and 2) pts with mCRPC without a t-SCNC component. Pts with adenocarcinoma enrolled in dose escalation and expansion are included in this analysis. **Methods:** Eligible pts had mCRPC, with progression on at least 1 ASI, with no prior chemotherapy for CRPC. Phase 1a pts received FOR46 0.1-3.0 mg/kg IV Q3 weeks (wks). The primary objectives in phase 1a were to assess adverse effects (AEs) and select the phase 1b dose; and in phase 1b to assess efficacy. For phase 1b, tumor biopsy in the CRPC setting for assignment to the 2 cohorts was required. CD46 expression was not required for inclusion in the expansion cohort, but was evaluated using a non-epitope specific CD46 polyclonal ab. Histology and CD46 expression were centrally reviewed. **Results:** Thirty-three pts were enrolled in phase 1a and 10 in phase 1b (including 6 treated in ph1a at the expansion dose or higher). Overall, 36 pts were treated at doses > 1.2 mg/kg. Following excess toxicity in pts with body mass indices > 30 (3 of 3 with Gr 4 neutropenia and 1 of 3 with Gr 3 fatigue at 2.4 mg/kg), further dosing was calculated using adjusted body weight (AJBW) rather than actual weight, allowing escalation to 3.0 mg/kg. The 2.7 mg/kg dose by AJBW was determined to be the MTD and phase 1b dose. The most common AEs at the 2.7 mg/kg dose were neutropenia (77% Gr 3 or 4), infusion reactions (37%, all < Gr 2), fatigue (31%, all < Gr 2) and peripheral neuropathy (24%, all < Gr 2)). Fourteen of 31 evaluable pts (45.2%) at > 1.2 mg/kg achieved a PSA_{50} response with 10 (32.3%) confirmed. Five pts were not evaluable for PSA response; 3 had no post-baseline PSA and 2 had baseline PSA < 1 ng/mL. The median duration of confirmed PSA_{50} response is >16 wks (range 6-48+ wks, with 4 ongoing at 12, 24, 25 and 48 wks). 18 pts had measurable lesions; 8 of 18 (44.4%) had tumor regression, with 4 (22.2%) confirmed partial responses (PR). The median duration of response is > 14 wks (range 9 -31+ weeks with 2 ongoing at 13 and 31 wks). Eight pts were evaluable for CD46 expression with a median H-score of 245 (range 0-300). Two pts with PRs had H-scores of 15 and 300; 4 with confirmed PSA_{50} had H-scores of 10, 15, 40 and 300. **Conclusions:** FOR46, a novel ADC targeting CD46, demonstrates clinical activity in mCRPC pts, with an acceptable safety profile, similar to other MMAE-containing ADCs. FOR46 merits further investigation in pts with mCRPC, alone and in combination with agents that enhance CD46 expression. Clinical trial information: NCT03575819. Research Sponsor: Fortis Therapeutics.

3002 **Oral Abstract Session**

Phase I, two-part, multicenter, first-in-human (FIH) study of DS-6000a in subjects with advanced renal cell carcinoma (RCC) and ovarian tumors (OVC). *First Author: Erika P. Hamilton, Sarah Cannon Research Institute/ Tennessee Oncology, PLLC, Nashville, TN*

Background: Cadherin 6 (CDH6) is part of the cadherin family, which is involved with cell-cell adhesion, organ development, and epithelial-mesenchymal transition. CDH6 is found to be overexpressed in various cancers, particularly RCC and OVC. DS-6000a is an antibody-drug conjugate, comprised of an humanized anti-CDH6 IgG1 monoclonal antibody attached to a topoisomerase I (TOP1) inhibitor payload via a cleavable linker. DS-6000a specifically binds to CDH6 on the surface of tumor cells and is internalized upon binding. The payload is then released, resulting in target cell apoptosis. In preclinical studies, DS-6000a inhibited tumor growth and induced tumor regression in CDH6-expressing RCC and OVC. Here, we report initial results from a phase I trial of DS-6000a in patients (pts) with advanced RCC and OVC (NCT04707248). **Methods:** This dose-escalation (Part A) and expansion (Part B) study will recruit pts with advanced RCC and OVC. DS-6000a is administered IV as monotherapy on Day 1 of 21-day cycles. Part A assesses safety, tolerability, and maximum tolerated dose or recommended dose for expansion (RDE) using Bayesian optimal interval design; additional pts are enrolled to examine safety and efficacy. The starting dose of DS-6000a is 1.6 mg/kg followed by 3.2, 4.8, 6.4, 8, and 9.6 mg/kg. Part B will assess safety, tolerability and efficacy at the RDE. **Results:** Part A interim results are presented. At data cutoff (19 NOV 2021), 22 pts had enrolled (7 RCC, 15 OVC). All RCC pts had received an immune checkpoint inhibitor and the majority of OVC had platinum resistant (Pt-R) disease; median age was 63.5 years (range, 41-78); median of 4 (range, 1-12) prior lines of therapy were administered; and median treatment duration was 8.0 wks (range, 3-33.14). Fifteen pts (68.2%) were ongoing at the cutoff date. Treatment-emergent adverse events (TEAEs) occurred in 19 pts (86.4%). Related TEAEs occurred in 17 pts (77.3%). The most common related TEAEs (>20%) were fatigue and nausea (45.5% each), and vomiting (27.3%). Grade ≥3 related TEAEs occurred in 4 pts (18.2%); the most common was neutropenia (13.6%). One patient (4.5%) had a Grade 3 febrile neutropenia. One dose-limiting toxicity of Grade 4 thrombocytopenia (9.6 mg/kg) occurred. There was no study drug discontinuation due to a TEAE. Among 15 evaluable pts, 2 partial responses (PRs; 1 confirmed in RCC and 1 unconfirmed PR in Pt-R OVC) were observed; 9 pts had stable disease. Moreover, 5 out of 11 OVC evaluable pts showed CA-125 responses using GCIG criteria and all CA-125 responders had Pt-R disease. **Conclusions:** The interim data from dose-escalation of this FIH study showed acceptable tolerability with early signals of efficacy in heavily pretreated pts with advanced RCC and Pt-R OVC, which support further clinical evaluation of DS-6000a in the planned dose-expansion cohorts in advanced RCC and OVC. Clinical trial information: NCT04707248. Research Sponsor: Daiichi Sankyo.

3003 **Oral Abstract Session**

First-in-human study of PC14586, a small molecule structural corrector of Y220C mutant p53, in patients with advanced solid tumors harboring a *TP53* Y220C mutation. *First Author: Ecaterina Elena Dumbrava, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The p53 tumor suppressor protein is a transcription factor that acts to maintain genome stability in response to cellular stress. Spontaneous mutation of the *TP53* gene leading to inactivation of the p53 protein is the most common mutational event across all human cancers. PC14586 is a novel, small molecule structural corrector that binds selectively to p53 Y220C mutant protein and restores the p53 wildtype conformation and transcriptional activity, resulting in potent preclinical antitumor activity. This Phase 1 multicenter dose escalation study assesses PC14586 safety, pharmacokinetics (PK), pharmacodynamics (PD) and preliminary efficacy in patients (pts) with advanced solid tumors that harbor the *TP53* Y220C mutation. **Methods:** Eligible adult pts with locally advanced or metastatic TP53 Y220C mutant solid tumors received increasing doses of oral PC14586 using the modified Toxicity Probability Interval design to estimate toxicity and to determine maximum tolerated dose and recommended phase 2 dose. Plasma PK was characterized using standard methods. Preliminary efficacy was assessed by RECIST v1.1. Reporting of interim results was approved by the study's Safety Review Committee. **Results:** As of 08 Feb 2022, 29 pts (62% female, median age 62 years) with a variety of *TP53* Y220C mutant solid tumor types (median number of prior lines of therapy 3; range 1 to 8) were treated in 7 dose cohorts of PC14586: 150 mg QD (3 pts), 300 mg QD (3 pts), 600 mg QD (4 pts), 1150 mg QD (5 pts), 2000 mg QD (7 pts), 2500 mg QD (4 pts) and 1500 mg BID (3 pts). PC14586 was generally well-tolerated; treatment-related AEs were observed in 79% of pts that were all Grade 1/2 in severity except 2 Grade 3 AEs (alanine aminotransferase increased and neutrophil count decreased). The most common AEs (≥15% of pts) were nausea (34%), vomiting (24%), fatigue (21%), and aspartate aminotransferase increased (17%). There were no dose limiting toxicities and enrollment continues. PK analysis showed dose proportional increases in Cmax and AUC. Amongst 21 efficacy evaluable pts, PRs were observed in 5 pts: 1 small cell lung and 1 breast with confirmed PR (cPR), both ongoing; 1 colorectal with unconfirmed PR (uPR), and 2 prostate with uPR and ongoing. In the 3 highest dose cohorts (total daily dose 2000 to 3000 mg), there were 3 PRs (2 uPR, 1cPR) and 7 SD out of 10 efficacy evaluable pts (all ongoing). Observations of decreasing p53 Y220C circulating tumor DNA and decreasing numbers of circulating tumor cells in pts further support on-target anti-tumor activity of PC14586. **Conclusions:** Enrollment to a Phase 1 study is feasible in a *TP53* mutation selective population. PC14586 is safe and tolerated up to 3000 mg daily. Preliminary efficacy was achieved in heavily pretreated pts. Additional safety, PK, PD and efficacy data will be reported at the annual meeting. Clinical trial information: NCT04585750. Research Sponsor: PMV Pharmaceuticals, Inc.

3004 **Oral Abstract Session**

A phase Ia/Ib, dose-escalation/expansion study of the MDM2–p53 antagonist BI 907828 in patients with solid tumors, including advanced/metastatic liposarcoma (LPS). *First Author: Mrinal M. Gounder, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The highly potent MDM2–p53 antagonist BI 907828 showed antitumor efficacy *in vivo*, particularly in *TP53* wild-type, *MDM2*-amplified de-differentiated LPS (DDLPS) patient-derived xenografts and syngeneic models. This phase I study (NCT03449381) is assessing BI 907828 monotherapy in patients with advanced solid tumors, including LPS. In Part A (dose escalation), patients received one of two BI 907828 dosing schedules: Arm A, day 1 of 21-day cycles (q3w); Arm B, days 1 and 8 of 28-day cycles. Based on previously reported results from Part A (LoRusso ASCO 2021), the MTD was 60 mg q3w and the recommended dose for expansion (RDE) was selected as 45 mg q3w. **Methods:** In Part B (dose expansion), patients received BI 907828 45 mg q3w. The primary endpoint was PFS. Secondary endpoints/objectives included objective response rate, overall survival, the number of patients with grade ≥3 treatment-related AEs, and PK parameters. Here, we report overall safety data and efficacy data in the subgroup of patients with advanced LPS. **Results:** As of January 10, 2022, 90 patients had been enrolled; 49 (54.4%) were male, 55 (61.1%)/34 (37.8%) were ECOG PS 0/1, the median number of prior systemic therapies was 2 (range, 0–11), 44 had advanced LPS (28 DDLPS, 16 well-differentiated LPS [WDLPS]). At data cut-off, 31/90 patients (34.4%) had received treatment for ≥6 months. In the 41 evaluable patients with advanced LPS, best response of PR or SD was observed in 24/27 patients with DDLPS (88.9%) and 13/14 patients with WDLPS (92.9%). Two DDLPS and 4 WDLPS patients achieved a PR; all had MDM2-amplified disease. In Part A, 5/11 DDLPS patients and 4/8 WDLPS patients have achieved PFS ≥10.5 months. In the 42 patients who received the RDE of 45 mg q3w, 18 patients (42.9%) had grade ≥3 AEs; the most common grade ≥3 AEs were neutropenia (23.8%), thrombocytopenia (21.4%), and anemia (11.9%). Seven patients (16.7%) had SAEs; the most common were thrombocytopenia (4.8%) and pyrexia (4.8%). PK analysis showed that mean plasma exposures (C_{max} and $AUC_{0\text{-}inf}$) increased with dose and showed no significant deviation from linearity in the dose range 10–60 mg. A correlation was observed between exposure and GDF-15 levels in plasma, as a target engagement marker. **Conclusions:** BI 907828 showed a manageable safety profile, high plasma exposure, target engagement and encouraging signs of antitumor activity in patients with advanced DDLPS and WDLPS. The Part B dose expansion is ongoing. Clinical trial information: NCT03449381. Research Sponsor: Boehringer Ingelheim.

3005 **Oral Abstract Session**

A phase 1 study of TPST-1120 as a single agent and in combination with nivolumab in subjects with advanced solid tumors. *First Author: Mark Yarchoan, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD*

Background: TPST-1120 is a first-in-class oral therapy that inhibits PPARα, a transcription factor that regulates fatty acid oxidation (FAO). TPST-1120 has diverse mechanisms of anti-tumor activity in preclinical studies, including inhibiting tumor proliferation, increasing the anti-angiogenic factor thrombospondin 1, and reducing T cell exhaustion. **Methods:** Subjects with advanced solid tumor malignancies received escalating doses of TPST-1120 as a single agent or in combination with nivolumab 480 mg IV every 4 weeks (combination cohort limited to RCC, cholangiocarcinoma [CCA] and HCC). Study objectives included evaluation of safety, pharmacokinetics, MTD, RP2D and anti-tumor activity as monotherapy and in combination with nivolumab. AEs were assessed per CTCAE v5 and efficacy per RECIST v1.1 **Results:** As of 14-Jan-2022, 35 subjects have been dosed (20 with TPST-1120 monotherapy at doses from 100 mg to 600 mg PO BID and 15 in combination with nivolumab at doses from 200 mg to 600 mg PO BID). Median prior lines of systemic therapy were 3 (2-11) in monotherapy and 2 (2-6) in combination cohorts. An MTD was not reached in monotherapy or combination, and the TPST-1120 RP2D was 600 mg PO BID for both cohorts. For TPST-1120 monotherapy, the most common treatment related AEs (TRAEs) were nausea (20%), fatigue (15%), and diarrhea (10%), all Grade 1-2. One monotherapy subject (5%) experienced a Grade 3 TRAE (hypertension). In the combination cohort the most common TRAEs related to either drug were fatigue (40%), diarrhea (27%) and nausea (20%), all Grade 1-2. Three combination subjects (19%) experienced Grade 3 TRAEs (one each arthralgia, hepatic enzyme increased, muscle spasms). A best response of stable disease was observed in 53% (10/19) of subjects treated with monotherapy. In combination, the ORR was 23% (3/13, all PRs) across all dose levels and 38% (3/8) at TPST-1120 dose levels ≥400 mg BID. These responses included 2 subjects with late-line RCC (2/2 RCC subjects enrolled, both with progression on prior anti-PD1 therapy) and one subject with heavily pre-treated CCA. At data cut off, 2 of 3 responding patients (CCA and one RCC) remained in PR and on study at 8.4 and 14 mo, respectively. **Conclusions:** TPST-1120 is a novel therapy designed to inhibit tumor proliferation and angiogenesis and stimulate anti-cancer immunity through inhibition of PPARα, a key regulator of FAO. The drug is well tolerated as a single agent and in combination with nivolumab. Promising objective responses have been observed in combination with nivolumab in subjects previously refractory to anti-PD-1 therapy, including 2/2 responders in late-line RCC, and a subject with heavily pretreated CCA, a tumor type generally not responsive to anti-PD-1 alone. Notably, all responders were treated at the two highest doses of TPST-1120 (ORR 38%). Updated study results including exploratory biomarkers will be presented. Clinical trial information: NCT03829436. Research Sponsor: Tempest Therapeutics.

3006 **Oral Abstract Session**

CRESTONE: Initial efficacy and safety of seribantumab in solid tumors harboring *NRG1* fusions. *First Author: Daniel R. Carrizosa, Levine Cancer Institute, Atrium Health, Charlotte, NC*

Background: *NRG1* fusions are rare oncogenic drivers found in ~0.2% of all solid tumors. These fusions elicit ERBB3/HER3 overactivation to drive tumor growth and cancer cell survival. Currently there are no approved targeted therapies for *NRG1* fusion-positive tumors. Furthermore, patients (pts) with tumors harboring *NRG1* fusions have poor outcomes with standard therapies. Seribantumab is a fully human anti-HER3 IgG2 monoclonal antibody that suppressed tumor growth in *NRG1* fusion-driven preclinical models. Here, we present initial clinical data from the CRESTONE study (NCT04383210). **Methods:** CRESTONE is a Phase 2, global, multicenter, open-label study of seribantumab in adult pts with locally advanced or metastatic solid tumors harboring *NRG1* fusions. A dose ranging phase established the RP2D as a 3g once weekly (QW) intravenous dose administered until treatment discontinuation criteria are met. In the expansion phase, cohort 1 will enroll at least 55 pts who had received at least one prior therapy and are naïve to ERBB-targeted therapy. Exploratory cohorts 2 or 3 will enroll pts previously treated with ERBB-targeted therapies and/or tumors harboring additional molecular alterations. The primary endpoint is objective response rate (ORR) by independent central review per RECIST v1.1. Initial data from cohort 1 pts who received seribantumab 3g QW with investigator (INV)-assessed response per RECIST v1.1 are reported. **Results:** By JAN-13-2022, 12 pts have received seribantumab 3g QW in cohort 1. Median age was 65 years (range 44–76), 67% were female, and median number of prior therapies was 1 (range 1–5). 92% (11/12) of pts had non-small cell lung cancer (NSCLC); 5 different NRG1 fusion partners (*ATP1B1*, *CD74*, *ITGB1*, *SDC4*, *SLC3A2*) were reported by local next-generation sequencing tests. Among 10 pts evaluable for INV-assessed response, the confirmed ORR was 30%, and the disease control rate was 90% (1 complete response, 2 partial responses, 6 stable disease, 1 progressive disease). 58% (7/12) of pts remain on study treatment, including 2 pts with NSCLC who achieved objective responses with an ongoing duration of response of 6 and 8.5 months. Seribantumab 3g QW was well tolerated with no drug discontinuations or dose reductions. Across all cohorts (n = 29), the most frequently (≥20%) reported treatment-related adverse events (TRAEs) were diarrhea (38%), fatigue (34%), and rash (24%), all were grade 1 or 2. One grade 3 TRAE of vomiting occurred; there were no Grade 4 or 5 TRAEs. Efficacy analysis is ongoing and updated efficacy data from evaluable pts in cohort 1 will be presented. **Conclusions:** Initial data indicate seribantumab induced durable responses in advanced solid tumors harboring *NRG1* fusions and has a favorable safety profile. These data support the continued evaluation of seribantumab in *NRG1* fusion-positive solid tumors in the ongoing CRESTONE study. Clinical trial information: NCT04383210. Research Sponsor: Elevation Oncology, Inc.

3007 **Oral Abstract Session**

Tumor agnostic efficacy and safety of erdafitinib in patients (pts) with advanced solid tumors with prespecified fibroblast growth factor receptor alterations (*FGFRalt*) in RAGNAR: Interim analysis (IA) results. *First Author: Yohann Loriot, Gustave Roussy, DITEP, Université Paris-Saclay, Villejuif, France*

Background: Erdafitinib (erda) is an oral selective pan-FGFR tyrosine kinase inhibitor approved to treat locally advanced or metastatic urothelial carcinoma (UC) in adults with susceptible *FGFR3/2alt* who have progressed during or after ≥ 1 line of platinum containing chemotherapy. *FGFRalt* are observed across a wide range of malignancies and may function as oncogenic drivers independent of the underlying tumor type. RAGNAR (NCT04083976) is an ongoing phase 2 open label, single arm tumor agnostic trial investigating the efficacy and safety of erda in pretreated adult and pediatric pts with advanced solid tumors and *FGFRalt*. Here, we report results from a planned IA of RAGNAR. **Methods:** Pts aged ≥ 6 y with advanced or metastatic solid tumors of any histology (except UC) with predefined *FGFR1-4alt* (mutations/fusions based on local/central test) and documented disease progression on ≥ 1 prior line of systemic therapy (tx) and no alternative standard tx received oral erda until disease progression or intolerable toxicity. The primary end point is objective response rate (ORR) by independent review committee (IRC). Secondary end points include investigator assessed ORR, duration of response (DOR), disease control rate (DCR), clinical benefit rate (CBR), PFS, OS, and treatment emergent adverse events (TEAEs). **Results:** As of the IA data cutoff, 178 pts were treated (median age 56.5 y [range 12-79], median 2 prior systemic tx). Only 9.0% of pts responded to last line of tx prior to study entry. ORR by IRC was 29.2% (95% CI, 22.7-36.5). Investigator assessed ORR was 26.4% (95% CI, 20.1-33.5). Responses were observed in 14 distinct tumor types, including gliomas, thoracic, gastrointestinal, gynecological, and rare tumors (Table). ORR in pts with *FGFR* mutations vs fusions was comparable (26.8% vs 27.0%, respectively). Median DOR, PFS, and OS were 7.1 mo (95% CI, 5.5-9.3), 5.2 mo (95% CI, 4.0-5.6), and 10.9 mo (95% CI, 7.9-14.3), respectively; DCR was 75.3% and CBR was 48.9%. All pts experienced TEAEs, including 69.1% with grade ≥ 3. Treatment-related serious TEAEs occurred in 7.3% of pts. **Conclusions:** RAGNAR data show, for the first time, evidence of efficacy for erda in heavily pretreated pts with a variety of hard to treat advanced *FGFR+* malignancies, including glioblastoma, pancreatic, and salivary gland cancers. Safety was consistent with the known erda safety profile. Clinical trial information: NCT04083976. Research Sponsor: Janssen Research & Development, LLC.

Tumor type	N (treated)	ORR* n (%)	Tumor type	N (treated)	ORR* n (%)
Total	**178**	**47 (26.4)**	**Esophageal**	6	1 (16.7)
Cholangiocarcinoma	31	13 (41.9)	**Low-grade glioma**	6	1 (16.7)
High-grade glioma	29	6 (20.7)	**Ovarian**	4	1 (25.0)
Breast	14	6 (42.9)	**Cancer of unknown primary**	8	2 (25.0)
Pancreatic	13	4 (30.8)	**Salivary gland**	5	5 (100.0)
Squamous NSCLC	11	3 (27.3)	**Duodenal**	1	1 (100.0)
Non–squamous NSCLC	7	1 (14.3)	**Thyroid**	1	1 (100.0)
Endometrial	6	2 (33.3)			

*Investigator assessed.

3008 **Oral Abstract Session**

Cobimetinib plus vemurafenib (C+V) in patients (Pts) with solid tumors with BRAF V600E/d/k/R mutation: Results from the targeted agent and profiling utilization registry (TAPUR) study. *First Author: Funda Meric-Bernstam, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: TAPUR is a phase II basket study evaluating anti-tumor activity of commercially available targeted agents in pts with advanced cancers with genomic alterations. Results in a cohort of pts with solid tumors with *BRAF* V600E/D/K/R mutation (mut) treated with C+V are reported. **Methods:** Eligible pts had advanced solid tumors, no standard treatment (tx) options, measurable disease, ECOG performance status (PS) 0-2, and adequate organ function. Genomic testing was performed in CLIA-certified, CAP-accredited site selected labs. Pts matched to C+V had various solid tumors with *BRAF* V600E/D/K/R mut, or other *BRAF* mut if approved by the Molecular Tumor Board, and no *MAP2K1/2, MEK1/2, NRAS* mut. Recommended dosing was C, 60 mg orally daily for 21 days, 7 days off and V, 960 mg orally every 12 hours. Primary endpoint was disease control (DC), defined as complete (CR) or partial (PR) response or stable disease at 16+ wks (SD 16+) (RECIST v1.1). Low accruing histology-specific cohorts with the same genomic target and tx were collapsed into a single histology-pooled cohort for this analysis. For histology-pooled cohorts with sample size of 28, the results are evaluated based on a one-sided exact binomial test with a null DC rate of 15% vs. 35% (power = 0.84; $\alpha = 0.10$) and one-sided 90% confidence interval (CI). Other efficacy endpoint estimates are presented with two-sided 95% CIs. Secondary endpoints were progression-free survival (PFS), overall survival (OS) and safety. **Results:** 31 pts with solid tumors (13 histologies; 6/31 ovarian cancer) with *BRAF* muts were enrolled from Dec 2016 to Jan 2021 and collapsed into one histology pooled cohort for analysis. 3 pts were not evaluable due to lack of post-baseline tumor evaluation and excluded from efficacy analyses. Demographics and outcomes are summarized in the Table. Pts had tumors with *BRAF* V600E mut (N = 26), G469V mut (N = 1), K601E mut (N = 2), N581I (N = 1) and T599_V600insT (N = 1). 2 CR (breast and ovarian cancer; V600E), 14 PR (13 V600E, 1 N581I), and 3 SD16+ (2 V600E, 1 T599_V600insT) were observed for a DC rate of 68% (90% CI: 54%, 100%) and an objective response (OR) rate of 57% (95% CI: 37%, 76%). CR durations were 5.1 (ovarian cancer) and 108.9 wks (breast cancer) and median duration of PR was 20.5 wks (range: 8.0, 176.0). 19 pts experienced ≥1 Grade 1-5 AE/SAE at least possibly related to tx including 1 death attributed to tx-related kidney injury. **Conclusions:** C+V demonstrated evidence of anti-tumor activity in pts with advanced solid tumors with *BRAF* V600E and other muts. Clinical trial information: NCT02693535. Research Sponsor: Genentech, Pharmaceutical/Biotech Company.

Demographics and baseline characteristics (N = 31) and efficacy outcomes (N = 28).

Median age, yrs (range)		63 (31, 79)
ECOG PS, %	0	23
	1	64
	2	13
Prior systemic regimens, %	0-2	48
	≥3	52
DC rate, % (OR or SD16+) (90% CI)		68 (54, 100)
OR rate, % (95% CI)		57 (37, 76)
Median PFS, wks (95% CI)		23.3 (13.3, 27.7)
Median OS, wks (95% CI)		60.9 (26.7, 116.3)

3009 **Poster Discussion Session**

Ulixertinib in patients with tumors with MAPK pathway alterations: Results from NCI-COG Pediatric MATCH trial Arm J (APEC1621J). *First Author: Kieuhoa Tran Vo, University of California, San Francisco, CA*

Background: The NCI-Children's Oncology Group (COG) Pediatric Molecular Analysis for Therapy Choice (MATCH) trial assigns patients age 1 to 21 years with relapsed or refractory solid tumors, lymphomas, and histiocytic disorders to phase 2 treatment arms of molecularly-targeted therapies based on genetic alterations detected in their tumor. Arm J evaluated the ERK1/2 inhibitor ulixertinib (BVD-523FB) in patients whose tumors harbored activating alterations in the MAPK pathway (*ARAF*, *BRAF*, *HRAS*, *KRAS*, *NRAS*, *MAPK1*, *MAP2K1*, *GNA11*, *GNAQ* hotspot mutations; *NF1*inactivating mutations; *BRAF* fusions). **Methods:** As there were no prior pediatric data, ulixertinib was initially tested in a dose escalation cohort using a rolling 6 design to establish the recommended phase 2 dose (RP2D) before proceeding with enrollment to the phase 2 cohort. Ulixertinib was administered at 260 mg/m^2/dose PO BID (dose level 1, DL1, n = 15) or 350 mg/m^2/dose PO BID (dose level 2, DL2, n = 5). Patients were treated on continuous 28-day cycles for up to 2 years, until disease progression or intolerable toxicity; response assessment occurred every 2-3 cycles. The primary endpoint was objective response rate; secondary endpoints included safety/tolerability and progression-free survival (PFS). **Results:** Twenty patients (median age 12 years; range 5-20) were enrolled between November 2018 and March 2021. All patients were evaluable for response. High-grade glioma (HGG, n = 7) was most common, with CNS tumors comprising 55% (11/20) of diagnoses; all CNS tumors except one (HGG with *KRAS* and *NF1* mutations) harbored *BRAF* fusions or V600 mutations. Rhabdomyosarcoma (n = 5) was the most frequent non-CNS diagnosis, with *NRAS* mutations detected in 4 tumors. DL1 was declared the RP2D after first-cycle dose limiting toxicities (DLTs) occurred in 1/6 DLT-evaluable patients at DL1 and 2/5 patients at DL2 in the dose escalation cohort. Any-cycle DLTs in 8 patients in the dose escalation and primary cohorts included fatigue, anorexia, rash, nausea, vomiting, diarrhea, dehydration, increased creatinine, hypoalbuminemia, hypernatremia, and hip fracture. No objective responses were observed. Six-month PFS was 37% (95% CI: 17%, 58%). Three patients with CNS tumors achieved stable disease > 6 months (HGG with *BRAF* fusion, 15 cycles; glioneuronal tumor with *BRAF* V600E, 9 cycles; low-grade glioma with *BRAF* fusion, 7 cycles). Analyses of correlative studies, including pharmacokinetics and circulating tumor DNA, are ongoing. **Conclusions:** The pediatric RP2D of ulixertinib was established as 260 mg/m^2/dose PO BID. There were no objective responses in this cohort of children and young adults with treatment-refractory tumors with activating MAPK alterations. Clinical benefit of prolonged disease control was observed in 3 patients with *BRAF*-altered gliomas and glioneuronal tumors. Clinical trial information: NCT03698994. Research Sponsor: U.S. National Institutes of Health.

3010 **Poster Discussion Session**

Phase II study of vismodegib in patients with *SMO* or *PTCH1* mutated tumors: Results from NCI-MATCH ECOG-ACRIN Trial (EAY131) Subprotocol T. *First Author: Anne S. Tsao, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: NCI-MATCH (EAY131) is a platform trial enrolling patients (pts) with solid tumors, lymphomas, or multiple myeloma to targeted therapies based on matching genomic alterations (NCT02465060). Subprotocol Arm T evaluated vismodegib (GDC0449), a hedgehog signaling pathway inhibitor with anti-tumor activity in pts with tumors harboring *PTCH1* and *SMO* mutations. **Methods:** Pts whose tumors had *SMO* or *PTCH1* mutations were eligible; results were confirmed by NCI-MATCH central labs if possible. Pts received oral vismodegib (150 mg daily) for 4-week cycles until progression/toxicity. Tumor response was assessed every 2 cycles. Primary endpoint was ORR; secondary endpoints included PFS, 6-month PFS, OS, and predictive biomarkers. Cutaneous basal cell carcinomas were excluded. **Results:** Of 34 pts enrolled (6/20/16 – 9/22/20); 2 were ineligible and 1 did not start therapy. The 31 analyzable pts' demographics were primary tumor sites/histology [gastrointestinal (n = 9), skin/soft tissue (n = 7), gynecologic (n = 5), lung (n = 4), unknown primary (n = 4), ductal breast (n = 1), meningioma (n = 1)]; median age 64 (range 19-81); 48.4% women; 61.3% (19/31) > 3 lines of prior therapy; 74% (23/31) > 1 co-occurring mutation [median 2 co-alterations (range 1-20)]. 8/31 > 4 co-occurring alterations. 9 pts had *SMO* mutant tumors (all SNVs); 5/9 had > 1 co-occurring gene alterations. 22 pts had *PTCH1* alterations (7 SNVs and 15 indels); 18/22 pts had > 1 additional gene alteration. Of 31 analyzable pts, 22 were MATCH-confirmed (i.e. had central confirmation of tumor *PTCH1/SMO* mutations). MATCH-confirmed pts had ORR 9.1% (2/22) while all analyzable pts had ORR 6.5% (2/31). 2 PRs were seen in pts with a skin/soft tissue sarcoma (*PTCH*) and a meningioma (*SMO*) with a median duration of response 14 months. The 6-month PFS rate was similar in MATCH-confirmed and analyzable pts (22.4% and 23.2% respectively) and median PFS was identical at 1.8 months. Median OS was 9.1 months in MATCH-confirmed and 7.3 months in analyzable pts. Within analyzable *SMO* variants: 1 PR, 3 SD, 4 PD, and 1 unevaluable responses were documented. Within analyzable *PTCH1* variants: 1 PR, 7 SD, 10 PD, and 4 unevaluable responses were seen. 4 pts (12.9%) discontinued therapy due to AE. Among 33 pts starting therapy, 18 (54.5%) had grade 1-2 toxicity, while 2 (6.1%) had grade 3 treatment-related toxicity. Most common toxicities: grade 1-2 fatigue (n = 11), anorexia (n = 8), weight loss (n = 7), alopecia (n = 7), and dysgeusia (n = 6). There were 4 on-study deaths, but none were treatment related. **Conclusions:** Although the primary endpoint was not reached, vismodegib was well-tolerated with mostly grade 1-2 toxicities and substantial responses were seen in patients with SMOPro641Ala and PTCHGlu947Ter alterations. Further study of the impact of concomitant molecular alterations may yield additional insights into vismodegib mechanisms of response. Clinical trial information: NCT02465060. Research Sponsor: U.S. National Institutes of Health, This study was coordinated by the ECOG-ACRIN Cancer Research Group (Peter J. O'Dwyer, MD and Mitchell D. Schnall, MD, PhD, Group Co-Chairs) and supported by the National Cancer Institute of the National Institutes of Health under award numbers: U10CA180820, U10CA180794, UG1CA233302, UG1CA233180, UG1CA233290, UG1CA233341, UG1CA233193, and UG1CA233329.

3011 **Poster Discussion Session**

A multicenter, open-label, single-arm, phase 1 dose-escalation study to evaluate the safety, tolerability, and anti-tumor activity of FCN-159 in adults with neurofibromatosis type 1. *First Author: Xiaojie Hu, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University, School of Medicine, Shanghai, China*

Background: Neurofibromatosis type 1 (NF1) is an autosomal-dominant genetic disease that increases susceptibility to malignant tumors. Up to 50% of patients with NF1 present with plexiform neurofibroma (PN). Surgery, a common treatment strategy for patients with PN, has limited efficacy. NF1 is caused by mutations in the gene that encodes neurofibromin; the NF1 mutation then leads to tumorigenesis via dysregulation of the Ras/Raf/MEK/ERK pathway. FCN-159 is anti-tumorigenic via highly potent, selective inhibition of MEK1/2. This study aims to assess the safety of FCN-159 in patients with NF1-related PN. **Methods:** This is a multicenter, open-label, single-arm, phase 1 dose-escalation and phase 2 dose-expansion study (NCT04954001). Patients with NF1-related PN that was not completely resectable or not suitable for surgery were enrolled in the study; they received FCN-159 monotherapy continuously in 28-day cycles. Here, we report safety and clinical efficacy data from adults enrolled in phase 1. **Results:** As of the data cutoff of December 1, 2021, 19 adults from 3 hospitals in China have been enrolled in the phase 1 dose-escalation study, 3 in 4 mg, 4 in 6 mg, 8 in 8 mg, and 4 in 12 mg. The most common neurofibroma-related complications were disfigurement and pain, occurring in 10 patients (52.6%) and 4 patients (21.1%) at baseline, respectively. Four patients experienced dose-limiting toxicity; G3 folliculitis was reported in 1 patient (16.7%) receiving the 8-mg dose and 3 (100%) patients receiving the 12-mg dose. The maximum tolerated dose was determined to be 8 mg. Study-drug-related treatment-emergent adverse events (TEAEs) were observed in all 19 patients (100%); the majority were grade 1 or 2 in severity. Nine (47.4%) patients reported grade 3 study drug-related TEAEs; 4 patients experienced paronychia and 5 experienced folliculitis, which were the most common causes of dose reduction (42.1%) and drug interruption (21.2%). One patient experienced a serious adverse event of rhegmatogenous retinal detachment, but this was considered unrelated to the study drug as it was preexisting at baseline. Of the 16 patients with at least 1 post-baseline tumor assessment, all (100%) had reduced tumor size and 6 (37.5%) had a reduction in tumor size of > 20%. Three out of 6 patients with a second tumor assessment result had further tumor shrinkage; tumor volumes in the remaining 3 patients were similar to those at first assessment. The largest reduction in tumor size was 84.2%. **Conclusions:** Overall, FCN-159 at 8 mg is well tolerated, with easy to manage adverse events, and showed promising anti-neurofibroma activity in phase 1; this warrants further investigation in a phase 2 study on efficacy and safety in this indication. Clinical trial information: NCT04954001. Research Sponsor: Fosun Pharmaceutical Development Co., Ltd.

3012 **Poster Discussion Session**

NCI 9938: Phase I clinical trial of ATR inhibitor berzosertib (M6620, VX-970) in combination with irinotecan in patients with advanced solid tumors. *First Author: Liza C Villaruz, University of Pittsburgh Medical Center, Hillman Cancer Center, Pittsburgh, PA*

Background: Ataxia telangiectasia and Rad3 related (ATR) is activated in response to replication stress from topoisomerase 1 inhibitors. Selective ATR inhibition with berzosertib potentiates the efficacy of irinotecan in colorectal mouse xenograft models. We hypothesized that berzosertib in combination with irinotecan is well tolerated, modulates the DNA damage repair response to irinotecan, and the combination is associated with clinical activity. **Methods:** This phase I study utilized a modified Storer's up and down dose escalation design. Dose Levels (DLs) combined berzosertib 60 to 270 mg/m^2 with irinotecan 180 mg/m^2, every 2 weeks in a 4-week cycle. The primary endpoint was identification of the maximum tolerated dose (MTD) and recommended phase II dose (RP2D). Activity, pharmacokinetics (PK), and pharmacodynamics (PD) were secondary endpoints. The identification of molecular subpopulations sensitized to the combination was exploratory. **Results:** Between July 2016 and July 2021, 51 patients (pts) enrolled, of whom 50 received treatment. Pts most commonly had colorectal cancer (CRC, 39%), pancreatic cancer (24%), small cell lung cancer (SCLC, 6%) and non-small cell lung cancer (6%). The median number of prior lines of therapy was 4 (range, 2 to 11). In Stage I, 1 of 3 evaluable pts experienced dose-limiting toxicity (DLT) of grade 3 lung infection at DL3 (berzosertib 180 mg/m^2 - irinotecan 180 mg/m^2), and Stage II was initiated enrolling cohorts of 5 pts. In Stage II, 4 of the first 11 pts treated at DL4 (berzosertib 270 mg/m^2 - irinotecan 180 mg/m^2) were unable to complete the DLT evaluation period due to clinically significant toxicity not meeting DLT criteria: grade 2 diarrhea (1 pt), grade 3 diarrhea (1 pt), and grade 3 neutrophil decrease (2 pts). The protocol was amended to limit dose escalation beyond DL4. At DL4, 1 of 21 evaluable pts experienced DLT (grade 4 febrile neutropenia). Most common treatment-related grade ≥ 3 toxicities were neutrophil decrease (34%), lymphocyte decrease (30%), WBC decrease (28%), anemia (20%), diarrhea (16%), fatigue (8%) and hypokalemia (8%). 2 partial responses were observed, occurring in pts with pancreatic cancer and *ATM* alterations: 32% decrease in an ATM E11828/ATM K1109* tumor lasting 15.3 months and 68% decrease in an ATM R3008H/germline ATM R1882* tumor ongoing at 11 months. An additional pt with ATM S214fs*40 mutant colorectal cancer (CRC) experienced a 26% decrease lasting 7.5 months. **Conclusions:** Berzosertib 270 mg/m^2 - irinotecan 180 mg/m^2 was declared the RP2D. The combination is associated with manageable side effects and promising disease activity in ATM mutant solid tumors. PK and PD studies are in process. Tumor biopsy studies are planned in a 15 pt dose expansion cohort at DL4, enrolling pts with CRC, pancreatic cancer, SCLC and DNA damage repair deficient tumors. Clinical trial information: NCT02595931. Research Sponsor: U.S. National Institutes of Health.

3013 **Poster Discussion Session**

First-in-human, phase I study of TT-00420, a multiple kinase inhibitor, as a single agent in advanced solid tumors. *First Author: Sarina Anne Piha-Paul, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: TT-00420 is a spectrum-selective multi-kinase inhibitor that targets cell proliferation, angiogenesis, and immune-oncology pathways by inhibiting Aurora kinases A/B and Janus kinases (JAK) involved in cytokine signaling and receptor tyrosine kinases (FGFRs and VEGFRs) involved in the tumor microenvironment. TT-00420 has demonstrated anti-tumor activity in both *in vitro* and *in vivo* preclinical models of solid tumors, including triple-negative breast cancer (TNBC) and cholangiocarcinoma (CCA). **Methods:** This phase I, first-in-human, dose escalation and expansion study of TT-00420 (NCT03654547) enrolled adult patients with advanced or metastatic solid tumors. Capsules in 1 mg or 5 mg formulation were administered orally once daily in 28-day cycles. Dose escalation was guided by Bayesian modeling with overdose control. The primary safety endpoints were to determine dose limiting toxicities (DLTs) and a dose recommended for dose expansion (DRDE). Secondary endpoints included pharmacokinetics (PK) and preliminary efficacy evaluated per RECIST v1.1 criterion. **Results:** As of February 7, 2022, 48 advanced solid tumor patients were enrolled in the study, and received at least one dose of TT-00420 in 7 dose levels: 1 mg *q.d.* (N = 1), 3 mg *q.d.* (N = 1), 5 mg *q.d.* (N = 4), 8 mg *q.d.* (N = 10), 10 mg *q.d.* (N = 6), 12 mg *q.d.* (N = 20), and 15 mg *q.d.* (N = 6). DLTs were observed in 3 out of 40 DLT-evaluable patients, including 1 patient at 8 mg *q.d.* who had Grade (Gr) 3 palmar-plantar erythrodysaesthesia syndrome and 2 patients at 15 mg *q.d.* who both had Gr 3 hypertension. Among the twenty (20) safety evaluable patients treated at 12 mg, the DRDE, drug-related TEAEs included hypertension (n = 11, 55.0%; Gr 3: n = 6, 30%); diarrhea (n = 7, 35%, Gr 3: n = 1, 5%); mucosal inflammation (n = 7, 35%; Gr 3: n = 1, 5%); palmar-plantar erythrodysaesthesia syndrome (n = 6, 30%; Gr 3: n = 0, 0%); and vomiting (n = 4, 20%; Gr 3: n = 0, 0%). No grade 4 suspected adverse events were reported. Out of 42 patients who had at least one post-baseline scan, 7 (16.7%) had a best response of partial response (PR) and 22 (52.4%) had stable disease (SD). Among 7 PRs, 3 were CCA patients (one for each treated at 8 mg, 10 mg, or 12 mg), 2 were TNBC patients (one for each at 10 mg, or 12 mg), 1 was HER2-negative BC patient at 12 mg, and 1 was CRPC patient at 12 mg. Sustainable stable disease for six months or longer was observed in patients with colon cancer (n = 1), head and neck cancer (n = 1), and peritoneal mesothelioma (n = 1). **Conclusions:** TT-00420 monotherapy was well tolerated and had favorable PK characteristics. The TEAEs observed in dose escalation and dose expansion cohorts were manageable with concomitant treatment and/or dose interruptions of TT-00420 and reversible upon the discontinuation of TT-00420 treatment. Taking safety, efficacy and clinical PK into consideration, 10 mg *p.o. q.d.* was recommended for phase II study of TT-00420 in patients with advanced CCA. Clinical trial information: NCT03654547. Research Sponsor: TransThera Sciences (Nanjing), Inc.

3014 **Poster Discussion Session**

Efficacy proof-of-concept from a phase 1 study of a novel therapeutic peptide, ST101, targeting the oncogenic transcription factor C/EBPβ in patients with refractory solid tumors. *First Author: T.R. Jeffry Evans, University of Glasgow, Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom*

Background: The oncogenic transcription factor CCAAT/enhancer-binding protein β (C/EBPβ) promotes tumor survival and proliferation and inhibits differentiation. ST101 is a peptide antagonist of C/EBPβ, with anti-tumor activity in prostate cancer (PC), glioblastoma (GBM), breast cancer (BC), melanoma, and other pre-clinical models. **Methods:** This phase 1 study enrolled patients (pts) with refractory solid tumors with varying histologies. The primary objective was to evaluate safety/tolerability of ST101 and to determine the recommended phase 2 dose (RP2D). Secondary and exploratory objectives included pharmacokinetics (PK), preliminary efficacy (RECIST 1.1), and pharmacodynamic (PD) evaluation. The study used a 3+3 dose-escalation design, with once-weekly IV infusion dosing of ST101 at 0.5, 1, 2, 4, 6, 9 mg/kg or a flat dose of 500 mg. **Results:** Enrollment in phase 1 was completed in November 2021 with a total of 25 pts with multi-metastatic disease that were refractory to standard therapy. As of February 15, 2022, five pts remain on study with a median treatment duration of 27 weeks' (16-77). There were no DLTs, dose modifications, or serious adverse events (SAEs) related to ST101. The only AEs of note were G1-2 histaminergic infusion-related reactions (IRRs), largely pruritis and urticaria, managed with antihistamines, montelukast, and interruption/slowing of infusion. IRRs affected 93% of pts on the first dose at ≥4mg/kg and led to prolongation of infusion time. Intensity and frequency of IRRs decrease with repeat dosing. No other AEs were consistently reported. There was no evidence of accumulation upon continued exposure of ST101 and no anti-drug antibodies. Tumor immunohistochemistry showed dose-proportionate staining for ST101 and decreased tumor proliferation in several pts represented by decreased Ki67 expression. Population PK analysis supported flat dosing in phase 2. Five pts continue on treatment with one confirmed partial response in a patient with cutaneous melanoma lasting >42 weeks and four pts with ongoing stable disease. **Conclusions:** ST101 demonstrated safety at all doses explored and evidence of efficacy across dose levels, particularly higher doses and in pts with melanoma. PK and PD support a dose relationship for efficacy and selection of 500 mg as the RP2D. Pts are now enrolling in phase 2 cohorts to assess response in cutaneous melanoma, GBM, castrate-resistant PC, and HR$^+$ BC. Clinical trial information: NCT04478279. Research Sponsor: Sapience Therapeutics.

Phase 1 pts demonstrating clinical benefit (SD, PR, CR).

Dose (mg/kg)	Tumor type	Response	Duration (weeks)
0.5	Signet ring adenocarcinoma	SD	77+
2	Small bowel adenocarcinoma	SD	18
2	Abdominal sarcoma	SD	9
4	Cutaneous melanoma	PR	42+
6	Hepatocellular carcinoma	SD	18
6	Esophageal adenocarcinoma	SD	9
9	Cutaneous melanoma	SD	27+
Flat dose (mg)			
500	Uveal melanoma	SD	16+
500	Mucosal melanoma	SD	16+

+indicates ongoing treatment.

3015 **Poster Discussion Session**

Expanding clinical actionability in individual patient profiles with the Molecular Oncology Almanac. *First Author: Brendan Reardon, Dana-Farber Cancer Institute, Boston, MA*

Background: The clinical care of oncology patients is routinely informed by tumor and inherited genetic profiles. This is accomplished by molecular pathologists synthesizing the growing body of clinical guidelines and scientific evidence that associates cancer genome alterations and therapeutic response, and applying that knowledge during case reviews. Many academic medical centers formalize this process in the form of molecular tumor boards. As the number of cases for review and literature continue to increase, there is opportunity to leverage clinical interpretation algorithms to computationally prioritize molecular features and both enhance and automate the sample contextualization process. Here, we present the Molecular Oncology Almanac (MOAlmanac) to enable the rapid assessment of tumor actionability. **Methods:** Molecular Oncology Almanac is an open source clinical interpretation algorithm and paired knowledge base for precision cancer medicine. It is used to rapidly characterize and identify genomic features related to therapeutic sensitivity and resistance and of prognostic relevance. This is performed by assessing not only individual genomic features (e.g. somatic variants, copy number alterations, germline variants, and fusions) but also interactions between these events as well as secondary features such as mutational burden, mutational signatures, MSI status, and aneuploidy. MOAlmanac summarizes all clinically relevant findings into a web-based actionability report. The underlying knowledge base can be accessed through our API endpoints and web browser, and entries may be recommended through either Github or our browser extension. In addition, we developed a cloud-based web portal on top of the Terra framework to increase accessibility. **Results:** A total of 32,108 samples from 30,607 patients across 66 cancer types received targeted sequencing to characterize somatic variants, copy number alterations, and fusions from PROFILE's Oncopanel and were evaluated with MOAlmanac. Based on Oncopanel's tier 1 and tier 2 criteria for clinical actionability, we observed that 8,285 samples (26%, 0 - 69% by cancer type) of patients harbored at least one alteration suggesting therapeutic sensitivity based on FDA approvals or clinical guidelines. Actionability increases to 18,117 samples (56%, 0 - 85% by cancer type) when considering an expanded set of evidence to include relationships captured from clinical trials, clinical, preclinical, and inferential evidence; consequently providing at least one therapeutic hypothesis to otherwise variant-negative patients. **Conclusions:** Clinical actionability of molecular tumor data was increased in individual patients by expanding the set of evidence considered. Source code and a web portal for this project are available at moalmanac.org. Research Sponsor: U.S. National Institutes of Health.

3016 **Poster Discussion Session**

Genomic landscape of acquired resistance to targeted therapies in patients with solid tumors: A study from the National Center for Precision Medicine (PRISM). *First Author: Arnaud Bayle, Gustave Roussy Cancer Center, Villejuif, France*

Background: Despite the effectiveness of the various targeted therapies currently approved in solid tumors, acquired resistance remains a persistent problem that limits the ultimate effectiveness of these treatments. Polyclonal resistance to targeted therapy has been described in multiple solid tumors through high throughput analysis of multiple tumor tissue samples from a single patient. However, biopsies at the time of acquired resistance to targeted agents may not always be feasible and may not capture the genetic heterogeneity that could exist within a patient. We used here sequencing of circulating tumor DNA (ctDNA) to characterize the landscape of secondary resistance mechanisms in a large cohort of patients with solid tumors. **Methods:** This study enrolled patients with advanced cancer from two institutional molecular profiling program STING (NCT04932525, sponsor: Gustave Roussy) or BIP (NCT02534649sponsor: Institut Bergonié). Genomic analysis was performed for each patient by using the Foundation One Liquid CDx Assay (324 genes, tumor mutational burden [TMB], microsatellite instability status). **Results:** 3435 patients with metastatic disease entered the study. Among them 992 patients (29%) received a targeted therapy matched to a specific molecular alteration before ctDNA. The main tumor types were: prostate cancer (349, 35%), luminal breast cancer (236, 24%), oncogene-addicted non-small cell lung cancer (129, 13%), *KRAS*-wild type colorectal cancer (126, 13 %). The most frequent class of targeted agents were androgen receptor pathway inhibitor (n = 350, 35%), aromatase inhibitor (236, 24%), anti-*EGFR* monoclonal antibodies (166, 17%), anti-*EGFR* tyrosine kinase inhibitors (83, 8%). ctDNA sequencing revealed DNA aberrations involved in secondary resistance in 308 patients (31%). The most frequent aberrations were *AR* mutations/amplifications, *ESR1* point mutations, *KRAS* point mutations, *EGFR* point mutations. Among patients with resistance mutation, polyclonal aberrations were identified in 123 patients (40%). The median number of polyclonal aberrations per patient was 2 (range: 2-16). Polyclonal aberrations involved at least 2 different genes in 32 patients (10%). Preliminary results suggest that patients with polyclonal aberrations had worse outcome in comparison with patients with one or no detected aberration and final data will be presented at the time of the congress. **Conclusions:** We report here the first comprehensive landscape of genomic aberrations in ctDNA involved in resistance to targeted therapies in cancer patients. Polyclonal secondary genomic aberrations represent a frequent clinical resistance mechanism that may explain the poor rate of sustained complete remission observed with targeted therapies and must guide the development of future combinatorial strategies. Research Sponsor: None.

3017 **Poster Discussion Session**

Dual tissue and plasma testing to improve detection of actionable variants in patients with solid cancers. *First Author: Matthew Mackay, Tempus Labs, Inc., Chicago, IL*

Background: Next generation sequencing (NGS) of tumor tissue and plasma (circulating tumor DNA [ctDNA]) are used clinically to identify actionable genomic alterations, with implications for treatment selection and disease surveillance. Early studies have observed that solid tumor tissue and ctDNA testing may capture both overlapping and complementary alterations. Using the Tempus database, we examined whether dual tissue and ctDNA testing, "dual testing", improved identification of actionable variants compared with either modality alone. **Methods:** We used Tempus Lens to retrospectively analyze 3153 de-identified stage 4 patients (breast [N = 644], colorectal [N = 841], non-small cell lung cancer (NSCLC) [N = 1232], and prostate [N = 436]). Each patient had dual testing—Tempus xF (ctDNA, 105 panel genes) and Tempus xT (tumor tissue, 595-648 panel genes), representing 6306 total samples. Samples were defined as concurrent if biopsied ≤30 days apart and longitudinal if plasma was collected between 31–365 days after tissue biopsy. All analyses were limited to single nucleotide variants and insertions/deletions that met the limit of detection criteria for both assays (104 genes). Indication matched actionable variants were defined by OncoKB Level 1 and 2 evidence, or R1 within both xF and xT (13 genes). **Results:** Of the 3153 patients with dual testing, 37% (1168) had actionable variants identified by at least one test. 94% (1100/1168) of these patients had variants identified via solid tumor profiling alone, 73% (856) had variants identified via ctDNA profiling alone, and 64% (745) had perfectly concordant variants. Thus, dual testing identified additional variants in 36% (423/1168) of these patients compared to any singular test. Of the 423 patients who had additional actionable alterations discovered through dual testing, ctDNA revealed unique alterations—which were not found in solid tissue testing—in 22% (95/423) of patients. Of these patients, 72% (68/95) had all actionable variants identified solely from ctDNA. Of the 251 patients with additional alterations identified by concurrent dual testing, 24% (61/251) had unique alterations identified in plasma. Similarly, of the 172 patients with additional alterations identified by longitudinal dual testing, 20% (34/172) had unique alterations identified in ctDNA alone. **Conclusions:** In the largest study of its kind, we show that dual tumor tissue and ctDNA testing—with samples collected either concurrently or longitudinally—identified more patients with actionable alterations than single modality testing alone and therefore should be considered as part of routine NGS testing. Additional studies to explore the genetic and intra-patient tumor heterogeneity of these variants as well as the impact of time between tissue and plasma sampling assessments and implications for timing of therapeutic recommendations are underway. Research Sponsor: None.

3018 **Poster Discussion Session**

Differential diagnosis of hematologic and solid tumors using targeted transcriptome and artificial intelligence. *First Author: Hong Zhang, Genomic Testing Cooperative, Irvine, CA*

Background: Diagnosis and classification of tumors is becoming increasingly dependent on biological and molecular biomarkers. RNA expression profiling using next generation sequencing (NGS) provides information on various biological and molecular changes in the cancer and in the microenvironment. We explored the potential of using targeted transcriptome and artificial intelligence (AI) in the differential diagnosis and classification of various hematologic and solid tumors. **Methods:** RNA from hematologic neoplasms (N = 2606) and solid tumors (N = 2038) as well as normal bone marrow and lymph node control (N = 806) were sequenced by NGS using a targeted 1408-gene panel. The hematologic neoplasms included 20 different subtypes. Solid tumors included 24 different subtypes. Machine learning is used for comparing two classes at a time. Geometric Mean Naïve Bayesian (GMNB) classifier is used to provide differential diagnosis across 45 diagnostic entities with assigned ranking. **Results:** Machine learning showed high accuracy in distinguishing between two diagnoses with AUC varied between 1 (Sarcoma vs GIST) and 0.841 (MDS vs normal control) (examples in Table). For differential diagnosis between all 45 different diagnoses, we used 3045 samples for training the GMNB algorithm and 1415 samples for testing. Correct first choice diagnosis was obtained in 100% of ALL, 88% of AML, 85% of DLBCL, 82% of colorectal cancer, 88% of lung cancer, 72% of CLL, and 72% of follicular lymphoma. The algorithm had difficulty in typically overlapping diagnoses and diagnosed as first choice 19% of MDS, 46% of normal, and 12% of MPN. Diagnosis improved significantly when second choice was considered. **Conclusions:** Targeted RNA profiling with proper AI can provide highly useful tools for the pathologic diagnosis and classification of various cancers. Additional information such as mutation profile and clinical information can improve these algorithms, reduce subjectivity, and minimize errors in pathologic diagnoses. Research Sponsor: None.

Two classes	AUC	% Sensitivity	% Specificity	Leave one out AUC
Normal (N) vs AML	0.971	95.2	91	0.967
N vs ALL	0.98	95.5	98.7	0.984
N vs CLL	0.988	97	97.3	0.998
N vs MPN	0.925	90.9	83	0.894
N vs MDS	0.841	82	70.1	0.818
Marginal vs CLL	0.987	98.7	91.6	0.983
CLL vs Mantle	0.993	96.6	95.8	0.99
AML vs MDS	0.883	86.1	69.8	0.871
Breast vs Colorectal	0.979	95.6	96.1	0.984
Lung vs Colorectal	0.972	98	92.9	0.979
Lung vs Breast	0.971	97.6	89.8	0.98
Breast vs Ovarian	0.966	100	91.2	0.987
Ovarian vs Endometrial	0.962	92	93.7	0.906
Pancreas vs Colorectal	0.978	98	91.9	0.979
Pancreas vs Esophageal	0.979	95.9	97.1	0.984
Hodgkin vs Normal LN	0.977	95.8	87.7	0.936
Hodgkin vs T-lymphoma	0.964	91.7	90.8	0.938
Hodgkin vs DLBCL	0.969	92.8	98.5	0.959
DLBCL vs Follicular	0.975	95.6	91	0.974
DLBCL vs T-lymphoma	0.963	91.1	89.7	0.944
Sarcoma vs Ovarian	0.983	94.9	98.4	0.984
Sarcoma vs Lung	0.99	98.6	96.3	0.99
Sarcoma vs GIST	1	99.3	100	1

3019 **Poster Discussion Session**

AI-enabled identification prediction of homologous recombination deficiency (HRD) from histopathology images. *First Author: Gowhar Shafi, iNDX.Ai, Cupertino, CA*

Background: Homologous recombination deficient (HRD) tumors are highly responsive to platinum-based chemotherapy and poly (ADP-ribose) polymerase inhibitor (PARPi) therapy. Pathogenic BRCA-1 and BRCA-2 (BRCA1/2) alterations are key members of the HR DNA repair pathway but genomic instability status, including loss of heterozygosity, telomeric allelic imbalance and large scale state transitions across the genome are also predictive of HRD. HRD testing is currently performed by next generation sequencing which can take 2-4 weeks for results, has a high failure rate, requires significant tissue and is costly. We developed and tested the ability of an AI enabled platform to predict HRD status from the analysis of whole slide imaging of the diagnostic H&E slide. This platform, iPREDICT-HRD is rapid, precise, and cost effective. **Methods:** The AI engine was trained on 120 H&E slides that were used to identify tumor prior to manual microdisseection for HRD assessment by NGS. Histopathological features were extracted, followed by feature mapping to predict HRD status based on the results of NGS testing. ResNet AI algorithm was trained to segment, annotate and predict HRD status. 10 lac tiles of 256x256 size at 40x magnification were generated per pathological class. 70% of the data set was used for training and 30% for validation of the AI model. **Results:** Using single blinded clinical samples, iPREDICT-HRD tool detected HRD + ve samples with 99.3% accuracy with 100% sensitivity and 99% specificity in the test set. Patch-level predictions of HRD status demonstrated intra-tumor heterogeneity within the H&E slides. Visual inspection of the heatmap suggested the presence of patches with high predictive ability of HRD status and this outperformed an average HRD score for slides with heterogeneity. **Conclusions:** AI-enabled prediction of HRD status can be accurately performed on diagnostic H&E slides potentially yielding results quickly and afforadably, even when limited tissue is available for testing. Research Sponsor: None.

3020 **Poster Discussion Session**

A clinical AI-driven multiplex immunofluorescence imaging pipeline to characterize tumor microenvironment heterogeneity. *First Author: Dmitry Zarubin, BostonGene, Waltham, MA*

Background: Understanding the underlying heterogeneity of the tumor microenvironment (TME) on a single-cell level is becoming increasingly important to predict a patient's response to immunotherapy. Conventional imaging methods can help reveal tissue heterogeneity, but are not optimal for identifying multiple cellular subpopulations or cellular interactions from a single slide image, limiting their use in clinical settings. Here, we present a clinical artificial intelligence (AI)-driven multiplex immunofluorescence (MxIF) imaging pipeline based on novel cell segmentation and cell typing methods to evaluate tumor cellular heterogeneity, immune cell composition, and cell-to-cell interactions. **Methods:** A machine learning (ML)-based cell segmentation algorithm was trained on a manually annotated dataset created from 219 different regions of interest (ROIs) that contained 85,991 cells from various tissues (colon, kidney, lung, lymph node, tonsil, and ureter). A dataset containing 58,676 cells from 146 ROIs was used for validation and accuracy was determined between automated and manually annotated images; accuracy was further evaluated by calculating the f1-score using available methods (DeepCell and Stardist). Marker stains with a low signal-to-noise ratio were automatically enhanced, allowing for adequate cell-to-cell interaction analysis. **Results:** An automated MxIF image processing workflow was developed. Validation of the trained cell segmentation model showed high accuracy (0.80 f1-score), demonstrating superior performance compared to other methods (DeepCell and Stardist - 0.55 and 0.78 f1-score, respectively). The pathologist-determined accuracy (0.84 mean f1-score) indicated a near-human performance of the developed method. Normalized expression values obtained from the cell typing model allowed automated cell recognition. We analyzed cellular heterogeneity across 3 regions of colorectal cancer (CRC), gastric cancer (GC), and non-small cell lung cancer (NSCLC) samples. While proportions of immune cells varied, proportions of malignant epithelial cells were stable across all regions of each sample, as concordant percentages of Ki67+ cells were identified (CRC-19%; GC-21%; NSCLC-5%). Analysis of cell-to-cell interactions and immune communities identified tumor-, immune-, and stromal-enriched communities in all tumor samples that were stable across regions. **Conclusions:** By analyzing complex tumor tissue at single-cell resolution with high accuracy, this AI-driven MxIF imaging technology is able to characterize tumor and microenvironment heterogeneity across cancer types. This novel AI-based tool is currently being integrated into several ongoing prospective clinical studies to aid in the development of predictive and prognostic biomarkers. Research Sponsor: None.

3021 **Poster Session**

First-in-human, phase I study of AK109, an anti-VEGFR2 antibody, in patients (pts) with advanced or metastatic solid tumors. *First Author: Nong Xu, The First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China*

Background: AK109 is a fully-human monoclonal antibody that specifically binds to vascular endothelial growth factor receptor 2 (VEGFR2), thereby block vascular endothelial growth factor (VEGF)/VEGFR2 signaling pathway to inhibit angiogenesis, endothelial cell migration and proliferation of tumor cells. This phase I study is the first-in-human trial of AK109, which was designed to evaluate safety, tolerability of AK109, to determine the maximum tolerated dose (MTD), recommend phase II dose (RP2D) and to gain preliminary data on pharmacokinetics (PK), pharmacodynamics, immunogenicity and clinical activity for AK109 in pts with advanced or metastatic solid tumors resistant to standard therapies (NCT04547205). **Methods:** This open-label, multi-center, phase I study included a dose escalation phase (part 1) using a 3+3 design to determine MTD and potential RP2D (n = 36 max), with planned dosing of 2, 4, 8, 12 and 18 mg/kg q2w and 15mg q3w, followed by a dose expansion phase (part 2), at 2 potential RP2Ds in q2w or q3w respectively (n = 24-30) . The PK characteristics, dose limiting toxicity (DLT), adverse events per CTCAE 5.0 and efficacy (ORR, DCR, DoR, PFS per RECIST v1.1, OS, etc.) of AK109 were evaluated. **Results:** As of December 30th, 2021 (median follow-up: 6.0 months), 40 pts (median age: 59.5 years) were enrolled, 16 pts in part 1 and 24 pts in part 2. No DLT was observed AK109 in part 1. Tumor types included gastric cancer (n = 9), non-small cell lung cancer (n = 8), hepatocellular carcinoma (n = 8), colorectal cancer (n = 5), pancreatic carcinoma (n = 2) and oesophagus cancer (n = 2), etc. Preliminary PK analyses showed systemic exposure in C_{max} and AUC_{last} increased dose proportionally at doses of 8 mg/kg and above, with a mean half-life of 8.5 to 10 days. 12mg/kg q2w and 15mg/kg q3w were selected as RP2Ds. Average exposure of AK109 was 6.9 cycles. Eight pts received over 10 cycles of AK109 . Treatment related adverse events(TRAE) occurred in 38 (95%) of all pts. Grade 3 and 4 TRAE occurred in 16 (40%) of all pts. The most common TRAEs were proteinuria (22/40, 55%), hypertension (13/40, 32.5%) and AST increased (11/40, 27.5%). Serious adverse event (SAE) occurred in 11 (27.5%) pts, 2 (5%) of which were AK109 related. ORR and DCR were 10.0% and 62.5%, respectively. The median PFS of non-small cell lung cancer (n = 8) and gastric cancer (n = 9) were 5.6 months (95% CI, 1.3, NE) and 5.5 months (95% CI, 1.4, NE), respectively. **Conclusions:** AK109 showed manageable safety and promising anti-tumor activity. Two phase II studies of AK109 combined with AK104 (anti PD-1/CTLA-4 bi-specific antibody) are ongoing to evaluate the efficacy of AK109 combined with AK104 in patients with multiple solid tumors (NCT05142423, NCT04982276). Clinical trial information: NCT04547205. Research Sponsor: Akeso Biopharma, Inc.

3022 **Poster Session**

Safety of the cyclin dependent kinase 9 (CDK9) inhibitor FIT039 for cervical intraepithelial neoplasia (CIN) 1 or 2 in a phase I/II trial. *First Author: Junzo Hamanishi, Kyoto University Graduate School of Medicine, Department of Gynecology and Obstetrics, Kyoto, Japan*

Background: Human papillomaviruses (HPVs) infect uterine cervical epithelial cells, leading to cervical intraepithelial neoplasia (CIN) and cervical cancer. However, there is no treatment for HPV infection in the uterine cervix prior to vaccination. We recently reported that cyclin dependent kinase 9 (CDK9) plays a critical role in viral RNA transcription of DNA viruses such as HPVs in host cells, and that FIT-039, a specific inhibitor of CDK9, suppresses the proliferation of several DNA viruses. Here, we evaluated the safety and antiviral effect of a FIT039-releasing vaginal tablet (FIT039CT) for CIN1 or 2 (CIN1/2). **Methods:** A multi-institutional, single-blind, placebo-controlled randomized phase I/II clinical trial involving 2 cohorts was designed to evaluate the safety of transvaginal FIT039CT for CIN1/2 as follows:. In the first cohort, 8 healthy women were randomized into FIT039CT (50mg/day or 100mg/day) or control group. In the second cohort, 14 women with a primary diagnosis of CIN1/2 were randomized into either FIT039CT (100mg/day) or control group. The primary endpoints were adverse events and plasma concentrations of FIT039. **Results:** 22 patients (8 volunteers, 11 CIN1 and 3 CIN2) were enrolled. There were no serious adverse events. Adverse events considered related to treatment were mild (vaginal discharge Grade 1: FIT039CT 16/17 women [94%] vs placebo 2/6 [33%]) and self-limiting in both cohorts. No patient discontinued this study due to adverse events. Maximum concentration (C max) and terminal elimination half-life (t 1/2) of serum FIT039 concentrations after single transvaginal treatment of FIT039CT were similar between the two doses as follows; C max (mean ± standard deviation) was 4.5 ± 0.5 ng/mL (50mg/day) and 4.4 ±1.4 ng/mL (100mg/day) at 6-7 hours; mean t1/2 was 14.8 ± 2.1 hours (50mg/day) and 12.1 ± 2.6 hours (100mg/day) hours. **Conclusions:** This study demonstrated the safety and validity of transvaginal FIT039CT once a day and may contribute to the development of an antiviral agent that can cure CIN1/2, and supports the design of the ongoing phase 2 clinical study. Clinical trial information: jRCT2051180201. Research Sponsor: Japan Agency for Medical Research and Development (AMED, 20lk0201081h0003), Pharmaceutical/Biotech Company.

3023 **Poster Session**

A phase I study to evaluate the safety, tolerability, and pharmacokinetics of MSB0254 in Chinese patients with solid tumors. *First Author: Tianshu Liu, Zhongshan Hospital of Fudan University, Shanghai, China*

Background: MSB0254 is a humanized vascular endothelial growth factor receptor 2 (VEGFR-2) monoclonal antibody. MSB0254 inhibits angiogenesis induced by either VEGF-A or –C. This trial is a phase I study to evaluate MSB0254's safety, tolerability and PK profiles, as well as early anti-cancer activities in Chinese patients with advanced solid tumors. **Methods:** In this phase I study (NCT04381325), locally advanced or metastatic solid tumor patients failed previous standard treatments were enrolled. In the dose escalation phase, following 3+3 rules, MSB0254 was given intravenously Q2W (every 2 weeks) at 4mg/kg , 8mg/kg, 12mg/kg, 16mg/kg, and Q3W at 20mg/kg. In the dose expansion phase, patients with selected tumor types will be treated with MSB0254 at 16mg/kg Q2W or 20mg/kg Q3W. Primary objectives were to evaluate the safety and tolerability and to identify maximum tolerable dose (MTD) and/or Recommended Phase 2 Dose (RP2D). Secondary objectives included the assessment of pharmacokinetics, immunogenicity, and preliminary efficacy per RECIST1.1. **Results:** As of 10th Jan, 2022, a total of 22 Chinese patients have been enrolled into the dose escalation phase and treated with MSB0254 at different dose levels from 4-16mg/kg Q2W or 20mg/kg Q3W. MTD was not reached. One DLT was reported in 12mg/kg Q2W dose cohort. A subject with intra-cholangial carcinoma developed G3 (grade 3) upper gastrointestinal hemorrhage on the C1D13. The adverse event was resolved after symptomatic treatment. The most common treatment-emergent adverse events (TEAEs) (>10%) included: hypertension (27.3%), AST increased (27.3%), γ-GGT increased (22.7%), neutrophil count decreased (18.2%), proteinuria (18.2%), WBC count decreased (13.6%), platelet count decreased (13.6%) and anemia (13.6%). Three subjects (13.6%) experienced G3 TEAEs: 1 upper gastrointestinal hemorrhage, 1 anemia and 1 Hypertriglyceridemia. No G4/5 TEAE was observed. And three subjects (13.6%) experienced 3 SAEs: 1 upper gastrointestinal hemorrhage, 1 G2 intestinal obstruction caused hospitalization and 1 G2 fatigue caused hospitalization. MSB0254 displayed a dose proportional pharmacokinetic profile between 4-16 mg/kg Q2W with calculated $T_{1/2}$ of 6-9 days. Eighteen subjects had at least one tumor assessment per RECIST 1.1 after MSB0254 treatment. Eleven subjects (61.1%) had best response of stable disease (SD). Four of them had stable disease for more than 6 months, including a neuroendocrine tumor (NET), a gastric cancer, an epithelioid hemangioendothelioma (EHE) and a submaxillary gland carcinoma patient. **Conclusions:** MSB0254 demonstrated a manageable safety profile and preliminary antitumor activity in patients with advanced solid tumors. 16mk/kg Q2W is recommended as RP2D. 20mg/kg Q3W is still under investigation. The study of MSB0254 on the expansion phase in selected tumor patients is ongoing. Clinical trial information: NCT04381325. Research Sponsor: Suzhou Transcenta Therapeutics Co., Ltd.

3024 **Poster Session**

VEGF inhibitors (VEGFi) activity in liver metastases (mets) regardless of primary cancer type: Meta-analysis and systematic review. *First Author: Ines Esteves Domingues Pires Da Silva, Melanoma Institute Australia, The University of Sydney, Sydney, Australia*

Background: Liver metastasis is a poor prognostic factor in several cancers and is associated with poor response to immunotherapy (IO) in melanoma and lung cancer. VEGFi have activity in hepatocarcinoma (HCC) and is hypothesized to be due the hypoxic microenvironment. Whether this is also true for liver mets is unknown. We sought to assess the efficacy of VEGFi in liver mets utilizing randomized-controlled clinical trials (RCTs) testing the efficacy of VEGFi, regardless of primary cancer site. **Methods:** Systematic searches of PubMed, Cochrane CENTRAL, and Embase were conducted from January 1, 2000, to January 1, 2022. All RCTs that compared a backbone of systemic therapy (chemotherapy [chemo] and/or IO and/or targeted therapy [TT]) or best supportive care (BSC) with vs without VEGFi in patients (pts) with liver mets from any cancer were selected. HCC trials were excluded. Study design, cancer type, number of pts, lines of treatment, study drugs and hazard ratios (HRs) with 95% CIs for overall survival (OS) and progression-free survival (PFS) were extracted. Pooled effects of VEGFi in pts with liver mets across different cancer types were estimated using random effect model with inverse variance. Heterogeneity between studies was assessed by I^2 statistics. Sensitivity analyses were performed considering prespecified subgroups of trials. **Results:** 3170 pts with liver mets from 19 RCTs were included in this meta-analysis: 8 colorectal cancer, 4 non-small cell lung cancer, 4 renal cell cancer & urothelial cancer, 1 pancreatic cancer, 1 GIST and 1 gastric cancer. Backbone systemic therapy in these trials included: chemo (11), TT (2), IO (2), chemo+IO (1), chemo+TT (1); and 2 BSC trials. Moderate heterogeneity between studies for both PFS (I^2= 55%) and OS (I^2= 46%) was seen. The addition of VEGFi to standard systemic therapy or BSC was associated with superior PFS (HR = 0.61; 95% CI, 0.50-0.74; p < 0.0001) and OS (HR = 0.86; 95%CI, 0.76-0.99; p = 0.0334) in pts with liver mets, regardless of whether pts had only liver mets or concurrent other sites of mets. In the subset of RCTs with data on pts without liver mets, the benefit with VEGFi was more pronounced in patients with liver mets (HR = 0.56) vs those without liver mets (HR = 0.64) for PFS, but not for OS. **Conclusions:** The addition of VEGFi to standard management improved survival outcomes in pts with liver mets across different cancer types and warrants further investigation. VEGFi added to IO may be effective in pts with resistant liver mets. Research Sponsor: None.

3025 **Poster Session**

Dose-finding and -expansion studies of trastuzumab deruxtecan in combination with other anti-cancer agents in patients (pts) with advanced/metastatic HER2+ (DESTINY-Breast07 [DB-07]) and HER2-low (DESTINY-Breast08 [DB-08]) breast cancer (BC). *First Author: Fabrice Andre, Gustave Roussy, Université Paris-Sud, Villejuif, France*

Background: Trastuzumab deruxtecan (T-DXd), an antibody-drug conjugate composed of a humanized anti-HER2 monoclonal antibody and a topoisomerase I inhibitor payload, is approved for pts with unresectable or metastatic HER2+ BC with ≥2 prior anti-HER2–based therapies. T-DXd showed improved progression-free survival vs trastuzumab emtansine (T-DM1) as an earlier-line treatment (tx) for pts with HER2+ metastatic BC in the phase 3 DESTINY-Breast03 trial (Cortes J, et al. *Ann Oncol*. 2021;32:S1283-S1346. Abstract LBA1). Preliminary antitumor activity of T-DXd was shown in heavily pretreated pts with HER2-low advanced/metastatic BC in the phase 1 DS8201-A-J101 trial (Modi S, et al. *J Clin Oncol*. 2020;38:1887-1896). We report preliminary results from the dose-finding phase of 2 trials investigating T-DXd combination tx in HER2+ or HER2-low metastatic BC. **Methods:** DB-07 (phase 1b/2; NCT04538742) and DB-08 (phase 1b; NCT04556773) are 2-part, modular, open-label, multicenter trials of T-DXd combined with other anticancer tx in pts with advanced/metastatic BC that is HER2+ (DB-07) or HER2 low (DB-08). Part 1 of each study is an ongoing dose-finding phase; pts must have ≥1 prior tx for metastatic BC. Part 2 of each study is a dose-expansion phase; pts must have no (DB-07) or ≤1 (DB-08) prior tx for metastatic BC. We report preliminary results from the T-DXd + pertuzumab module of DB-07 part 1 (data cutoff: Oct 15, 2021) and T-DXd + anastrozole and T-DXd + fulvestrant modules of DB-08 part 1 (data cutoff: Sep 27, 2021); pts in the DB-08 modules must be hormone receptor positive. The part 1 primary objective was to assess safety and tolerability and determine the recommended phase 2 dose (RP2D) according to the modified toxicity probability interval-2 algorithm. Pts were followed up beyond the 21-day dose-limiting toxicity (DLT) period (28 days for T-DXd + fulvestrant) for safety events. **Results:** In DB-07, 7 pts were enrolled and received T-DXd 5.4 mg/kg + pertuzumab 420 mg (loading dose: 840 mg) every 3 wk (q3w; not evaluable for DLTs, n = 1). In DB-08, 6 pts were enrolled and received T-DXd 5.4 mg/kg q3w + anastrozole 1 mg daily (not evaluable for DLTs, n = 1); another 6 pts were enrolled and received T-DXd 5.4 mg/kg q3w + fulvestrant 500 mg every 4 wk (loading dose: 500 mg cycle 1 days 1 and 15). For all 3 modules, no DLTs were reported in any DLT-evaluable pts; the dose levels used in part 1 were approved to be the RP2Ds for use in the dose-expansion part of each corresponding module. No deaths on study or cases of interstitial lung disease/pneumonitis were reported to date. **Conclusions:** The RP2Ds for the T-DXd combinations were the standard doses for BC of each individual drug. These studies are ongoing, with additional T-DXd combinations being evaluated and further follow-up underway. Clinical trial information: NCT04538742; NCT04556773. Research Sponsor: This study is funded by AstraZeneca Pharmaceuticals. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201).

3026 **Poster Session**

Safety, pharmacodynamic, and clinical response evaluation of nilotinib and paclitaxel in adults with refractory solid tumors. *First Author: Sarah Shin, Developmental Therapeutics Clinic/Early Clinical Trials Development Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD*

Background: The combination of the BCR-Abl kinase inhibitor nilotinib and the anti-tubulin agent paclitaxel was identified in the NCI-ALMANAC study to have greater-than-additive activity in the NCI-60 cell line panel and greater-than-single-agent antitumor activity in xenograft models, in which this combination induces tumor epithelial-mesenchymal transition (EMT). A phase 1 study was initiated to establish the safety, tolerability, and recommended phase 2 dose (RP2D) of this combination in patients (pts) with advanced solid tumors and to examine the pharmacokinetic (PK) and pharmacodynamic (PD) effects of the combination to understand the mechanism of action (NCT02379416). The dose escalation phase established the RP2D as 300 mg oral nilotinib twice daily and 80 mg/m^2 intravenous paclitaxel on days (D) 1, 8, and 15 of each 28-day cycle. Here, we report the safety, preliminary PD, and efficacy data for this combination. **Methods:** Nilotinib and paclitaxel were administered as noted above, with a 1-day (escalation cohort) or 2-day (expansion cohort) paclitaxel-only run-in during the first cycle to enable comparison of the PK and PD effects of the combination vs. single-agent paclitaxel. Paired biopsies to assess tumor molecular response were collected from expansion cohort pts at baseline, cycle (C) 1 D2, and C1D28, with an optional biopsy at progression; accrual continued until ≥ 12 sufficient-quality paired biopsies were obtained. Blood specimens to assess molecular responses in circulating tumor cells (CTCs) were obtained at several timepoints during C1 and longitudinally every cycle thereafter. EMT biomarkers were measured in tumor and CTC specimens using quantitative immunofluorescence microscopy assays. **Results:** A total of 44 pts were enrolled. Three pts had partial responses (PR), and 1 had an unconfirmed PR (9%); 23 pts (52%) had a best response of stable disease (SD), including 7 pts on study for ≥ 10 cycles. The most common grade (Gr) 3-4 treatment-related adverse events were hematologic and hypophosphatemia. No pts experienced Gr ≥ 3 peripheral neuropathy. The median time on treatment was 67 days. Two pts with granulosa cell ovarian carcinoma had durable responses, completing 74+ and 64 cycles. Multiple patient biopsies and corresponding CTC specimens exhibited treatment-induced EMT. Longitudinal analysis of CTC EMT phenotypes in the 2 pts with extended PR revealed a substantial increase in mesenchymal-like CTCs prior to progression for the pt on study for 64 cycles; such increases were not observed in the pt still on study after 74+ cycles. Further PD analyses are ongoing. **Conclusions:** The combination of nilotinib and paclitaxel demonstrates promising disease control with durable response in select patients. Tumor PD analyses to discover the underlying pharmacology of this active regimen are ongoing. Funded by NCI Contract No. HHSN261201500003I. Clinical trial information: NCT02379416. Research Sponsor: U.S. National Institutes of Health.

3027 **Poster Session**

TLD-1, a novel liposomal doxorubicin, in patients (pts) with advanced solid tumors: Dose escalation and expansion part of a multicenter open-label phase I trial (SAKK 65/16). *First Author: Dagmar Hess, Cantonal Hospital St. Gallen, St. Gallen, Switzerland*

Background: TLD-1 is a novel liposomal doxorubicin that compared favorably to conventional liposomal formulations of doxorubicin in preclinical in vivo mouse breast cancer models. This phase I first-in-human trial is aiming to determine the recommended phase II dose (RP2D), toxicity profile, pharmacokinetics and preliminary activity. **Methods:** Patients with a maximum of 3 prior lines of systemic chemotherapy and preferably anthracycline-sensitive disease were eligible. TLD-1 was administered on day 1 iv over 60-90 minutes (depending on individual dose) q 21 days, for up to 6 or 9 cycles (according to prior anthracycline-exposure) with premedication of 8mg dexamethasone. Dose escalation with dose levels (DL) 1-7 of 10, 16, 23, 30, 35, 40 and 45mg/m^2 started with an accelerated titration design, treating one pt at each DL up to DL6 (40mg/m^2) followed by a modified continual reassessment method at DL7 due to observed toxicity. **Results:** 30 pts (F:M = 24:6) have been treated, one each at DLs 1-6, 15 pts at DL7 and an additional 9 pts at DL6. Most frequent tumor types included breast (n = 13), ovarian (n = 6), cervical cancer (n = 2) and cholangiocarcinoma (n = 2). Median age was 67.5 years (range:38-83), 13 pts were exposed to prior anthracyclines. The median number of cycles was 4 (range:1-9). No dose-limiting toxicities (DLT) occurred during cycle 1. At DLs 1 to 5, no treatment-related G3 AEs (TRAE) were observed. At DL6, there was one case of mucositis G3, one of palmar-plantar-erythrodysesthesia (PPE) G3 and one of anemia and neutropenia G3 each. One patient with pre-existing valvular cardiopathy developed symptoms of heart-failure G3 after 8 cycles. Echocardiography showed severe mitral regurgitation with normal LV-EF. In addition one case of urinary-tract infection G3 was seen. Dose-modifications or -delays due to AEs occurred in 7/50 cycles. At DL7, one case of mucositis G3, 3 events of PPE G3 and one case of fatigue G3 were reported. In addition, one case of infection with shingles occurred. Dose-modifications or -delays due to AEs occurred in 12/61 cycles. Shingles and heart failure were reported as SAEs. All toxicities listed above were categorized as TRAE. 29/30 pts were evaluable for response. Three breast cancer pts had a partial response, 2 at DL7 and 1 at DL6, 14 pts had stable disease. **Conclusions:** No DLT was observed up to DL7. RP2D was defined at 40mg/m^2 due to cumulative PPE G3 at DL7. The trial is ongoing with a comparative PK-part evaluating the two iv liposomal formulations of doxorubicin TLD-1 and Caelyx. Clinical trial information: NCT03387917. Research Sponsor: InnoMedica Holding AG.

3028 **Poster Session**

Phase 1 study of OBT076, a first-in-class anti-DEC205 ADC, in patients with advanced/metastatic solid tumors: Safety, efficacy, and PK/PD results. *First Author: Olivier Rixe, Quantum Santa Fe, Santa Fe, NM*

Background: OBT076, an Antibody Drug Conjugate (ADC) consisting of a fully human IgG1 antibody conjugated via a cleavable linker to the derivative microtubule inhibitor DM4. It has specificity for the CD205/Ly75 target antigen which is an endocytic receptor overexpressed on the cell surface and immunosuppressive dendritic cells. This phase 1 study evaluates safety, tolerability, PK/PD and preliminary efficacy of OBT076 in solid tumor patients with high expression of target protein CD205 (CAP-CLIA validated centralized IHC test). **Methods:** Open label, two parts trial in patients with metastatic CD205+ve solid tumors who progressed on standard therapy. Part 1 of the study consisted in dose escalation from 1.6 mg/kg to 3.5 mg/kg. An mTPI design is used to guide to determine the maximum tolerated dose (MTD) Treatment was given on day 1 every 3 weeks followed by GCSF on day 8. Blood samples and flow cytometry were used to assess PK/PD. Tumor response was assessed every three cycles. Part 2 of trial is an expansion basket trial enriched in indications where preliminary efficacy has been shown. **Results:** The study completed Part 1 dose escalation. Part 2 expansion phase is ongoing. Between Dec 2019 and January 2022, 20 patients were enrolled (18 patients in the dose escalation and 2 in the ongoing expansion). The median age 61, 9 patients were males and 9 had ECOG PS 0. All patients had at least one metastatic site and 90% received at least 2 lines of chemotherapy in the metastatic setting. Recommended dose for the expansion phase is 3.0 mg/kg. No other significant side effects have been observed. PK data showed that Cmax of 40.000-90.000 ng/ml was achieved between 2.5 and 3.5mg/kg dose and is comparable to the therapeutic dose in mouse models. In part 1 of the study, 7 patients derived clinical benefit despite being in disease progression at trial entry. One patient with gastric cancer with linitis plastica experienced major improvement with complete disappearance of ascites and metastatic adenopathy after cycle 3. The six other patients had lasting stable disease and received between 5-14+ cycles with median of 5 cycles. Two patients with low PD-L-1 expression received checkpoint inhibitor treatment with pembrolizumab after 2 and 5 cycles of OBT076, both patients experienced near complete response after only one to two cycles. **Conclusions:** OBT076 at 3.0mg/kg has shown favorable safety profile with manageable neutropenia. The preliminary efficacy has shown preliminary antitumoral single agent activity in gastric, ovarian and lung cancer. The two patients who received a sequential administration of pembrolizumab after OBT076 showed major tumor activity. Sequential administration of OBT076 followed by a PD-1 inhibitor was also supported by PD markers and warrants further evaluation. Clinical trial information: NCT04064359. Research Sponsor: Oxford Biotherapeutics.

dose cohort (mg/kg)	1.6	2.5	3.5	3.0
N (patients)	3	9	3	3
DLTs	0	1*	1*	0

Neutropenia was the DLT*.

3029 **Poster Session**

First-in-human study of OBI-999: A globo H-targeting antibody-drug conjugate in patients with advanced solid tumors. *First Author: Apostolia Maria Tsimberidou, Department of Investigational Cancer Therapeutics, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: OBI-999 is a novel antibody-drug conjugate, composed of a humanized monoclonal IgG1 antibody which targets the tumor-associated carbohydrate antigen Globo H, conjugated with monomethyl auristatin E (MMAE, vedotin). Upon binding to Globo H, OBI-999 is internalized into the tumor cell, and the linker (Thiobridge) connecting MMAE (an ultrapotent antimitotic agent) to the monoclonal antibody is cleaved by cathepsin B to release MMAE, thereby causing cell cycle arrest by inhibiting tubulin polymerization. We conducted a first-in-human, phase 1, dose-escalation study of OBI-999 monotherapy in patients with advanced cancer (NTC04084366). **Methods:** OBI-999 was administered intravenously at doses of 0.4, 0.8, 1.2, and 1.6 mg/kg on Day 1 of a 21-day cycle. Patients received study treatment until disease progression, unacceptable toxicity, or up to 2 years of treatment. **Results:** Overall, 15 adult patients were treated. OBI-999 administered on Day 1 of each 21-day cycle was well tolerated up to 1.2 mg/kg, the maximum tolerated dose (MTD). Treatment-related AEs (TRAEs) were noted in 40% (6/15) of patients. TRAEs ≥Grade 3 were noted in 27% (4/15) of patients; of whom 3 had neutropenia and 2 had anemia. OBI-999 exhibited non-linear pharmacokinetics from 0.4 mg/kg to 1.6 mg/kg, with lower clearance at higher doses. A retrospective validated automated immunohistochemistry assessment indicated 50% of patients with advanced solid tumors had high Globo H staining (H-score cutoff ≥100). Of 3 patients treated at the 1.6 mg/kg dose level; 2 developed Grade 4 neutropenia during Cycle 1 and the third developed Grade 4 neutropenia on Cycle 2 Day 15. One patient (1.6 mg/kg) with Grade 4 neutropenia also developed Grade 4 renal insufficiency and died from progressive disease (direct bilirubin, 3.5 mg/dL). Five (33.3%) patients had stable disease (SD), including 1 patient with adenoid cystic carcinoma of the oropharynx (SD for 13 cycles); 1 patient with gastroesophageal junction adenocarcinoma (SD for 8 cycles), and 3 patients with other tumor types (SD for 4, 2, and 2 cycles). **Conclusions:** We completed the dose-escalation portion of the study. OBI-999 was well tolerated. The recommended phase 2 dose was determined to be 1.2 mg/kg once every 3 weeks. Dose-dependent, non-cumulative neutropenia was dose limiting. We are currently enrolling patients with high Globo H expressing solid tumors (H-score ≥100) in the expansion phase of the study, which includes pancreatic, colorectal, and cancers of other histologic subtypes. Clinical trial information: NTC04084366. Research Sponsor: OBI Pharma Inc.

3030 **Poster Session**

Safety, pharmacokinetics, and clinical activity of OBI-3424, an AKR1C3-activated prodrug, in patients with advanced or metastatic solid tumors: A phase 1 dose-escalation study. *First Author: Apostolia Maria Tsimberidou, Department of Investigational Cancer Therapeutics, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: OBI-3424 is a novel nitrogen mustard prodrug that can be selectively converted in the presence of the AKR1C3 enzyme into the bis-alkylating agent OBI-2660, which forms intra- and inter-strand DNA crosslinks resulting in cell death. This selective mode of activation distinguishes OBI-3424 from traditional alkylating agents, and potentially improves the safety profile and antitumor activity against chemo- and radio-resistant tumors. We conducted a first-in-human, phase 1, dose-escalation study of OBI-3424 monotherapy in patients with advanced solid tumors (NCT03592264). **Methods:** OBI-3424 was administered intravenously at doses of 1, 2, 4, 6, 8, or 12 mg/m^2 (Days 1 and 8 every 21 days, Schedule A) or 8, 10, 12, or 14 mg/m^2 (Day 1 every 21 days, Schedule B). A "3+3" design was used for dose escalation. Patients received study treatment until disease progression, unacceptable toxicity, or up to 2 years of treatment. **Results:** Overall, 39 adult patients were treated. In patients receiving Schedule A, the maximum tolerated dose (MTD) of OBI-3424 was determined to be 8 mg/m^2. Dose limiting toxicities (DLTs) were reported at the 12 mg/m^2 dose level, including thrombocytopenia (Grade 3-4, 5 of 6 patients) and anemia (Grade 3-4, 5 of 6 patients). Platelet count nadirs were noted on Day 15 or Day 22. These cytopenias led to dose modification and resulted in protocol amendment (Schedule B). In Schedule B, the MTD was not reached at the maximum dose tested (14 mg/m^2). Grade 3 or higher anemia was noted in 3 of 6 patients treated at 14 mg/m^2; the recommended phase 2 dose (RP2D) is 12 mg/m^2 (Day 1 every 21 days). Treatment-related AEs (TRAEs) were noted in 82% (32/39) of patients. The most common TRAEs were anemia (64%), thrombocytopenia (51%), nausea (26%), and fatigue (21%). No patient had a fatal TRAE, 49% had ≥Grade 3 TRAEs, including 3 patients who had serious TRAEs. OBI-3424 showed linear pharmacokinetics from 1 to 14 mg/m^2, with minimal accumulation after repeated dosing. A retrospective validated automated immunohistochemistry assessment indicated that 27% of patients had high AKR1C3 staining (H-score ≥135). Best confirmed response was stable disease in 21 patients (54%). **Conclusions:** We completed the dose-escalation portion of the study. The RP2D was determined to be 12 mg/m^2 once every 3 weeks. OBI-3424 was well tolerated. Dose-dependent, non-cumulative thrombocytopenia and anemia were dose limiting. We are currently enrolling patients with pancreatic cancer and other tumor types with overexpression of AKR1C3 (H-score ≥135) in the expansion phase of the study. Clinical trial information: NCT03592264. Research Sponsor: OBI Pharma Inc.

3031 **Poster Session**

BOLD-100-001 (TRIO039): A phase 1b dose-escalation study of BOLD-100 in combination with FOLFOX chemotherapy in patients with advanced gastrointestinal solid cancers: Interim safety, tolerability, and efficacy. *First Author: Jennifer L. Spratlin, Alberta Health Services, Edmonton, AB, Canada*

Background: BOLD-100 is a first-in-class ruthenium-based anticancer agent in Phase 1b / 2 clinical development for the treatment of advanced gastrointestinal (GI) cancers in combination with FOLFOX. Being developed primarily as a combinational agent, BOLD-100 induces cellular stress through modulation of the unfolded protein response, production of reactive oxygen species and induction of DNA damage. BOLD-100 demonstrates synergy in established preclinical models in combination with various anticancer therapies, particularly in resistant cell lines. **Methods:** This is a prospective, Phase 1b dose-escalation (Part A) and Phase 2 dose-expansion (Part B) study of BOLD-100 in combination with FOLFOX for colorectal (CRC), pancreatic (PDAC), gastric (GC) and biliary tract (BTC) cancers. Patients (pts) receive BOLD-100 with FOLFOX on day 1 of each 14-day cycle. In Part A, pts are enrolled in a 3+3 design to determine the combination recommended Phase 2 dose (RP2D), with BOLD-100 dose-escalation (420, 500 and 625 mg/m2) up to dose level 3. Part B comprises 5 cohorts treated at the RP2D until progressive disease or unacceptable toxicity. In Part A, reported here, the primary endpoints are safety, tolerability and maximum tolerated dose; the Part B endpoints are efficacy (primary), pharmacokinetic (PK) and pharmacodynamic parameters (secondary), and duration of response (exploratory) (NCT04421820). **Results:** As of 07 Feb 2022 (contains Part A preliminary data), 19 pts (mean age 65 years) were treated: 9 (47%) CRC, 5 (26%) BTC, 4 (21%) PDAC, 1 (5%) GC. Patients had a median of 3 prior systemic therapies, and 18 (95%) were enrolled with stage IV disease. Median number of cycles completed was 5 (range 1-15). 18 pts reported ≥1 treatment-emergent adverse events (AEs), most commonly fatigue (n = 12, 63%), nausea (n = 9, 47%) and stomatitis (n = 8, 42%). The majority of AEs were grade (G) 1-2. 7 G4 AEs (all neutropenia), and 1 unrelated G5 AE of pulmonary embolism occurred. There were 8 serious AEs in 6 different pts, with 1 SAE of dyspnea reported as related to BOLD-100. 2 pts experienced infusion-related reactions, related to chemotherapy. 2 dose-limiting toxicities have been observed: G3-4 neutropenia complicated by fever > 38.5°C or infection (n = 1, cohort #2) and inability to receive planned doses due to AEs (n = 1, cohort #3). To date for evaluable pts (n = 16), disease control rate of 75%, 1 partial response (48% target lesion reduction) and 11 stable disease have been observed. **Conclusions:** BOLD-100 plus FOLFOX is well-tolerated with no clinically significant safety findings. Dose-escalation data supports a BOLD-100 RP2D of 625 mg/m2 for the expansion phase. Progression-free survival, overall survival, and PK data are forthcoming. Clinical trial information: NCT04421820. Research Sponsor: Bold therapeutics.

3032 **Poster Session**

Increased systemic toxicities from antibody-drug conjugates (ADCs) with cleavable versus non-cleavable linkers: A meta-analysis of commercially available ADCs. *First Author: Carrie Wynn, University of Mississippi Medical Center, Jackson, MS*

Background: Though in theory ADCs should deliver high-dose chemotherapy directly to target cells with few systemic effects, in clinical practice numerous side effects have been observed. We hypothesized that ADCs with cleavable linkers would have more systemic toxicities than those with non-cleavable linkers due to the increased free payload released systemically. To compare their side effect profiles, we conducted a meta-analysis of adverse events (AEs) of commercially available ADCs. **Methods:** Systematic review yielded 12 phase II/III clinical trials that led to the FDA approval of commercially available ADCs. Polatuzumab vedotin was not included because it was only studied in combination with other agents. Any grade AEs and grade ≥3 AEs occurring in at least 5% of patients in each study were recorded. The estimated inverse variance weighted absolute average risk and 95% confidence interval (CI) were estimated for each AE. Absolute risk differences and 95% CIs were estimated by linker type. **Results:** Data from 2,417 patients treated with 9 ADCs were pooled. 7 ADCs had cleavable linkers (N = 1,082), and 2 had non-cleavable linkers (N = 1,335). At least half of studies reported thrombocytopenia, neutropenia, anemia, increased AST and ALT, nausea, vomiting, diarrhea, hypokalemia, headache, and fatigue, as well as rates of all grade and grade ≥3 AEs. AEs ≥ grade 3 occurred in 43% of patients overall, 47% in the cleavable linker arms and 34% in the non-cleavable arms. This was significantly different (weighted risk difference -12.9%; 95% CI -17.1% to -8.8%). There was also a significant difference favoring non-cleavable linkers for ≥ grade 3 neutropenia (-9.1%; 95% CI -12% to -6.2%) and ≥ grade 3 anemia (-1.7%; 95% CI -3.3% to -0.1%). Cleavable linkers were significantly associated with increased AST all grade (3.9%; 95% CI 0.3% to 7.5%) and increased ALT all grade (3.7%; 95% CI 0.2% to 7.3%), though notably the CI approached 0 on the low end of difference for each. There was no significant difference in rates of all grade AEs or in rates of discontinuation due to AEs. There was no significant difference in rates of all grade nausea, vomiting, diarrhea, hypokalemia, or headache. Finally, there was no significant difference in rates of grade ≥3 thrombocytopenia, increased AST/ALT, or fatigue. **Conclusions:** Cleavable linkers appear to have significantly higher rates of ≥ grade 3 AEs and neutropenia within the limitations of this non-randomized comparison and treatment of heterogeneous malignancies. The increased payload in the circulation likely accounts for this; however, it may also make them more efficacious, as suggested by the results of the DESTINY-Breast03 trial. In the final analysis, we will compare the efficacy of cleavable vs non-cleavable ADCs indirectly using the standard of care for each tumor and line of therapy, with the exception of breast cancer. Research Sponsor: None.

3033 **Poster Session**

Enabling circulating cell-free mRNA theranostics from PD-L1, ALK, ROS1, NTRK to transcriptomic profiling. *First Author: Chen-Hsiung Yeh, Circulogene Theranostics, Birmingham, AL*

Background: Circulating cell-free mRNA (cfmRNA) expression can be considered as a compendium of transcripts collected from all organs. It has the capability of integrating functional and genetic information of tissues, highlighting this analyte's unique potential as a non-invasive biomarker in early detection, therapy selection and patient follow-up of cancer management. Plasma cfmRNA is usually made up of degraded small fragments of smaller than 200 nucleotides, very low concentration, and with different terminal modification, these properties make it difficult to detect. We have developed, validated and automated a cfmRNA clinical testing workflow for simultaneous measurement of PD-L1 expression, ALK, ROS1 and NTRK fusions. This proprietary real-time qPCR-based process is exosome-free, highly sensitive and requires only half milliliter of plasma with 72-hour turnaround. A plasma cfmRNA profiling database covering 750 genes in 9 major cancer pathways was also established with novel cancer type-specific characteristics. **Methods:** Circulating cfRNA was extracted from 400 uL of plasma and reverse transcribed to cDNA. The cDNA pool then served as the universal source for multi-biomarker tests. All target primer and probe sets were selected based on RNA secondary structures. Plasma PD-L1 expression, ALK, ROS1, NTRK fusions and transcriptomic profiling were performed by Circulogene CLIA/CAP-complied testing platform. **Results:** Limit of detection (LOD) for PD-L1, ALK/ROS1 and NTRK were 1.0 copy/uL, 17.5 copies/uL and 28 copies/uL, respectively. For scoring of PD-L1 expression, based on Keynote trials, we used the 30th percentile Ct value as cutoff in qPCR which corresponded to IHC ≥ 50% TPS; while the 66th percentile Ct value corresponded to IHC ≥ 1% TPS. PD-L1 cfmRNA was demonstrated to be an excellent surrogate marker of tissue PD-L1 protein for clinical outcomes with immunotherapy. In a global cfmRNA landscape, a functional transcriptomic databank was also established, including differential gene expression, classification, functional clustering and cancer type-specific signatures. **Conclusions:** Liquid biopsy qPCR tests targeting PD-L1 expression, ALK, ROS1 and NTRK fusions are commercially available and filling the gap of tissue-based assays and NGS. Our groundbreaking cfmRNA work has research, clinical, and diagnostic value, and provides greater dimensionality to the current knowledge of cfmRNA research and makes a significant jump into understanding and devising strategies to tailor cancer Dx and Rx. Research Sponsor: None.

3034 **Poster Session**

Multicancer early detection with a spectroscopic liquid biopsy platform. *First Author: Matthew Baker, Dxcover Ltd., Glasgow, United Kingdom*

Background: A rapid, low-cost, sensitive, multi-cancer early detection (MCED) test would be transformational in the diagnostics field. Earlier cancer detection and instigation of treatment can increase survival rates. An effective test must accurately identify the small proportion of patients with typically non-specific symptoms who actually have cancer. Such symptoms don't easily segregate by organ system, necessitating a multi-cancer approach. **Methods:** In this large-scale study (n = 2094 patients) we applied the Dxcover Cancer Liquid Biopsy to differentiate cancer against non-cancer, as well as organ specific tests to identify cancers of the brain, breast, colorectal, kidney, lung, ovary, pancreas, and prostate. The test uses Fourier transform infrared spectroscopy to analyze all macromolecules in a minute volume of patient serum, and machine learning to build a classifier of the resultant spectral profiles for calling the likelihood of cancer. **Results:** For the overall cancer classification, our model achieved 90% sensitivity with 61% specificity when tuned for sensitivity, with detection rates of 93% for stage I, 84% for stage II, 92% for stage III and 95% for stage IV. We also tuned for maximum sensitivity or specificity, whilst the other statistic was fixed above a minimum value of 45%. This resulted in 94% sensitivity with 47% specificity, and 94% specificity with 48% sensitivity, respectively. For organ specific cancer classifiers area under the curve values were calculated for all cancers: brain (0.90), breast (0.74), colorectal (0.91), kidney (0.91), lung (0.90), ovarian (0.85), pancreatic (0.81) and prostate (0.85). **Conclusions:** Cancer treatment is often more effective when given earlier and this low-cost strategy can facilitate the requisite earlier diagnosis. With further development, the Dxcover MCED test could have a significant impact on early detection of cancer, which is vital in the quest for improved survival and quality of life. Research Sponsor: Dxcover Ltd.

3035 **Poster Session**

Blood-based detection of actionable alterations from NCI-MATCH patients with no tissue results. *First Author: Robin Harrington, Molecular Characterization Laboratory, Frederick National Laboratory for Cancer Research, Frederick, MD*

Background: The National Cancer Institute Molecular Analysis for Therapy Choice (NCI-MATCH) multi-arm phase II clinical trial tested tumor tissue from 5,954 patients with advanced refractory cancer to assign treatment based on the molecular profile. Molecular profiling was successful for 93% of patients. For 267 of the patients who were not enrolled because molecular profiling was not successful, plasma cfDNA was evaluated to provide insight into the potential utility of blood-based testing in a broad spectrum of histologies when tissue is not evaluable. **Methods:** Cell-free DNA was extracted from plasma collected from Streck blood tubes and quantitated. Libraries were constructed using ^{3} 15 ng cfDNA into the Illumina TruSight Oncology 500 ctDNA RUO Assay, including unique molecular identifiers and duplex barcodes for error correction. Libraries were sequenced on the NovaSeq 6000 with S4 XP flow cells. **Results:** Of the 267 samples, 250 samples (94%) were evaluable, representing 72 histologies, including colorectal cancer (N = 36), lung adenocarcinoma (N = 15), pancreatic adenocarcinoma (N = 14), and invasive breast carcinoma (N = 12). Of these, 231 (92%) had ^{3} 1 OncoKB annotated mutation, with 208 patients (83%) having putative somatic mutations detected in genes not commonly associated with clonal hematopoiesis. The most common somatic mutations were in *TP53*, *KRAS*, *APC*, and *PIK3CA*, reported in 51%, 20%, 12%, and 12% of patients respectively. A total of 109 patients (44%) had ^{3} 1 actionable mutation of interest (aMOI) reported that could have been used for treatment assignment in the NCI-MATCH clinical trial. After applying histology and molecular exclusions, 75 patients (30%) had ^{3} 1 aMOI. The most common assignable treatment arms were *Z1B/Z1BX1* (palbociclib with *CCND1/2/3*, N = 13), Z1F (copanlisib with *PIK3CA* Mutations, N = 13), S1/S1X1 (trametinib with *NF1* mutation, N = 12), and Z1C/Z1CX1 (palbociclib with *CDK4/CDK6* Amplification and Rb Expression by IHC, N = 10). Mutations in genes commonly associated with clonal hematopoiesis (CH) were prevalent in this population. Along with the expected high frequency of *DNMT3A* (21% of patients) and *TET2* (11%) mutations, *PPM1D* mutations were the highest amongst CH genes, with 61 patients (24%) having ^{3} 1 *PPM1D* mutation, likely due to the heavily pre-treated nature of these patients. **Conclusions:** Variants observed in the blood are consistent with what is reported in the tissue. Using liquid biopsy when tissue is not evaluable can expand the ability of patients to obtain mutation information that can inform treatment compared to using tumor tissue only. Cell-free DNA provided valuable mutation information for these patients and could have resulted in up to an additional 75 patients being eligible for treatment selection based on their mutation profile. These results indicate that blood-based screening could be a tool for future NCI-sponsored clinical studies. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

3036 **Poster Session**

Test performance and clinical validity of circulating tumor DNA (ctDNA) in predicting relapse in solid tumors treated with curative intent therapy. *First Author: Abhenil Mittal, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Studies have explored the prognostic value of ctDNA in predicting relapse in solid tumors treated with curative intent. These studies have evaluated ctDNA at specific 'landmark' timepoint or over numerous 'surveillance' time points. However, variable results have led to uncertainty about the clinical validity of this tool. Here, we quantify the predictive and discriminatory accuracy of ctDNA and explore sources of heterogeneity at both landmark and surveillance time points across different tumor sites. **Methods:** A search of MEDLINE (host: PubMed) identified studies evaluating ctDNA after curative intent therapy in solid tumors. Odds ratios (OR) for disease recurrence at both landmark and surveillance time points for each study were calculated and pooled in a meta-analysis using the Peto method. Pooled sensitivity and specificity weighted by individual study inverse variance were estimated and meta-regression utilizing linear regression weighted by inverse variance was performed to explore associations between patient and tumor characteristics and the OR for disease recurrence. **Results:** Of 23 studies identified; 16 (750 patients) and 14 studies (853 patients) reported on landmark and surveillance time points respectively. The median time from completion of definitive therapy to landmark testing was 51.5 days (range 3-120). The pooled OR for recurrence at landmark was 22.22 (95% CI 14.82-33.30) and at surveillance was 27.51 (95% CI 19.1-39.63). The pooled sensitivity for ctDNA at landmark and surveillance time points were 59.9% and 73.2%. The corresponding specificities were 90.9% and 86.6%. Subgroup results are shown in the table. There was lower predictive accuracy with the use of tumor site specific panels, in patients receiving adjuvant chemotherapy and in lung cancer. Meta-regression showed that longer time to landmark and higher number of surveillance blood draws were associated with higher prognostic accuracy, as was a history of smoking. **Conclusions:** Although ctDNA at both landmark and surveillance time points shows high prognostic accuracy, it has low sensitivity, suboptimal specificity and therefore weak discriminatory accuracy to predict relapse in patients with solid tumors treated with curative intent. Testing methodology, time points and patient populations need to be optimized before it can be incorporated routinely in clinical practice. Research Sponsor: None.

Surveillance Studies by Subgroup (studies/patients)	OR (95% CI)	Subgroup difference p
Disease site		
1. Lung (5/176)	11.37 (6.13-21.06)	0.001
2. Breast (3/187)	27.76 (13.53-56.95)	
3. Colorectal (5/426)	53.36 (28-101.70)	
4. Bladder (1/64)	104.64 (26.64-410.95)	
Panel		
1. Patient specific (8/605)	51.70 (31.4-85.14)	< 0.001
2. Tumor sitespecific (6/248)	13.28 (7.77-22.70)	
Adjuvant chemotherapy		
1. No (5/287)	58.74 (27.46-125.66)	
2. Yes (9/566)	21.92 (14.46-33.24)	0.03

3037 **Poster Session**

An ultra-sensitive assay using cell-free DNA fragmentomics for multi-cancer early detection. *First Author: Yang Shao, Geneseeq Research Institute, Nanjing Geneseeq Technology Inc., Nanjing, China*

Background: Although most cancer can benefit from early detection by more effective treatments and better prognosis, current screening programs are only limited to tumor-specific tests for a subset of common cancers. To benefit a broader population and outweigh the risks of single-cancer tests, an effective and affordable multi-cancer test should be developed for sensitive early detection of multiple cancers and accurate prediction of cancer tissue of origin simultaneously. **Methods:** In this study, we enrolled 971 cancer patients of the most prevalent and lethal cancer types, including primary liver cancer (PLC, *N*= 381), colorectal adenocarcinoma (CRC, *N*= 298), and lung adenocarcinoma (LUAD, *N*= 292), as well as 243 healthy controls. The participants were randomly divided into a training cohort and a test cohort in a 1:1 ratio. Five fragmentomic features representing cfDNA fragmentation size, motif sequence, and copy number variation were extracted from processed whole-genome sequencing (WGS) data of the participants to build the base models. Each base model implemented five machine learning algorithms for model training, and the optimal base models were used to create the final multi-dimensional model through ensemble stacked machine learning. The integrated multi-cancer model is composed of the first-level binary cancer detection model and the second-level multi-classification cancer origin model. The training cohort was used to train the models with 10-fold cross-validation. The test cohort remained untouched during model construction and was solely used for performance evaluation. **Results:** Our cancer samples are highlighted by mostly early-stage diseases (early-stage PLC: 88.5%; CRC: 100.0%; LUAD: 100.0%). The cancer detection model reached an area under the curve (AUC) of 0.983 for differentiating cancer patients from healthy individuals in the test cohort. At 95.0% specificity, the sensitivity of detecting all cancer is 95.5%, and 100.0%, 94.6%, and 90.4% for PLC, CRC, and LUAD, respectively. Its sensitivity is consistently high for early-stage, small-size tumors. The cancer origin model demonstrated an overall 93.1% accuracy for predicting tissue of origin in the test cohort (97.4%, 94.3%, and 85.6% for PLC, CRC, and LUAD, respectively). Furthermore, the model's cancer detection and origin classification performance remained robust when reducing sequencing depth to 1× (cancer detection: ≥ 91.5% sensitivity at 95.0% specificity; cancer origin: ≥ 91.6% accuracy). **Conclusions:** We utilized multiple plasma cfDNA fragmentomic features to build an ensemble stacked machine learning model. The assay reached ultrasensitivity and accuracy for multi-cancer early detection, shedding light on leveraging cfDNA fragmentomics for early screening in clinical practice. Research Sponsor: None.

3038 **Poster Session**

Utilization of cell-free DNA fragmentomics in minimal residual disease detection for non-small cell lung cancer. *First Author: Rong Yin, Department of Thoracic Surgery, Jiangsu Key Laboratory of Molecular and Translational Cancer Research, Jiangsu Cancer Hospital & Nanjing Medical University Affiliated Cancer Hospital & Jiangsu Institute of Cancer Research, Nanjing, China*

Background: Non-small-cell lung cancer (NSCLC) is the leading cause of worldwide cancer-related deaths. Currently, ~30-55% of the NSCLC patients develop recurrence due to minimal residual disease (MRD) after receiving surgical resection of the tumor. Therefore, there is an urgent clinical need to accurately predict the MRD risk in post-surgical NSCLC patients. However, the current targeted ctDNA mutation profiling method is limited by the cost of design and synthesis of patient-specific panels and relatively low sensitivity. Cell-free DNA (cfDNA) fragmentomics have recently shown great accuracy and affordability in early cancer detection. This retrospective study aims to develop an ultra-sensitive and affordable fragmentomic assay for MRD detection in NSCLC patients. **Methods:** A total of 116 NSCLC patients (54 stage I, 21 stage II, 40 stage III and 1 stage IV), who received curative surgical resections (32 patients relapsed during follow-up, median relapse time: 315.5 days), enrolled in the Lung Cancer Tempo-spatial Heterogeneity (LuCaTH) cohort. A total of 231 plasma samples, collected at 7 days post-surgery and 3 months thereafter, were used for whole-genome sequencings (~5X). The cfDNA fragment size profile was used to fit a Regularized Cox Regression model. A leave-one-out cross-validation (LOOCV) was used to evaluate the model's predictive performance, and the optimal cutoff for predicting relapse was determined by identifying the Youden index to the predicted relative risk for all samples. **Results:** Our machine learning model showed an excellent performance in detecting patients with a high risk of recurrence. At 7 days post-surgery, the high-risk patients detected by our model showed an increased risk of 3 times compared to the low-risk patients (hazard ratio [HR] = 3.2, $p < 0.001$). Multivariate analysis confirmed that the association between model-determined high-risk status and patient relapses was not affected by the baseline clinical variables (age, sex, smoking, stage, etc.). Furthermore, the longitudinal analysis showed that our model was capable of detecting high-risk patients who were 11 times more likely to develop recurrence, independent from other clinical factors (multivariate HR = 11.8, $p < 0.001$). Overall, our model was able to identify high-risk status in 26 of 32 relapsed patients (81.2% sensitivity), preceding radiographic relapse by a median of 216 days. Furthermore, the sensitivity for MRD detection reached 91% while combining the model prediction with mutation-based ctDNA results. **Conclusions:** We have developed a predictive model for patient recurrence by detecting the fragmentomic profiling of plasma cfDNA contributed by the MRD. Despite being limited by the relatively small cohort size, our model has shown great sensitivity in predicting patient recurrence, therefore exhibiting a great potential to guide adjuvant therapy decisions. Research Sponsor: National Science Foundation of China.

3039 **Poster Session**

Plasma first: Accelerating lung cancer diagnosis through liquid biopsy. *First Author: Miguel Garcia Pardo, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Molecular profiling of tumor tissue is the gold standard for treatment decision making in advanced non-small cell lung cancer. Results may be delayed or unavailable due to insufficient tissue samples or prolonged wait times for biopsy, pathology assessment and testing. We piloted the use of plasma molecular testing as part of the initial diagnostic work-up for patients with suspected advanced lung cancer (NCT04863924). **Methods:** Patients with radiologic evidence of advanced lung cancer referred to the lung rapid diagnostic program underwent plasma circulating tumor DNA (ctDNA) testing using InVisionFirst-Lung, a next-generation sequencing (NGS) assay targeting 37 genes. Standard tissue testing was performed with comprehensive NGS (Oncomine). The primary endpoint was time to treatment in stage IV NSCLC patients compared to an historical pre-COVID-19 cohort (2018-9). Secondary endpoints included actionable targets identified in plasma, % of patients starting targeted therapy based on liquid biopsy and result turnaround time (TAT). **Results:** Between July 1 to December 31, 2021, 60 patients were enrolled. Median age was 70 years (range 33-91), 52% were female, 57% Caucasian, 48% never smokers. Of these, 73% had NSCLC, 12% small cell, 10% non-lung pathology and 5% declined tissue biopsy. Of 44 NSCLC patients, 5 (11%) had early-stage disease and underwent curative therapy. Most stage IV patients (79%) had systemic treatment. Median time to treatment initiation in the study cohort was 34 days (n = 31, range 10-90) versus 62 days (n = 101, range 13-159) in the historical cohort ($p<0.0001$). Two thirds (N = 23) of stage IV NSCLC patients had actionable alterations identified, (30% in current/ex-smokers); 18 started targeted therapy including 10 based on plasma results before tissue results were available. Median TAT was 7 days for plasma from blood draw to reporting (range 4-14) and 26 days for tissue molecular testing (range 11-42), $p<0.0001$. Concordance was high between plasma and tissue testing (70%). Liquid biopsy identified actionable alterations for 3 patients not identified by tissue NGS. In 4 cases, plasma testing failed to identify actionable alterations detected in tissue, due to undetectable plasma ctDNA. **Conclusions:** Liquid biopsy in the initial diagnostic workup of patients with suspected advanced NSCLC leads to faster molecular results and shortens time to treatment compared to tissue testing alone. Supplementing the current standard of tissue molecular testing with a plasma-first approach during the diagnostic work up of patients with suspected advanced lung cancer may increase access to precision medicine and improve patient outcomes. Clinical trial information: NCT04863924. Research Sponsor: Lung Health Foundation, Pharmaceutical/Biotech Company, Princess Margaret Cancer Foundation (Invest in Research Grant), the Division of Medical Oncology/Hematology Fellowship Award, and Merck LCIC.

Actionable alterations detected in stage IV NSCLC (n = 39).	
Molecular alteration	**N (%)**
***EGFR* L858R**	7 (18)
***EGFR* exon 19 deletion**	5 (13)
***KRAS* G12C**	4 (10)
***EGFR* exon 20 insertion**	2 (5)
***ERBB2* exon 20 insertion**	2 (5)
***EGFR* L861Q**	1 (2.5)
***MET* exon 14 skipping mutation**	1 (2.5)
ALK fusion	1 (2.5)

3040 **Poster Session**

A cell-free RNA-based next-generation sequencing (NGS) assay for the detection of actionable gene fusions in patients with non–small cell lung cancer (NSCLC). *First Author: Yukti Choudhury, Lucence Diagnostics, Singapore, Singapore*

Background: Gene fusions and alternate RNA splice forms represent clinically actionable driver and resistance-conferring alterations in NSCLC and other cancers. Where tissue samples are inadequate for molecular testing, liquid biopsies could address the gap in detection of clinically relevant gene fusions. Targeted cell-free (cf) DNA-based NGS methods are typically used for non-invasive blood-based testing of gene fusions, but have limited sensitivity if fusion breakpoints involve long intronic regions or repetitive sequences (e.g. *NTRKs* and *NRG1*). RNA-based approaches are not affected by introns, can identify expressed fusion genes and can discriminate splicing. We developed an NGS assay optimized for cfRNA analyte for the detection of actionable gene fusions and exon deletion/skipping events in liquid biopsies. **Methods:** A highly multiplexed molecular-barcoded primer panel was designed for cfRNA-based detection of actionable fusion genes in NSCLC (*ALK*, *BRAF*, *FGFR2*, *FGFR3*, *MET* (including exon 14 skipping), *NRG1*, *NTRK1/2/3*, *RET* and *ROS1*) covering > 90% of reported driver and partner gene exons in COSMIC database. The panel also targets housekeeping genes as endogenous sample controls. We developed a custom bioinformatics pipeline to call fusions and exon skipping based on split and spanning reads. **Results:** In initial analytical validation using fragmented RNA from pre-characterized reference material (representing 32 unique fusions at known copy numbers), the assay could detect as low as 10 fusion copies with a sensitivity of 97.6% and a specificity of 100%. For clinical testing, cfRNA co-eluted with cfDNA in nucleic acid extracts from plasma was used. In plasma samples (n = 103) from advanced NSCLC, 76% (15/21) of fusions (5 *ALK*, 3 *RET*, 2 *ROS1*, 5 *MET* ex14 skipping, 1 *FGFR3-TACC3*) detected in a clinically validated cfDNA assay (LiquidHALLMARK) were also detected in corresponding cfRNA. In a subset of samples that were driver-negative untreated or tyrosine kinase-inhibitor treated, the cfRNA assay yielded 9 gene fusions or breakpoints (1 *CD74-NRG1*, 4 *BRAF*, 2 *MET*, 2 *FGFR3-TACC3* fusions) that could not be detected by the cfDNA assay. This represents an increase of 8.7% (9/103) of actionable alterations (driver or resistance) identified using cfRNA. Together cfRNA and cfDNA resulted in 30 fusion events to be detected compared to 21 by the cfDNA assay alone, representing a 42.8% (9/21) increase in fusion-specific detection of the combined assay. **Conclusions:** This novel cfRNA assay can detect actionable gene fusions and exon skipping events in liquid biopsies with high sensitivity. Combining cfRNA with more routine cfDNA testing can increase the total actionable diagnostic information from non-invasive testing in NSCLC patients where tissue samples are lacking, especially for gene fusions not amenable to detection in cfDNA. Research Sponsor: Lucence Diagnostics.

3041 **Poster Session**

Early detection of cancer using cell-free DNA (cfDNA) size analysis on a multiplexed amplicon-based next-generation sequencing (NGS) platform. *First Author: Yukti Choudhury, Lucence Diagnostics, Singapore, Singapore*

Background: Tumor-derived cfDNA fragments are observed to be shorter in length than normal cfDNA. This size (length) difference can be analyzed as a tumor-specific signal. Whole genome or probe hybridization-based NGS methods can capture cfDNA fragments of native sizes. However, amplicon-based NGS assays are not directly amenable to cfDNA size analysis due to predetermination of amplicon sizes by design. Here we present a method to extract relative distribution of cfDNA fragment lengths from a targeted amplicon-based assay and show its utility in cancer detection. **Methods:** The LiquidHALLMARK cfDNA assay is an amplicon-based NGS test for the sensitive detection of genomic alterations in 80 genes. Although panel design is optimized for cfDNA with average amplicon length of ~150 bp, the consecutive tiling design of amplicons for genes with contiguously targeted regions, e.g. *BRCA* permits the formation of longer amplicons (> 150 bp) from physically subsequent primer pairs, provided longer template cfDNA molecules are present. Cancer samples (n = 281), clinically tested by LiquidHALLMARK during Sep 2020-Sep 2021, and healthy samples (n = 28) were included for analysis. For each sample, fragment lengths were inferred from sequencing alignment files, and binned into "short" (0-150 bp) and "long" (151-500 bp) groups. A relative "size ratio" of the total number of short vs. long fragments per sample was calculated, and examined with clinical features, plasma cfDNA concentration (cfDNA/ml) and highest mutation allele frequency (AF%), in a model to predict cancer. **Results:** Calculated size ratios (relative abundance of short fragments) were higher in cancer than normal samples (median 47.6 vs. 31.2, $p < 0.001$). Cholangiocarcinoma and colorectal cancer samples had the highest size ratios (medians: 62.9 and 60.9, respectively) in agreement with a genome-wide NGS study that profiled cfDNA sizes. Size ratios were higher in metastatic (n = 143) compared to early stage (n = 30) lung cancers ($p = 0.0039$), indicating a stage-dependent accumulation of shorter cfDNA fragments. Size ratio was correlated with cfDNA/ml ($r = 0.63$, $p < 0.01$) and AF% ($r = 0.42$, $p < 0.01$). In 20-fold cross-validation of a logistic regression model trained to predict cancer, average area under curve (AUC) was 0.82 using size ratio, 0.86 using cfDNA/ml, and increased to 0.95 with the two features combined. **Conclusions:** Our analysis shows that it is feasible to derive meaningful cfDNA fragment size information from amplicon-based NGS data. Importantly, relative fragment size distributions observed in cancer and healthy plasma samples by this method are concordant with alternate target capture methods. Fragment size ratios derived from relatively small, targeted amplicon panels are a novel feature that, combined with other molecular and clinical features, can enhance non-invasive methods of cancer detection. Research Sponsor: Lucence Diagnostics.

3042 **Poster Session**

Detection of homologous recombination deficiency (HRD) in cell-free DNA (cfDNA) using an amplicon-based next-generation sequencing (NGS) assay. *First Author: Jonathan Poh, Lucence Diagnostics, Singapore, Singapore*

Background: Homologous recombination (HR) deficiency is characterized by tumor genomic instability, often due to alterations in *BRCA1/2* and other HR-related genes. HRD predicts sensitivity to PARP inhibitors (PARPi) in prostate, ovarian and breast cancers. For the subset of cancers that have genomic instability without detectable alterations in HR genes, profiling biomarkers of HRD such as loss of heterozygosity (LOH) could identify additional HRD positive (HRD+) patients that may benefit from PARPi. Here, we present a novel cfDNA NGS assay that can detect tumor LOH non-invasively to improve assessment of HRD+ status. **Methods:** An amplicon-based HRD NGS assay covering > 1000 SNPs was developed to detect LOH both globally and on the gene level in cfDNA. Analytical validation was done using LOH+ *BRCA*-mutant cell lines in limiting dilution admixtures. Clinical performance was assessed by benchmarking findings from 46 tumor tissue DNA samples against results from an orthogonal NGS-based genomic scarring assay. Clinical utility of the HRD assay was evaluated in 75 cfDNA samples, including 72% (54/75) from *BRCA*-associated cancers (36 breast, 12 prostate, 4 ovarian, 2 pancreatic) and 28% from other cancer types. All cfDNA samples were previously clinically tested by an NGS assay that included *BRCA1/2* (LiquidHALLMARK). A subset of cfDNA samples identified as HRD+ were further assessed for alterations in 26 key HR genes (*ARID1A, ATM, ATR, ATRX, BAP1, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCA, FANCC, FANCG, FANCL, MRE11, NBN, PALB2, PTEN, RAD51, RAD51B, RAD51C, RAD51D, RAD54L,* and *XRCC2*). **Results:** In analytical validation, the assay could detect HRD in admixtures with as low as 18% tumor fraction. In tissue samples, overall concordance of HRD status with the orthogonal test was 91.3% (42/46), with a positive percent agreement of 94.4% (34/36) and negative percent agreement of 80.0% (8/10). In cfDNA, 26.7% (20/75) of samples were HRD+, including 29.6% of *BRCA*-associated cancers (16/54; 12 breast, 2 prostate, 1 ovarian, and 1 pancreatic) and 19.1% (4/21) of other cancer types. In the three HRD+ breast cancers with pathogenic *BRCA* mutations, the assay also identified *BRCA*-specific LOH. Nine HRD+ breast cancers (two *BRCA*+ and seven *BRCA*-) were further analyzed for alterations in 26 HR genes. Of the two *BRCA*+ HRD+ breast cancers, one harbored an additional *PTEN* loss-of-function (LOF) mutation. Of the seven *BRCA*- HRD+ breast cancers, one harbored biallelic *PALB2* and *CDK12* LOF mutations, while another harbored a *CDK12* LOF mutation. **Conclusions:** LOH detection in cfDNA provides additional diagnostic yield of HRD+ status in multiple cancer types, even in the absence of pathogenic HR gene alterations. Further clinical studies to evaluate the utility of HRD detection in cfDNA using LOH and to determine concordance with tumor tissue are ongoing. Research Sponsor: Lucence Diagnostics.

3043 **Poster Session**

Systemic levels of the soluble co-inhibitory immune checkpoints, CTLA-4, LAG-3, PD-1/PD-L1, and TIM-3 are markedly increased in basal cell carcinoma. *First Author: Bernardo Leon Rapoport, Department of Immunology, Faculty of Health Science, University of Pretoria, Pretoria, South Africa*

Background: Although co-inhibitory immune checkpoint proteins are primarily involved in promoting inhibitory cell-cell interactions in adaptive immunity, especially tumor immunity, the soluble cell-free variants of these molecules are also detectable in the circulation of cancer patients where they retain immunosuppressive activity. Nevertheless, little is known about the systemic levels of these soluble co-inhibitory immune checkpoints in patients with various subtypes of basal cell carcinoma (BCC), which is the most invasive and treatment-resistant type of this most commonly occurring malignancy. **Methods:** In the current study, we have measured the systemic concentrations of five prominent co-inhibitory immune checkpoints, namely CTLA-4, LAG-3, PD-1/PD-L1 and TIM-3, as well as those of C-reactive protein (CRP) and vitamin D (VD), in a cohort of patients (n = 40) with BCC, relative to those of a group of control participants (n = 20), using the combination of multiplex bead array, laser nephelometry and ELISA technologies, respectively. **Results:** The median systemic concentrations of CRP and VD were comparable between the two groups; however, those of all five immune checkpoints were significantly elevated ($P = 0.0184$ - $P \leq 0.00001$), with those of CTLA-4 and PD-1 being highly correlated ($r = 0.87$; $P < 0.00001$). **Conclusions:** This seemingly novel finding not only identifies the existence of significant systemic immunosuppression in BCC, but also underscores the therapeutic promise of immune checkpoint targeted therapy, as well as the potential of these proteins to serve as prognostic/predictive biomarkers in BCC. Research Sponsor: University of Pretoria, South Africa.

3044 **Poster Session**

Dysregulation of immune checkpoint proteins in patients with newly diagnosed early breast cancer. *First Author: Bernardo Leon Rapoport, The Medical Oncology Centre of Rosebank, Johannesburg, South Africa*

Background: Checkpoint proteins regulate the immune system. Breast cancer (BC) cells can up-regulate or down-regulate these proteins to evade anti-tumor immune responses. Soluble forms of immune checkpoint molecules (ICMs) can be measured in human plasma. The study aimed to measure the systemic levels of a series of co-stimulatory and co-inhibitory ICMs at diagnosis, post-neo-adjuvant chemotherapy (NAC) and post-surgery in newly- diagnosed BC patients (pts) relative to those of a healthy control group. **Methods:** Soluble ICMs were measured using multiplex bead array technology in plasma from 72 BC pts and 45 healthy controls. Data was prospectively obtained and levels compared between pre-treatment, post-NAC, and post-surgery using non-parametric tests (Mann-Whitney & Kruskal-Wallis). **Results:** Pre-treatment levels of the soluble stimulatory molecules *viz.* GITR ($p<0.0001$), GITRL ($p< 0.020$), CD27 ($p< 0.024$), CD40 ($p< 0.021$), ICOS ($p< 0.009$), as well as the inhibitory molecules PD-L1 ($p< 0.0001$), CTLA-4 ($p< 0.005$), TIM-3 ($p< 0.0004$), HVEM ($p< 0.0004$) were significantly lower in early BC pts compared to controls. Post-treatment, there were significant increases in most ICM levels (Table), with the exception of CTLA-4, which decreased significantly following treatment. On the other hand, pre-treatment plasma concentrations of CCL5 (RANTES) (84.22 vs. 48.72 pg/mL, $p<0.0001$), M-CSF (84.41 vs 13.34 pg/mL, $p<0.0001$), FGF-21 (24.36 vs. 8.64 pg/mL, $p<0.001$) and GDF-15 (806.82 vs. 430.03 pg/mL, $p<0.0001$) were significantly increased in the breast cancer pts compared to healthy controls. A pathological complete response (pCR) was documented in 65% of pts (mostly TNBC). There were no correlations between pre-treatment ICM levels, CCL5, M-CSF, FGF-21 and GDF-15 and pCR. **Conclusions:** We identified low levels of stimulatory and inhibitory ICMs in newly-diagnosed, non-metastatic BC pts compared to healthy controls. Following treatment, with the exception of CTLA-4, most of these pre-treatment abnormalities of systemic ICM levels corrected. NAC is associated with up-regulation of sPD-L1 and most other ICMs. These results indicate that early BC is associated with down-regulation of soluble stimulatory and inhibitory ICMs. Newly-diagnosed early BC pts appear to have generalized immune-suppression independent of subtype and stage. To our knowledge, this is the first study to describe the effect of treatment on systemic ICMs in early BC pts. Research Sponsor: CANSA, Pharmaceutical/Biotech Company.

ICM	Control Median (pg/mL)	Diagnosis (Group A) Median (pg/mL)	Post-NAC (Group B) Median (pg/mL)	Post-surgery (Group C) Median (pg/mL)	Group A vs Group B
CD80	2329	1678	3048	3611	P < 0,0001
CTLA-4	2618	1566	598	687	P < 0,0001
LAG-3	150416	131275	464880	500133	P < 0,0001
PD-L1	3342	1647	4794	5215	P < 0,0001
TIM-3	5047	3897	9975	9615	P < 0,0001
CD27	4577	3342	5351	5427	P < 0,0001
CD28	46135	32914	44277	50058	P < 0,0415
GITR	3797	1497	4035	4434	P < 0,0001
ICOS	26506	15123	26586	29746	P < 0,0001

3045 **Poster Session**

Characterization of genomic landscape using comprehensive circulating cell-free tumor DNA next generation sequencing in advanced thyroid carcinoma. *First Author: Valentina Tarasova, Department of Head and Neck-Endocrine Oncology, Moffitt Cancer Center, Tampa, FL*

Background: Availability of targeted therapies in thyroid carcinoma (TC) has challenged the conventional treatment algorithms and established urgency for timely identification of targetable genetic abnormalities. Tissue-based next generation sequencing (NGS) is often limited by tumor insufficiency and slow turn-around time. Plasma-based circulating tumor DNA (ctDNA) NGS overcomes these barriers and has been widely adopted across advanced-stage solid tumors. To date, plasma-based NGS characterization of genomic alterations in TC has not been determined. Herein, we profile potential actionable mutations detected via ctDNA in patients with advanced TC subtypes. **Methods:** A retrospective analysis of Guardant Health, Inc database was performed using the commercially available Guardant360 plasma-NGS test on advanced metastatic TC samples collected between 2016 and 2021. Patients with papillary TC (PTC), follicular TC (FTC), poorly differentiated TC (PDTC), medullary TC (MTC), and anaplastic TC (ATC) were clustered into four groups (G1: ATC, G2: PTC, FTC, and PDTC, G3: MTC, and G4: unspecified TC). The landscape of genetic alterations, frequencies of alterations in clinically relevant genes, and tumor mutation burden (TMB) were analyzed. **Results:** Of the 1,108 patients included, 47.1% were male. The median age was 65 years old (range 13-98), and 0.18% (n = 5) patients were under 18 years old. Alteration frequencies of selected, clinically relevant genes are demonstrated in the table below. TMB analysis was performed on 315 samples, and the mean TMB was higher in G1 compared to G2, G3, and G4 ($p= 0.0029$, 0.0826, and 0.0112, respectively). **Conclusions:** Plasma-based comprehensive NGS by Guardant360 may be utilized in patients with advanced metastatic TC for detecting clinically relevant genetic alterations for the selection of available targeted therapies, immunotherapy, or determination of the clinical trial eligibility. Future validation of the clinical utility by analysis of paired tumor and plasma samples is warranted. Research Sponsor: None.

	Group 1 ATC n = 93	Group 2 PTC, FTC, PDTC n = 99	Group 3 MTC n = 34	Group 4 Unspecified TC n = 882	Total n = 1108
BRAF	28.0%	17.2%	5.9%	15.3%	16.2%
RAS (HRAS/KRAS/NRAS)	16.1%	15.2%	2.9%	15.6%	15.3%
RET mutations	2.2%	0	38.2%	4.3%	4.8%
RET fusions	1.1%	0	0	0.9%	0.8%
ALK fusions	0	0	2.9%	0.3%	0.4%
NTRK fusions	0	0	0	0.2%	0.2%
PTEN	7.5%	2.0%	0	4.3%	4.2%
TERT	18.3%	14.1%	0	11.0%	11.5%
TP53	58.1%	29.3%	8.8%	34.9%	35.3%

3046 **Poster Session**

Identification of markers for tumor- and immune-derived extracellular vesicles (EVs) in preclinical models. *First Author: Dove-Anna Johnson, NIH, Bethesda, MD*

Background: Extracellular Vesicles (EV) are of broad interest as carriers of molecular signatures of tumor progression and cancer treatment response. EVs, which contain nucleic acids, lipids, and proteins, are released from cells for waste excretion and communication. Numerous proteins and markers are expressed within and on the surface of EVs, but classification markers for murine EV subsets are lacking. To identify tumor and dendritic cell- derived EV markers for preclinical models of breast cancer, we investigated surface marker repertoires of EVs produced by the murine breast cancer and dendritic cell lines, 4T1 and DC2.4. **Methods:** Cells were cultured in serum free media for 2 days. EVs were harvested and isolated by ultrafiltration followed by size exclusion chromatography. EV particle size and concentration were estimated by nanoparticle tracking analysis and microBCA. To identify highly expressed EV markers, a mouse EV multiplex flow cytometry assay was performed using detection antibodies, CD9, CD63, and CD81, with sets of >35 barcoded capture beads, representing more than 100 specific capture: detection combinations. EV marker expression was analyzed using the FCM_{PASS}/MPA_{PASS} software (nano.ccr.cancer.gov). > 250 beads were assessed for each capture- and detection- antibody combination for each EV type and dilution tested; mean fluorescent intensity was determined; and pairwise comparisons between test and control sample sets were evaluated by t-tests. **Results:** Breast cancer (4T1)-derived EVs but not dendritic cell (DC2.4)-derived EVs were strongly detected with CD326 (EpCAM) and CD49b (integrin alpha5, VLA-2) capture beads, using each of the three tetraspanin antibodies. Both types of EVs were detected with anti-CD9 and anti-CD81 when captured by anti-CD44 and anti-CD49e (integrin beta1, VLA-5) beads. DC2.4 EVs were distinctively identified by CD11b capture. CD63 capture and detection antibodies robustly recognized EVs from 4T1 but provided minimal recognition of DC2.4 EVs. Mouse serum EVs from non-tumor bearing mice, showed minimal or no detectable CD326 or CD11b. **Conclusions:** Multiparametric MPA_{PASS}-processed EV repertoire analysis of EVs from murine breast cancer and dendritic cell lines identified CD9, CD81, CD44, and CD49e as common epitopes among both types of evaluated EVs. CD326, CD49b, and CD63 distinguished 4T1 from DC2.4 EVs, and CD11b distinctively identified the DC2.4 EVs. The absence of detected CD326+ and CD11b+ in the serum of non-tumor bearing mice indicates the potential of these two markers for detection of specific tumor and antigen presenting cell EV subsets in serum from mice bearing CD326+ tumors such as 4T1. These results establish a foundation for further tests of detection and tracking of tumor-specific CD326+ EVs as "liquid biopsies" in blood samples as correlates to tumor progression and/or response to treatment. Research Sponsor: U.S. National Institutes of Health.

3047 **Poster Session**

Cell-free RNA in liquid biopsy and biomarkers profiling of hematologic and solid tumors. *First Author: Maher Albitar, Genomic Testing Cooperative, Irvine, CA*

Background: Expressed RNA can capture mutations, changes in expression levels due to methylation, and provide information on cell of origin, growth, and proliferation status. We developed an approach to isolate fragmented RNA from peripheral blood plasma and explored its potential to be used in liquid biopsy. **Methods:** Peripheral blood cfRNA was extracted from patients with neoplasms in B-cell (#105), T-cell (#16), Myeloid (#73), and from solid tumors (#44), Normal individuals (#51), and reactive post-transplant (#137). RNA was sequenced using a 1459-gene panel. Expression profile was generated using Cufflinks. **Results:** cfRNA levels of various solid tumor biomarkers (CA-125, CA-15-3, CEA 8, Keratin19, Keratin6A...) were significantly higher ($P < 0.0001$) in samples from solid tumors as compared with normal control. Similarly, cfRNA lymphoid markers (CD19, CD22, CD79A, and CD79B...) and cfRNA myeloid markers (CD33, CD14, CD117, CD56...) were all higher in B-cell lymphoid neoplasms and myeloid neoplasms, respectively ($P < 0.0001$), as compared with control. In evaluating the host immune system, cfRNA CD4:CD8B and CD3D:CD19 ratios in normal controls were as expected (median: 5.92 and 6.87, respectively) and were significantly lower in solid tumors (median 3.40 and 2.23, respectively, $P < 0.0002$). Solid tumor cfRNA showed CTLA4:CD8B ratio significantly higher in tumors than in normal (median 0.74 vs 0.19, $P = 0.0001$), while there was no difference in cfRNA PD-L1:CD8B ratio (median 1.45 vs 1.77, $P = 0.96$). Similar distinct patterns are noted for various cytokine and chemokines. cfRNA was highly predictive of diagnosis (AUC > 0.98) of solid tumors, B-cell lymphoid neoplasms, T-cell lymphoid neoplasms, and myeloid neoplasms as compared with normal control. When a specific neoplastic disease was considered against all cases including control and other neoplasms, the AUC varied between 0.77 and 0.949. **Conclusions:** This data shows that liquid biopsy using targeted sequencing of cfRNA in patients with various types of cancer provides comprehensive and reliable information on the neoplastic disease as well as the host. Research Sponsor: None.

Groups	AUC	Sensitivity (%)	Specificity (%)	No. of genes	Leave one out AUC
Normal (N) vs B-cell Lymphoid	0.984	96.3	98	60	0.995
N vs Myeloid	0.996	96.6	98	30	0.994
N vs Solid tumors	0.997	97.8	98	30	0.98
N vs T-lymphoid	0.999	100	98	30	0.98
N vs Reactive	0.77	82.9	53.7	200	0.624
B-Lymphoid vs all others	0.783	86.8	59	200	0.725
Myeloid vs all others	0.754	78.1	60.7	8	0.743
Solid tumors vs all others	0.817	88.9	62.7	450	0.729
T-Lymphoid vs all others	0.949	93.8	86.9	10	0.881
Reactive vs all others	0.77	82.9	53.4	200	0.641

3048 **Poster Session**

Combining cell-free RNA (cfRNA) with cell-free total nucleic acid (cfTNA) as a new paradigm for liquid biopsy. *First Author: Maher Albitar, Genomic Testing Cooperative, Irvine, CA*

Background: Expressed RNA can capture mutations, gene fusions, and biomarker profiles. In principle, each abnormal cell has one copy of mutated gene, but numerous copies of mutated RNA. Cell-free RNA (cfRNA) is not used due to the assumption that it is degraded. Next Generation Sequencing (NGS) by design is particularly adaptable for fragmented DNA and RNA. We developed an approach to isolate cell-free total nucleic acid (cfTNA) and cell-free RNA (cfRNA) from peripheral blood. Using targeted sequencing, we explored the potential of this approach to detect mutations, fusion mRNA, and copy number variation (CNV) in solid tumors and hematologic neoplasms. **Methods:** Peripheral blood cfTNA and cfRNA were extracted from B-cell lymphoid neoplasms (#105), T-cell neoplasms (#16), Myeloid neoplasms (#73), solid tumors (#44), and Normal individuals (#51), and sequenced using a targeted panel of 1459 genes. **Results:** Numbers of mutations detected in solid tumors and hematologic neoplasms were significantly ($P > 0.0001$) higher in cfRNA (No. = 1229) than in cfTNA (No. = 1004). Overall variant allele frequency (VAF) was significantly higher in cfRNA than in cfTNA ($P < 0.0001$). However, numerous mutations detected by RNA were not detected by cfTNA and vice versa. In general, nonsense mutations were more likely to be detected by cfTNA than by cfRNA and at higher VAF. Low-level mutations (VAF < 10%) were more likely to be detected by cfRNA than by cfTNA. For example, 136 mutations in TP53 gene were detected using cfRNA and only 70 mutations were detected in cfTNA. KRAS mutations were also higher in cfRNA (#33) as compared with cfTNA (#21). In contrast, when most of the mutations were nonsense, as in ASXL1 gene, more mutations were detected by cfTNA (24 vs 23). When mutations were detected in both cfRNA and cfTNA, mutation load (level of mutant copies) was overall slightly higher in cfTNA ($P = 0.06$), likely due to higher degradation of RNA, but varied significantly dependent on the type of mutated gene and type of mutation. cfRNA was reliable in detecting fusion transcripts in solid tumors and in hematologic neoplasms (SLC34A2-ROS1, DDX5-BCL6, ETV6-RUNX1, RUNX1T1-RUNX1, PML-RARA, RUNX1-ZFPM2, DEK-NUP214, EP300-ZNF384) irrespective of the breakpoint or partner gene. The cfTNA detected various CNVs expected by cytogenetic analysis when tumor fraction was adequate (VAF > 10%). **Conclusions:** This data demonstrates that using cfRNA and cfTNA provides complementary comprehensive information for evaluating mutations, fusion genes, and CNV. This approach increased sensitivity and reliability of liquid biopsy. Furthermore, the cfRNA provides critical information on relative expression of various genes that can be used as biomarkers in characterizing the neoplastic process (see ASCO abstract, Liquid Biopsy Based on Cell-Free RNA and Biomarkers profiling of hematologic and solid tumors). Research Sponsor: None.

3049 **Poster Session**

Serum concentrations of oncometabolite, 2-hydroxyglutarate (2HG), as biomarkers for isocitrate dehydrogenase *(IDH1/2)* mutations in cholangiocarcinoma (ICCA). *First Author: Cha Len Lee, Department of Medical Oncology and Haematology, Toronto, ON, Canada*

Background: Mutations in IDH1/2 genes are common in low-grade glioma (GM) and occur in approximately 20% of intrahepatic cholangiocarcinoma (ICCA). Mutant IDHs leads to preferential accumulation of the R-relative (R2HG) to the S-enantiomer (S2HG) of 2HG. We investigated the utility of circulating R2HG, total R2HG+S2HG (tRS) and ratio of R2HG/S2HG (rRS) as biomarkers in GM and ICCA patients (pts). **Methods:** Blood and tumor tissues samples were obtained from pts with IDH1/2-mutant GM and ICCA. IDH mutation was confirmed by either immunohistochemistry (GM pts) or next generation sequencing (ICCA pts). Samples were analyzed for S2HG and R2HG using a validated HPLC tandem mass spectrometry method. Tissue and serum R2HG, tRS and rRS were compared with paired t-tests for GM pts. Serum S2HG, R2HG, tRS and rRS were compared with unpaired t-tests between GM and ICCA pts. A $p<0.05$ was considered statistically significant. **Results:** Blood and tumor samples were collected from 21 pts (GM = 11, ICCA=10). Tumor tissues were insufficient for analysis in 1 GM and 8 ICCA pts. Tissue S2HG, R2HG, tRS, and rRS were 0.72±0.68 ng/g, 48.92±58.92 ng/g, 66.87±80.35 ng/g and 55.77±36.23 for GM pts. There were no differences in R2HG and tRS between tissue and serum samples, while S2HG was significantly higher in serum samples ($p = 0.001$) and rRS was significantly higher in tissue samples for GM pts ($p = 0.01$). rRS were 144.8 and 244.9 respectively in 2 ICCA pts with sufficient tissues. There was no difference in serum S2HG between GM and ICCA pts. However, serum R2HG, tRS and rRS were significantly higher in ICCA pts. **Conclusions:** In *IDH1/2* mutant GM and ICCA pts, R2HG was increased relative to S2HG in tumor tissues. In GM pts, the accumulation of R2HG in tumor tissues was not reflected in blood, likely due to the inability of 2HG to diffuse across the blood-brain barrier. Serum R2HG, tRS and rRS were significantly elevated in ICCA pts. These biomarkers have no clinical utilities in GM pts. However, they can potentially be used to identify IDH mutations in ICCA pts, especially given the inability to obtain tumor tissue in some ICCA pts. Clinical trial information: NCT03991832. Research Sponsor: University Health Network, Toronto.

Comparison of S2HG, R2HG, tRS, and rRS in the serum of IDH1/2-mutant ICCA vs. GM pts. SD = standard deviation.

Biomarkers	IDH-mutant ICCA (n = 10)	IDH-mutant GM (n = 11)	p-value
Serum S2HG (SD) (ng/mL)	81.5 ± 48.9	60.8 ± 39.1	0.29
Serum R2HG (SD) (ng/mL)	461.9 ± 397.4	55.0 ± 20.0	0.003
Serum tRS (SD) (ng/mL	543.4 ± 392.7	115.9 ± 54.7	0.002
Serum rRS	7.70 ± 8.58	1.08 ± 0.48	0.02

3050 **Poster Session**

A circulating miRNA-based AI prediction system to identify multiple types of cancer. *First Author: Chih-Hsun Wu, Artificial Intelligence and E-Learning Center, National Chengchi University, Taipei City, Taiwan*

Background: Cancer is a major problem for human health. Development of an early diagnostic tool can increase the survival of cancer patients. Liquid biopsies have many advantages over traditional tumor tissue biopsies. Circulating microRNAs (miRNAs) are one type of liquid biopsies in part because they regulate the expression and thus functions of their target genes. Circulating miRNAs are stable, non-invasive and changes in their expression are detectable in the early stage of cancer progression, often before clear evidence of tissue biopsy/image tests. To date, there are few liquid biopsy-based tools for multiple-cancer diagnosis and their performance is unsatisfactory. The development of a non-invasive, effective early detection system for cancers is urgently needed. **Methods:** We integrated and investigated circulating miRNA expression data of 5046 non-cancer samples along with 3856 cancer samples of 6 major cancer types downloaded from publicly available databases. We used these expression data along with gender to establish a multiple cancer type AI prediction system. Furthermore, we built comprehensive interaction networks (miRNA-drug, miRNA-target gene) and performed functional enrichment analysis. **Results:** We constructed high-performance AI prediction model that can detect and differentiate 6 cancer groups from one non-cancer group. A median of sensitivity of 93.84% in test data was achieved for the multiple cancer classification task. A panel of gender and 15 most important circulating miRNAs was further shown to achieve excellent performance (sensitivity = 90.44%), with just a bit of decrease in the sensitivity of using the full set (gender and 2565 miRNAs). The 15 key circulating miRNAs worked well for the early stage (stage 1: sensitivity = 88%), much better than other liquid-biopsy results reported in the literature. This is important because these miRNAs and the AI system can be used to significantly decrease clinical cost and increase efficiency of early diagnosis, not to mention it is non-invasive. Finally, we constructed comprehensive interaction networks (drug/ target gene) for these key miRNAs to explore potential therapeutic strategies and understand the underlying biological mechanisms. **Conclusions:** In the study, we constructed the multiple-cancer prediction AI system to classify groups of normal individuals and cancer patients of multiple types, while finding key circulating miRNAs. As several key circulating miRNAs were shown to be potential drug targets or serve as diagnosis biomarkers to fulfill the aim of cancer precision medicine, this work represents a significant step toward achieving the goal of developing a non-invasive tool for early diagnosis of cancers. Research Sponsor: Taipei, Taichung, Kaohsiung Veterans General Hospital, Tri-Service General Hospital, Academia Sinica Joint Research Program.

3051 **Poster Session**

Circulating tumor DNA (ctDNA) in HER2 exon 20 insertion mutations and responses in NSCLC HER2 exon 20 insertion treated with poziotinib. *First Author: Arunthi Thiagalingam, Spectrum Pharmaceuticals, Boston, MA*

Background: ctDNA levels in plasma samples permits temporal assessment of tumor mutational status and tumor burden during therapy. Poziotinib is an oral HER2 TKI in development for NSCLC patients harboring HER2 exon 20 insertion mutations. We assessed serial plasma samples for changes in HER2 exon 20 insertion mutations and other driver mutations in first- and second-line patients comparing to clinical response per RECIST1.1. **Methods:** NSCLC patients harboring HER2 exon 20 insertion mutations were enrolled into the poziotinib ZENITH20 using tumor tissue based NGS. Serial plasma samples were collected at baseline, at C3D1, at Day 1 of every other cycle until disease progression. The Guardant360[a] 74-gene liquid biopsy assay was used to assess changes in tumor-associated somatic variants including the target variant HER2 exon20 insertion as well as other emergent driver mutations in ctDNA as expressed as percent variant allele frequency (%VAF). **Results:** 23 first- and second-line NSCLC patients were evaluable with tumor tissue confirmation of HER2 exon 20 insertion mutations. 22 of 23 (96%) had baseline plasma samples with detectable ctDNA. 21 of 22 samples had detectable HER2 exon 20 insertion mutations (mean % VAF 20±5) resulting in a concordance of 95% versus tissue based NGS. 7 patients had serial testing through C7D1 permitting assessment of ctDNA dynamics and comparison to clinical responses. 5 of 7 (71%) serially tested patients treated with poziotinib at 16mg QD had undetectable HER2 exon 20 insertion at C3D1 which was associated with a tumor response PR. Tumor escape (PD) was observed in 2 of the 5 patients which correlated with increases in target HER2 exon 20 insertion VAF in the plasma with the remaining 3 patients ≥PR. Notably, the rise in HER2 exon 20 in ctDNA occurred prior to tumor escape. In one patient treated with poziotinib at 16 mg QD we observed undetectable levels of the HER2 exon 20 insertion in ctDNA at C3D1 which continued through C16. This patient's responses correlated with patient tumor response of SD at C2 which then became PR through C9 and CR through C17. **Conclusions:** Poziotinib treatment resulted in reductions in HER2 exon 20 insertion mutations in ctDNA preceded and correlated with the clinical tumor response. Increases in ctDNA HER2 exon 20 insertion mutations were observed prior to confirmation of tumor escape. Serial monitoring of ctDNA is a potential predictive biomarker for treatment response and disease progression. Future evaluation in a larger population is required to confirm the impact of these findings. Research Sponsor: Spectrum Pharmaceuticals Inc.

3052 **Poster Session**

PD-L1 is overexpressed on tumorspheres cultured from circulating cancer stem cells in patients with breast cancer. *First Author: Monika Pizon, Transfusion Center Bayreuth, Bayreuth, Germany*

Background: Circulating cancer cells, and in particular their very rare subpopulation, circulating cancer stem cells (cCSCs), are responsible for recurrence and metastasis. The exact role of cCSCs in escape of cancer from immunosurveillance is still unknown, but recent studies revealed that enhanced PDL-1 expression in cancer stem cells is linked to immune evasion and could crucially contribute to the maintenance of CSC self-renewal. Understanding the mechanisms behind this PDL-1 overexpression in cancer stem cells is critical for developing more effective anti-PD-1/PD-L1 therapy. Therefore the aim of the study was to determine the number of tumorspheres and expression of PD-L1 on tumorspheres cultured from cCSC in breast cancer patients. **Methods:** 110 patients with breast cancer in different stages of disease were included in this study. The determination of circulating cancer stem cells was performed using the sphere-forming assay. Additionally anti-PDL-1 antibody staining was applied to examine PDL-1 expression on breast tumorspheres. **Results:** We have developed an innovative *in vitro* platform for detection of cCSCs from peripheral blood of cancer patients. The number of tumorspheres increased significantly with tumor progression and aggressiveness of primary tumor. Patients with metastatic disease had statistically more tumorspheres as compared to patients without metastasis (30 vs 10/100µl blood, $p < 0.05$). Patients with multiple metastasis had more tumorspheres compared to patients with single metastases (60 vs 30/100µl blood, $p < 0.05$). The number of tumorspheres was positively correlated with Ki-67, Her2 status and grade score in primary breast tumors. We observed high PDL-1 expression and their considerable heterogeneity in enriched tumorspheres. **Conclusions:** The number of tumorspheres cultured from peripheral blood directly reflects aggressiveness and proliferation capacity of primary tumor. The presence of tumorspheres with expression of PDL-1 might suggest their immunregulatory potential. Better understanding of the interaction between cCSCs and tumor immunology may help to identify strategies to eradicate the minor subpopulation that escapes conventional therapy attack, thus providing a solution to the problem of drug resistance and metastasis. Research Sponsor: None.

3053 **Poster Session**

Prospective characterization of circulating tumor cell kinetics in patients treated with radiation therapy per definitive intent oligometastatic paradigm. *First Author: Shivani Sud, University of North Carolina at Chapel Hill, Chapel Hill, NC*

Background: Definitive intent oligometastatic paradigm describes a state with limited metastatic sites amenable to comprehensive radiation therapy (RT). We characterized circulating tumor cell (CTC) kinetics in response to definitive RT among patients with oligometastatic cancer and identify a CTC kinetic profile associated with progression free survival (PFS). **Methods:** In this single-institution prospective correlative biomarker study, we enrolled patients with any solid malignancy, ≤ 5 metastatic sites in ≤3 anatomic organ systems undergoing definitive intent RT to all disease sites. Blood specimens were collected prior to RT (baseline), during RT and at follow up visits up to 24 months post RT. Additional lines of therapy were administered per standard of care. CTCs were captured and enumerated using a previously reported nanotechnology-based assay functionalized with aEpCAM, aHER-2, and aEGFR to facilitate biomimetic cell rolling and dendrimer-mediated multivalent binding. Disease status was assessed per RECIST 1.1 criteria. On exploratory analysis disease status was correlated with CTCs as a continuous and ordinal variable (cut-point upper bound of the 3rd quartile). A favorable CTC clearance profile was defined as a decrease in CTC count between pre-treatment and end of treatment - an unfavorable CTC clearance profile was defined as the opposite. **Results:** We enrolled 43 patients with median follow up of 14.3 months corresponding to 255 CTC measurements. Median baseline CTC count was 28 CTCs/ml (range 0.17-1085). Thirty four patients (79%) received stereotactic body radiation therapy. On Wilcoxon signed-rank test there was no association between pre-treatment CTC count and number of disease sites (median 1 metastatic site/patient, range 1-5) nor metastases site (bone, brain, visceral), $p > 0.05$. Thirty one patients (72%) experienced local or systemic progression at subsequent time points. For 90% of patients, a CTC count <15/ml < 100 days post-RT corresponded to durable local control of irradiated lesions. Patients with a favorable versus unfavorable clearance profile had significantly longer PFS (median 13 vs 4 months, log rank test, $p = 0.0011$). During the post-RT period 24 patients (56%) went on to receive systemic therapy (cytotoxic chemotherapy, hormone therapy, immunotherapy, kinase inhibitors). On logistic regression, CTC > 15/ml at a given time point was associated with clinical disease progression within the subsequent 6 months (odds ratio 3.31, $p = 0.007$). An increase in CTCs to > 15/ml preceded radiographic or biochemical progression in 8 of 31 (26%) of patients experiencing disease progression. **Conclusions:** Our data suggests CTCs may serve as a biomarker for disease control in oligometastatic disease and may predict disease progression prior to standard assessments for patients receiving diverse therapies. Clinical trial information: NCT03161821. Research Sponsor: None.

3054 **Poster Session**

Monitoring engorgement of phagocytic circulating stromal cells during chemo-radiotherapy induction predicts survival in unresectable stage 2/3 NSCLC. *First Author: Kirby P Gardner, Creatv MicroTech, Inc., Monmouth Junction, NJ*

Background: Circulating stromal cells, ie Cancer Associated Macrophage-Like cells (CAMLs), are prevalent in the circulation of non-small cell lung carcinoma (NSCLC) patients (pts), appearing as giant phagocytic macrophages that represent an inflammatory pro-tumorigenic microenvironment. Previously it was shown that pts with engorged CAMLs of ≥50µm after treatment are prognostic for poor clinical outcomes. However, analyzing the dynamic changes in CAMLs over time or in response to treatment, ie chemoradiation (CRT) and immunotherapy (IMT) has not been evaluated. We monitored n = 182 unresectable NSCLC stage II/III pts treated with CRT alone (n = 91) or with concurrent IMT (n = 91) to evaluate changes in CAMLs before and after CRT induction at it relates to progression free survival (PFS) or overall survival (OS). **Methods:** We prospectively procured pts from 3 different regimes, treated with CRT alone (n = 91), treated concurrently with CRT & Atezolizumab (n = 40, clinical trial NCT02525757), or treated concurrently with Durvalumab (n = 51). We recruited 182 pts with pathologically confirmed stage II/III unresectable NSCLC. A total of 15 mL blood samples were drawn prior to start of therapy at baseline (BL) and ~5 weeks (T1) after CRT induction. Blood filtration was done using CellSieve filters, then CAMLs were identified and measured to evaluate PFS & OS hazard ratios (HRs) by censored univariate and multivariate analyses at 2 years. **Results:** CAMLs were found in 89% of all samples tested. Increases in CAML size between BL & T1 were significantly correlated with worse clinical outcomes, with higher CAML increases correlated with increasingly worse outcomes, including CAML increases >10μm resulting in PFS HR=1.7 $p = 0.027$ & OS HR=1.9 $p = 0.045$, through increases >40μm resulting in PFS HR=2.1 $p = 0.013$ & OS HR=2.5 $p = 0.020$. Increases of CAMLs >35μm was optimal at stratifying pts PFS HR=2.2 $p = 0.005$ & OS HR=2.8 $p = 0.005$. Specifically, pts treated with only CRT and increasing CAMLs >35μmhad significantly worse PFS HR=2.7 $p = 0.029$ & OS HR=4.1 $p = 0.013$. In parallel, pts treated with CRT+IMT and increasing CAMLs >35μm had near significance for worse PFS (HR=2.1 $p = 0.073$) & OS (HR=2.3, $p = 0.147$), though follow up clinical data is ongoing. **Conclusions:** Our data suggest that in unresectable stage II/III NSCLC, tracking the increase of pro inflammatory immune cells (CAMLs) in circulation during therapy induction can identify pts less responsive to CRT or PD-L1/PD-1 IMTs. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

3055 **Poster Session**

Defining resistance mechanisms to CDK4/6 inhibition in hormone receptor-positive HER2-negative metastatic breast cancer (MBC) through a machine learning approach applied to circulating tumor DNA (ctDNA). *First Author: Lorenzo Gerratana, Department of Medical Oncology, Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano, Italy*

Background: Although cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) are a primary treatment for hormone receptor-positive/HER2 negative MBC, data regarding resistance mechanisms are still an unmet need. The aim of the study was to highlight new resistance pathways using machine learning (ML) to detect multiparametric patterns in complex datasets. **Methods:** The study retrospectively analyzed a cohort of 610 hormone receptor positive HER2 negative MBC patients (pts) at Northwestern University, Massachusetts General Hospital and Washington University in St. Louis between 2015-2020 with baseline ctDNA testing by Guardant360. Pathways were defined based on previous work (Sanchez-Vega F et al, Cell. 2018) (i.e., RTK, RAS, RAF, MEK, NRF2, ER, WNT, MYC, P53, cell cycle, notch, PI3K). Only pathogenic variants according to OncoKB were included in the models. Associations among single nucleotide (SNVs) and copy number (CNVs) variations, pathway classification and previous exposure to CDK4/6i were explored through logistic regression and Gradient boosted machines (GBMs) ML algorithm. **Results:** at baseline, 322 pts (52.8%) were previously treated with CDK4/6i. The most detected pathway alterations were SNVs in PI3K (37.1%), P53 (31.8%), ER (29.2%) and RTK (22.3%). After stepwise logistic regression, RB1, NF1 and ESR1 SNVs were associated with previous exposure to CDK4/6i (respectively OR: 3.55 $P = 0.017$; OR: 3.06 $P = 0.026$ and OR: 1.82 $P < 0.001$), while SNVs in the ER pathway were associated with CDK4/6i (1.56 $P < 0.001$). Two GBMs models were designed based on gene variants (training AUC: 0.695, cross validation AUC: 0.631) and oncogenic pathways (training AUC: 0.713, cross validation AUC: 0.619). The highest relative importance (RI) was observed for ESR1 SNVs (RI: 35.35), TP53 SNVs (RI: 11.33), NF1 SNVs (RI: 3.45), SMAD4 SNVs (RI: 3.39) and RB1 SNVs (RI: 3.33). Alterations at a pathway level with the highest RI were ER SNVs (RI: 33.50), P53 SNVs (RI: 14.98), PI3K SNVs (RI: 14.40), RTK SNVs (RI: 10.55), RTK CNVs (RI: 10.26), cell cycle CNVs (RI: 6.99), cell cycle SNVs (RI: 6.77) and RAS SNVs (RI: 6.54). Of the previously highlighted pathway alterations, a significant impact on PFS after ctDNA collection was observed among *de novo* pts treated with CDK4/6i (165 pts) for ER SNVs ($P < 0.0001$), RTK SNVs ($P = 0.0011$), RTK CNVs ($P = 0.0006$), Cell cycle CNVs ($P = 0.0010$) and Cell cycle SNVs ($P = 0.0143$). No impact was observed on PFS for pts who had not received a CDK4/6i-based regimen. **Conclusions:** The combination of ctDNA-based datasets and machine learning algorithms defined novel resistance pathways for patients treated with CDK4/6i. Although preliminary, these results suggest that alterations of the ER, RTK and Cell cycle pathways might be crucial to optimize treatment strategy and drug development. Research Sponsor: Lynn Sage Breast Cancer Foundation.

3056 **Poster Session**

Tracking changes in circulating stromal cells and circulating tumor cells predicts responsiveness of new line induction in metastatic breast cancer after 1 cycle of therapy. *First Author: Daniel L Adams, Creatv MicroTech, Inc., Monmouth Junction, NJ*

Background: In metastatic Breast Cancer (mBC), Circulating Tumor Cells (CTCs) are established prognostic indicators of patients (pts) not responding to new lines of therapy and who have poor clinical outcomes. However, CTCs are typically found in < 20% of mBC pts and many pts without CTCs will also progress. Recently an inflammatory pro-tumorigenic macrophage emanating from tumor stroma (i.e. Cancer associated macrophage-like cell [CAML]) was found in > 90% of mBC pts and were also indicative of poor clinical outcomes. As CTCs & CAMLs are isolated in conjunction from a single blood sample, and both are prognostic for therapy response, we evaluated CTCs & CAMLs before and after initiation of new therapies in mBC to determine their combined prognostic/predictive values. **Methods:** An observational prospective 2-year multi-institutional study was undertaken to evaluate CTCs & CAMLs before, and after, induction of any new line of therapy in pts with diagnosed mBC (n = 101). Anonymized and blinded blood samples were taken at baseline (BL), prior to starting a new systemic therapy, and a 2nd sample (T1) taken after therapy initiation (~30 days). Blood was filtered by CellSieve filtration. The quantities and subtypes of CTCs & CAMLs were analyzed based on RECIST v1.1 for progression-free survival (PFS) and overall survival (OS) hazard ratios (HRs) by censored univariate & multivariate analysis at 2 years. **Results:** CTCs were identified in 35% (n = 35/101) of pts at BL & 24% (n = 24/101) at T1, with a single CTC at T1 being highly prognostic for worse PFS HR = 6.2 95%CI 3.0-13.2, p < 0.001 & OS (HR = 5.1 95%CI 2.0-13.4, p = 0.002. In parallel, CAMLs were found in 93% of BL and 86% of T1 samples, and whose decreases were significantly prognostic for improved PFS (HR = 2.7, 95%CI 1.4-5.1, p = 0.006) and OS (HR = 4.4 95%CI 1.5-13.2, p = 0.018) when CTCs were absent. Overall ≥1 CTC at T1 (n = 24) had median PFS = 2.4 & mOS = 4.8 months (mos), however, in pts without CTCs plus an increase in CAMLs (n = 36) had mPFS = 5.9 & mOS = 14.1 mos, while in pts without CTCs plus a decrease in CAMLs (n = 41) had mPFS = 14.8 & mOS = 18.8 mos. **Conclusions:** Our data confirms that pts with persistent CTCs have the worst clinical outcomes. Further, simultaneous CAML quantification provided a new dynamic predictive blood based biomarker in pts without detectable CTCs which may be useful to better individualize therapy and improve outcomes, though future studies are need to validate these findings. Research Sponsor: DARPA DOD, Pharmaceutical/Biotech Company.

3057 **Poster Session**

Resolution ctDx FIRST plasma assay as a companion diagnostic for adagrasib and its application to longitudinal monitoring. *First Author: Ira Pekker, Resolution Bioscience, Inc., Kirkland, WA*

Background: KRAS is one of the most commonly mutated oncogenes in cancer. There is a significant need for new treatment options for patients with non–small cell lung cancer (NSCLC) harboring the *KRAS* G12C mutation. Adagrasib is an investigational, highly selective, oral small molecule inhibitor of KRAS G12C that has demonstrated clinical benefit in patients with *KRAS G12C*–mutant NSCLC and CRC. Detection of KRAS G12C in cfDNA is minimally invasive and is of benefit to NSCLC patients, many without lesions accessible by tissue biopsy testing. **Methods:** Resolution ctDx FIRST is a 113 gene comprehensive genomic profiling assay that identifies oncogenic alterations including substitutions, insertions, deletions, gene fusions, and homozygous deletions using targeted NGS sequencing of cfDNA. The Resolution ctDx FIRST assay is being developed as a companion diagnostic for adagrasib in NSCLC patients of the Mirati Study 849-001. **Results:** The LOD95 for SNVs and indels in KRAS and EGFR at a cfDNA input level of 15ng ranged from 0.34% to 0.82%. No false positives were detected in any samples from healthy donors (N = 60). A total of 230 NSCLC plasma samples were orthogonally tested using a ddPCR assay for *KRAS* G12C, using 76 plasma samples from Study 849-001 where KRAS G12C positive results had previously been obtained by a tissue assay, and 154 commercially procured NSCLC samples representative of the trial population. The PPA and NPA for Resolution ctDx FIRST plasma testing relative to ddPCR assay (95% CI) were 87.0% (75.1–94.6%) and 97.6% (94.1–99.4%) respectively. Of 112 Study 849-001 patients, 71 (63.4%) were tested for KRAS G12C mutations with Resolution ctDx FIRST in pretreatment plasma samples. Seventy-four commercially procured matched tissue and plasma samples were tested by Resolution ctDx FIRST and tissue assay. The PPA and NPA for Resolution ctDx FIRST plasma testing relative to tissue assay (95% CI) were 66.2% (54.0-77.0%) and 100% (94.7-100%) respectively. The detection of *EGFR* variants in the Resolution ctDx FIRST assay was compared to results from a ddPCR assay for each variant. A total of 165 NSCLC plasma samples generated a total of 317 comparative valid results. PPA was 100% for EGFR L858R, 88.9% for EGFR T790M, and 91.3% for EGFR Exon 19 Deletions. NPA was 97.8% for EGFR L858R, 100% for EGFR T790M, and 100% for EGFR Exon 19 Deletions. Application of the assay in longitudinally collected NSCLC and CRC patient samples will be presented highlighting changes of VAF over time including identification of oncogenes involved in emerging resistance. **Conclusions:** The Resolution ctDx FIRST assay offers highly sensitive, specific, and robust test results, and meets analytical requirements for clinical applications. Research Sponsor: Mirati Therapeutics, Inc.

Variant	LoD95 (%MAF)	95% CI (%MAF)
KRAS G12C	0.50%	0.379%, 0.667%
EGFR exon 19 deletions	0.34%	0.241%, 0.476%
EGFR L858R	0.38%	0.289%, 0.493%
EGFR T790M	0.82%	0.680%, 0.989%

3058 **Poster Session**

T-cell receptor repertoire analysis based on RNA sequencing data from tumor cells and tumor-infiltrating lymphocytes. *First Author: Cheng Du, Department of oncology, General Hospital of Northern Theater Command, Shenyang, China*

Background: T-cell receptor (TCR) repertoire has been thought to be indicative in cancer progression and treatment response. Previous methods mainly focused on peripheral blood or fresh tumor tissue, which were sometimes logistically limited in clinical settings. Tumor-infiltrating lymphocytes (TILs), which harbored TCR characteristics, were also mingled with tumor cells (TCs), which brought hurdles in extracting TCR signals from bulk RNA sequencing data. Here we employed a set of RNA sequencing data from paired FFPE tumor samples and their micro-dissected TILs, to analyze and compare the TCR features in tumor cells and TILs. **Methods:** RNA sequencing data of 14 tumor cell samples and matched TILs were downloaded from NCBI-SRA (accession: PRJEB36554). Raw data were cleaned up by Trim Galore (v0.6.2). TCR clonotypes were assembled and quantified from clean fastq files by MiXCR (v3.0.4). Diversity and clonality metrics were analyzed using VDJtools (v1.2.1) and in-house Pearl scripts. **Results:** The median mapping rates of sequencing reads to TCR regions were 0.29% and 1.80% for TCs and TILs respectively (p = 0.00051). TCR diversity of TCs and TILs was characterized by Shannon and Simpson index respectively. The median Shannon index was 1.889 and 2.694 in TCs and TILs (p = 0.00034, unpaired Wilcoxon rank-sum test); the median Simpson index was 0.8724 and 0.9420 in TCs and TILs (p = 0.0058). **Conclusions:** RNA isolated from clinical FFPE samples could be used for TCR analysis. Micro-dissection of TILs could enhance TCR signals of unprocessed tumor tissues. Research Sponsor: None.

3059 **Poster Session**

Imaging of solid tumors using 68Ga-FAP-2286. *First Author: Thomas A. Hope, University of California, San Francisco, San Francisco, CA*

Background: Fibroblast Activation Protein (FAP) is a transmembrane protein overexpressed on cancer associated fibroblasts (CAFs), and is abundantly present in many epithelial cancers, suggesting FAP is an attractive imaging and therapeutic target. FAP-2286 is a cyclic peptide that binds to FAP and is currently being evaluated as a radioligand therapy to treat patients (pts) with FAP-positive solid tumors. The role of 68Ga-FAP-2286 as a diagnostic agent is unknown. We present an interim analysis of the ability of 68Ga-FAP-2286 to detect metastatic disease across multiple cancer types. **Methods:** This is a first in human Phase I/II study of 68Ga-FAP-2286 (NCT04621435) with a planned total enrollment of 65 pts across 3 cohorts: dosimetry cohort (n = 5), cohort with RECIST measurable disease (n = 30) and a cohort at risk for metastases without measurable disease (n = 30). By the cutoff date of February 12, 2022, 27 pts were enrolled (3 in cohort 1, 15 in cohort 2 and 9 in cohort 3). For each pt, the five largest lesions were included for analysis, and for each lesion, the maximum standardized uptake value (SUVmax) of the 68Ga-FAP-2286 and the size (short axis for lymph nodes) were documented. In pts who had an available FDG PET performed within 8 weeks of 68Ga-FAP-2286 PET, uptake on the two scans was compared. **Results:** Of the 27 enrolled pts, 9 had bladder cancer, 5 sarcoma, 4 head and neck squamous cell cancer (HNSCCA), 3 breast cancer (BC), and 3 castration resistant prostate cancer (CRPC). Most pts (89%, 24/27) had tumors positive for uptake on 68Ga-FAP-2286 PET, including 30 lesions < 1.5 cm, and 17 less than 1.0 cm. 16 pts had a paired FDG PET. In these pts, the average SUVmax on 68Ga-FAP-2286 PET was 244% higher than on FDG PET. Only two pts had higher uptake on FDG PET than on 68Ga-FAP-2286 PET (HNSCCA and DSRCT). The highest relative uptake was seen in 2 pts with BC (both 3.4 times higher on 68Ga-FAP-2286 PET); the average SUVmax in BC was 16.6. The lowest uptake on 68Ga-FAP-2286 PET was CRPC with an average SUVmax of 7.0. Sarcoma had variable uptake with one pt having an SUVmax of 4.5 (Ewing's), while two pts had an SUVmax over 30 (both undifferentiated pleomorphic). Although sarcoma had high uptake on 68Ga-FAP-2286 PET, it was similar to FDG PET uptake across the 5 pts (ratio to FDG PET = 1.0). **Conclusions:** 68Ga-FAP-2286 is a promising imaging agent across cancers, although its benefit is not seen equally. BC had the highest absolute uptake and highest relative uptake compared to FDG PET; prostate cancer had the lowest uptake. Further work should be undertaken to define the settings where 68Ga-FAP-2286 PET may inform clinical decision making, and which pts may benefit from FAP-targeted radioligand therapy. Clinical trial information: NCT04621435. Research Sponsor: Clovis Oncology.

3060 **Poster Session**

Frequency of practice-changing findings identified by comprehensive genomic profiling in non-myeloid hematologic malignancies. *First Author: Katherine I. Zhou, Department of Medicine, Duke University School of Medicine, Durham, NC*

Background: Comprehensive genomic profiling (CGP) is increasingly used to guide management of myeloid and advanced solid malignancies, but its role in non-myeloid hematologic malignancies is less clear. Studies have found a high rate of potentially actionable variants by CGP in this population, but these do not always translate into clinical practice changes. We aimed to determine the rate at which variants found on CGP changed clinical practice. **Methods:** We retrospectively reviewed a cohort of 101 consecutive patients with non-myeloid hematologic malignancies at Duke, comprising a total of 105 samples that were sent for CGP by FoundationOne Heme (104) or HemeComplete (1) in 2014–2021. We identified variants of clinical significance and classified them by evidence level according to the AMP/ASCO/CAP 2017 guidelines (e.g., for therapies, level A: FDA-approved / in guidelines; B: expert consensus; C: clinical trial / FDA-approved in different tumor type; D: preclinical data). We further identified documented changes in clinical practice that occurred in direct response to CGP results. **Results:** Commonly cited reasons for CGP included guiding therapy selection (27), identifying resistance mutations (19), refining prognosis (14), and clarifying diagnosis (11). Of the 105 samples sent for sequencing, 92 (88%) yielded at least one pathogenic or likely pathogenic variant. CGP resulted after death in 12 patients and within 1 month of death in another 11 patients. Seventy-three out of 101 patients (72%) had at least one variant with therapy sensitizing, diagnostic, or prognostic significance (levels A–C) or associated with therapy resistance (levels A/D). While 61 patients (60%) had a therapy sensitizing variant, only 6 patients (10%) were offered a biomarker-directed therapy. In contrast, the presence of a resistance mutation led to discontinuation of current therapy or influenced future therapy selection in 9 of 13 patients (69%). The absence of a resistance mutation influenced choice of therapy in another 4 patients. Sequencing results also helped clarify a previously uncertain diagnosis in 4 patients and led to medical genetics referrals in 3 patients. **Conclusions:** Comprehensive genomic profiling of non-myeloid hematologic malignancies identified variants of clinical significance in 72% of patients and led to changes in practice in 22% of patients. CGP was often sent late in the clinical course. Research Sponsor: U.S. National Institutes of Health.

	# Patients	# Therapy sensitizing (# acted on)	# Therapy resistant (# acted on)	# Diagnostic significance (# acted on)	# Prognostic significance
CLL	46	C: 32	A: 8 (6), D: 5 (3)	B: 1 (1)	A: 14
B-cell NHL	15	C: 11 (3)	0	B: 4, C: 7 (1)	C: 3
T-cell NHL	15	C: 8 (2)	0	C: 2	C: 2
Histiocytic Neoplasms	11	B: 3, C: 2 (1)	0	C: 1 (1)	0
Plasma Cell Neoplasms	5	C: 4	0	0	B: 1
Other	9	C: 1	0	B: 3, C: 2 (1)	A: 1
Total	101	B: 3, C: 58 (6)	A: 8 (6), D: 5 (3)	B: 8 (1), C: 12 (3)	A: 15, B: 1, C: 5

3061 **Poster Session**

Molecular typing and clinical characteristics of synchronous multiple primary colorectal cancer. *First Author: Jun Huang, Department of Colorectal Surgery, The Sixth Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China*

Background: Synchronous multiple primary colorectal cancer (sMPCC) is clinically rare while its incidence was increasing in the past decade. However, little was known about molecular and clinical features of sMPCC, which might be different from single primary colorectal cancer (CRC). **Methods:** From November 2012 to April 2021, 239 sMPCC from a total of 13276 CRC patients operated in the 6th Affiliated Hospital of Sun Yat-sen University were enrolled in this study. Mismatch repair (MMR) status in each lesion of all 239 patients was examined by immunohistochemistry (IHC). Totally 78 sMPCC patients and 94 single primary CRC patients conducted an 831-gene panel based next-generation sequencing (NGS) (OncoPanscan, Genetronhealth). Somatic mutations and potential pathogenic germline variants were analyzed. Microsatellite instability (MSI) and tumor mutation burden (TMB) were calculated. **Results:** We found that dMMR/MSI-H frequencies in sMPCC were significantly higher than those in single primary CRC, which were confirmed by both IHC (50/239 vs 872/13037, $p < 0.001$) and NGS (17/78 vs 5/94, $p = 0.0022$). According to the MMR/MSI status at different lesion in sMPCC patients, they were further divided into all MSI-H, MSI-H & MSS and all MSS group, with incidences of 16.7%, 4.2% and 79.1%, respectively. With NGS analysis, we found that the most enriched gene mutation type in sMPCC patients was C > T (G > A), and their most frequently mutated genes were *APC* (65%), *KRAS* (46%), *TP53* (31%), *PIK3CA* (25%), *EGFR* (23%), *ARID1A* (18%), *NF1* (18%), *SOX9* (18%), *FAT4* (16%), and *TCF7L2* (15%), whereas those genes in single primary CRC patients were *APC* (71%), *TP53* (64%), *KRAS* (40%), *FBXW7* (20%), *PIK3CA* (13%), *SMAD4* (12%), *ARID1A* (11%), *FAT4* (11%), *CREBBP* (11%), and *NF1* (10%). Moreover, we found that higher TMB was correlated with higher MSI in sMPCC rather than single primary CRC patients. Furthermore, we found that the mutated genes were different among three subgroups. The top 5 mutated genes in MSI-H group were *APC* (68%), *FAT4* (64%), *TCF7L2* (59%), *KMT2B* (55%), *ARID1A* (45%), whereas those in MSI-H & MSS group were *APC* (57%), *KMT2B* (43%), *KMT2C* (43%), *ATM* (43%), *PRKDC* (43%), and those in MSS group were *APC* (66%), *KRAS* (49%), *TP53* (36%), *PIK3CA* (21%), *EGFR* (20%). Finally, we also found that patients with pathogenic/likely pathogenic germline mutations were comparable between sMPCC and single primary CRC, indicating that sMPCC may not be resulted from germline changes. **Conclusions:** Our results revealed that incidences of dMMR/MSI-H in sMPCC were significantly higher than those in single primary CRC. We proposed that MMR/MSI status of each lesion in sMPCC patients should be verified before treatment and these patients could be divided into three subgroups according to their MMR/MSI status. Our findings indicated that sMPCC patients with different MMR/MSI status might be treated with personalized therapies for better management of their disease. Research Sponsor: National Natural Science Foundation of China [Grant No. 81972885] and the 1010 project of the 6th Affiliated Hospital of Sun Yat-sen University [1010CG (2020)-20].

3062 **Poster Session**

Evaluating the utility of fluorine-18 fluorodeoxyglucose (^{18}F-FDG)-positron emission tomography (PET)/ computed tomography (CT) scan in cancer of unknown primary. *First Author: Tharani Sivakumaran, Peter MacCallum Cancer Centre, Melbourne, Australia*

Background: Cancer of unknown primary (CUP) represents a heterogeneous group of metastatic tumours where standardized diagnostic work-up fails to identify the tissue of origin (TOO). Small studies, to date mainly focused on cervical lymph node squamous cell CUP patients, have shown ^{18}F-FDG-PET/CT can change patient management and identify the TOO. We aimed to describe the Peter MacCallum Cancer Centre experience with ^{18}F-FDG PET/CT in CUP with respect to detection of a TOO and its impact on management. A secondary aim was to compare the overall survival (OS) in patients where TOO is detected with those without TOO detection. **Methods**: Retrospective analysis of CUP patients treated between 2014-2020. Patients were identified from medical oncology clinics and PET/CT records. Information regarding demographics, clinicopathological details, CUP subtype as per ESMO guidelines, genomic analysis (If known), suspected TOO as per clinician pre- and post-FDG PET/CT, treatment details pre- and post FDG PET/CT and follow-up were collated from electronic medical records. Clinical details and genomic analysis were used to determine the clinically suspected TOO and compared against independent blinded nuclear medicine specialist FDG-PET/CT reads to determine sensitivity, specificity, accuracy and detection rate of TOO. **Results:** One hundred and forty-seven patients were identified of whom 65% had undergone molecular profiling. The median age at diagnosis was 61 years (range 20-84) and the median follow-up time was 69 months (range, 26–83). The predominant histological subtype was adenocarcinoma (54%). Eighteen percent of patients had a prior cancer history and 29% had a 1st degree relative with a history of cancer. Ninety-three percent were ECOG 0-1, and the dominant metastatic site was lymph nodes (35%). Eighty-one percent were classified as unfavourable CUP subtype as per ESMO guidelines. FDG PET/CT demonstrated a TOO detection rate of 34% with high specificity (98%) and moderate accuracy (78%). FDG PET/CT resulted in a change in management in 22% of patients and identified occult disease sites in 37% of patients. The median OS for all patients was 17.8 months. Median OS was not reached and 12.5 months for favourable and unfavourable CUP subtypes, respectively ($p < 0.0001$). Median OS when a potential TOO was identified on an FDG-PET/CT scan was 25.4 months compared with 9.1 months when a TOO remained elusive. ($p < 0.0001$). Multivariable analysis of survival adjusted for age and sex remained significant for FDG-PET identification of TOO ($p = 0.004$), favourable CUP ($p < 0.001$) and ECOG ≤ 1 ($p < 0.001$). **Conclusions**: ^{18}F-FDG PET/CT plays a complementary role in CUP diagnostic work-up and was able to determine the likely TOO in a third of cases. OS is improved with TOO identification, demonstrating the value of access to a diagnostic PET/CT scan for CUP patients. Research Sponsor: None.

3063 **Poster Session**

Baseline tumor size as prognostic index in patients with cancer receiving experimental targeted agents. *First Author: Paolo Tarantino, Division of Early Drug Development, European Institute of Oncology IRCCS, University of Milan, Milan, Italy*

Background: Several studies showed that high baseline tumor size (BTS) is associated with worse outcomes in cancer patients treated with immunotherapy (IO). However, the prognostic impact of BTS for patients receiving targeted therapies (TT) remains uncertain. **Methods:** We collected clinical data for patients with solid tumors consecutively treated within early phase trials at our institution from 01/2014 to 04/2021. Treatments were categorized as IO-based (if any IO-agent was included) or TT-based (biomarker-matched or not). BTS was calculated as the sum of RECIST 1.1 baseline target lesions. Progression-free survival (PFS), overall survival (OS) and objective-response rate (ORR) were compared between patients with high BTS (> median) and low BTS (≤median). **Results:** 444 patients were eligible for the analysis (220 IO, 151 TT biomarker-matched, 73 TT biomarker-unmatched). Median age was 56 years (interquartile range, IQR 48-64) and median BTS was 69 mm (IQR 40-100). Most represented tumor types were breast (49%), lung (9%), melanoma (5%) stomach, colorectal, head and neck and ovarian (4% each). Patients with low BTS were more often female ($p < 0.001$), had a better performance status (PS, $p = 0.008$), lower LDH ($p < 0.001$), lower neutrophile/lymphocyte ratio (NLR, $p < 0.001$) and higher albumin ($p = 0.003$). OS was significantly longer for patients with low BTS (16.6 vs 8.2 months, $p < 0.001$), including when restricting at those receiving IO (12 vs 7.5 months, $p = 0.005$). Among patients receiving TT, those with lower BTS experienced longer PFS (4.7 vs 3.1 months, $p = 0.002$) and OS (20.5 vs 9.9 months, $p < 0.001$) as compared with those with high BTS. However, BTS was only prognostic among patients receiving biomarker-matched TT, with improved PFS (6.2 vs 3.3 months, $p < 0.001$) and OS (21.2 vs 6.7 months, $p < 0.001$) in the low-BTS subgroup, despite a similar ORR (28% vs 22%, $p = 0.57$). BTS was instead not prognostic among patients receiving unmatched TT, with similar PFS (3.7 vs 4.4 months, $p = 0.30$), OS (19.3 vs 11.8 months, $p = 0.20$) and ORR (33% vs 28%, $p = 0.78$) in the two BTS groups. Multivariate analysis confirmed that BTS was independently associated with PFS ($p = 0.03$) and OS ($p < 0.001$) but not with ORR ($p = 0.11$), regardless of tumor site, treatment category, PS, NLR, sites of metastases and number of prior lines. **Conclusions:** Patients receiving biomarker-matched TT experience longer PFS and OS if having a lower BTS, whereas response rate is not affected by this variable. This difference may reflect the faster emergence of molecular mechanisms of resistance among patients with higher baseline burden. Lower BTS is also confirmed to be associated with longer survival among patients receiving experimental IO. BTS has instead no prognostic value among patients receiving unmatched TT. Research Sponsor: None.

3064 **Poster Session**

A large-scale, multi-center molecular characterization of *MET* fusions in a real-world Chinese population. *First Author: Yutao Liu, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China*

Background: *MET* is a driver gene notable in its diversity of clinically relevant aberrations, including exon 14 skipping, copy number gain, point mutations, and gene fusions. Compared with the former two, *MET* fusions are severely under-reported, leaving unanswered a series of fundamental questions. In this study, we addressed this knowledge gap by screening for and characterizing *MET* fusions in a real-world, multi-center population of Chinese cancer patients. **Methods:** We retrospectively included patients with solid tumors and available genome profiles acquired between August 2015 to May 2021. *MET* fusion-positive (*MET*+) patients were subsequently selected for clinical and molecular characterization. **Results:** A total of 79816 patients across 27 tumor types were screened. We detected 155 putative *MET* fusions from 122 patients, resulting in an overall prevalence of 0.15%. Lung cancer comprised the majority of *MET*+ patients (92, 75.4%). Prevalence was markedly higher in liver, biliary tract cancer, and renal cancer (range 0.52%-0.60%) and lower in ovarian cancer (0.06%). A substantial proportion (48/58, 82.8%) of unique partners were reported for the first time. The fusion partners also turned out to be highly heterogeneous, with *ST7, HLA-DRB1,* and *KIF5B* as the three most common partners. Mutational landscape analysis of lung adenocarcinoma patients (n = 32) revealed high prevalence of aberrant *TP53* in *MET*+ patients as well as *EGFR* L858R, L861Q and *MET* amplification as concurrent alterations. **Conclusions:** This study is, to our knowledge, currently the largest in characterizing *MET* fusions. Our findings warrant further clinical validation and mechanistic study that may translate into therapeutic avenues for *MET* fusion-positive cancer patients. Research Sponsor: Beijing Medical Award Foundation.

3065 **Poster Session**

Independent validation of a novel noninvasive 4-microRNA diagnostic model for multicancer early detection. *First Author: Andrew Zhang, Del Norte High School, San Diego, CA*

Background: Cancer early detection is critical to reduce mortality as treating early stage cancers is more likely to have better outcomes. We previously developed a diagnostic model based on 4 serum cell-free microRNAs (miRNAs) capable of detecting 12 cancer types with high accuracy (AACR 2022, Poster 2890; Manuscript submitted). In the current study, we aimed to validate this diagnostic model using independent serum microRNA microarray datasets. **Methods:** Four microarray datasets assessing the expression of 2588 serum miRNAs in patients with esophageal squamous cell carcinoma, gastric cancer, prostate cancer and glioma, as well as non-cancer healthy controls with a standardized platform were identified from Gene Expression Omnibus (GEO). The datasets were combined, cases that were redundant among them or with the cases used in our previous study (correlation > 0.99) were excluded. The 4-miRNA model was applied to the final combined dataset to calculate a diagnostic index and make prediction of cancer vs. no-cancer using previously determined algorithm and cut-point. The performance of the diagnostic model was assessed using Receiver Operating Characteristic (ROC) analysis, sensitivity and specificity. **Results:** After excluding redundant cases, the final combined dataset consisted of 3877 subjects, including 447 esophageal, 1267 gastric, 769 prostate and 196 glioma cancer patients, as well as 1198 healthy controls. The 4-miRNA model demonstrated an area under the curve (AUC) of 0.986, 0.995, 0.992 and 0.990 in the ROC analysis, with a sensitivity of 85.0%, 99.6%, 90.6% and 86.7% for esophageal, gastric, prostate and glioma cancers, respectively, while achieving a 99.1% specificity. These performance metrics were highly consistent to those reported in our previous study (Table). **Conclusions:** The study provided an independent validation of the previously developed 4-miRNA model, further demonstrating that the diagnostic model we developed has the potential to be developed into a simple, inexpensive and noninvasive blood test for multi-cancer early detection with high accuracy. Research Sponsor: None.

Comparison of sensitivities of the 4-miRNA diagnostic model in the four cancer types between our previous study vs. the current study.

	Previous Study			Current Study		
Cancer Type	**N**	**AUC**	**Sensitivity**	**N**	**AUC**	**Sensitivity**
Esophageal Squamous Cell Carcinoma	124	0.990	84.7%	447	0.986	85.0%
Gastric Cancer	150	0.999	100%	1267	0.995	99.6%
Prostate Cancer	40	0.996	92.5%	769	0.992	90.6%
Glioma	40	0.996	87.5%	196	0.990	86.7%

3066 **Poster Session**

Comparative analysis of microsatellite instability-high (MSI-H) *BRAF* V600E-mutated versus MSI-H *BRAF* wild type colorectal cancers (CRC), including tumor microenvironment (TME), associated genomic alterations, and immunometabolomic biomarkers. *First Author: Mohamed E. Salem, Levine Cancer Institute, Atrium Health, Charlotte, NC*

Background: The $BRAF^{V600E}$ mutation is associated with the hypermethylator phenotype CIMP, which can also lead to the MSI-H phenotype. $BRAF^{V600E}$ mutation and MSI-H/dMMR status seem to be biologically intertwined; however, the impact of coexisting $BRAF^{V600E}$ mutations on the TME and immunometabolomic features of MSI-H/dMMR CRC tumors is not well characterized. **Methods:** A retrospective review of deidentified records of patients with MSI-H/dMMR CRC tumors was conducted using next-generation sequencing data (Tempus lxT assay: DNA-seq of 595-648 genes at 500x coverage, and full transcriptome RNA-seq). Several immune markers of tumor immunogenicity in *BRAF* wild-type ($BRAF^{wt}$) vs. V600E-mutated ($BRAF^{V600E}$) tumors were assessed, including tumor mutational burden (TMB), neoantigen tumor burden (NTB, ScanNeo), PD-L1 expression, immune infiltration, and canonical immuno-metabolomic pathways (82 geneset signatures). **Results:** A total of 459 MSI-H/dMMR CRC tumors were analyzed, of which 123 (27%) tumors harbored $BRAF^{V600E}$mutations, and 336 (73%) were $BRAF^{wt}$. MSI-H/dMMR $BRAF^{V600E}$ tumors were more frequently identified in females (69% vs. 55%; P= 0.01), non-Hispanic or non-Latino (100% vs. 73%; P =0.001), and older patients (median age: 76 yrs vs. 62 yrs; P< 0.001). Compared to $BRAF^{WT}$, $BRAF^{V600E}$ tumors exhibited significantly higher TMB (Median: 49 mut/MB vs. 36 mut/MB; P < 0.001) and were more frequently associated with TMB-High status (> 10 mut/MB; 100% vs. 95%; P = 0.008); however, no significant differences were observed with tumor NTB, immune score, or T cell infiltration (CD4 or CD8). NK cell infiltration was higher in the $BRAF^{V600E}$cohort (< 0.001). When compared to $BRAF^{WT}$ tumors, $BRAF^{V600E}$ tumors harbored a greater frequency of mutations in *MSH6*(42% vs. 20%), *B2M* (33% vs. 16%), *BRCA2* (31% vs. 12%), *ATM* (23% vs. 12%), and *TP53* (30% vs. 19%) but a lower frequency of *MSH2* (3.3% vs. 11%), all P< 0.05. Pathway enrichment analysis identified 10 significantly altered signaling pathways, most of which related to stromal/immune cell signaling and metabolism. Five were upregulated among $BRAF^{V600E}$ tumors: glycerophospholipid, galactose, cyclin-dependent cell signaling; Nucleotide, and TH1 inflammation. Five pathways were downregulated (Wnt, Notch, TH17 inflammation, amino sugar, and cancer stem cell signaling). **Conclusions:** MSI-H/dMMR $BRAF^{V600E}$ CRCs undergo broad metabolic reprogramming (e.g., glycerophospholipidgalactose, nucleotide). A rise in lipid metabolism, particularly with NK inflammation, suggests that $BRAF^{V600E}$mutated tumors may be associated with a non-classical immune component. $BRAF^{V600E}$ and $BRAF^{wt}$ CRCs exhibited similar NTB and T cell infiltration, suggesting that both are likely to benefit from immune checkpoint inhibitors. Research Sponsor: None.

3067 **Poster Session**

Impact of *RAS* mutations on immunologic characteristics of the tumor microenvironment (TME) in patients with microsatellite instability-high (MSI-H) or mismatch-repair–deficient (dMMR) colorectal cancer (CRC). *First Author: Mohamed E. Salem, Levine Cancer Institute, Atrium Health, Charlotte, NC*

Background: The KEYNOTE-177 trial demonstrated pembrolizumab's superiority over first-line chemotherapy in patients with MSI-H/dMMR mCRC. However, in a subgroup analysis, patients with *KRAS* or *NRAS* mutations did not show the same favorable PFS benefit with PD-1 blockade therapy (HR 1,19; CI 0.68-2,07). The impact of *RAS* mutations on the immunologic characteristics of the TME of MSI-H/dMMR CRC has not been well characterized. **Methods:** A retrospective review of deidentified records of patients with MSI-H/dMMR CRC tumors was conducted using next-generation sequencing data (Tempus lxT assay, DNA-seq of 595-648 genes at 500x coverage, and full transcriptome RNA-seq). MSI-H determined by assessment of 239 loci by NGS. Several immune markers were assessed, including tumor mutational burden (TMB), neoantigen tumor burden (NTB, ScanNeo), PD-L1 expression, immune infiltration, and canonical immune pathways (82 geneset signatures). **Results:** A total of 463 MSI-H/dMMR CRCs were analyzed, of which 110 (24%) tumors harbored *RAS* mutations (RAS^{mut}) [*KRAS*: 93%, *NRAS* 6% and *HRAS* 1%), while 353 were *RAS*-wild-type (RAS^{WT}). Compared to MSI-H/dMMR RAS^{WT}, MSI-H/dMMR RAS^{mut} tumors were more frequently identified in males (53% vs. 38%; P= 0.005), and younger patients (median age: 57 yrs vs. 71 yrs, P< 0.001). Although there were no significant differences in median TMB (40 mut/MB for both, p = 0.9) or frequency of TMB-high status (≥10 mut/MB) between the two groups, RAS^{mut}tumors tended to have a lower tumor NTB (16 vs. 12 neoAg/Mb, P <0.001) and lower % CD8 T cell but higher % CD4 T cell infiltration (P < 0.05). Significant differences were observed in genomic alterations co-occurring with RAS^{mut} compared to RAS^{WT} (e.g., *MLH1* (23% vs. 8.8%, P < 0.001), *MSH6 (36% vs. 24%, P = 0.017), APC* (60% vs. 20%, P< 0.001), *ARID1A* (54% vs 30%, P< 0.001), *PIK3CA* (36% vs 19%, P< 0.001), *and TP53* (32% vs. 19%, P = 0.014). Pathway enrichment analysis identified 14 differentially expressed pathways among RAS^{mut} tumors. Four pathways showed significant upregulation, including Hedgehog, Wnt, *TGFβ*, and cancer stem cell pathways. Ten pathways of interest showed significant downregulation among RAS^{mut} tumors. The majority (9/10) were immune-related, including cytokine signaling [*JAK-STAT, TGFβ, TH1*], innate immune [*NK cells*], and adaptive immune events *(CD8 T cell, Tregs*)]. **Conclusions:** MSI-H/dMMR CRCs harboring RAS^{mut} exhibited overall upregulated *WNT/SHH* pathway activity, coupled with reduced NTB, cytokine signaling, and innate and adaptive immune events. *TGFβ* is pleiotropic, and different members were associated with variable modulation. These data suggest that MSI-H/dMMR CRCs harboring *RAS* mutations are less immunogenic and appeared to contain a TME that is less sensitive to immune checkpoint blockade than MSI-H/dMMR RAS^{wt} CRCs. Research Sponsor: None.

3068 **Poster Session**

Lesion-specific radiomics analysis shows promising results for early-stage efficacy assessment of IOA-244 in uveal melanoma. *First Author: Martin Gueuning, Radiomics, Liege, Belgium*

Background: Radiomics is an image based approach that allows for characterization and quantification of tumor lesions in cancer patients. Radiomics has been proven capable of potentially adding value in the diagnostic and prognostic patient managment. In this study we evaluated the potential of Radiomics to bring additional insight also in early drug development. **Methods:** All the visible malignant lung and liver metastasis lesions of 7 uveal melanoma patients (86% of women, 60±11y) treated with IOA-244 (EudraCT 2019-000686-20) were manually segmented and analyzed in their size and shape *via* a radiomics approach. The CT scans at baseline and first follow-up (8 weeks) were included in the study and compared. Descriptive statistics and linear mixed effect (LME) models were used to quantify volumetric lesion-specific response to treatment. Response has been defined both as continuous variable and in three discrete categories (lesion shrinkage, stable and progressive disease for a volume change of [-100%;-0%];[0%-+25%] and > 25%, respectively). The influence of lesion shape at baseline (e.g. compactness, elongation or surface roughness among others) on the treatment response has been explore through LME models as well. **Results:** We identified and segmented 126 metastatic lesions (70 lung and 56 liver) from baseline scans and 122 lesions (71 lung and 51 liver) from post treatment scans. Of those, 64% could be consistently mapped between visits, resulting in a total of 147 matching lesions on which the radiomics analysis was performed. We found 19% of complete response and 16% of new lesions appearing. 8 weeks after treatment start, we observed non progressive disease in 61% of all lesions, of which 42% was shrinking. LME did not show a significant change in lesion volume between visits, but the mean difference between visits was negative. LME did show that lesion shape is significantly different between progressors and non-progressors at baseline for lung lesions (compact and irregular lesions are more likely to respond), and that there are moderate correlations (0.4-0.7) between tumor shape and volume change for liver lesions (compact lesions have a larger volume drop). **Conclusions:** This work demonstrates both the clinical potential of IOA-244 for treatment of Uveal Melanoma patients with lesions in the lung and in the liver and the potential of radiomics individual lesion analysis for clinical research in the very early stages of drug development. Lesion evolution volumetric assessment has allowed a more accurate and sensitive understanding of IOA-244 efficacy and impact across different lesions, in both lung and liver. Radiomics showed a promising response of selected population to IOA-244 over the first time point (W0-W8). A further radiomics analysis on next follow-up scans would allow a radiological proof of treatment-induced changes and long-term patient outcome prediction. Research Sponsor: None.

3069 **Poster Session**

The HERPET study: Imaging HER2 expression in breast cancer with the novel PET tracer [^{18}F]GE-226, a first-in-patient study. *First Author: Laura M. Kenny, Imperial College London, London, United Kingdom*

Background: Over-expression the human epidermal growth factor receptor-2 (HER2) is seen in 20% of breast cancers; this is an adverse prognostic factor and used to guide therapy selection. At present HER2 expression can only be determined using biopsy material using immunohistochemistry or fluorescence in situ hybridisation. Heterogeneous expression of HER2 is now being recognised as a cause of treatment resistance but is difficult to characterise. A non-invasive method for determining HER2 expression could have several advantages and help select appropriate therapy for patients. GE-226 is a novel radiolabelled GE-Affibody radioligand which binds to the HER2 receptor with high affinity at a different epitope than trastuzumab. **Methods:** Patients with locally advanced or metastatic breast cancer were recruited and scanned for 65 mins after iv injection of 200MBq of GE-226 (mean activity injected for each patient 202MBq (range 164-223MBq, mean radiochemical purity 94%) of radioligand, over one bed position for dynamic imaging, followed by a half-body scan. Blood sampling was used to measure metabolism of the tracer. Safety was assessed. HER2-extracellular domain (ECD) domain was measured in blood. Tumoural uptake was quantified by semi-quantitative and fquantitative parameters in HER2 positive and HER2 negative tumours. Patients had routine baseline FDG imaging. **Results:** Twenty patients completed the study. GE-226 scans were well tolerated. There were no serious adverse events. GE-226 was slowly metabolised into a single metabolite in the liver; 97% of parent remained at 60 minutes post injection (range 82-100). There was a significant difference in tumoural radioligand uptake between biopsy proven HER2 positive and HER2 negative tumoural patients as measured by SUV_{mean} and SUV_{max} ($p < 0.001$). Comparing HER2 positive to HER2 negative cases, there was also a significant difference between tumour to normal tissue uptake ratios SUV_{mean}. Heterogeneous uptake was observed in three patients, two with interlesional uptake variation and one with intralesional heterogeneity. Tumoural uptake increased over time. Normal physiological uptake in salivary glands and the thyroid gland was noted. GE-226 was able to differentiate between lymphadenopathy due to sarcoidosis and cancer in one patient and was superior to FDG which had shown widespread uptake in the benign and malignant nodes. **Conclusions:** [18F]GE-226 imaging is well tolerated and shows promise for imaging of HER2 positive breast cancer. Further studies with this agent are now planned. Clinical trial information: NCT03827317. Research Sponsor: Medical Research Council (UK), Pharmaceutical/Biotech Company, Medical Research Council.

3070 **Poster Session**

[^{18}F]Fluorothymidine(FLT)-PET imaging of thymidine kinase 1 pharmacodynamics in non-small cell lung cancer treated with pemetrexed. *First Author: Preetha Aravind, Imperial College London, London, United Kingdom*

Background: Imaging of tumor proliferation has been studied with FLT-PET in various tumor types including NSCLC. Pemetrexed inhibits thymidylate synthase(TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT). TS inhibition upregulates the thymidine salvage pathway including relocalisation of ENT1 to membrane and TK1 activation as a transient "flare" response. We hypothesise that this can be detected as an increase in FLT tumoral uptake that subsequently decreases with reduced proliferation. This study was conducted to assess FLT uptake as an early pharmacodynamics(PD) marker of pemetrexed response. **Methods:** This was an open-label imaging study in 21 patients with Stage 3/4 NSCLC treated with pemetrexed and platinum-based chemotherapy. Patients underwent FLT PET/CT scan at baseline and 4h after administration of pemetrexed. Platinum component of treatment was administered on the day after second FLT scan for cycle 1. Plasma for TK1 activity expression were collected before each scan time point and analysed by ELISA. Percentage change in standardized uptake value (%ΔSUV) was calculated as [SUV(PET2) – SUV(PET1)]/SUV(PET1)*100. Treatment response calculated by RECIST 1. 1 and survival data were collected. **Results:** 17 patients had evaluable PET/CT scans for pemetrexed response. Median percentage difference for SUVmean and SUVmax in tumour lesions increased by 3% and 10.3% respectively. 5 patients showed homogeneous FLT flare at 4h after pemetrexed, 2 patients had decrease, 10 patients had heterogeneous FLT response (regardless of platinum doublet). There was no significant correlation between plasma TK1 activity and FLT flare. At 9 weeks, 4 patients had partial response, 9 stable disease and 4 progressive disease. Baseline and weighted average ΔSUVmax were not associated with survival. The 5 patients with FLT flare in all lesions showed a median OS of 31 months, unlike the group with heterogenous or decrease uptake(15 months). FLT uptake in bone marrow and small bowel significantly increased at 4h (t test p = 0.004, p = 0.004, respectively) indicating increased thymidine salvage activity. Early FLT uptake was not predictive for tumour RECIST response or OS. In multivariable cox regression analysis, pre-treatment TK1 activity, adjusted for performance status, smoking history and age, independently affected survival in this group (p = 0.011). **Conclusions:** Early FLT flare at 4h was seen in NSCLC post pemetrexed administration indicating activation of thymidine salvage pathway. Median overall survival of patients with an FLT flare response was more than twice longer than patients with mixed or no response. However, the small sample size lacked power to show statistical significance in the OS comparison. Further studies should evaluate this and the relationship to other prognostic variables in a larger cohort of patients. Clinical trial information: NCRI UK badge 9249. Research Sponsor: Medical Research Council, UK.

3071 **Poster Session**

Differential expression of somatostatin receptor (SSTR) subtypes across a spectrum of neuroendocrine neoplasms (NENs). *First Author: Emil Lou, Masonic Cancer Center/ University of Minnesota School of Medicine, Minneapolis, MN*

Background: Targeted therapy of NENs based on the presence of SSTRs fills a unique niche in tumor biology and clinical treatment of patients with solid tumors. SSTRs have multiple isoforms and are collectively expressed in the majority of NENs. However, subtypes are still not routinely tested and thus not assessed for clinical decision-making, especially for patients meriting consideration of targeted radionucleotide therapy. Clarifying the landscape of SSTR subtypes using molecular techniques more sensitive than immunohistochemistry (IHC)-the standard of testing, and identifying associated genomic biomarkers that differ between them, will pave the way for more sophisticated decision-making in the future. Additionally, leveraging transcriptomics to better assess mitotic markers such as Ki-67 to assess tumor grade, would increase diagnostic accuracy. Here we provide initial validation across a spectrum of NENs. **Methods:**1595 NENs were analyzed using Next Generation Sequencing (592 gene panel, NextSeq), Whole Exome and Transcriptome Sequencing (NovaSeq), and IHC at Caris Life Sciences (Phoenix, AZ). Significance was determined using chi-square, Fisher-Exact or Mann-Whitney U and p-adjusted for multiple comparisons ($q<0.05$) where applicable. **Results:** In a subset of 492 NENs with accompanying tumor grading information, a median *MKI67* (gene encoding Ki-67) TPM value of 2.27 for low-grade (LG-), and 38.7 for high-grade NENs (HG-NENs) was observed ($q<0.05$). Using ROC curve analysis, a threshold of *MKI67* expression (13.4375 TPM) differentiated LG- from HG-NENs, with a true positive rate of 86.84%, a false positive rate of 11.9% and an AUC of 95% and was subsequently applied to the entire cohort to infer HG/LG. Compared to HG-NENs (n = 862), LG-NENs(n = 733) expressed higher levels of SSTR 1(3.5-fold),2 (2.9-fold) and 5 (1.67-fold) and lower levels of SSTR4 (0.28-fold)($q<0.05$). Further, the expression of SSTRs 3 and 4 in HG-NEN (r_s= 0.63) and SSTRs 1 and 2 in LG-NENs (r_s= 0.64) were positively correlated. Overall, the prevalence of altered *TP53*, *RB1*, *PIK3CA*, *APC*, *KRAS* was higher and *MEN1* was lower in HG-vs LG-NENs ($q<0.05$). For each SSTR subtype, we established high and low cohorts based on median expressions. In LG-NENs, increased alterations in *TP53* and *RB1* were associated with increased expression of SSTRs 1 and 2 and reduced expression of SSTRs 3 and 4. In HG-NENs, increased alterations in APC were associated with increased expression of SSTR 1 and 4 and reduced expression of SSTRs 3 and 5. Additional subtype- and grade-specific alterations were also observed. **Conclusions:** This study provides evidence that WTS and NGS can be leveraged to predict grade of NENs and define characteristic differences in the genomic landscape across SSTR subtypes in HG and LG NENs. Incorporating the molecular profiling of NENs can thus aid in advancing the development of more tailored therapeutic strategies. Research Sponsor: Caris LLC.

3072 **Poster Session**

Image-based detection of *FGFR3*-fusion in urothelial bladder cancer. *First Author: Nir Peled, Oncology Division, Shaare Zedek Medical Center, Jerusalem, Israel*

Background: Fibroblast growth factor receptor-3 (FGFR3) is a transmembrane protein, somatically altered in a large spectrum of cancer types. Chromosomal rearrangement resulting in *FGFR3* gene fusions leads to a constitutively active tyrosine kinase, mediating tumorigenesis. *FGFR3*-fusion is a prognostic and predictive marker as well as a validated therapeutic target in urothelial bladder cancer. Both FISH and RT-PCR assays can be used for the detection of *FGFR3* rearrangements while immunohistochemistry lacks sufficient sensitivity and specificity. In recent years advances in next-generation sequencing improved their ability to detect these alterations in clinical settings. However, systemic screening of these alterations is still expensive, time-consuming, and requires expertise personnel for data analysis and interpretation. In this study, we aimed to develop and validate an alternative machine learning (ML) based method for the detection of *FGFR3*-fusions directly from routine pathology hematoxylin and eosin (H&E) slides. **Methods:** A cohort of 388 H&E whole slide images of bladder urothelial carcinoma samples, obtained from the TCGA Research Network (https://www.cancer.gov/tcga) was used. Cases were randomly divided into training (n = 238) and testing (n = 150) sets. Advanced Convolutional Neural Network (CNN) was used to generate the *FGFR3*-fusion classifier on the training set following validation on the testing set. **Results:** Validation of the *FGFR3*-fusion classifier was performed on a cohort of 150 cases from 19 different centers, including three positive cases of *FGFR3-TACC3* fusions and 147 negative cases. The AI-classifier performance was measured in comparison to the TCGA dataset. The model demonstrated 100% sensitivity and 94% specificity, with an Area Under the Curve (AUC) of 0.96. **Conclusions:** Herein, we demonstrate a real-time ML-based genomic testing solution for *FGFR3*-fusion detection in bladder cancer directly from H&E stained slide images. Utilization of such an alternative method can facilitate fast, accurate, and systemic screening of patients if integrated within the routine pathological pipeline supporting targeted therapy treatment for these patients. Research Sponsor: Imagene-AI.

3073 **Poster Session**

Molecular therapy selection in treatment-refractory advanced cancers: A retrospective cohort study determining the utility of TOPOGRAPH knowledge base. *First Author: Frank Po-Yen Lin, NHMRC Clinical Trials Centre, University of Sydney, Sydney, NSW, Australia*

Background: Comprehensive genomic profiling (CGP) is increasingly used to guide therapy selection in advanced cancer patients who have exhausted standard therapy options. Here we assess the utility of Therapy Oriented Precision Oncology Guidelines for Recommending Anticancer Pharmaceuticals (TOPOGRAPH) to guide matching of drug treatments based on CGP in this setting. **Methods:** This study was conducted in an Australia-wide precision oncology program, the Molecular Screening and Therapeutics Study (MoST, ANZCTR registration ACTRN12616000908437). All patients with advanced cancer after exhausting standard treatments underwent CGP in 2016-2021 were stratified into cohort A (no further therapy received) and B (received ≥1 therapy after CGP). The primary outcome was overall survival (OS) estimated by the Kaplan-Meier method, using the log rank test to assess between-group differences. TOPOGRAPH matched the treatment history to the CGP results, stratified into clinically active (Tiers 1-3, T1-3), investigational (T3B/4), inactive (R2) or unmatched groups. **Results:** Over a median follow-up of 21.7 months (mo) for 2852 patients (75% with rare cancers, n = 2150), the median OS (mOS) from the date of CGP result was 7.0 mo (95% CI 6.4-7.6) for cohort A (n = 1562) and 15.8 mo (95% CI 14.5-16.9) for cohort B (n = 1290). In both cohorts, patients with CGP results matching any TOPOGRAPH tier (T1-4) had shorter OS compared to patients without a matching tier (A: 6.4 v 20.5 mo, hazard ratio for death [HR] 2.15, p<0.001; B: 14.7 v 23.6 mo, HR 1.43, p<0.001). Patients in cohort B receiving matched therapy (n=342, 27%) had a longer mOS than 948 patients who received only unmatched therapy (16.9 v 10.4 mo, HR 0.70, p<0.001). For CGP results matched to T1-3, 122 patients who received a T1-3 therapy had a significantly longer mOS than those who received unmatched therapy (22.1 v 9.8 mo, HR 0.51, p<0.001). For CGP results matched only to T3B/4, a trend toward longer mOS was observed in patients receiving matched therapy in T3B/4 (n = 138, 14.5 v unmatched 10.0 mo, HR 0.81, P = 0.07). In tier-matched analysis, the mOS were not significantly different between patients who received genomics matched v unmatched therapy in T3B (matching outside cognate histotypes, n = 48 v 508, 11.9 v 9.7 mo, HR 0.84, p = 0.36) and T4 (n = 32 v 134; therapy with preclinical/early clinical evidence, 17.1 v 12.2 mo, HR 0.69, p = 0.17). **Conclusions:** TOPOGRAPH is prognostic and likely predictive of treatment effect based on CGP, supporting its utility in guiding molecular therapy selection in patients who have exhausted standard treatment options. Research Sponsor: Office for Health and Medical Research, State of New South Wales and Australian Federal Government.

OS from the next therapy after CGP in cohort B (n = 1290).

Therapy received post CGP	Overall Matched N	mOS (mo)	Tier-matched analysis Matched N	Tier-matched analysis Matched mOS (mo)	Unmatched N	mOS (mo)	HR	P
T1-3	122	22.1	122	22.1	296	9.8	0.51	<0.001
T3B/4	220	14.5	138	14.5	584	10.0	0.81	0.07
Untiered	913	10.5						
R2	35	9.4						

3074 **Poster Session**

Development and validation of Duoseq as a novel diagnostic and companion assay for lymphoma and other cancers. *First Author: Chrissie Rozzi, Data Driven Bioscience, Durham, NC*

Background: While NGS applications of DNAseq and RNAseq have proven to be powerful tools for genomic discovery, NGS remains underutilized in the clinic. We hypothesized that the clinical translation of NGS would be greatly improved by addressing two critical issues: first, having a single assay for both DNA and RNA sequencing, and second, including all the bioinformatics to enable rapid analysis and reporting of clinically relevant findings within 2 days rather than 2-3 weeks which remains the widespread standard. We developed Duoseq to address these issues. **Methods:** In most cancer biopsies, RNA constitutes nearly 80% of the total nucleic acid and DNA only 20%. Duoseq incorporates interfering factors that make the ligation of sequencing barcodes to RNA much less efficient than that to DNA to, in effect, invert the proportion of DNA and RNA from the sample. This enables the efficient generation of high quality DNA and RNA libraries. The assay targets over 450 recurrently altered genes in hematologic cancers. We developed secure bioinformatics software that connects to an Illumina sequencer to render four major classes of clinical measurements: mutations, gene expression (cell of origin in DLBCL), Epstein Barr virus (EBV) status and and common translocations (BCL2, BCL6, MYC, IRF4, CCND1). **Results:** Technicians at three different CLIA labs were trained to perform Duoseq at the respective sites using a local Illumina sequencer. The assay was performed on 111 FFPE lymphoma cases including diffuse large B cell lymphoma, and other B and T cell lymphomas that were characterized using clinical standard assays. The standards included Sanger sequencing or Foundation One testing (mutations), in situ hybridization (EBV), immunohistochemistry or Nanostring (expression) and fluorescent in situ hybridization (translocation). The included Duoseq software provided the bioinformatics results as well as annotations. With a minimum input of 50ng of nucleic acid/sample, Duoseq generated a mean depth of coverage of 438X. We found that, compared to clinical standards, Duoseq performed accurately for mutations (95.9%), EBV status (96.5%), translocations (94.1%) and expression (100%). In addition, Duoseq provided information on clonality, specific translocation partners and identified novel fusions that were not available from standard assays. **Conclusions:** Duoseq accurately recapitulates the clinical workup of lymphomas replacing the need for single analyte tests such as FISH, while providing a wealth of additional data. The simplicity of the assay and the included bioinformatics software enables its performance at any clinical lab without the need for specialized personnel or computing infrastructure. We anticipate the application of Duoseq as a diagnostic assay, as well as in clinical trial selection and companion diagnostic applications owing to its high accuracy and short turnaround time. Research Sponsor: Data Driven Bioscience.

3075 **Poster Session**

Real-world utilization of ctDNA in the management of colorectal cancer. *First Author: Kristin M. Zimmerman Savill, Cardinal Health, Dublin, OH*

Background: The utilization of circulating tumor DNA (ctDNA) as a non-invasive biomarker for the detection of minimal residual disease, prediction of recurrence in the post-operative setting, and real-time monitoring of treatment efficacy has the potential to vastly improve the care and outcomes of patients with colorectal cancer (CRC). In August of 2020, ctDNA testing first gained approval for use in solid tumors and its prognostic benefit after curative intent surgery has been demonstrated to exceed that of prior standard of care clinicopathological criteria in CRC patients. The comprehensive integration of validated ctDNA approaches into the routine clinical care of patients with CRC would not only fundamentally change how risk of recurrence is assessed but could also reduce treatment with unneeded/unwarranted toxic therapies and allow for earlier recognition and treatment in cases with a high risk of relapse. This survey-based study aimed to evaluate the utilization of ctDNA testing in the management of CRC among practicing community oncologists in the U.S. **Methods:** Questions related to ctDNA utilization for patients with CRC were presented to community oncologists during a virtual meeting held in July 2021. Descriptive statistics were used to analyze the results. **Results:** Of 55 participating oncologists geographically distributed across the U.S., 49% indicated not using ctDNA to make treatment decisions in CRC. A proportion of physicians reported using ctDNA to detect recurrence (27% of physicians); make decisions around post-resection adjuvant therapy (25%); monitor disease progression/relapse (18%); and track tumor resistance during treatment (9%). The most frequently cited barriers to ordering ctDNA testing for patients with metastatic CRC were reimbursement issues (reported by 56% of oncologists), insufficient clinical evidence (46%), and limited familiarity with ctDNA use (28%). Oncologists reported that the following would increase their utilization of ctDNA testing: more clinical evidence of the utility of ctDNA (reported by 66% of physicians), increased education on methodology (60%), more education on the use of ctDNA (57%), more financial aid and reimbursement support for patients (49%), more decision support tools (47%), and better communication between physicians and vendors (26%). **Conclusions:** These findings demonstrate limited adoption of ctDNA testing by community oncologists in the care of CRC patients. Insufficient demonstration of clinical utility, limited familiarity with methodology, and reimbursement issues were cited as barriers to uptake. Education for community oncology providers about ctDNA testing and its demonstrated clinical utility, and increased financial support for patients may improve its utilization and adoption in CRC to improve patient outcomes and care. Research Sponsor: None.

3076 **Poster Session**

Repeat large panel genomic sequencing identifies actionable alterations and characterizes the genomic landscape in patients with metastatic solid tumors. *First Author: Niamh Coleman, The University of Texas MD Anderson Cancer Center, Houston*

Background: The implementation of genomic profiling with next generation sequencing has revolutionized the field of precision oncology. Comprehensive genomic testing of tumors to identify actionable genomic alterations is now commonly performed in the care of patients with advanced/metastatic disease. Although the genomic profile of tumors has been shown to evolve with progression and intervening treatments, the role of repeat genomic testing is not well established. We sought to determine the evolution of actionable genomic alterations in patients undergoing repeat genomic testing on the same comprehensive genomic panel. **Methods:** We retrospectively examined the molecular profiles and medical records of 262 patients with metastatic solid tumors treated in MD Anderson who underwent genomic testing on the same panel (Oncomine, Thermo Fisher) for the detection of somatic mutations in the coding sequence of 143 cancer-related genes, on at least 2 separate occasions. Genomic alterations were reviewed by a central Precision Oncology Decision Support (PODS) team in order to provide annotations at the alteration level on the functional significance. **Results:** 262 patients underwent repeat genomic testing using the same genomic panel on samples collected at different time points from July 2010 to Dec 2021 across tumor types. Changes in alterations (gain or loss) were identified on repeat testing in most patients (66%) We then specifically assessed changes in alterations that were categorized as actionable if annotated by the PODS team at the time of reporting. A gain or loss of an actionable alteration was detected in 38% (100/262) patients. New actionable alterations were frequently identified (73%; 73/100), while 41% had loss of an actionable alteration (41/100). 14% had both loss and gain of actionable alteration on repeat testing; 58% had new actionable alteration identified alone; 27% had loss of actionable alteration only. Actionable alterations identified on repeat testing included alterations in *PI3K/AKT* (27%), *EGFR* (15%), and *MAPK (*16%). On repeat testing, changes in $^{3}2$ actionable alterations were frequently identified in the same test (43%). **Conclusions:** Repeat large panel genomic testing identifies both gain and loss of actionable alterations in patients with advanced metastatic cancers. Actionable aberrations frequently coexist with alterations in a variety of other genes, which highlights the complexities of treating patients with metastatic cancer on progression of disease and suggests that tailored combination strategies may be necessary in these patients. Research Sponsor: None.

3077 **Poster Session**

Use of clinical RNA-sequencing in the detection of actionable fusions compared to DNA-sequencing alone. *First Author: Jackson Michuda, Tempus, Chicago, IL*

Background: While targeted DNA-seq can detect clinically actionable fusions in tumor tissue samples, technical and analytical challenges may give rise to false negatives. RNA-based, whole-exome sequencing provides a complementary method for fusion detection, and may improve the identification of actionable variants. In this study, we quantify this benefit using a large, real-world clinical dataset to assess actionable fusions detected from RNA in conjunction with DNA profiling. **Methods:** Using the Tempus Research Database, we retrospectively analyzed a de-identified dataset of ~80K samples (77.4K patients) profiled with the Tempus xT assay (both DNA-seq with fusion detection in 21 genes and whole exome capture RNA-seq). Only patients that had successful RNA- and DNA-seq were included. Fusions were detected using the Tempus bioinformatic and clinical workflow. Candidate fusions were filtered based on read support thresholds, fusion annotation (*i.e.,* breakpoints, reading frame, conserved domains), and manual review. OncoKB was used to select fusion alterations in levels 1 and 2 and to identify those indication-matched to targeted therapies. **Results:** We identified 2118 level 1 and 2 fusion events across 1945 patients across 20 different cancer types. Most fusions were observed in non-small cell lung cancer (NSCLC) (25%) and biliary cancer (9%) samples. Of the 2118 fusion events, 29.1% (616) were detected only through RNA-seq while 4.8% (101) of the events were identifiable only through DNA-seq. Notably, 69.4% of fusions in low-grade glioma and 58.2% in sarcomas were detected only by RNA-seq. When evaluating specific gene fusion events, RNA-seq consistently improved the detection of fusions compared to DNA-seq alone (Table) across all cancer types. A total of 1106 fusions were classified as targetable by OncoKB indication-matched therapies with 19% (214) of these identifiable through RNA-seq alone, 5% (54) by DNA-seq alone, and 76% (838) identifiable through RNA- and DNA-seq. Overall, fusions identified through RNA-seq alone led to a 24% increase in the number of patients who were eligible to receive matched therapies (214 / 892). This included imatinib for patients with CML/BLCL (69.8%), crizotinib for NSCLC (40.3%) and entrectinib for *NTRK* and *ROS1* fusions (32.5%). **Conclusions:** The addition of RNA-seq to DNA-seq significantly increased the detection of fusion events and ability to match patients to targeted therapies. Results support consideration of combined RNA-DNA-seq for standard-of-care fusion calling. Research Sponsor: None.

All fusion events.

Fusion	N	% Both RNA+DNA	% DNA only	% RNA only
ALK-*	386	78.0	4.1	17.9
FGFR2-*	384	69.3	9.1	21.6
FGFR3-*	307	73.6	2.9	23.5
BRAF-*	289	30.4	1.4	68.2
NTRK1/2/3-*	198	65.7	11.1	23.2
RET-*	191	85.3	4.2	10.5
BCR-ABL	130	87.7	1.5	10.8
ROS-*	113	70.8	1.8	27.4
Others	118	28.0	3.4	68.6
All	**2118**	**66.1**	**4.8**	**29.1**

3078 **Poster Session**

Pathogenic fusion detection in solid malignancies utilizing RNA-DNA based comprehensive genomic profiling (CGP) testing. *First Author: Brian Piening, Earle A. Chiles Research Institute at Robert W. Franz Cancer Center, Providence Cancer Institute, Portland, OR*

Background: Gene fusions caused by chromosomal rearrangements comprise a key category of oncogenic driver mutations. However, given the diverse array of potentially novel loci where each proto-oncogene can translocate, many assays including DNA-based CGP have technical limitations that disallow the detection of all relevant fusion partners potentially leading to false negatives. Hybrid Capture RNA sequencing renders a more comprehensive evaluation of genes and allows detection of novel and known fusion partners. Here we assessed the impact of utilizing in-house CGP testing with a paired RNA-DNA hybrid assay in the identification of pathogenic fusions and their potential clinical actionability for patients with solid tumors across a large US health system. **Methods:** Patients in the Providence health system diagnosed with advanced solid tumor malignancies over a two-year period (2019-2021) received reflex CGP testing at the time of diagnosis utilizing an internally validated workflow. DNA/RNA sequencing results as well as histology and staging information were curated from deidentified electronic medical records and in-house databases, and tumor types were mapped to OncoTree tissue categories. Potential clinical actionability was assessed based on OncoKB therapeutic levels 1-3 and clinical trial eligibility matched to the biomarker inclusion criteria for ASCO TAPUR, NCI-MATCH and MyPathway studies (both without time limits and at time of testing). **Results:** The median patient age at diagnosis was 67 years, 52% of patients were female, and the majority (80%) were white. Across all tested advanced solid tumors, 6.7% (217/3218) were found to harbor a pathogenic fusion. The tumor types most enriched in this set of pathogenic fusions were prostate (30%), lung (27%), CUP (10%) and breast (9%). 29% (n = 64) of the identified pathogenic fusions were identified as actionable based on OncoKB criteria (levels 1-3), and 31% (n = 69) matched to one or more arms in the ASCO TAPUR, NCI-MATCH or MyPathway basket clinical trials. The most frequent actionable fusion driver genes identified were *ALK* (12%), *FGFR 1-3* (12%), *RET* (7%) *NTRK 1-3* (3%), and *ROS1* (2%) and a subset of these key drivers were fused with novel gene pairs. A subset of fusions co-occurred with other targetable biomarkers, with the most common comprising tumor mutational burden high (TMB-H) (13%), *PIK3CA* (7%) and high microsatellite instability (MSI-H) (2%). **Conclusions:** In-house CGP testing utilizing an RNA-DNA based assay identified actionable fusion targets across tumor types, with many novel fusion partners that may be undetectable by prior generation sequencing assays. While many of these actionable targets are rare individually, the expanding totality of actionable gene alterations supports the growing utility of CGP for identifying patients who are candidates for approved targeted therapies and clinical trials. Research Sponsor: Illumina grant.

3079 **Poster Session**

DNA methylation profiling to determine the primary sites of metastatic cancers using formalin-fixed paraffin-embedded tissues. *First Author: Hongcang Gu, Zhejiang ShengTing Biotech Co. Ltd/Institute of Health and Medical Technology, Hefei Institutes of Physical Science, Chinese Academy of Sciences, Hefei, Anhui, China*

Background: Metastatic cancers with uncertain primary sites account for a significant portion of new cases. Among them, 3-9% are eventually assigned to cancer of unknown primary (CUP) site after a comprehensive diagnostic workup. Accurate identification of the primary site is the starting point for cancer diagnosis worldwide, and it is critical to guide the subsequent treatments of metastatic cancers. Here we presented a new DNA methylation sequencing-based method to predict the tissues of origin for metastatic cancers, including CUP. **Methods:** Cancer diagnosis relies substantially on histological and immunohistochemical analyses of formalin-fixed paraffin-embedded (FFPE) tissues. To take advantage of sample accessibility, we developed an optimized and streamlined method that was particularly used to generate reduced represent bisulfite sequencing (RRBS) libraries for genome-wide DNA methylation profiling with degraded DNA fragments. After confirming that data quality generated using the new FFPE-RRBS method was comparable with regular RRBS, we created an RRBS database using 541 fresh frozen samples across ten most common cancer types and 58 tumor-adjacent normal tissues. By incorporating four distinct methylation summary scores and seven machine learning approaches, 28 models were trained and compared for multi-class classification using our database. Lastly, we selected the best classifier to predict the tissues of origin utilizing 249 FFPE samples across ten metastatic cancer types and 12 FFPE samples from CUP patients. Meanwhile, the classifier was also cross-validated using a DNA methylation microarray data set of 4702 patients diagnosed with corresponding primary cancers in the TCGA project. **Results:** FFPE-RRBS allowed to construct decent libraries with heavily degraded genomic DNA within 20 hours. Comparable DNA methylation metrics were obtained for the RRBS libraries of paired primary cancer tissues (fresh frozen vs. FFPE) and the libraries of paired FFPE samples derived from primary and metastatic tissues. Among the 28 methylation-based classifiers, the mean methylation-based LinearSVC model performed the best, achieving an overall accuracy of 81% with an AUC of 0.95 in determining the primary sites of 10 metastatic cancers. In a cross-validation assay using the TCGA data set of 4702 cancer patients, the overall prediction accuracy and AUC were 92% and 0.99, respectively. Lastly, our model successfully identified the tissues of origin in 10 of 12 CUP patients in a prospective study. **Conclusions:** The FFPE-RRBS is a novel method for efficient profiling of heavily degraded FFPE samples and the mean methylation-based LinearSVC model can predict the tissues of origin for metastatic cancers and CUP with high accuracy. Research Sponsor: Affiliated Hangzhou First People's Hospital, Cancer Center, Zhejiang University School of Medicine.

3080 **Poster Session**

A first-in-human phase I study of CTX-712 in patients with advanced, relapsed or refractory malignant tumors. *First Author: Toshio Shimizu, Department of Experimental Therapeutics, National Cancer Center Hospital, Tokyo, Japan*

Background: CTX-712 is a first in class, orally available, highly potent and selective small-molecular inhibitor of CDC2-like kinase (CLK), a key regulator of the RNA splicing process that plays a critical role in driving cell growth. CTX-712 demonstrated potent inhibition of proliferation in a variety of human tumor cell lines in vitro and elicited robust antitumor activity in vivo in multiple xenograft models. The objectives of this study are to determine the recommended dose (RD) by evaluating maximum tolerated dose (MTD) and dose limiting toxicity (DLT), safety, pharmacokinetics (PK) and pharmacodynamics (PD) profiles, and preliminary efficacy of CTX-712 in patients with solid tumors (ST) and hematologic malignancies (HM). **Methods:** This study consists of ST and HM dose escalation cohorts to identify MTD and ST dose expansion cohort to identify RD. The ST dose escalation cohort was initiated with accelerated titration and then switched to a 3+3 design (10, 20, 40, 70, 105, 140 and 175 mg/body twice a week in 28-day cycles). The initial dose of HM dose escalation cohort was decided from the safety information of ST dose escalation cohort. A 3+3 design was used in HM dose escalation cohort. **Results:** As of Dec. 31, 2021, 30 patients were enrolled (16 in the ST dose escalation cohort (10/20/40/70 mg [1], 105/175 mg [3], 140 mg [6]), 10 in the ST expansion cohort, and 4 in the HM dose escalation cohort). In the ST dose escalation cohorts, DLTs were observed in 2 patients (140 mg [platelet count decreased, hypokalemia], 175 mg [dehydration]) and MTD was determined to be 140 mg. Based on this safety information, the ST dose expansion cohort and the HM dose escalation cohort were initiated with the dose of 105 mg twice a week. Among all enrolled patients, the common any-grade Adverse Events (AEs) (≥30%) were nausea (97%), vomiting (63%), diarrhoea (63%), decreased appetite (57%), blood creatinine increased (40%), dysgeusia (37%), constipation (33%), pyrexia (33%) and white blood cell count decreased (30%). The most common Grade 3 or higher AEs were hypokalemia (10%), amylase increased and platelet count decreased (7%). In PK analysis, a dose-dependent increase in systemic exposure of CTX-712 was observed. PD response was assessed in RNA extracted from peripheral blood cells. Dose dependent increases of exon skipping in two marker RNAs were detected. Two Partial Responses and two Complete Responses were observed in ST and HM, respectively. **Conclusions:** CTX-712 demonstrated an acceptable safety profile with early signs of clinical antitumor activity, establishing the initial proof of concept of the CLK inhibitor. Observed DLTs included dehydration, platelet count decreased, and hypokalemia. Investigation is ongoing to determine RD. Clinical trial information: JapicCTI-184188. Research Sponsor: Chordia Therapeutics Inc.

3081 **Poster Session**

First-in-human phase 1/2 dose escalation and expansion study evaluating first-in-class eIF4A inhibitor zotatifin in patients with solid tumors. *First Author: Funda Meric-Bernstam, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Zotatifin (eFT226) is a first in class, potent and sequence selective inhibitor of RNA helicase eIF4A1 that promotes stable mRNA:eIF4A:drug ternary complex at specific polypurine motifs within the 5'-UTR, preventing ribosome docking and thus, efficient translation of select transcripts. In preclinical models zotatifin treatment simultaneously down-regulated translation of numerous oncogenes with complex 5' mRNA structures, including ERBB2, FGFR1/2, EGFR, KRAS, and CCND1. **Methods:** Patients (pts) with select advanced solid tumors harboring mutations/amplification of ERBB2, FGFR1, FGFR2, EGFR, or KRAS or with pancreatic cancer were enrolled into 3+3 dose escalation portion of the protocol (Part 1), and indication specific expansions continue to enroll at recommended phase 2 dose (RP2D; Part 2). The primary endpoints of Part 1 include determination of safety, tolerability, and maximum tolerated dose (MTD)/RP2D; additional endpoints include characterization of pharmacokinetic, pharmacodynamic (including from blood-based assay during escalation and from pre- and on-treatment biopsy at/near MTD with reverse phase protein array (RPPA)), and initial efficacy. **Results:** As of cut-off date Jan 13, 2022, Dose escalation phase (Part 1) included 37 patients treated with zotatifin at dose levels: 0.005, 0.01, 0.02, 0.035 mg/Kg IV weekly, and 0.035, 0.05, 0.07, 0.1 mg/kg IV 2 weeks-on and 1 week-off. DLTs were observed in 3 patients: Gr 2 thrombocytopenia (0.035 mg/kg weekly), Gr 3 anemia (0.1 mg/kg) and Gr 3 gastrointestinal bleed resulting in anemia (0.1 mg/kg). MTD/RP2D is 0.07 mg/Kg IV 2 weeks-on and 1 week-off. The most common treatment emergent adverse events (TEAEs) in Part 1 include: fatigue, anemia, diarrhea and dyspnea. The most common AEs at RP2D (n = 16 pts; Part 1 and Part 2) include: anemia (25% all gr 1 or 2), fatigue (25% all gr 1 or 2) and dyspnea (19%; 13% Gr 3) diarrhea (13%, all Gr 1 or 2). Pharmacokinetics were generally linear and dose proportional and exposures at MTD/RP2D are consistent with target pharmacologic levels in preclinical models. Blood based biomarkers showed dose- and time- dependent evidence of target engagement. Pre- and on-treatment biopsy data in expansion patients showed decreased expression of target proteins. No patient in dose escalation experienced an objective tumor response; initial efficacy data from Part 2 and at RP2D will be presented. **Conclusions:** eIF4A inhibitor zotatifin achieves pharmacologically relevant exposures with on-target AEs that are manageable at the MTD, with evidence of target knockdown from on-treatment biopsies. Part 2 indication-specific expansions (including in ER+ FGFR-amplified MBC as single agent, ER+ MBC in combination with fulvestrant and abemaciclib, and KRAS NSCLC in combination with sotorasib) are on-going. Clinical trial information: NCT04092673. Research Sponsor: eFFECTOR Therapeutics.

3082 **Poster Session**

Circulating tumor DNA (ctDNA) determinants of improved outcomes in patients (pts) with advanced solid tumors receiving the ataxia telangiectasia and Rad3-related inhibitor (ATRi), RP-3500, in the phase 1/2a TRESR trial (NCT04497116). *First Author: Ezra Rosen, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: RP-3500 is a selective and potent oral ATRi in development for advanced solid tumors harboring loss-of-function (LOF) alterations in genes associated with ATRi sensitivity. We determined whether ctDNA can facilitate enrollment/monitoring of pts treated with RP-3500. **Methods**: Serial plasma samples collected at baseline (BL, 99 pts) and early timepoints on therapy (89 pts, 3-9 weeks [wks]) were profiled for ctDNA (Tempus xF or Guardant360). Targeted next generation sequencing (NGS) (SNiPDx panel) was performed on matched peripheral blood mononuclear cells and tumor samples collected at BL. Molecular ctDNA response (MR) was defined as ≥50% reduction in mean variant allele frequency (VAF) from BL to any timepoint ≤9 wks on-therapy. Clonal hematopoiesis (CH) or germline alterations were excluded from the analysis. Efficacy was assessed in pts treated with > 100 mg RP-3500/day with ≥1 post-BL response assessment. Endpoints included progression-free survival (PFS) and clinical benefit rate (CBR; CR/PR by RECIST1.1 or PSA/CA-125, or > 16 wks on treatment). **Results:** BL ctDNA was detected in 82% (81/99) of pts. Eligibility alterations were evaluable by the ctDNA panel in 61% (60/99) of pts, excluding structural/copy number variants and genes/exons not on the panel. Percent agreement between BL ctDNA and local eligibility NGS test was 93% (56/60). CH variants were identified in 26 pts (1-14 per pt); median VAF was 0.4% (0.1-12.4%). Two pts with pathogenic ataxia-telangiectasia mutated (*ATM*) alterations were determined to be from CH. MRs were observed in 44% (24/55) of pts with median time to MR of 3.3 wks and were across tumors harboring *ATM* (10/20), *BRCA2* (7/10), *BRCA1* (4/15), *CDK12* (1/3), *PALB2* (1/3) and *RAD51C* (1/1) pathogenic alterations. Four pts with BRCA1 mutant tumors had MRs, 2 of whom (breast cancer) had received prior PARPi and had confirmed BRCA1 reversion mutations and clinical benefit (CB). One pt with g*ATM* pancreatic cancer with CB had > 90% reduction in *KRAS* mutant VAF at 3 wks. MR was associated with longer mPFS (29 vs 12 wks, p = 0.0002) and significantly higher CBR (17/22 (77%) vs. 8/28 (29%); p = 0.001) than those without MR. Pts with MRs not achieving CB (N = 5) included 4 with RP-3500 dose interruptions/reductions and 1 who discontinued early (10 wks) due to clinical progression but with decreased target lesions and stable disease. **Conclusions:** ctDNA testing is a reliable method to detect DNA damage repair LOF alterations but is limited to alterations and genes/exons covered by the ctDNA test. CH alterations are frequent, especially for ATM, thus matched normal analysis is preferred. Changes in ctDNA as early as 3 wks were associated with improved outcomes and may be useful for evaluating drug activity in heterogenous tumors outside of traditional efficacy endpoints. Clinical trial information: NCT04497116. Research Sponsor: Repare Therapeutics.

3083 **Poster Session**

Pharmacokinetic and pharmacodynamic activity evaluation of MAK683, a selective oral embryonic ectoderm development (EED) inhibitor, in adults with advanced malignancies in a first-in-human study. *First Author: Vincent Ribrag, Gustave Roussy, Villejuif, France*

Background: Polycomb Repressive Complex 2 (PRC2) regulates transcription via trimethylation of histone H3 at lysine 27 (H3K27me3). Its dysregulation and over-expression are associated with tumorigenesis in several conditions. MAK683 is a potent oral inhibitor of PRC2 activation, allosterically targeting the EED–H3K27me3 binding site. **Methods:** NCT02900651 is an ongoing first-in-human dose-escalation study of MAK683 in adults with advanced malignancies. MAK683 was administered fasted once (QD) or twice daily (BID) on a continuous schedule in 28-day treatment cycles. The pharmacokinetic (PK) profile of MAK683 was assessed in sequential blood samples on Days 1, 8 and/or 15 of Cycles 1–6. MAK683 pharmacodynamic activity in Cycle 1, measured by change in H3K27me3, was evaluated in peripheral blood monocytes on Days 1, 8, and 15 by flow cytometry and in tumor biopsies at baseline and Day 15 by H-score. **Results:** As of Aug 30, 2021, 125 patients had received MAK683 at doses of 10–800 mg QD or 60–450 mg BID. MAK683 was well absorbed with a median T_{max} of ~1-4 hours across cohorts. PK exposure (C_{max}, AUC) increased generally with dose over the entire dose range with no major deviation from dose proportionality, taking into account the sample size and PK variability. Apparent terminal half-life (geometric mean) was 2.5–6.6 hours across cohorts and constant over time. MAK683 accumulation of ~0.9-2.2-fold (QD) or ~1.3-2.0-fold (BID) was seen with repeat dosing. Peripheral monocytes showed substantial on-treatment reductions from baseline in the H3K27me3/H3 ratio across doses. Maximum percentage reduction was proportional to cumulative MAK683 AUC, with a trend towards greater reductions at higher baseline H3K27me3. H3K27me3 H-score reductions from baseline > 40 were observed in 7/10 patients with diffuse large B-cell lymphoma (n = 4) or epithelioid sarcoma (n = 6) and paired baseline–Day 15 biopsies. RNA-seq characterization of biopsy samples is ongoing. **Conclusions:** MAK683 has a PK profile supportive of QD or BID dosing in patients with advanced malignancies. Analysis of H3K27me3 in blood monocytes and tumor biopsy confirm the *in vivo* pharmacodynamic activity of MAK683. Clinical trial information: NCT02900651. Research Sponsor: Novartis.

3084 **Poster Session**

Phase 1 results of a phase 1/2 trial of CYT-0851, a first-in-class inhibitor of RAD51-mediated homologous recombination, in patients with advanced solid and hematologic cancers. *First Author: Ryan C Lynch, University of Washington/Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: Homologous recombination (HR) is an essential, high-fidelity mechanism to repair DNA double strand breaks (DSBs) in cancer cells. CYT-0851 inhibits HR leading to an accumulation of unrepaired DSBs and tumor cell death. We are reporting the completed Phase 1 dose-escalation results and RP2D selection to support ongoing development of CYT-0851. **Methods:** Patients (pts) with advanced hematologic and solid tumors were treated with continuous 28-day cycles of increasing doses of CYT-0851 following a 3+3 design. The primary objective was determining the maximum tolerated dose. Secondary objectives included safety, pharmacokinetics, and anti-tumor activity. **Results:** As of a 15 Nov 2021 data cutoff (DCO), 73 pts with advanced cancers (NHL n = 18; Sarcoma n = 16; Pancreas n = 11; Breast n = 8; HNSCC n = 6; Ovarian n = 4; SCLC n = 4; Other n = 4; Myeloma n = 2) were treated in 12 cohorts (total daily doses: 30 mg to 1200 mg). One pt experienced a dose-limiting toxicity (DLT) of reversible metabolic acidosis at 1200 mg. Two of 3 pts at 800 mg experienced reversible DLT-like events in Cycle 2 of Gr3 dry skin and Gr3 myalgia and polyarthritis, respectively. Three of 10 pts treated at 600 mg experienced DLT-like events in Cycle 1: 1 pt experienced an SAE of Gr3 anorexia with Gr3 stomatitis, vomiting, and dehydration and 2 pts had Gr3 fatigue. No DLTs occurred at 400 mg daily which was selected as the RP2D. 42 pts (57.5%) experienced a CYT-0851-related adverse event (AE), including 12 (16.4%) with a Gr3/4 AE. There were no treatment-related deaths. AE leading to CYT-0851 withdrawal were reported in 2 pts (2.7%) treated with 600 and 800 mg. The most common CYT-0851-related AEs were primarily Gr1/2 and included fatigue (20.5%), hyperuricemia (11%), nausea (11%), alopecia (9.6%), constipation (8.2%) and headache (8.2%). CYT-0851 exposure was approximately dose-proportional across the evaluated doses with an effective half-life of ~3 days. Exposure at 400 mg daily was consistent with efficacy in preclinical models. 46 pts were evaluable for response at the DCO. 12 pts with NHL were evaluable by Lugano and included 1 CR in FL and 1 PR in DLBCL treated for 393+ and 244 days respectively. 34 pts with solid tumors were evaluable by RECIST v1.1 with 1 PR in a pt with myxofibrosarcoma treated for 313 days and 16 pts with stable disease. Fifteen pts were treated for 100+ days and 5 for 180+ days. **Conclusions:** CYT-0851 has demonstrated promising and broad clinical activity in a Ph 1 population of pts with advanced cancers. The safety profile is favorable as characterized by events that were infrequent, primarily Gr1/2, and reversible. Six expansion cohorts (DLBCL, Follicular Lymphoma, Myeloma, Pancreatic, Ovarian and Sarcoma) are enrolling to characterize activity at the RP2D. Ph 1 evaluation of CYT-0851 in combination with 3 chemotherapy backbones is also ongoing. Clinical trial information: NCT03997968. Research Sponsor: Cyteir Therapeutics.

3085 **Poster Session**

Interim phase 1 results for SQ3370 in advanced solid tumors. *First Author: Sant P. Chawla, Sarcoma Oncology Research Center, Santa Monica, CA*

Background: SQ3370, a novel therapy, utilizes Shasqi's proprietary Click Activated Protodrugs Against Cancer (CAPAC) platform where mutually-reactive click chemistry groups release Doxorubicin (Dox) at the tumor site minimizing systemic exposure. In animals, SQ3370 enhanced survival, T-cell infiltration and antitumor responses in injected and non-injected tumors. Minimal to no toxicity, including no cardiotoxicity was seen in up to 9-fold dose increases in animals. Conventional Dox can induce cardiomyopathy at incidences of 1-20% for cumulative doses from 300-500 mg/m^2 in humans and re-treatment with Dox is less effective in heavily pre-treated patients (pts). Here we report interim results of the Phase 1 (NCT04106492). **Methods:** SQ3370 has 2 components: 1) Intratumoral injection of a protodrug-activating biopolymer (SQL70: 10 mL or 20 mL); 2) 5 consecutive daily IV infusions of an attenuated protodrug of Dox (SQP33). Key eligibility includes locally advanced or metastatic solid tumors, ≤300 mg/m^2 prior exposure to Dox, ECOG 0-1 and no limit to prior systemic therapies. Primary objectives include safety and determining Phase 2 dose. Dose escalation was assessed in 2 stages: 1) accelerated titration; 2) 3+3 design. **Results:** As of 31JAN2022 data cut, 26 pts were treated, 21 with 10 mL biopolymer (bp) and 5 with 20 mL bp over 9 dose escalation protodrug cohorts. MTD has not been reached. Median age was 61 years (26-84), 62% were females, and 69% were ECOG 1. Prior procedures included surgery (89%) and radiation (62%). At study entry, 77% of pts had metastases with a median number of metastatic sites being 2 (1-5); most frequently lung (50%). Tumors were sarcoma (73%), breast cancer (7.7%), gyne (7.7%) and other (11.5%). Twenty-four of 26 (92%) pts received prior systemic therapies with 50% receiving prior Dox. Median number of prior systemic therapies was 2 (1-7). Of the 26 pts, 62% received > 500 mg/m^2 cumulative Dox given as SQP33. Median duration of treatment was 2 cycles (1-12). Most frequent AEs, regardless of causality, for the 10 mL bp group included nausea (n = 11), fatigue (n = 9) and anemia (n = 6), and for the 20 mL bp group included anemia (n = 3) and nausea (n = 2). Ejection fraction (LVEF) remained normal during the study period. No AEs that led to discontinuation or death were related to SQ3370 by investigator. At a median follow-up of 9.2 wks (3-37), 21 pts were evaluable. SD was best response in 71%. Median duration of SD was 80-dys (37-186) corresponding to an overall disease control rate (CR+ PR+ SD x 30-dys) of 71% (68% in 10 mL bp; 100% in 20 mL bp). The remainder of pts had PD as best response. Over 38% of pts remain on drug. **Conclusions:** SQ3370 with 10 mL or 20 mL biopolymer was well tolerated in pts with half being re-treated with Dox. Although > 60% of pts received > 500 mg/m^2 cumulative Dox given as SQP33, LVEF remained normal. Preliminary evidence of disease control was observed in pts despite heavy prior pre-treatment and high cancer burden. Dose escalation is ongoing. Clinical trial information: NCT04106492. Research Sponsor: Shasqi, Inc., U.S. National Institutes of Health.

3086 **Poster Session**

Safety, tolerability, pharmacokinetics and preliminary efficacy of MIL93, an anti-Claudin18.2 monoclonal antibody, in patients with advanced solid tumors: A phase 1 clinical study. *First Author: Jing Huang, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: Claudin18.2 (CLDN18.2) is specifically expressed in the tight junction of gastric epithelial cells, and has been identified as a promising target in gastric and pancreatic cancer as well as several other malignancies. MIL93 is a humanized IgG1 monoclonal antibody targeting CLDN18.2. From January 2021, we started a multicenter, dose escalation and expansion phase 1 study of MIL93, for the treatment of patients with advanced solid tumors (Protocol number MIL93-CT101, Beijing Mabworks Biotech Co. Ltd.) at 6 clinical study sites in China. Currently the study is still ongoing. **Methods:** We already enrolled 13 pts aged 18 years or older with advanced solid tumors whose disease had progressed after standard systemic treatments. Pts were required to have measurable lesion as per RECIST v1.1; ECOG PS score of 0-1 and adequate organ functions. In the dose escalation phase, 6 dose levels (0.3mg/kg, 1mg/kg, 3mg/kg, 10mg/kg, 20mg/kg and 30mg/kg, Q3W) of MIL93 were planned for assessment. Accelerated titration was adopted for the first 2 dose levels, and the 3+3 design was used afterwards. In the dose expansion phase, pts with CLDN18.2-positive cancers received the selected RP2D. The primary objectives were the safety and tolerability, dose limiting toxicities (DLTs) and maximum tolerated dose (MTD) of MIL93. Secondary objectives included pharmacokinetics, immunogenicity and preliminary efficacy. **Results:** At the data cut-off date (February 14, 2022), 13 pts were enrolled between April 23, 2021 and February 9, 2022. MIL93 was well-tolerated for the dosages tested (0.3mg/kg through 20mg/kg Q3W) as no DLTs were observed, and dose escalation was ongoing at 30mg/kg. In particular, Grade 3 nausea and vomiting occurred in 2 cases in the third dose group, so preventive antiemetic treatment was given from the fourth dose group. 9 pts (69.2%) experienced at least one treatment-emergent adverse event (TEAE) with no Grade 4 or Grade 5 AEs. The most common treatment-related adverse events (TRAEs) occurring in ≥10% of pts were nausea (46.2%), vomiting (46.2%), fatigue (15.4%), anemia (15.4%). Serious adverse events (SAEs) were observed in 3 (23.1%) pts, and MIL93-related SAEs occurred in 1 pt (7.7%, Grade 3 nausea). Among the 10 pts who had at least one post-treatment radiological evaluation, 1 pt with CLDN18.2-positive gastric cancer achieved PR and 3 pts had SD, including 1 case of gastric cancer, 1 case of gastroesophageal junction cancer and 1 case of gallbladder cancer. **Conclusions:** MIL93 had a favorable safety profile with no DLTs observed through 20mg/kg Q3W. Pts with CLDN18.2-positive gastric cancer responded to the treatment. Dose escalation and expansion in selected tumor types is currently underway. Clinical trial information: NCT04671875. Research Sponsor: Mabworks Biotech Co.Ltd.

3087 **Poster Session**

Molecular landscape and actionable alterations in a genomic-guided cancer clinical trial: First analysis of the ROME trial. *First Author: Andrea Botticelli, Department of Radiology, Oncology and Pathology, "Sapienza" University of Rome, Rome, Italy*

Background: The Rome Trial is a randomized, prospective, multicenter, multi-basket, Phase II clinical trial (EudraCT n° 2018-002190-21; NCT04591431). The aim is to evaluate the efficacy of Tailored Therapy (TT) vs Standard of Care (SoC) in patients (pts) with metastatic solid tumors who received at least one and no more than two lines of treatment. Pts with a molecular alteration were discussed in a Molecular Tumor Board (MTB), assigned to one or a combination of the 20 available treatments, and randomized to TT or SoC. **Methods:** Tissue (collected within 6 months) and blood samples from pts with refractory solid tumors were analyzed centrally with next generation sequencing (NGS, FoundationOneCDx and FoundationOneLiquid). MTB discussed all screened pts with any actionable genomic alterations using common mutational database and ESCAT. Genomic data, MTB reports and treatment outcomes were collected. The 3 outcomes of the MTB were: A) assignment of a TT and randomization, B) screening failure (SF) C) SF for the trial but with relevant information from the genomic test. Outcome C was divided into 3 groups: 1) indication to receive a personalized standard treatment different from the planned one, 2) indication to access to another clinical trial/compassionate use/expanded access, 3) indication to perform a germline test (GT). **Results:** From Oct 2020 to Dec 2021, 497 pts were enrolled in 38 Italian accrual sites, 303 (61.0%) had relevant genomic alterations and were discussed to the MTB. Molecular profiling was determined both on tissue and liquid biopsy in 262/303 (86.5%) pts, while in 11 (3.5%) and 30 (10.0%) only on tissue or liquid, respectively. After applying clinical and molecular exclusion criteria and considering multiple actionable or resistance-conferring mutations (detected in 95 and 70 out of 303 patients): 135 pts (45%) were randomized (outcome A), 19 (30%) were SF (outcome B), and 78 (25%) SF but with an additional indication (outcome C). Of them, 14 patients (18%) were group 1 and 42 (54%) had indication to a target therapy outside from the trial (group 2). MTB suggested a GT to 60/303 pts (20%, group 3). To date, 8 out of 9 GT performed confirmed a germline mutation (4 BRCA1/2, 2 PALB2, 1 MUTHY, 1 ATM). Finally, 213 pts, 71% of those discussed to MTB and 43% of the entire screened population, were randomized or received at least one specific indication following the extended molecular assessment with NGS. **Conclusions:** We demonstrated the feasibility of screening a large numbers of pts from numerous accruing sites in a complex trial to test investigational therapies for moderately frequent molecular targets. Co-occurring resistance mutations were common and endorse to investigate combination targeted-therapy regimens. The Rome trial MTB, even when no actionable alterations were detected, provided a therapeutic and diagnostic indication with a potential impact on patient's outcomes. Clinical trial information: NCT04591431. Research Sponsor: Roche, Bristol Myers Squibb, Incyte, Takeda, Pfizer, Novartis.

3088 **Poster Session**

Characterizing the genomic landscape of *PIK3CA* alterations from 121,221 adult patients with cancer: The next tissue-agnostic target? *First Author: Niamh Coleman, The University of Texas MD Anderson Cancer Center, Houston*

Background: The PI3K–AKT–mTOR signaling pathway is frequently dysregulated in cancer and small molecule inhibitors targeting various nodes in the pathway have been pursued for decades. Activating mutations in *PIK3CA* are recognized potent drivers of oncogenesis, though the landscape of *PIK3CA* fusions and amplifications has yet to be well-defined. The field has been hampered by issues such as resistance and poor tolerance, however several isoform-specific PI3K inhibitors have now received regulatory approval and allosteric pan-mutant and specific mutant selective Inhibitors of PI3Kα are being investigated in early phase clinical trials. Here, we present a comprehensive analysis of *PIK3CA* alterations in pan-cancer adult malignancies. **Methods:** We analyzed 136096 samples from 121221 patients available from AACR Project GENIE v.11 database for the prevalence of PIK3CA mutations, fusions and copy number alterations in a range of cancer types. **Results:** 15712 alterations in *PIK3CA* were detected in profiled tumor samples (12%), in 14774 of patients profiled (12%), most frequently in endometrial (44% of 4135 cases), anal (35% of 286 cases), breast (35% of 14218 cases), cervical (27% of 761 cases) and colorectal cancer (20% of 3743 cases).*PIK3CA* alterations identified included 17740 mutations (11%) (including duplicate mutations in patients with multiple samples). 16685 missense mutations were identified (12%);14953 were identified as missense in driver mutation (likely oncogenic)(90% of missense); 1,732 were missense of variants of uncertain significance (VUS) using OncoKB database (11%). Missense mutations most frequently involved codons 545(3347, 20% of missense), codon 1047 (3644, 22%) and codon 542 (1881, 11%). 237 truncating mutations were identified (0.2%), 442 in-frame deletions, 29 in-frame insertion mutations. PIK3CA fusions were observed in 0.06% of tumor samples and were most identified in breast, colorectal, lung, GBM and ovarian cancer (24%, 17%, 13%, 7% and 6% of identified *PIK3CA* fusions respectively). PIK3CA fusions were most commonly intragenic fusions(36%);common fusion partners included *TBL1XR1*, *FNDC3B* and *NAALADL2*(17%, 7%, 5% of identified *PIK3CA* fusions, respectively). *PIK3CA* fusions were identified as VUS, aside from *KMT2C-PIK3CA* (2%). *PIK3CA* amplification high level gain occurred in 0.5% of samples tested(662), deletion occurred in 0.16%(21). **Conclusions:** Activating *PIK3CA* mutations occur frequently across cancer types and could be considered for tissue-agnostic drug development. *PIK3CA* fusion and amplification events are extremely rare. Most *PIK3CA* missense mutation variants are described as oncogenic, while fusions are described as VUS, which may limit the impact of precision oncology for patients with this alteration. Further functional characterization of *PIK3CA* variants and basket trial enrollment are warranted. Research Sponsor: None.

3089 **Poster Session**

A phase I/II study of first-in-human trial of JAB-21822 (KRAS G12C inhibitor) in advanced solid tumors. *First Author: Jian Li, Department of Gastrointestinal Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Beijing, China*

Background: KRAS G12C mutation occurs in approximately 4% of non-small cell lung cancer (NSCLC), 1-2% of colorectal cancer (CRC) and other solid tumors in China. JAB-21822 (Jacobio, Beijing, PRC) is a highly selective, covalent oral inhibitor of KRAS G12C. **Methods:** NCT05009329 is an ongoing first-in-human, open label phase I/II study of JAB-21822 in patients with advanced solid tumors. The primary objective is to evaluate the safety and tolerability of JAB-21822. Other objectives include preliminary efficacy, pharmacokinetics, and biomarkers. Here we report the results from the dose escalation phase of the trial. **Results:** As of January 28th, 2022, 53 patients with a median age of 62 years (39-79) were enrolled in 5 different dose levels: 200mg QD, 400mg QD, 800mg QD, 400mg BID and 400mg TID. Most patients (55%) had $\geq$ 2 prior lines of therapy. No dosing-limiting toxicities were observed. Two treatment-related adverse events (TRAEs) were G4 neutropenia (1 in 400mg BID and 1 in 400mg TID). The most common TRAEs ($\geq$ 10%) included anemia (24.5%), total bilirubin increase (20.8%), direct bilirubin increase (15.1%), proteinuria (13.2%) and indirect bilirubin increase (11.3%). Only Grade 1 and 2 TRAEs were observed in the QD cohorts. A total of 33 patients (22 NSCLC, 9 CRC and 2 pancreatic cancer) had at least 1 post-baseline tumor assessment; in the 800mg QD cohort, overall response rate (ORR) and disease control rate (DCR) were 50% (5/10) and 100% (10/10), respectively, including 4 non-confirmed partial response (PR); in the 400mg QD cohort had an ORR and DCR of 80% (4/5) and 100% (5/5) respectively, including 2 non-confirmed PR. Patients with NSCLC (400mg QD and 800mg QD), the ORR and DCR were 70% (7/10) and 100% (10/10), respectively, including 5 non-confirmed PR. With respect to the pharmacokinetics analysis, JAB-21822 was rapidly absorbed with an average T_{max} of 2 hr and reached higher plasma exposures (C_{max} and $AUC_{0\text{-}24h}$) after a single dose and multiple doses at C1D8. **Conclusions:** JAB-21822 was well tolerated with impressive preliminary efficacy in patients with heavily treated solid tumors harboring KRAS G12C mutation. The study is enrolling patients in the expansion phase. Multiple JAB-21822-based combination trials are also ongoing. Clinical trial information: NCT05009329. Research Sponsor: Jacobio Pharmaceuticals Co., Ltd.

3090 **Poster Session**

Dose optimization for MORAb-202, an antibody-drug conjugate (ADC) highly selective for folate receptor-alpha (FRα), using population pharmacokinetic (PPK) and exposure-response (E-R) efficacy and safety analyses. *First Author: Seiichi Hayato, Eisai Co. Ltd., Tokyo, Japan*

Background: MORAb-202 is an ADC consisting of farletuzumab (an antibody that binds to FRα) paired with eribulin mesylate (a microtubule dynamics inhibitor) conjugated via a cathepsin B-cleavable linker. A phase 1 dose-escalation and expansion study in patients with advanced solid tumors evaluated MORAb-202 doses ranging from 0.3 mg/kg to 1.2 mg/kg IV every 3 weeks (Shimizu 2021, *CCR*). The dose-expansion part included starting doses of 0.9 mg/kg and 1.2 mg/kg in an ovarian cancer (OC) cohort. Objective response rates (ORR) by investigator per RECIST v1.1 and rates of all-grade interstitial lung disease (ILD), an adverse event of interest, were lower at the 0.9 mg/kg dose vs the 1.2 mg/kg dose. To support dose optimization for clinical benefit while reducing the risk of ILD, a MORAb-202 PPK model was developed to characterize the pharmacokinetics and to obtain model-predicted exposure measures. **Methods:** Exposure was predicted for different dosing scenarios: flat dosing, bodyweight (BW)-based dosing with or without a dose cap, adjusted ideal BW dosing, and body surface area (BSA)-based dosing. E-R analyses for efficacy (ie, ORR) and safety (ie, ILD by expert review) were conducted using logistic-regression analysis. Simulations (N = 1000) were performed using a BW distribution from a previous phase 3 farletuzumab study in OC (Vergote 2016, *JCO*) to predict the probability of ORR and ILD in patients treated with MORAb-202. **Results:** MORAb-202 exposures were dose proportional, and the pharmacokinetics were described by a 2-compartment model with zero-order IV infusion and first-order elimination. Patients with higher BW had less-than-proportional increases in clearance (allometric exponent [AE] 0.571) and distribution volume (AE 0.524). MORAb-202 demonstrated a positive exposure (based on area under the curve [AUC]) dependence to ORR and ILD. The probability of achieving a tumor response was higher with higher AUC (odds ratio [OR] for an AUC unit change of 1000 $\mu g \bullet h$/mL: 1.73 [95% CI 1.06–3.11]). The probability of an ILD event was higher with higher AUC (OR for an AUC unit change of 1000 $\mu g \bullet h$/mL: 3.50 [95% CI 1.89–7.81]). Simulations across BW ranges (34.2–144 kg) indicated that BSA-based dosing (33 mg/m^2), compared with BW-based dosing (0.9 mg/kg), yielded similar predicted median (90% prediction interval) rates for ORR (33.7% [19.3–62.2] vs 37.9% [20.6–67.5]) and all-grade ILD (46.8% [18.2–88.2] vs 55.1% [20.7–91.9]). However, BSA-based dosing is predicted to reduce ILD in the highest BW quartile (> 80–144 kg) by approximately 35% compared with BW-based dosing. **Conclusions:** Based on this assessment, BSA-based dosing is predicted to lower the exposure-dependent ILD risk in patients with higher BW and is being further evaluated in ongoing clinical studies. Clinical trial information: NCT03386942. Research Sponsor: Eisai Inc., Nutley, NJ, USA.

3091 **Poster Session**

Adaptive response analysis of colorectal cancer cells to low-dose oxaliplatin as a tool to deciphering mechanisms of synergistic drug interaction. *First Author: Diego Tosi, Medical Oncology Department, Institut du Cancer de Montpellier, Montpellier, France*

Background: Using an *in vitro* dose matrix approach, we previously showed in multiple colorectal cancer cell lines a striking cytotoxic synergism between oxaliplatin at very low concentrations and the ATR inhibitor VE-822. We confirmed this finding *in vivo*, and, surprisingly, in this setting the oxaliplatin-induced cell addiction to VE-822 persists over several days after oxaliplatin elimination. We tried to elucidate the molecular mechanism of the latter phenomenon. **Methods:** We evaluated by RNAseq the gene expression changes induced *in vitro* by low-dose oxaliplatin in the colorectal cancer cell line HCT-116 after 24 and 48 hours of treatment. In order to untangle the functional significance of the adaptive response to oxaliplatin, we performed on the RNAseq data an extensive gene set enrichment analysis (GSEA) using gene set from all Molecular Signature Database v7.4 collections with the exception of C7. For ontology-based gene set collections, we clusterized the enriched gene sets using the semantic similarity methodology in order to increase the readability of global functional response. **Results:** Extensive GSEA showed that after 24 hours of oxaliplatin treatment cancer cells upregulate several gene sets involved in aspecific responses to cellular stress or to various type of extracellular stimulations, including other organisms, oxygen-containing compounds, abiotic stimuli and hypoxia. In addition, several gene sets involved in proteolysis and autophagy are upregulated, suggesting a rewiring of cell machinery. After 48 hours of oxaliplatin treatment, we observed the activation of ribosome function, mitochondrial assembly and synthesis of aminoacids and ribonucleosides. Finally, a widespread negative enrichment of gene sets involved in DNA repair-related was detected both at 24 and at 48 hours, with a far greater negative enrichment at 48 hours, which suggest a commitment of cancer cell to a major limitation of DNA repairing capability lasting several days following a DNA damaging insult. Analysis of leading edge genes from the DNA repair gene sets showed a profound repression both at 24 and 48 hours of the transcripts of BRCA1, BRCA2, ATM, CHK1, WEE1, BARD1, BRIP1, NEHJ1, RAD51, XRCC2, CLSPN, GEN1, DNA2, EXO1, TOPBP1, POLE, RMI1. Interestingly, ATR mRNA was minimally repressed both at 24 and at 48 hours, which could explain the long-standing *in vivo* dependence of cancer cell to ATR after a brief oxaliplatin exposure. **Conclusions:** Extensive GSEA was able to elucidate the molecular mechanism underlying synergistic interaction between oxaliplatin and VE-822. The impact of profiling cancer cell adaptive responses by extensive GSEA should be further evaluated in the setting of rational development of drug combinations. Research Sponsor: None.

3092 **Poster Session**

^{64}Cu-SAR-Bombesin PET-CT imaging in the staging of ER+/PR+/HER2- metastatic breast cancer: Safety, dosimetry, and feasibility in a phase I trial. *First Author: Keith Wong, Department of Theranostics and Nuclear Medicine, St. Vincent's Hospital, Sydney, NSW, Australia*

Background: Breast cancers are most frequently oestrogen receptor (ER) and progesterone receptor (PR) positive and ^{18}F-Fluorodeoxyglucose PET-CT (FDG) used in conventional staging of breast cancer has lower sensitivity for these subtypes. Gastrin releasing peptide receptors (GRPR) are a potential alternative diagnostic and theranostic target for ER+/PR+ breast cancers due to their overexpression of GRPR. This phase 1 study aims to assess the safety and potential of the novel radiotracer ^{64}Cu-Sarcophagine(SAR)-Bombesin (BBN) in the re-staging of recurrent metastatic ER+/PR+/human epidermal growth factor 2 negative (HER2-) breast cancer. **Methods:** Patients with confirmed recurrent or primary metastatic ER+/PR+/HER2- breast cancer undergoing staging prior to a new treatment underwent ^{64}Cu-SAR-BBN PET-CT with imaging at 1, 3 and 24 hours post-injection. Bloods and vital signs were acquired for patients at baseline, 1, 3 and 24 hours post-injection timepoints, and electrocardiogram (ECG) performed 1 hour pre and 1 hour post injection. Blood tracer-clearance and dosimetry was performed. GRPR receptor status was assessed in 4/7 patients from metastatic-site biopsy samples. Staging of the patients was assessed by conventional imaging (FDG, bone scan and diagnostic CT) within 3 weeks of ^{64}Cu-SAR-BBN imaging. All PET scans were assessed visually, and quantitatively using MIM Software. **Results:** 9 patients were enrolled. 7/9 patients underwent all imaging modalities, while 2/9 did not undergo BBN imaging. 1/7 patient who underwent all imaging had de- novo metastatic ER+/PR+/Her 2- breast cancer and 6/7 recurrent metastatic disease. 2/7 had lobular subtype. There were no adverse events reported, and ECG, vitals and haematological, biochemical and coagulation markers remained unchanged. All 7 patients were positive on conventional imaging, while 6/7 were positive on FDG. BBN was positive in 5/7 patients. Both BBN negative patients had disease identified on FDG. Conversely, 1 patient was BBN positive but FDG negative. 4/7 patients were BBN positive and FDG positive. In these 4 patients, mean SUVmax was higher for BBN than FDG (15 vs. 12). In classical lobular subtype (2/7), BBN was highly avid compared to FDG (SUV max 20 vs 11, and 20 vs <3) and with a higher tumor volume compared to FDG (2034 vs 504, and 634 mL vs FDG negative). **Conclusions:** ^{64}Cu-SAR-Bombesin is a novel tracer which appears safe and may have a diagnostic and theranostic role in patients with metastatic ER+/PR+/HER2- breast cancer, particularly lobular subtype. Further evaluation appears warranted. Research Sponsor: Clarity Pharmaceuticals.

3093 **Poster Session**

Theranostic pairing: ABY-025/251 targeting HER2 with ^{68}Ga and ^{188}Re—Minimized radioligands using Affibody peptide scaffold technology. *First Author: Yongsheng Liu, Uppsala University, Uppsala, Sweden*

Background: HER2 expressing tumors such as subsets of metastatic breast cancer and gastro-esophageal tumors can be targeted using specific antibodies or antibody-drug-conjugates (ADCs). However, some tumors remain refractory to treatment. External radiation therapy is unsuited to advanced metastatic disease. Targeted molecular radiation therapy has proven useful in other tumors such as neuroendocrine tumors or prostate cancer using ^{177}Lu. ^{188}Re is a beta emitting isotope that when chelated to the ABY-251 Affibody molecule has the potential to precisely target HER2 expressing tumors locally. The ABY-251 Affibody molecule is a very small, structured protein scaffold with a molecular weight of only 7 kDa targeting HER2 with high affinity (K_D = 100pM). ABY-251 can be manufactured by chemical synthesis. A diagnostic analog molecule ABY-025 was also developed with chelation to ^{68}Ga ideal for PET visualization. **Methods:** A pre-clinical study in mice was conducted to investigate tumor/tissue uptake, followed by a clinical diagnostic study for visualization in HER+ patients with metastatic breast cancer, to be followed by a theranostic study in humans. **Results:** Pre-clinical Study: A preclinical study in mice has previously demonstrated high contrast uptake in HER2 tumor tissue using the diagnostic analog ABY-025. Off target accumulation was seen in kidney tissue using the diagnostic ABY-025, which in the ABY-251 therapeutic molecule has been reduced by further engineering of the molecule. This molecule has now been proven to increase survival in mice bearing HER2+ tumors. Median survival in the treated animals was 68 days as compared to 29 and 27.5 days in animals treated with vehicle and non-labelled peptide respectively. Clinical diagnostic study ph1/2: ABY-025 was studied in HER2+ patients with metastatic breast cancer. In a study of 16 women with refractory metastatic breast cancer (>2 prior lines of therapy, 12 IHC positive and 4 IHC negative) 9 out of 10 patients showed high HER2 expression levels as measured with ABY-025 PET despite ongoing treatment with HER2 targeted therapy. Persistent high ^{68}Ga-ABY-025 tumor uptake in patients despite treatment with standard HER2-targeted therapies is a sign of therapeutic drug resistance. These patients would be eligible for treatment with the therapeutic analog ABY-251 using ^{188}Re generated beta radiation for tumor eradication. Clinical therapeutic study (planned): ABY-251 is in development to soon enter therapeutic clinical Ph1/2a trials in patients with refractory HER2+ tumors and positive tumor imaging using ABY-025 as a theranostic pair. **Conclusions:** A radiopharmaceutical theranostic approach diagnosing HER2+ patients with metastatic disease using ^{68}Ga-ABY-025 for targetability and subsequent treatment using ^{188}Re-ABY-251 seems feasible and is currently in clinical trials. Clinical trial information: NCT01858116. Research Sponsor: Uppsala University and Affibody AB.

3094 **Poster Session**

Tumor agnostic efficacy of selpercatinib in patients with *RET* fusion+ solid tumors: A global, multicenter, registrational trial update (LIBRETTO-001). *First Author: Vivek Subbiah, Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Selpercatinib, a first-in-class highly selective and potent RET kinase inhibitor, is approved in multiple countries for the treatment of lung and thyroid cancer with *RET* fusions and medullary thyroid cancer with *RET* mutations. We provide an efficacy and safety update with more patients (pts) and longer follow-up (data cut-off: 24Sep2021) in *RET* fusion+ solid tumors with histologies other than lung/thyroid. **Methods:** The phase 1/2 LIBRETTO-001 trial (NCT03157128) enrolled pts with locally advanced/metastatic *RET* fusion+ solid tumors. Following dose escalation, pts received the recommended dose of 160 mg orally twice daily. The efficacy analysis set consisted of pts enrolled ≥6 months (mo) prior to the cut-off date. If a pt achieved response, an additional ≥6 mo follow-up from the initial response was required. There was no additional follow-up required for non-responders. Response was assessed per RECIST 1.1. Primary endpoint was objective response rate (ORR) by independent review committee (IRC). Secondary endpoints included ORR by investigator (INV), duration of response (DoR), progression-free survival (PFS), time to response (TTR), and safety. **Results:** Forty-five pts with 14 unique *RET* fusion+ tumor types received ≥1 dose of selpercatinib: 12 pancreatic, 10 colon, 4 salivary, 3 unknown primary, 3 sarcoma, 2 each of breast, carcinoma of the skin, xanthogranuloma, and cholangiocarcinoma, and 1 each of lung carcinoid, rectal neuroendocrine, small intestine, ovarian, and pulmonary carcinosarcoma. Median age was 53 years (range 21-85). Forty-one pts received prior systemic therapy (median prior lines: 2, range 0-9); 31% received ≥3 lines. In 41 efficacy-evaluable pts, confirmed ORR by IRC was 44% (18/41, 95% CI: 29-60). Clinical benefit was observed in 63% (26/41) of pts: 2 complete responses (breast, small intestine), 16 partial responses, and stable disease ≥16 weeks in 8 pts by IRC. Responses were observed across a variety of fusion partners. Median TTR was 1.9 mo by IRC. Median DoR was 24.5 mo (95% CI: 9.2-NE) with 50% (9/18) of responses ongoing at a median follow-up of 14.9 mo by IRC. Median PFS by IRC was 13.2 mo (95% CI: 7.4-26.2), with 34.1% alive and progression-free at a median follow-up of 16.4 mo. No new safety signals were identified in this cohort compared to broader safety database. Three grade 5 AEs were observed (unrelated to treatment by INV), and 4 pts discontinued treatment due to AEs (1 deemed related to treatment by INV). **Conclusions:** Selpercatinib continued to demonstrate durable antitumor activity in pts with *RET* fusion+ cancers across multiple tumor types. No new safety signals were identified. These results emphasize the importance of comprehensive genomic profiling to identify actionable oncogenic drivers, including *RET* fusions. The LIBRETTO-001 study continues to enroll pts. Clinical trial information: NCT03157128. Research Sponsor: Eli Lilly and Company.

3095 **Poster Session**

A phase Ia/Ib, dose-escalation/expansion study of BI 907828 in combination with BI 754091 (ezabenlimab) and BI 754111 in patients (pts) with advanced solid tumors. *First Author: Noboru Yamamoto, Department of Experimental Therapeutics, National Cancer Center Hospital, Tokyo, Japan*

Background: Preclinical data show that combining a murine double minute 2–tumor protein 53 (MDM2–p53) antagonist with immune checkpoint inhibitors produces anti-tumor effects in multiple tumor types. This Phase Ia/Ib study (NCT03964233) is assessing BI 907828, a MDM2–p53 antagonist, combined with immune checkpoint inhibitors in *TP53* wild-type cancers. **Methods:** In Phase Ia (dose escalation), pts with advanced/metastatic solid tumors received escalating doses of BI 907828 guided by a Bayesian Logistic Regression Model (starting dose 10 mg orally) plus ezabenlimab 240 mg (anti-PD-1 antibody) and BI 754111 600 mg (anti-LAG-3 antibody) every 21 days (q3w). Primary endpoint was the maximum tolerated dose (MTD) of BI 907828 based on the number of pts with dose-limiting toxicities (DLTs) during cycle one. During Phase Ia, other studies indicated a lack of added efficacy when BI 754111 was combined with ezabenlimab; therefore, the study design was updated to switch the dose escalation to the doublet combination of BI 907828 plus ezabenlimab. **Results:** A total of 11 pts received the triplet combination at 10/20/30/45 mg dose levels (DL; n = 3/3/3/2 respectively); all have discontinued treatment. No DLTs were reported in cycle one; MTD was not reached. As of 20th January 2022, 15 pts have received the doublet combination at 30/45 mg DLs (n = 10/5 respectively). One pt (45 mg) had a DLT during cycle one: G2 neutropenia. Four DLTs were reported after cycle one: G3 anemia (30 mg); G2 thrombocytopenia (45 mg); and G3 neutropenia and G4 thrombocytopenia (45 mg). G≥3 adverse events occurred in eight pts; most commonly anemia (n = 6), thrombocytopenia (n = 4) and lymphopenia (n = 3). There were no notable safety findings with BI 907828 45 mg q3w, the recommended dose for expansion (RDE) for BI 907828 monotherapy. Nine of the 15 pts who received doublet therapy were evaluable for response; four had a confirmed partial response (PR; 30 mg, n = 1; 45 mg, n = 3), two biliary tract carcinoma, one urothelial carcinoma, and one myxoid liposarcoma; one had an unconfirmed PR (30 mg) with adenocarcinoma (primary site intrahepatic cholangiocarcinoma). Four pts with liposarcoma and gastric cancer had stable disease. MTD will be reported. In Phase Ib, pts will receive the RDE of BI 907828 plus 240 mg ezabenlimab (q3w). Pts will be recruited to two cohorts: soft tissue sarcomas (liposarcoma, undifferentiated pleomorphic sarcoma, myxofibrosarcoma, synovial sarcoma and leiomyosarcoma) and selected MDM2-amplified tumors (NSCLC, gastric adenocarcinoma, urothelial carcinoma, and biliary tract carcinoma). Primary endpoints are progression-free survival and objective response (RECIST 1.1). **Conclusions:** The doublet combination of BI 907828 plus ezabenlimab showed a manageable safety profile and early signs of anti-tumor activity. Eleven pts remain on treatment; recruitment is ongoing. Clinical trial information: NCT03964233. Research Sponsor: Boehringer Ingelheim.

3096 **Poster Session**

Interim safety and efficacy results from a phase 1 study of NT219 in adults with advanced solid tumors. *First Author: Alberto Bessudo, Pacific Oncology Hematology Associates Inc., Encinitas, CA*

Background: NT219 is a small molecule, effecting IRS1/2 degradation and inhibiting STAT3 phosphorylation. IRS1/2 and STAT3 are major signaling junctions regulated by various oncogenes, altered during epithelial to mesenchymal transition (EMT) and drug resistance, and play an important role in the tumor and its microenvironment. A Phase 1/2 study (NCT04474470) includes a dose escalation of NT219 administered weekly for the treatment of relapsed and/or refractory cancer patients. **Methods:** In the dose escalation part of the study involving a conventional 3+3 design, patients with recurrent and/or metastatic solid tumors were administered intravenously with NT219 at 3, 6, 12 and 24mg/kg. Safety was assessed according to CTCAE v5 and anti-tumor activity was assessed by the investigators according to RECISTv1.1 using CT/MRI. The primary objectives of this part of the study are to evaluate safety, tolerability, PK and determine the recommended Phase 2 dose (RP2D). The study includes evaluation of potential biomarkers including measurements of STAT3, IRS1/2 phosphorylation, and TILs in biopsy specimens. **Results:** As of data cutoff date of February 8, 2022, a total of 13 patients were enrolled to 4 NT219 dose levels (3 - 24mg/kg) in the dose escalation phase, of which 11 were evaluable for dose limiting toxicity (DLT) determination, including 4 with colorectal cancer (CRC), 2 with pancreatic cancer, 2 with breast cancer, and one of each of the following cancers: gastroesophageal junction (GEJ), esophageal, appendiceal, papillary thyroid, and mesothelioma. Median number of prior treatment regimens for metastatic disease was 4 (2-11). Six Grade 3 adverse events (AEs) were observed, including alkaline phosphatase increase, aspartate aminotransferase increase, toxic encephalopathy, worsening back pain, abdominopelvic ascites, closed displaced fracture of right femoral neck, with the first 2 considered as possibly related to NT219. No Grade 4 AEs or treatment related deaths were reported. For the 11 evaluable patients, best overall response included one confirmed PR (GEJ patient, 5.5 months duration of response), and 3 SD (3 of 4 CRC patients; duration of 5.2, 4, and 2 months with ongoing follow up) with two patients awaiting follow up MRI/CT scans. As of the cutoff date, 9/11 patients that completed the DLT period are either on treatment or in follow up (range 1.1 to 14.7 months). **Conclusions**: Interim analysis of safety results obtained in 4 NT219 dose levels found NT219 to be well tolerated without DLTs in advanced cancer patients. The observed durable PR in a GEJ patient and SDs in 3 CRC patients are an encouraging initial signal of efficacy. Combination treatment of cetuximab with escalating NT219 doses in patients with recurrent/metastatic CRC and squamous cell carcinoma of the head and neck (SCCHN) has begun. An expansion cohort in patients with recurrent/metastatic SCCHN will be initiated at the conclusion of this part. Clinical trial information: NCT04474470. Research Sponsor: Purple Biotech Ltd.

3097 **Poster Session**

A phase 1, first-in-human, dose-escalation and biomarker trial of liposomal gemcitabine (FF-10832) in patients with advanced solid tumors. *First Author: Erkut Hasan Borazanci, HonorHealth, Scottsdale, AZ*

Background: FF-10832 is a stable liposomal formulation of gemcitabine (GEM) shown to overcome resistance through increased plasma stability and enhanced tumor drug delivery. Macrophage uptake and immune activation in the tumor microenvironment (TME) play a role in the superior efficacy of FF-10832 compared to GEM, with selective, marrow-sparing biodistribution contributing to an improved safety profile. **Methods:** A 3+3 design determined the safety, maximum tolerated dose (MTD), dose-limiting toxicities (DLT), pharmacokinetics (PK), and recommended Phase 2 dose (RP2D). FF-10832 was administered IV once or twice per cycle on a 28 or 21-day schedule until disease progression or unacceptable toxicity. Circulating immune cell populations were measured over time by flow cytometry. **Results:** Patients (pts) [n = 73, 26M/47F; median age, 64 (range, 26–84); # prior therapies, 3 (1–11); prior GEM, 60%] received FF-10832 on Day 1 and 15 Q28 days (1.2–30 mg/m^2), Day 1 and 8 Q21 days (12–23 mg/m^2), or Day 1 only Q28 or 21 days (30–55 mg/m^2); median # cycles = 2 (1–14) & time on study = 8.3 (4–60) weeks. Common drug-related adverse events were Grade (Gr) ≤2 rash (22%), nausea (22%, 1 Gr 3), and pyrexia (21%, 2 Gr 3). Dose-limiting Gr ≥3 cellulitis/skin ulcers were observed at ≥23 mg/m^2 with twice per cycle dosing and those regimens discontinued. Dose frequency was reduced to Day 1 only, which was well-tolerated without significant skin toxicity. Gr ≥3 thrombocytopenia and pneumonitis were observed at 55 mg/m^2 Q21 days and the MTD confirmed at 40 (Q21) and 48 mg/m^2 (Q28). Median OS = 25.3 (95%CI: 16–27.1) weeks and PFS = 9.6 (95%CI: 7.9–17.6) weeks. Three of 35 evaluable pts achieved a partial response (PR): one pt with gallbladder cancer who previously progressed on GEM achieved a 50%↓ by Cycle 13 at 40 mg/m^2 Q28 days & maintains response on study at 60 weeks; two pts with pancreatic cancer had ≥30%↓: one adenocarcinoma after 2 cycles at 4.8 mg/m^2 Days 1 & 15 Q28 days, and one acinar cell after 7 cycles at 40 mg/m^2 Q28 days who remains on study. Stable disease (SD) was observed in 16 pts; 9 for ≥20 weeks. AUC increased in proportion to dose without accumulation. An extended plasma $t_{1/2}$ (hrs) for released (39) & total GEM (26) with a free fraction < 1% of total GEM concentrations suggests continuous release in the TME. Pts with PR or SD had dose and time-related log decreases in Ki67+ regulatory T cells relative to total CD4+ cells with increases in anti-tumor CD8+ cells, suggesting a shift to a more immunocompetent environment. **Conclusions:** FF-10832 was well-tolerated in heavily pre-treated pts with solid tumors, with evidence of anti-tumor activity in pts who progressed on prior GEM. Prolonged, continuous exposure and enhancement of anti-tumor immunity may contribute to improved efficacy. Expansion is ongoing in biliary tract cancer pts treated at the RP2D/schedule of 40 mg/m^2 Day 1 of a 21-day cycle. Clinical trial information: NCT03440450. Research Sponsor: FUJIFILM Pharmaceuticals U.S.A., Inc.

3098 **Poster Session**

The bi-steric mTORC1-selective inhibitor RMC-5552 in tumors with activation of mTOR signaling: Preclinical activity in combination with RAS(ON) inhibitors in RAS-addicted tumors, and initial clinical findings from a single agent phase 1/1b study. *First Author: Howard A. Burris III, Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN*

Background: RMC-5552 is a potent bi-steric mTORC1-selective inhibitor that activates the downstream tumor suppressor 4EBP1, thereby inhibiting initiation of protein translation. This novel therapeutic moiety addresses a key limitation of rapalogs, which do not effectively inhibit phosphorylation of 4EBP1. RMC-5552 has previously demonstrated significant anti-tumor activity in preclinical models of human cancers with mTOR pathway activation. Additionally, mTOR signaling plays a key role in therapeutic response and resistance in RAS-addicted cancers, which represent a significant unmet medical need. **Methods:** We examined the combination of bi-steric mTORC1 inhibitors (RMC-5552 and the research tool compound RMC-6272) with direct inhibitors of active RAS (RAS(ON) inhibitors) in mutant KRAS-driven models. To enable the clinical testing of RMC-5552 as a companion inhibitor for RAS(ON) inhibitors, a Phase 1/1b dose-escalation trial of RMC-5552 monotherapy is currently testing a once-a-week IV schedule. **Results:** RMC-5552 and RMC-6272 demonstrated marked combinatorial anti-tumor activity with RAS(ON) inhibitors across a series of preclinical models of KRAS mutated non-small cell lung cancer. The combination enhanced tumor apoptosis and resulted in durable tumor regressions as compared to tumor growth inhibition resulting from single agents alone. As of 13 January 2022, a total of 14 patients with solid tumors have been evaluated in an ongoing Phase 1/1b trial over 5 dose levels ranging from 1.6 to 12 mg IV weekly. Median age was 62 years and the majority received ≥3 prior therapies. The most common (> 25%) drug-related adverse events were mucositis/stomatitis (43%) and decreased appetite (29%). The most common grade 3 drug-related adverse events were mucositis/stomatitis observed in 3 patients in dose levels ≥ 10 mg (21%) and were dose-limiting. The dose of 6 mg IV weekly was well tolerated. Plasma exposures of RMC-5552 were dose-proportionate at lower dose levels up to 6 mg but increased above dose proportionality with higher dose levels. Plasma exposures at 6 mg and above were consistent with those resulting in inhibition of tumor p4EBP1 in preclinical models. Of 5 patients evaluable for efficacy at doses of 6 mg and higher, one confirmed PR was observed in a patient with head and neck cancer with a pathogenic mutation in *PTEN* (ORR 20%) and 3 patients had a best response of SD. Dose-optimization is ongoing. **Conclusions:** RMC-5552 is clinically active in tumors with mTORC1 signaling activation at a tolerable dose and schedule and has the potential to be a companion inhibitor of choice for RAS(ON) inhibitors in RAS-addicted tumors. Clinical trial information: NCT04774952. Research Sponsor: Revolution Medicines.

3099 **Poster Session**

Updated analysis of the efficacy and safety of entrectinib in patients (pts) with locally advanced/metastatic *NTRK* fusion-positive (*NTRK*-fp) solid tumors. *First Author: Maciej Jerzy Krzakowski, Lung and Thoracic Cancer Department, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland*

Background: *NTRK* gene fusions, coding for chimeric TRK proteins, are oncogenic drivers in many solid tumors. In an integrated analysis of three phase 1/2 trials (ALKA-372-001 [EudraCT 2012-000148-88]; STARTRK-1 [NCT02097810]; STARTRK-2 [NCT02568267]), entrectinib, a potent CNS-active TRK inhibitor, showed durable systemic and intracranial responses in pts with *NTRK*-fp solid tumors. We report updated data from a larger cohort with longer follow-up (clinical cutoff 2 Aug 2021). **Methods:** Pts with locally advanced/metastatic *NTRK*-fp solid tumors and ≥12 months' follow-up from first tumor assessment were efficacy evaluable. The safety cohort also included pts from TAPISTRY (NCT04589845). Tumor responses were assessed by blinded independent central review (BICR) per RECIST v1.1 at Week 4 and every 8 weeks thereafter. Primary endpoints: objective response rate (ORR) and duration of response (DoR). Progression-free survival (PFS), overall survival (OS), intracranial (IC)-ORR and safety were also assessed. **Results:** The efficacy-evaluable cohort comprised 150 adults (vs 121 previously) with 17 different solid tumor types. Median age was 58.5 years; 91% of pts had ECOG PS 0–1 and 37% had received ≥2 prior lines of therapy. Median survival follow-up was 30.6 months. ORR was 61.3% (n = 92/150; 95% CI: 53.1–69.2), including 25 complete responses. Responses were observed in all tumor types with n>1 (Table). Median DoR, PFS and OS were 20.0 months (95% CI 13.2–31.1), 13.8 months (95% CI 10.1–20.0), and 37.1 months (95% CI 27.2–not estimable [NE]), respectively. In pts with and without investigator-assessed baseline CNS metastases (n = 31 / n = 119), ORR was 61.3% (95% CI 42.2–78.2) and 61.3% (95% CI 52.0–70.1) respectively. IC-ORR was 69.2% (n = 9/13) in pts with BICR-assessed measurable CNS metastases; median IC-DoR was 17.2 months (7.4–NE). In the safety population (N = 235: all treated pts), most treatment-related adverse events (TRAEs) were grade 1/2 and not serious; the most frequent were dysgeusia (36.6%), diarrhea (29.8%) and weight increase (28.5%). TRAEs led to dose interruption, reduction and discontinuation in 32.8%, 24.3% and 7.2% of pts, respectively. **Conclusions:** In this updated analysis, entrectinib continued to demonstrate deep and durable responses and was well tolerated in pts with *NTRK*-fp solid tumors with or without baseline CNS metastases. Clinical trial information: STARTRK-2 [NCT02568267]. Research Sponsor: F. Hoffmann-La Roche Ltd.

NTRK-fp tumor type (N ≥ 5)	ORR, n/N (%)
Sarcoma	19/32 (59.4)
Non-small cell lung cancer	20/31 (64.5)
Mammary analogue secretory carcinoma	22/26 (84.6)
Thyroid	10/16 (62.5)
Colorectal	3/11 (27.3)
Breast	6/9 (66.7)
Head and neck	3/5 (60.0)
Neuroendocrine	2/5 (40.0)

Other tumor types included in efficacy-evaluable population: pancreatic (N = 4); carcinoma of unknown primary (N = 3); gynecological (N = 2); adrenal, cholangiocarcinoma, gastrointestinal tract, neuroblastoma, penile and prostate (N = 1 each).

3100 **Poster Session**

Long-term efficacy and safety of larotrectinib in a pooled analysis of patients with tropomyosin receptor kinase (TRK) fusion cancer. *First Author: Alexander E. Drilon, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions are oncogenic drivers in multiple tumors. Larotrectinib is a highly selective, central nervous system (CNS)-active tropomyosin receptor kinase (TRK) inhibitor, approved to treat adult and pediatric patients (pts) with TRK fusion cancer. In an integrated analysis of 206 pts with non-primary CNS TRK fusion cancer, larotrectinib demonstrated an investigator-assessed objective response rate (ORR) of 75%; median progression-free survival (PFS) was 35.4 months (mo; Hong et al, ASCO 2021). We report updated efficacy and safety data based on central review assessments in an expanded dataset. **Methods:** Data were pooled from three clinical trials (NCT02576431, NCT02122913, and NCT02637687) of pts with non-primary CNS TRK fusion cancer treated with larotrectinib. Larotrectinib was administered until disease progression, withdrawal, or unacceptable toxicity. ORR was assessed by independent review committee (IRC) per RECIST v1.1. Data cut-off was July 20, 2021. **Results:** As of data cut-off, 244 of 269 larotrectinib-treated pts were evaluable for efficacy by IRC. There were 25 different tumor types. The most common were soft tissue sarcoma (STS [43%], including infantile fibrosarcoma [18%] and other STS [25%]), thyroid (11%), lung (10%), salivary gland (9%), and colorectal (7% [colon, n = 18; rectal, n = 1]). Ninety-four (35%) pts were aged < 18 years; 175 (65%) were ≥18 years. Pts had gene fusions involving *NTRK1* (46%), *NTRK2* (3%), or *NTRK3* (51%). A total of 27%, 28%, and 45% of pts had 0, 1, and ≥2 prior lines of systemic therapy, respectively. The ORR was 69% (95% confidence interval [CI] 63–75): 64 (26%) complete response (CR), including 13 (5%) pathological CR, 104 (43%) partial response,41 (17%) stable disease, 20 (8%) progressive disease, and 15 (6%) not determined. Median time to response was 1.8 mo (range 0.9–16.2). Median duration of response (DoR) was 32.9 mo (95% CI 27.3–41.7); median follow-up was 28.3 mo. Median PFS was 29.4 mo (95% CI 19.3–34.3); median follow-up was 29.3 mo. At a median follow-up of 32.2 mo, median overall survival (OS) was not reached; the 48-mo OS rate was 64% (95% CI 55–73). Treatment duration ranged from 0.1 to 67.9 months. Treatment-related adverse events (TRAEs) were mainly Grade 1–2; 50 (20%) pts had Grade 3–4 TRAEs. Five (2%) pts discontinued treatment due to TRAEs. To exclude the possible confounding effect of ongoing enrollment on median DoR, we conducted an exploratory analysis in the subset of 164 pts who were analyzed as of July 2019. The ORR was 74% (95% CI 67–81) and median DoR was 34.5 mo (95% CI 27.6–43.3); median follow-up was 34.1 mo. **Conclusions:** With longer follow-up, larotrectinib continued to demonstrate rapid and durable responses, extended survival benefit, and a favorable safety profile. These results highlight the importance of testing for *NTRK* gene fusions in cancer pts. Clinical trial information: NCT02576431, NCT02122913, NCT02637687. Research Sponsor: Bayer HealthCare and Loxo Oncology.

3101 **Poster Session**

A first-in-human phase 1 dose escalation study of FF-10850 (liposomal topotecan) in patients with advanced solid tumors. *First Author: Ursula A. Matulonis, Dana-Farber Cancer Institute, Boston, MA*

Background: FF-10850 (liposomal topotecan) was developed using a unique dihydrosphingomyelin-based carrier to enhance tumor drug delivery and retention, leading to improved efficacy and safety. Preclinical studies demonstrated superior antitumor activity with less myelosuppression compared to topotecan, with a pharmacokinetic (PK) profile supporting a twice-monthly dosing schedule. **Methods:** Accelerated titration followed by a 3+3 dose escalation design was used to determine the safety, maximum tolerated dose (MTD), dose-limiting toxicities (DLT), PK, and recommended Phase 2 dose. FF-10850 was administered IV on Day 1 and 15 of a 28-day cycle until disease progression or unacceptable toxicity. **Results:** Patients (pts) [n = 29; 4M/25F; median age, 64 (range, 37–79) and # prior therapies, 4 (range, 1–8)] received FF-10850 at doses of 1, 2, 2.5, 3, 3.5 and 5 mg/m^2; median # of cycles, 2 (range, 1–11). FF-10850 was well-tolerated at doses up to 2 mg/m^2. Common drug-related adverse events (AEs) included anemia (83%, 51% Gr≥3), thrombocytopenia (62%, 35% Gr≥3), neutropenia (59%, 45% Gr≥3), nausea (38%), fatigue (24%, 7% Gr≥3), alopecia (24%), and hypokalemia (17%, 3% Gr≥3). Dose-limiting Gr≥3 thrombocytopenia, neutropenia, anemia, and fatigue were observed at doses ≥2.5 mg/m^2. Eight pts required dose reductions due to AEs. The median time on study was 8.3 (1.6–45) weeks, with a median PFS of 9.4 weeks and median OS at least 26 weeks. Of 24 pts evaluable for response, two achieved a partial response (PR). One pt with ovarian cancer treated at 3.5 mg/m^2 achieved a complete response in target lesions by Cycle 2 with stable non-target lesions, and maintained response for > 30 weeks (8 cycles) before progressing; dose was reduced in this pt to 2.6 mg/m^2 at Cycle 2 due to Gr 4 thrombocytopenia. Another pt with refractory metastatic Merkel cell carcinoma tolerated therapy well at 2 mg/m^2 and achieved a 48% reduction in target lesions that was maintained for > 30 weeks (8 cycles). Stable disease was observed in an additional 9 pts for ≥10 weeks (5 ovarian, 2 uterine and 2 cervical); five who maintained disease control for ≥24-45 weeks including one (ovarian) who had previously progressed on topotecan. An extended plasma $t_{1/2}$ for topotecan of 25-30 hours was observed with no apparent dose-dependency or accumulation; < 1% of circulating topotecan was in the free (released) form. **Conclusions:** FF-10850 was well-tolerated up to 2 mg/m^2 with antitumor activity demonstrated in heavily pre-treated pts with solid tumors including ovarian cancer, and an improved PK profile allowing less frequent dosing compared to topotecan. Expansion is ongoing in pts with ovarian and Merkel cell carcinoma at the RP2D of 2 mg/m^2 IV on Day 1 & 15 of a 28-day cycle. Clinical trial information: NCT04047251. Research Sponsor: FUJIFILM Pharmaceuticals U.S.A., Inc.

3102 **Poster Session**

A study of senaparib in combination with temozolomide for the treatment of patients with advanced solid tumors and extensive-stage small cell lung cancer. *First Author: Bo Gao, Blacktown Cancer & Haematology Centre, Blacktown Hospital, Sydney, NSW, Australia*

Background: Senaparib (or IMP4297) is a PARP inhibitor with a novel chemical structure. Preliminary data demonstrate senaparib has significant antitumor activity with good tolerability in some patients with advanced solid tumors. DNA damage caused by temozolomide, a non-classic oral alkylating agent, can sensitize tumors to the effects of PARP inhibitors. In a xenograft model, synergistic antitumor effect was observed with the combination of senaparib and temozolomide, supporting this trial (NCT04434482). **Methods:** This is a phase Ib/II dose-escalation and dose-expansion study. Patients with advanced solid tumors were enrolled for dose escalation to evaluate the safety, tolerability using a modified "3+3" design. Low dose temozolomide (20 to 30 mg, once daily, days 1 to 21) in combination with continuous senaparib (40 to 80 mg, once daily, days 1 to 28) of each 28-day cycle was evaluated. Dose expansion will establish anti-tumor activity and safety of the combination in patients with extensive stage small cell lung cancer (ES-SCLC). **Results:** A total of 14 patients were enrolled for dose escalation as follows: Cohort 1 (1 patient; senaparib 40 mg plus temozolomide 20 mg), Cohort 2 (3 patients; senaparib 60 mg plus temozolomide 20 mg), Cohort 3 (7 patients; senaparib 80 mg plus temozolomide 20 mg), Cohort 4 (3 patients; senaparib 80 mg plus temozolomide 30 mg). One DLT (Grade 4 thrombocytopenia) was observed in Cohorts 3 and 4. The MTD and RP2D were determined as: senaparib 80 mg plus temozolomide 20 mg. Anaemia, neutropenia and thrombocytopenia were the only Grade ≥3 TEAEs occurring in > 1 patient. All AEs were manageable, and no treatment related deaths were reported. The ORR was observed in 3 of 12 (25.0%) evaluable patients, including 2 confirmed PR and 1 unconfirmed PR. The DCR was 83.3% (10 of 12 evaluable patients). Two patients remain on treatment for more than 1 year. **Conclusions:** Preliminary results suggest that low dose temozolomide (D1-21 of a 28-day cycle) in combination with continuous senaparib is generally well tolerated with encouraging anti-tumor activity. Recruitment for dose expansion for ES-ECLC patients has commenced (Sep 2021). Clinical trial information: NCT04434482. Research Sponsor: None.

3103 **Poster Session**

A CRUK first-in-human phase I trial of LY3143921, a novel CDC7 inhibitor, in patients with advanced solid tumors. *First Author: Peter F. Gallagher, Queen's University Belfast, Belfast, United Kingdom*

Background: CDC7, a protein with key roles in regulating cell-cycle progression is often over-expressed in malignant cells, particularly those with *TP53* mutations. LY3143921, an orally administered ATP-competitive CDC7 inhibitor, demonstrated favorable pre-clinical anti-cancer activity in colorectal cancer (CRC) and squamous non-small cell lung cancer (sqNSCLC), particularly in *TP53* mutant models. **Methods:** Phase Ia (dose escalation) recruited patients (pts) with advanced solid tumors enriched for malignancies associated with *TP53* mutation. Pts received LY3143921 OD or BD continuously on a 21-day schedule, using an accelerated 3+3 escalation design, starting at 30 mg OD. Phase Ib recruited pts with CRC or sqNSCLC treated continuously at RP2D, or pts with other advanced tumors treated at RP2D on days 1-3 every 7 days. Radiological assessment was performed every 2 cycles initially. Pts in phase Ib could consent to pre- and on-treatment skin +/- tumor biopsies. Primary objectives: assess safety/tolerability and determine MTD and RP2D of LY3143921. Secondary objectives: evaluate preliminary efficacy and pharmacokinetic (PK) profile of LY3143921. Exploratory objective: correlate efficacy to baseline molecular/genetic alterations, including *TP53* mutation and measure markers including pMCM2 in pre- and on- treatment tumor and skin samples. **Results:** 68 pts were recruited and 67 treated (38 phase Ia, 29 phase Ib). Most frequent drug-related CTCAEs (all grades): nausea (75%), orthostatic hypotension (50%), vomiting (47%), fatigue (45%) & diarrhea (44%). Grade 3-4 LY3143921 related AEs occurred in 17 pts. In phase Ia 8 DLTs occurred in 5 pts (G3 nausea, vomiting, fatigue & hyponatraemia and G2 diarrhea, anorexia & lethargy). RP2D was 360 mg BD (continuous non-fasted dosing schedule). 37 pts were evaluable for radiological response with no complete or partial responses seen, and stable disease (SD) was observed in 24 pts (65%). In phase Ia 3 pts achieved long term SD of 1, 2.5 and 3+ years duration. For evaluable pts treated in phase Ib, SD was seen in 8/12 CRC pts, 1/2 sqNSCLC pts and 2/2 pts treated with the intermittent schedule (median duration 15 weeks, range 6-18+). 2 pts remain on-study. Recruitment ceased due to lack of radiological response according to RECIST. Dose-dependent increases in LY3143921 exposure (C_{max} & $AUC_{0\text{-}24}$) were seen. IHC analyses of skin biopsies demonstrated reductions in pMCM2, indicating on-target activity of LY3143921. Pre-clinical testing of combination with standard of care agents is ongoing. Additional PD and PK data will be presented. **Conclusions:** LY3143921 is well tolerated, exhibits dose-dependent increases in plasma exposure and demonstrates evidence of target inhibition. Significant monotherapy clinical activity was not observed; further analyses should investigate potential predictive response biomarkers and rational combination approaches. Clinical trial information: NCT03096054. Research Sponsor: Cancer Research UK.

3104 **Poster Session**

Mechanisms of acquired resistance to TRK inhibitors. *First Author: Guilherme Harada, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: First-generation TRK tyrosine kinase inhibitors (TKIs) are approved in a tumor-agnostic fashion in more than 40 countries for patients with *NTRK* fusion-positive adult and pediatric cancers. While resistance to these agents has previously been described, the exact frequency with which major mechanisms of resistance emerges is not clearly understood. **Methods:** Patients with an *NTRK*-fusion-positive tumor who received a first-generation TRK TKI were eligible. We retrospectively identified those patients that had post-progression tumor tissue analyzed by next-generation sequencing (NGS). The pattern of serial resistance to a second-generation TKI was analyzed when available. **Results:** Eighteen patients were identified. The median age was 46 years (range 2-67). Nine unique fusions were detected in ten different tumor types. *NTRK1*, *NTRK2*, and *NTRK3* fusions were found in eight (44%), one (6%), and nine (50%) patients, respectively. Thirteen patients (72%) were treated with larotrectinib and five patients (28%) received entrectinib. NGS (MSK-IMPACT n = 17, Foundation One n = 1) carried out on post-progression tissue revealed the following profile of acquired resistance: on-target resistance (83%, n = 15/18), off-target resistance (11%, n = 2/18), and no identifiable mechanism (6%, n = 1/18). Among patients with on-target resistance, the most common mutation involved the solvent front (87%, n = 13/15: n = 7 *NTRK3* G623R, n = 4 *NTRK1* G595R, n = 1 *NTRK2* G639L, n = 1 *NTRK3* G623E) followed by the gatekeeper region (13%, n = 2/15: n = 1 *NTRK1* F589L, n = 1 *NTRK3* F617I). Two patients developed off-target alterations. One acquired *BRAF* V600E mutation and the other *MET* amplification. Interestingly, solvent front mutation loss was observed in two patients who transitioned to and progressed on a second-generation TRK TKI. One patient with a baseline *NTRK1* G595R mutation developed polyclonal resistance with acquisition of *KRAS* G12A and *NTRK1* G667A alterations as well as *NTRK1* G595R loss. The other patient with *NTRK3* G623R developed an *NTRK3* F617I gatekeeper mutation with *NTRK3* G623R loss. **Conclusions:** In *NTRK* fusion-positive cancers, on-target resistance preferentially involving the solvent front is more frequent than off-target resistance to first-generation TKI therapy. Furthermore, the sequential use of second-generation therapy appears to alter the evolutionary kinetics of mutation retention and acquisition. Research Sponsor: U.S. National Institutes of Health.

3105 **Poster Session**

A phase 1 dose-escalation study of the ABN401 (c-MET inhibitor) in patients with solid tumors. *First Author: Dae Ho Lee, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea*

Background: *MET* is a proto-oncogene encoding a receptor tyrosine kinase c-MET for hepatocyte growth factor (HGF). Dysregulated MET signaling by *MET* exon14 skipping, *MET* gene amplification and c-MET overexpression in cancer plays a critical role in the development of primary oncogenesis, acquired drug resistance and metastasis. This is a first-in-human trial, phase 1 dose-escalation study of the highly selective MET kinase inhibitor, ABN401. ABN401was evaluated in subjects with advanced solid tumors in South Korea and Australia. **Methods:** Patients with advanced solid tumors were enrolled in escalating dose cohorts using an accelerated titration design. ABN401 was orally administered daily with 21-day cycle. The primary objective was to evaluate safety and tolerability to define dose-limiting toxicity (DLT), maximum tolerated dose (MTD) according to CTCAE v5. Secondary objectives included pharmacokinetic, recommended phase II dose (RP2D), and preliminary efficacy assessments. Tumor assessment was determined using Response Evaluation Criteria in Solid Tumors (RECIST 1.1). **Results:** Out of 28 screened patients, 16 patients with 6 different tumor types were treated with ABN401 at daily dose levels of 50, 100, 200, 400, 800 and 1200 mg, 15 patients were evaluated for DLT and one unevaluable. No DLT was observed in all 6 dose levels and the MTD has not been reached. No drug related grade ≥ 3 AEs were observed: only one drug-related SAE (transient peripheral edema) was reported. For treatment response, 5 patients with stable disease, and 2 with partial response were observed. These two patients with partial response had non-small cell lung cancer (NSCLC) with c-MET overexpression and had been treated with ABN401 for 10 and 18 months, respectively. **Conclusions:** ABN401 dosed up to 1200 mg QD was well tolerated with an acceptable safety profile and promising preliminary antitumor activity in patients with advanced solid tumors. The extension (pilot expansion) for additional efficacy assessment is under way at 800 mg daily dose with c-MET altered NSCLC patients in South Korea and Australia. In addition, a phase 2 expansion study is to start in the United States and South Korea. Clinical trial information: NCT04052971. Research Sponsor: None.

3106 **Poster Session**

Safety, pharmacokinetics (PK), and clinical efficacy of ICP-723, a highly selective next-generation pan-TRK inhibitor, in patients with solid tumor. *First Author: Xiao-Li Wei, Department of Medical Oncology, Sun Yat-sen University Cancer Centre, Guangzhou, China*

Background: NTRK gene fusion resulting from NTRK1/2/3 genetic alterations occurs in various adult and pediatric cancers, which is one of the most defined driving factors of carcinogenesis. Patients with NTRK fusion positive cancers treated by earlier generation TRK inhibitors achieve rapid and durable responses but can develop on-target resistance. ICP-723 is a highly selective next-generation TRK inhibitor. In preclinical studies, ICP-723 not only markedly inhibits the activity of the wild type TRKA/B/C, but also shows robust activity against resistant mutations, e.g., G595R, F589L or G667C/A/S. A first-in-human clinical study is currently ongoing to evaluate the safety, tolerability, pharmacokinetics (PK) characteristics and efficacy of ICP-723. **Methods:** This is a multi-center, open-label phase I/II clinical trial, which includes a phase I dose escalation part and a phase II dose expansion part. In the phase I dose escalation, patients with advanced solid tumor, who failed from clinical standard of care or for whom there is currently no effective therapy, will be enrolled. The modified "3+3" method is followed for dose escalation. **Results:** As of 11Feb2022, a total of 17 patients in phase I dose escalation were treated with ICP-723 at doses of 1 mg QD to 8 mg QD. The median age of the enrolled patients was 54 yrs, (range: 31 to 69 yrs) and ECOG performance status was between 0-1 (58.8% had ECOG PS of 1). Six of 17 patients were confirmed as NTRK gene fusion positive tumors by either prior gene test reports or the central lab gene test. There is no DLT observed in the 6 dose groups. Most AEs were manageable and grade 1-2. The most common TRAEs (> 20%) were asthenia (23.5%), increased ALT (29.7%), increased AST (29.7%) and anemia (29.7%). Gr ≥3 TRAEs were increased ALT (5.9%), increased AST (5.9%), increased CPK (11.8%), neutrophil count decreased (5.9%) and pain (5.9%). The plasma exposure to ICP-723 increased in a dose proportional manner across the observed dosage levels. According to RECIST 1.1 criteria, among the 6 patients with NTRK fusion, the overall response rate (ORR) was 66.7% (4 patients with partial response (PR)), the disease control rate (DCR) was 100%. It is worth noting that one patient with measurable brain metastasis achieved PR with the target brain lesion shrunk from 10 mm to 3 mm. All patients who achieved PR responded to ICP-723 at the first tumor assessment after 4-week treatment and maintained sustained responses to the date of data cutoff. **Conclusions:** ICP-723 is safe and well-tolerated in patients with advanced solid tumors. Encouraging clinical efficacy including intracranial activity was demonstrated in patients with NTRK gene fusion in various tumor types. Enrollment in phase I is ongoing until the final RP2D is determined, then phase II expansion will be conducted in patients with defined gene alterations. Clinical trial information: NCT04685226. Research Sponsor: InnoCare Pharma Limited.

3107 **Poster Session**

First-in-human (FIH) phase I study of the highly selective phosphoinositide 3-kinase inhibitor delta (PI3Kδ) inhibitor IOA-244 in patients with advanced cancer: Safety, activity, pharmacokinetic (PK), and pharmacodynamic (PD) results. *First Author: Anna Maria Di Giacomo, Center for Immuno-Oncology, University Hospital of Siena, Siena, Italy*

Background: T regulatory (Tregs) cells contribute to immune suppression in cancer. The highly selective inhibitor of PI3Kδ, IOA-244, blocks the activity of Tregs among other things, thus reprograms the anti-tumor immune response. **Methods:** IOA-244 was investigated in a two-part FIH study. Part A explored the continuous daily dosing of IOA-244 at 10, 20, 40 and 80 mg. Part B consists of expansion cohorts of specific tumor indications, including pre-treated uveal melanoma patients (pts). Primary objective: safety of the anticipated biologically effective dose (BED), or the recommended phase 2 dose (RP2D). Secondary objectives: PK; PD (e.g., inhibition of CD63 expression on basophils, changes in immune cell subsets in peripheral blood); RECIST 1.1.-based responses; PFS and OS. Exploratory studies: changes in circulating immune cells by Cytometry by Time of Flight (CyTOF); response assessments by radiomics **Results**: Part A Solid Tumor (completed): Sixteen pts were treated in 4 cohorts each with 4 pts. Pts characteristics: uveal melanoma (9/16; 56%), cutaneous melanoma (5/16; 31%) and pleural mesothelioma (2/16; 13%). Four pts had at least one serious TEAE, none considered related to IOA-244. There was no treatment-emergent adverse events (TEAE) leading to study drug discontinuation, immune related toxicity or Dose Limiting Toxicity. CTCAE v5 Grade 1 and 2 were observed, including 2 cases of transient diarrhoea and 2 of AST/ALT elevation. Part A (Completed) – Subgroup Uveal Melanoma Pts (progressed ≥1 line prior therapy): 9 pts treated (3/9 pts ongoing). Mean time on treatment: 7.7 mo (range: 1.8-16.0 mo with 3 pts ongoing). ORR (RECIST 1.1): CR+PR: 0/9 (0%); SD: 6/9 (67%). Median OS: 5.4 mo - not determined (% alive at 1 year: 44% with 3 pts ongoing). CT images from 7/9 patients were assessed for changes in their metastatic lesions by radiomics (baseline and Week 8). Based on 147 matched lesions, 19% had complete responses and 16% had new lesions. In the liver, non-progressive disease was observed in 61% of all lesions, including 42% with either complete response or volume reduction of more than 30%. Using CyTOF, circulating Tregs were reduced while CD8 and NK cells were increased. Part B Uveal Melanoma Expansion Cohort (ongoing): 7 patients (7/7 pts ongoing); mean time on treatment 3.7 mo. ORR (RECIST 1.1): SD in 4/7 pts (57%). Part A Follicular Lymphoma Cohort (ongoing): At 20 mg: 4/4 pts. No DLT. At 80 mg: recruiting. **Conclusions:** In addition to being well tolerated, IOA-244 at the 80 mg dose shows reduction in peripheral blood Tregs and anti-tumor responses based on radiomics. Therefore, RECIST 1.1.-derived SD may underestimate anti-tumor activity of IOA-244 in treatment-resistant uveal melanoma. Additional patients will be treated to further refine this radiomics-based observation. Clinical trial information: NCT04328844. Research Sponsor: iOnctura SA.

3108 **Poster Session**

Phase Ib study of selinexor and eribulin combination in advanced solid tumors and triple-negative breast cancer. *First Author: Blessie Elizabeth Nelson, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Selinexor (KPT-330) is potent inhibitor of Exportin-1. *In vitro*, Selinexor was found to be synergistic with eribulin in triple negative breast cancer (TNBC) cell lines and enhanced antitumor activity of eribulin in TNBC patient-derived xenografts (PMID 28810913). **Methods:** We conducted a phase Ib trial in combination of selinexor and eribulin using 3 + 3 design in dose escalation for patients with advanced solid tumors and in TNBC in dose expansion cohort. Eribulin could be discontinued after combination for 6 cycles at physician discretion. Primary objectives: Safety, Recommended Phase 2 Dose (RP2D). Secondary Objectives: Objective Response Rate (ORR), Duration of Response (DOR), Disease Control Rate (DCR), Overall Survival (OS) and Progression Free Survival (PFS). **Results:** 31 patients, TNBC (n = 19), sarcoma (n = 8), others (n = 4) enrolled in dose escalation (n = 10) and dose expansion phases (n = 21). Median prior therapies:4 (1–6). Study initiated selinexor at 60mg twice weekly and eribulin 1.4mg/m^2 on Day1, Day8 every 3 weeks which led to 1 Dose Limiting Toxicity (DLT) and hence, selinexor 80mg once weekly and eribulin 1mg/m^2 was elected as RP2D due to efficacy and tolerability. As of 01/15/2022, of 29 patients (94%) who have discontinued treatment, 24 (77%) were due to progressive disease, 3 (10%) withdrew consent and 2 (6%) due to toxicities (G1 pneumonitis; G3 neutropenia) while 2 (6%) remain on trial. All 31 patients had at least one treatment emergent adverse event (TEAE) while most prevalent TEAEs (all grades) were leukopenia (77%), nausea (71%), anemia and neutropenia (68%) and fatigue (48%). The most common G3/4 TEAE were leukopenia (26%) and neutropenia (29%). 2 DLTs occurred; 1 in first dose level (DL); 1 in second DL dosed at selinexor 80 mg once weekly due to G3 neutropenia. ORR for all was 10% while DCR (SD+PR+CR) > 6 months seen in 3 (15%) TNBC and 2 (20%) sarcoma patients. The median OS and PFS for all were 12.3 (7.3, 27.3) months and 2.3 (1.6, 4.1) months. In dose escalation cohort, ORR was 10% where one patient (3%) with vaginal SCC had confirmed PR (-44%) for 2.1 months. Five patients (62.5%) with sarcoma had stable disease (SD). One patient with high grade sarcoma has SD for 68 months and remains on selinexor after 4 months of eribulin and selinexor. In TNBC dose expansion (n = 19), ORR was 10.5% with 2 confirmed PRs and median duration of response (DOR) of 10.8 months. One patient who has remained on treatment for 18 months, and after receiving 8 months of eribulin and selinexor, remains on selinexor with 100% target regression and an indeterminate brain lesion. **Conclusions:** Selinexor with eribulin is safe with manageable toxicity profile and modest overall clinical efficacy. Durable responses and disease control were observed with metastatic TNBC. Further study is needed to examine the determinants of response to this combination. Clinical trial information: NCT02419495. Research Sponsor: Karyopharm Therapeutics, , U.S. National Institutes of Health, Clinical and Translational Sciences Award (1UL1TR003167) (NIH/NCATS), and MD Anderson Cancer Support Grant (P30CA016672) (NIH-NCI).

3109 **Poster Session**

Central nervous system (CNS) outcomes and progression patterns in patients with *RET* fusion-positive lung cancers treated with selpercatinib. *First Author: Yonina R. Murciano-Goroff, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Selpercatinib, a potent/selective RET inhibitor, is approved for the treatment of *RET* fusion-positive non-small cell lung cancers. While the drug is known to have substantial intracranial activity (intracranial ORR 82%) in patients with existing brain metastases, (1) central nervous system (CNS) outcomes in patients without brain metastases and (2) CNS progression patterns in patients with brain metastases have not been explored. **Methods:** Patients with advanced *RET* fusion-positive lung cancers were prospectively treated with selpercatinib on the registrational LIBRETTO-001 trial (NCT03157128) or the LIBRETTO-201 multi-center expanded access program (EAP, NCT03906331). Key overall and CNS eligibility criteria were previously presented. Patients with and without pre-selpercatinib brain metastases who underwent serial CNS and extracranial imaging were eligible for analysis. The data cutoff was November 24, 2020. Cumulative incidence rates (CIRs) were calculated using a competing risk model with systemic progression of disease (PD) or death as competing risks; patients with simultaneous CNS and systemic PD were treated as having had CNS PD. **Results:** Sixty-two patients (48 LIBRETTO-001, 14 EAP) were identified. Median age was 64. Thirty-two (52%) were female and 47 (76%) were never smokers. The most common 5' fusion partner was *KIF5B* (68%). The median number of prior therapies was 2 (range 1-11); 34% received prior multikinase inhibitor therapy. The median time on treatment was 21.8 months. Thirty-one (50%) patients had no baseline brain metastases. In these patients, the CIR of CNS metastasis was 0% at 6 months and 12 months; none of these patients developed CNS metastasis during selpercatinib treatment. The 9 patients that progressed did so extracranially. Of the 31 patients with baseline brain metastases, 12 (39%) had prior CNS radiation and 3 (10%) had prior CNS surgery. At the time of data cut-off, 23 patients had some evidence of progression, including 8 in both the CNS and systemically, 6 only in the CNS, and 9 only systemically. Overall, 17 of the 31 patients with baseline brain metastasis did not develop evidence of CNS progression as of the data cut. Among patients with baseline brain metastasis, the CIR for evidence of CNS PD was 6.7% at 6 months and 27.4% at 12 months. **Conclusions:** In patients with *RET* fusion-positive lung cancers without baseline brain metastases, new CNS metastases were not observed during selpercatinib therapy. Among patients with baseline brain metastasis, a substantial number did not experience progression in the CNS on treatment. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

3110 **Poster Session**

Phase I dose-escalation study of IBI351 (GFH925) monotherapy in patients with advanced solid tumors. *First Author: Qing Zhou, Guangdong Lung Cancer Institute, Guangzhou, China*

Background: IBI351(GFH925) is an irreversibly covalent inhibitor of KRAS^{G12C}. In this first-in-human dose-escalation study, we report the preliminary safety and anti-tumor activity of IBI351 (GFH925) in patients (pts) with advanced solid tumors harboring the KRAS p.G12C mutation. **Methods:** Pts with locally advanced, recurrent or metastatic solid tumors with KRAS^{G12C} mutation for whom standard therapy had failed were enrolled. Phase I dose escalation had an accelerated titration design for dose level 250mg QD and a BOIN design with 450/700/900mg QD. The primary end points were safety and tolerabilityThe secondary end points were pharmacokinetics (PK) and anti-tumor activity of IBI351(GFH925) monotherapy per RECIST v1.1. **Results**: As of Feb 07 2022, 15 pts (13 men, 2 women; median age: 62 yrs, range: 48–74 yrs) were enrolled, among whom 12 had non-small cell lung cancer (NSCLC), and 3 had colorectal cancer (CRC). 4 pts had ≥3 prior lines of treatment (tx). Median tx duration was 66.5 ds (range: 21–98 ds). No dose-limiting toxicity (DLT) or any ≥grade 3 treatment-related adverse events were observed in any dose cohorts. A total of 12 patients (80.0%) had treatment-related adverse events (grade 1, n = 6; grade 2, n = 6). By investigator-assessment, tumor response was evaluated in 9 pts (4 with ≥2 assessments); 6 pts had not reached their first assessment. 2 pts had PR (1 NSCLC at wks 12, 450mg, tx ongoing; 1 CRC at wks 6, 700mg, tx ongoing), 4 pts (NSCLC) had SD, and 3 pts had PD (1 NSCLC at wks 12, 2 CRC at wks 6). As data cut-off date, 11 pts were continuing to receive IBI351 (GFH925). **Conclusions**: IBI351(GFH925) was well-tolerated without unanticipated adverse events across all doses explored in pts with advanced solid tumors harboring the KRAS p.G12C mutation. The data also demonstrated the preliminary efficacy signal of IBI351 (GFH925) in previously treated advanced NSCLC and CRC. Clinical trial information: NCT05005234. Research Sponsor: Innovent Biologics, Inc., China.

3111 **Poster Session**

Baseline predictors of hematological toxicity in patients with advanced cancer treated with ATR inhibitors in phase I/II clinical trials. *First Author: Natalie Ngoi, Department of Investigational Cancer Therapeutics, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Ongoing trials are exploring ATR inhibitors (ATRi) in genomically selected contexts. However, myelosuppression, particularly anemia, has limited the therapeutic window of this class of drugs. We sought to discover clinical biomarkers predicting severe hematological toxicity from ATRi. **Methods:** We retrospectively analyzed clinical parameters and peripheral blood cell indices retrieved from complete blood count (CBC) reports of patients (pts) pre- and during treatment with an oral ATRi on phase I/II trials at our center. Pts received ATRi monotherapy or in combination with a PD1 inhibitor (PD1i) or a PARP inhibitor (ATRi+PARPi) in dose-escalation and expansion cohorts, which included ATRi at potentially toxic doses. **Results:** 37553 indices from 2209 CBC reports of 141 pts treated with an ATRi from 10/2017 to 1/2022 were analyzed. 132 (93.6%) pts received ATRi +/- PD1i; 9 (6.4%) pts received ATRi+PARPi. The incidences of ≥ grade (G) 3 anemia, neutropenia and thrombocytopenia were 47.5%, 31.9% and 11.4%. 73/141 (51.8%) pts received red cell transfusion. Baseline risk factors predicting ≥G3 anemia on univariate analysis included: lower median (med) hematocrit (Hct) (hazard ratio (HR) (95% confidence interval) = 3.05 (1.82, 5.13) ≤med vs > med; p < 0.0001), hemoglobin (Hb) (HR = 2.74 (1.64,4.57) ≤med vs > med; p = 0.0001), mean corpuscular Hb concentration (HR = 1.85 (1.11,3.10) ≤med vs > med; p = 0.019); and higher median immature reticulocyte fraction (HR = 0.43 (0.25,0.71) ≤med vs > med; p = 0.0012), reticulocyte count (ct) (HR = 0.59 (0.35,0.97) ≤med vs > med; p = 0.037) and red cell distribution width (RDW) (HR = 0.54 (0.33,0.88) ≤med vs > med; p = 0.015). On multivariate analysis, lower median Hct (HR = 3.76 (2.15, 6.6) ≤med vs > med; p < 0.0001), higher immature granulocyte ct (HR = 1.71 (1.30, 2.25) per 1 fold increase; p = 0.0001), higher RDW (HR = 7.83 (1.70, 36.03) per 1 fold increase; p = 0.0082) and higher ATRi starting dose (HR = 1.40 (1.05, 1.86) per 1 fold increase; p = 0.022) significantly predicted ≥G3 anemia risk. Baseline risk factors for ≥G3 neutropenia on univariate analysis included: lower median absolute neutrophil ct (ANC) (HR = 2.26 (1.18, 4.33) ≤med vs > med; p = 0.015) or white blood cell ct (WBC) (HR = 2.73 (1.40, 5.33) ≤med vs > med; p = 0.0032). On multivariate analysis, lower median WBC (HR = 2.85 (1.45, 5.59) ≤med vs > med; p = 0.0024) was associated with higher risk of neutropenia, while ATRi+PARPi increased risk of neutropenia (ANC < 0.75) (HR = 4.15 (1.40, 12.3); p = 0.01) and thrombocytopenia (HR = 3.90 (1.47, 10.4); p = 0.0064). **Conclusions:** ≥G3 anemia was frequent in pts receiving ATRi. At baseline, lower median Hct and higher RDW predict severe anemia, while lower WBC predicts neutropenia from ATRi. ATRi+PARPi has increased risk of neutropenia and thrombocytopenia vs ATRi +/- PD1i. These indices may inform patient selection and CBC monitoring for future ATRi trials. Research Sponsor: None.

3112 **Poster Session**

A phase Ib study of the combination of alisertib (Aurora A kinase inhibitor) and MLN0128 (dual TORC1/2 Inhibitor) in patients with advanced solid tumors, final expansion cohort data. *First Author: S. Lindsey Davis, University of Colorado Cancer Center, Aurora, CO*

Background: In prior work, senescence and up-regulation of genes in the PI3K/AKT/mTor pathway were observed in patient-derived xenograft models treated with alisertib to resistance, and tumor growth inhibition was observed when MLN0128 (sapanisertib) was added to alisertib. In a previously reported dose escalation cohort of patients with advanced solid tumors treated with the combination of alisertib and MLN0128, the maximum tolerated dose (MTD) was alisertib 30mg BID days 1-7 of a 21-day cycle and MLN0128 2mg daily on a continuous schedule. Presented here are final results from the dose expansion portion of this clinical trial. **Methods:** Three cohorts of patients were treated with the combination at the MTD. Patients with advanced solid tumors, refractory to standard therapy, were assigned to either single-agent treatment with alisertib (Group 1) or MLN0128 (Group 2) on days 1-7 of Cycle 1. For the remainder of the study, patients received combination treatment. Group 3 enrolled patients with refractory pancreatic adenocarcinoma who were treated with standard dosing of the combination. Biopsies were performed in Groups 1 and 2 prior to treatment initiation and after both the single-agent lead-in and 7 days of combination treatment, with assessment of pharmacodynamic markers. Functional imaging was performed pre-treatment and after Cycle 1. **Results:** A total of 31 patients with refractory cancers were treated. Group 1 included patients with breast (5), colorectal (2), ovarian (2), and pancreatic (1) cancers. Group 2 included patients with breast (4), colorectal (2), pancreatic (2), uterine (1), and kidney (1) cancers. Eleven patients with refractory pancreatic cancer were treated in Group 3. Median time on study was 11.6 weeks in Group 1, 6 weeks in Group 2, and 9 weeks in Group 3. One partial response was documented in Group 1. One patient with pancreatic cancer in Group 1 continued on study for 47 weeks, and another pancreatic cancer patient in Group 3 continued on study for 28 weeks. Toxicity was similar across cohorts, with mucositis, fatigue, hyperglycemia and neutropenia reported as most common. Biopsy results were significant for increased apoptosis and tumor-infiltrating immune cells noted in tissues from 4 patients treated with the MLN0128 lead-in. Decreased F18-FDG uptake on PET/CT, often with increased ADC values in diffusion MRI, was observed in metastatic liver lesions in 4 patients after Cycle 1. **Conclusions:** In an expansion cohort of 31 patients treated with the combination of MLN0128 and alisertib at the previously defined MTD, treatment was tolerable with an expected toxicity profile. Prolonged stable disease was observed in 2 patients with pancreatic cancer. Increased apoptosis and tumor-infiltrating immune cells were noted in tissues from patients treated with a lead-in of MLN0128. Clinical trial information: NCT02719691. Research Sponsor: Investigator Initiated Trial Agreement between Dr. Jennifer Diamond and Takeda Pharmaceutical Company.

3113 **Poster Session**

Pan-cancer analysis of exogenous (microbial) sequences in tumor transcriptome data from the ORIEN consortium and their association with cancer and tumor microenvironment. *First Author: Daniel Spakowicz, Division of Medical Oncology, Department of Internal Medicine & Department of Biomedical Informatics, Ohio State University, Columbus, OH*

Background: The tumor microbiome holds great potential for its ability to characterize various aspects of cancer biology and as a target for rational manipulation. For many cancer types, little is known about the role of microbes and in what contexts they affect clinical outcomes. Non-human (i.e. exogenous) sequences can be observed in low abundance within high throughput sequencing data of tumors. Here, we describe a collaboration among members of The Oncology Research Information Exchange Network (ORIEN) to leverage tumor biopsy RNAseq data collected under a shared protocol and generated at a single site to better understand the tumor microbiome, its association with prognostic features of the tumor microenvironment (TME) such as hypoxia, and how it may be used to improve clinical outcomes. **Methods:** Tumor RNAseq samples from 10 primary source locations including the tissues colon, lung, pancreas, and skin from ORIEN and similar cancers from The Cancer Genome Atlas (TCGA) were processed through the exoTIC (exogenous sequencing in tumors and immune cells) pipeline to identify and count exogenous sequences, filter contaminants, and normalize across datasets. Gene expression signatures of the TME, such as hypoxia, were calculated using 'tmesig'. Microbe relative abundances were modeled with primary tumor location and hypoxia score using a gamma-distributed generalized linear regression via the stats package in R. **Results:** We analyzed RNA-seq data of 2892 and 2720 tumors from ORIEN and TCGA, respectively. Patients' ages were significantly greater in the ORIEN than the TCGA dataset (62 vs 58 yo, t-test p<0.001). The ORIEN data contained more sarcoma samples than TCGA (n = 691 vs 259) with roughly equivalent numbers in other cancer types. Fewer microbes were significantly associated with the hypoxia score than with cancer type (n = 32 vs 210). This trend was observed in both the ORIEN and TCGA datasets. The largest effect sizes were observed between microbes and small cell lung cancer. **Conclusions:** We found microbial sequences in all ORIEN and TCGA tumor RNA-seq samples tested. Cancer type showed more significant associations with microbes than a hypoxia signature. These observations merit further investigation into the interaction between microbes and the TME. Research Sponsor: None.

Cohort summary.

	ORIEN	TCGA	p
n	2892	2720	
Age (mean (SD))	58.49 (14.49)	62.02 (14.36)	<0.001
Sex = male (%)	1418 (49.0)	1371 (50.5)	0.297
Top Cancers (%)			<0.001
Thyroid Carcinoma	539 (18.6)	502 (18.5)	
Colon Adenocarcinoma	500 (17.3)	478 (17.6)	
Sarcoma	691 (23.9)	259 (9.5)	
Metastatic (%)	643 (22.2)	0 (0.0)	<0.001
Treatment Naive (%)	2284 (79.0)	2695 (99.2)	<0.001

3114 **Poster Session**

Temsirolimus (T) in patients (pts) with solid tumors with mTOR mutation: Results from the Targeted Agent and Profiling Utilization Registry (TAPUR) Study. *First Author: Gordan Srkalovic, Sparrow Cancer Center, Michigan Cancer Research Consortium, Ypsilanti, MI*

Background: TAPUR is a phase II basket study evaluating anti-tumor activity of commercially available targeted agents in pts with advanced cancers with genomic alterations. Results in a cohort of solid tumor pts with *mTOR* mutation (mut) treated with T are reported. **Methods:** Eligible pts had solid tumors, no standard treatment (tx) options, measurable disease, ECOG Performance Status (PS) 0-2, and adequate organ function. Genomic testing was performed in CLIA-certified, CAP-accredited site selected labs. Pts matched to T had various solid tumors with *mTOR* mut. After antihistamine pre-treatment, 25 mg T was infused over 30-60 minutes weekly until disease progression. Primary endpoint was disease control (DC), defined as complete (CR) or partial (PR) response, or stable disease at 16+ weeks (wks) (SD 16+) (RECIST v1.1). Low accruing histology-specific cohorts with the same genomic alteration and tx were collapsed into a single histology-pooled cohort for this analysis. For histology-pooled cohorts with sample size ≤28, the results are evaluated based on a one-sided exact binomial test with a null DC rate of 15% vs. 35% ($\alpha = 0.10$ and power=0.86 for N = 26) and one-sided 90% confidence interval (CI). Other efficacy endpoint estimates are presented with two-sided 95% CIs. Secondary endpoints were progression-free survival (PFS), overall survival (OS) and safety. **Results:** 29 pts with solid tumors (11 histologies) with *mTOR* mut were enrolled from June 2016 to June 2020. 3 pts were not evaluable (2 pts, no post-baseline tumor eval; 1 pt, no measurable disease) and excluded from efficacy analyses. The Table shows demographics and outcomes. 2 PR and 10 SD16+ were observed for a DC rate of 46% (one-sided 90% CI: 32% to 100%) and an objective response (OR) rate of 8% (95% CI: 1% to 25%); the null hypothesis of a 15% DC rate is rejected (p<0.001). 5/10 pts with SD16+ had CRC or biliary cancer. Of the 2 pts with PR, one had uterine cancer and T1977R mut and the other had head and neck cancer and I1636V mut. The durations of PR were 12.3 and 23.9 wks, respectively, and median duration of SD was 34.5 wks (range: 18.7, 90.0) for pts with SD16+. 8 pts experienced grade 3 or grade 4 AEs or SAEs at least possibly related to T, including acute kidney injury, epistaxis, hyperglycemia, hypertension, hypertriglyceridemia, mucositis, leukopenia, thrombocytopenia, and pneumonitis. **Conclusions:** Monotherapy T showed evidence of anti-tumor activity in pts with advanced solid tumors with *mTOR* mut. Additional study is warranted to confirm the efficacy of T in pts with *mTOR* mut. Clinical trial information: NCT02693535. Research Sponsor: Pfizer, Pharmaceutical/Biotech Company.

Demographics and baseline characteristics (n = 29) and efficacy outcomes (n = 26).

Median age, yrs (range)		61 (36, 78)
ECOG PS, %	0	52
	1	45
	2	3
Prior systemic regimens, %	1-2	21
	≥3	79
DC rate, % (OR or SD16+) (one-sided 90% CI)		46 (32, 100)
OR rate, % (95% CI)		8 (1, 25)
Median PFS, wks (95% CI)		13.6 (8.1, 27.7)
Median OS, wks (95% CI)		45.3 (27.4, 61.4)

3115 **Poster Session**

Genomic and clinical characteristics of *MET* alterations in solid tumors among the 10,475 Chinese patients. *First Author: Yaping Li, AcornMed Biotechnology Co., Beijing, China*

Background: Somatic alterations of the MET oncogene are emerging as an attractive target in human cancers, thus, understanding the molecular epidemiology of MET alterations is essential. While the occurrence of MET exon 14 skipping mutations (MET ex14) in US lung cancer patients is well defined, it is not widely published for Chinese patients. In addition, reports on the occurrence of METex14 outside lung cancer and other clinically relevant MET alterations across all cancers are limited. **Methods:** The *MET* ex14 alterations and amplification data of 10475 Chinese cancer patients from 16 types of cancer were obtained in Acronmed database, including non-small cell lung cancer (NSCLC, n = 5719), Hepatocellular carcinoma (HCC, n = 511), colorectal cancer (CRC, n = 1779), renal cell carcinoma (RCC, n = 1169), Gastric carcinoma (GC, n = 679), etc. Genomic profiling of DNA was performed through a next-generation sequencing. **Results:** Of all pan-cancer patients, 141 cases (1.3%) with *MET* alterations were identified, including *MET* Amp (0.9%) and *MET* ex14 (0.7%). Compared to Western population (~3%), the frequency of *MET* alterations is much lower in Chinese cancer patients (1.3%). *MET* Amp were most commonly found in HCC (1.7%), GC (1.3%), NSCLC (0.7%), RCC (0.7%), CRC (0.2%). *MET* ex14 occurred most in NSCLC (0.5%), HCC (0.3%), CRC (0.2%). HCC were significantly to have *MET* Amp than NSCLC (P = 0.01), while *MET* ex14 mutations were more likely to be observed in NSCLC (p = 0.02). We further analyzed the *MET* mutation characteristics of NSCLC. The most frequently co-mutated genes in *MET* ex14 cohort were *TP53* (48%,15/31), *KMT2B* (23%,7/31) and *EGFR* (16%, 5/31). Except for *TP53* (65%,22/34) and *EGFR* (56%,19/34) mutations. Interestingly,other gene mutations were rare in the patients with *MET* Amp. In addition, *MET* ex14 patients showed significant lower *EGFR* mutation comparing to the *MET* amp patients (P = 0.002). **Conclusions:** Our study demonstrated a landscape of *MET* alterations among the Chinese population. *MET* mutations occurs in a variety of solid tumors, indicating that these patients may benefit from *MET* inhibitors. Research Sponsor: None.

3116 **Poster Session**

Variable detection of actionable alterations across racial groups and association with testing patterns. *First Author: Emma Sturgill, Sarah Cannon Research Institute, Nashville, TN*

Background: Molecular landscape studies are critical to biomarker discovery and precision oncology research. However, non-White patients (pts) have historically been under-represented. In this study, we examine clinico-genomic data from a network of community oncology clinics to evaluate real-world mutational frequencies in Black, White, and Asian pts with cancer. **Methods:** We utilize Genospace, a precision medicine software, to harmonize clinical data from the Sarah Cannon research network of U.S. community oncology practices with genomic data from commercial NGS vendors. Pts with known race and NGS test results from September 2015 to November 2021 are assessed. Variants of uncertain significance (called by NGS vendor) are excluded. Asian pts are not evaluable in all instances because of low pt number. Statistical analyses include Chi squared and two sample test of proportions with Benjamini-Hochberg false discovery rate correction. **Results:** A total of 18,399 pts are assessed, with 7% Black (n = 1,319), 92% White (n = 16,903), and 1% Asian (n = 177) pt representation. The most common tumor types include non-small-cell lung (NSCLC; 27% of Black pts, 30% of White pts, 33% of Asian pts), colorectal (15% of Black pts, 12% of White pts, 14% of Asian pts), breast (14% of Black pts, 11% of White pts, 9% of Asian pts), and prostate (6% of Black pts, 5% of White pts, 3% of Asian pts) at roughly equal proportions across racial groups. In NSCLC, EGFR mutations and ALK fusions significantly enrich in Asian pts while KRAS G12C is detected more frequently in Black patients (see table for details; Black: n = 353, White: n = 5,127, Asian: n = 58). In both prostate and breast cancers, plasma-based NGS is less common in Black pts than White pts (plasma-to-tissue ratio = 1.1 (Black prostate: n = 82); 1.5 (White prostate: n = 863); 0.6 (Black breast: n = 178); 0.9 (White breast: n = 1,918)). In prostate, AR mutations are detected less frequently in Black pts. However, when considering plasma-NGS results alone the detection frequency is roughly equal. Similarly, the gap in ESR1 detection frequencies in breast decreases when considering plasma-NGS results alone. **Conclusions:** Actionable alterations are detected across racial groups at variable frequencies with potential biological and technical underpinnings. In scenarios where plasma-NGS is commonly used to monitor for resistance mutations, discrepancies in NGS ordering patterns likely affect detection frequencies. Research Sponsor: None.

Select gene alteration frequencies across racial groups.

	Black	White	Asian
NSCLC EGFR mutation*	9%	9%	43%
NSCLC KRAS G12C	11%	9%	5%
NSCLC ALK fusion*	1%	1%	5%
Prostate AR mutation	13%	17%	-
Prostate AR mutation (plasma)	22%	22%	-
Prostate AR mutation (tissue)*	3%	8%	-
Breast ESR1 mutation	11%	18%	-
Breast ESR1 mutation (plasma)	20%	25%	-
Breast ESR1 mutation (tissue)	3%	11%	-

*$p < 0.05$.

3117 **Poster Session**

Stress keratin 17 as a novel biomarker of response in immune checkpoint blockade–treated head and neck squamous cell carcinoma. *First Author: Taja Lozar, University of Wisconsin-Madison, Madison, WI*

Background: Low response rates in immune checkpoint blockade (ICB) treated head and neck squamous cell carcinoma (HNSCC)drive a critical need for robust clinically validated biomarkers that can predict response to ICB. Stress keratin 17 (K17) is a known prognostic marker in various types of cancer, including HNSCC; however, its predictive value for ICB response has not been investigated. Preclinical studies suggest K17 suppresses macrophage-mediated CXCL9/CXCL10 chemokine signaling involved in attracting activated CD8+ T cells into tumors. Furthermore, knocking out K17 results in restored response to ICB in a HNSCC mouse model. Here, we evaluated if K17 protein expression predicts response to ICB in human HNSCC patients. **Methods:** We conducted a retrospective analysis of 26 HNSCC patients that received at least one cycle of pembrolizumab at the University of Wisconsin-Madison Carbone Cancer Center. Pretreatment, archival, formalin-fixed, paraffin-embeded samples were stained by immunohistochemistry using a K17 monoclonal antibody. Clinical outcomes were investigator-assessed for all patients with at least one post-treatment scan or evidence of clinical progression after treatment initiation. Based on independent pathology review, cases were categorized into K17 high vs K17 low based on a cut-off of > 5% strong cytoplasmic staining intensity of tumor cells in the invasive carcinoma component. Correlation between K17 expression and clinical outcomes was assesed using Fischer's exact test and log rank test. **Results:** The 26 patients included in this study were 85% male, median age 60.5 years, 74% ECOG performance status < 2, with 80% having received prior chemotherapy. Primary site included oral cavity (54%), oropharynx (23%), larynx (4%), or other (19%). Seventeen tumors (65%) showed high K17 expression, and 9 tumors (35%) showed low K17 expression. Eleven patients (42%) had programmed death ligand 1 (PD-L1)+ tumors as determined by combined positive score. Six patients (23%, all K17 low) achieved clinical benefit, while 20 patients (77%, 17 K17 high and 2 K17 low) had progressive disease. High K17 expression was associated with lack of clinical benefit ($p < 0.001$), shorter time to treatment failure ($p < 0.001$), progression-free ($p = 0.004$) and overall survival ($p = 0.02$). PD-L1 expression by immunohistochemistry (clone 22C3) did not correlate with K17 expression or clinical outcome. **Conclusions:** Our findings suggest that K17 expression may predict clinical benefit from ICB in HNSCC patients, thus supporting further validation studies. Research Sponsor: U.S. National Institutes of Health.

Response Status	K17 High		K17 Low		Total	
Clinical benefit	0	(0.0%)	6	(75.0%)	6	**(23.1%)**
Progressive disease	18	(100.0%)	2	(25.0%)	20	**(76.9%)**
All	**18**		**8**		**26**	

3118 **Poster Session**

Genomic landscape of SMARCA4-deficient lung tumors by clinical RNA sequencing. *First Author: Brian Pham, University of California-Davis, Sacramento, CA*

Background: SMARCA4-deficient lung cancer is an undifferentiated lung cancer subtype associated with poor prognosis and morphological features that make them challenging to distinguish from sarcoma. These tumors are known to be resistant to standard of care surgery, radiation, and chemotherapy. Recent case reports suggest that these tumors might be resistant to immunotherapy. An assessment of the genomic and transcriptomic features of *SMARCA4*-deficient thoracic tumors may identify potential novel targets and treatment strategies for this new WHO lung cancer classification. **Methods:** We retrospectively analyzed de-identified NGS data from 8,484 thoracic formalin-fixed, paraffin-embedded tumor biopsies from lung cancer patients sequenced using the TempuslxT solid tumor assay (DNA-seq of 595-648 genes at 500x coverage; whole-exome capture RNA-seq). Tumor-normal match sequencing was performed for all tumors, enabling the detection of incidental germline alterations across 46 genes. SMARCA4-deficiency was defined as tumors with a pathogenic or likely pathogenic *SMARCA4* single nucleotide variant, insertion/deletion, or copy number alteration. Statistical significance was determined using Fisher's exact test and Wilcoxon rank-sum tests. **Results:** *SMARCA4*-deficiency was detected in 370 (4.4%) tumors, of which over 80% were stage III or IV. *SMARCA4*-deficient tumors included more male patients (63% vs 49%, $p < 0.001$) and younger age at diagnosis (median 64 vs 68 years, $p < 0.001$). There were more patients with high tumor mutational burden (TMB-H, ≥10 mutations per megabase) (34% vs 15%, $p < 0.001$), and fewer patients with positive PD-L1 immunohistochemical staining (44% vs 54%, $p = 0.009$) compared to *SMARCA4* wild-type tumors. Microsatellite instability status occurred at similar low frequencies across SMARCA4-deficient vs wild-type tumors (0.8% vs 0.5%, $p = 0.5$). *SMARCA4*-deficient tumors showed enrichment for somatic mutations in *TP53* (71% vs 47%, $q < 0.001$), *STK11* (22% vs 6.8%, $q < 0.001$), *KEAP1* (15% vs 4.2%, $q < 0.001$), and *CDKN2A* (15% vs 5.9%, $q < 0.001$) compared to wild-type. Tumor normal-match sequencing identified incidental germline mutations in *MUTYH* (2.2%), *ATM* (1.1%), *ATP7B* (0.5%), and *MSH6* (0.5%) for *SMARCA4*-deficient tumors. RNA-sequencing analysis confirmed reduced transcriptional expression of *SMARCA4* ($p < 0.001$), *CD274* (PD-L1; $p < 0.001$), *TNFRSF18* ($p < 0.001$), and *TNFRSF4* ($p = 0.035$) in deficient tumors vs wild-type. Furthermore, *SMARCA4*-deficient tumors revealed reduced infiltration of CD4+ T cells (19% vs 22%, $p < 0.001$). **Conclusions:** This study reveals the unique genomic and transcriptional characteristics of *SMARCA4*-deficient lung tumors. Further studies are needed to assess the impact of immunotherapies and targeted therapies among this patient population. Research Sponsor: Tianhong Li.

3119 **Poster Session**

Clinical utility of tumor next-generational sequencing (NGS) panel testing to inform treatment decisions for patients with advanced solid tumors. *First Author: Lucia Bogdan, Department of Internal Medicine, University of Toronto, Toronto, ON, Canada*

Background: There is limited information about the clinical utility of targeted NGS panel testing to inform decision-making for patients with advanced solid tumors. The Ontario-wide Cancer Targeted Nucleic Acid Evaluation (OCTANE) is an ongoing prospective study that enrolled over 4,500 solid tumor patients for NGS panel testing. We performed a retrospective survey of 21 medical oncologists enrolling OCTANE patients at a single academic institution to evaluate the impact of NGS testing on treatment decisions. **Methods**: Patients and treating oncologists were identified at the Princess Margaret Cancer Centre between 2016-2021. Tumor-only sequencing was performed using a custom hybridization capture panel of 555 cancer genes (Hi5) or a commercial 161-gene amplicon DNA/RNA panel (Oncomine Comprehensive v3). Oncologists were asked to review testing results for individual patients and complete a survey indicating whether NGS testing impacted treatment decisions. Mutations were defined as actionable based on clinical judgment and compared to classifications provided by OncoKB, an FDA-recognized precision medicine knowledgebase. The primary outcome of this study was rate of treatment change based on mutation results. Patient, test, and physician factors were evaluated for association with treatment changes using univariate analyses and a mixed effects model. **Results:** Two cohorts were surveyed, the first between 2017-2019 and the second in 2021. Of the 582 surveys sent, 394 (67.7%) were completed. Each physician completed a median of 19 surveys (range, 9-48). We found that 188 (47.7%) patients had a mutation classified as actionable by the oncologist, of whom 134 (71.3%) had ≥1 OncoKB-defined actionable mutation(s). 62/394 (15.7%) patients were matched to a treatment, of whom 37 were enrolled in a clinical trial, 13 received an approved drug, 4 were prescribed off-label therapy and 8 avoided ineffective treatment. 127/188 (67.5%) patients with actionable mutations did not receive treatment due to lack of available therapy, stability on current regimen, clinical deterioration or patient decision. Rate of treatment change was highest for bowel (15/37, 40.5%), breast (14/52, 27.5%), biliary tract (6/22, 27.3%) and lung (4/17, 23.5%) cancers. Treatment decisions were not associated with patient age, gender, physician clinical experience, physician gender, testing experience, OncoKB mutation level or time from biopsy to sequencing. There was no difference in overall survival between patients with matched vs. no matched treatment ($p = 0.55$, median survival not reached). **Conclusions:** OCTANE testing led to a change in drug treatment in 15.7% of patients, supporting the clinical utility of NGS panel testing for patients with advanced solid tumors. Patient, test, and physician characteristics were not significantly associated with treatment change. Research Sponsor: This study was conducted with the support of the Ontario Institute for Cancer Research through funding provided by the Government of Ontario and by the Princess Margaret Cancer Foundation.

3120 **Poster Session**

Pan-cancer association between increased iron utilization and poor prognosis highlights potential of transferrin receptor-targeting therapies in multiple tumor types. *First Author: Asaad Trabolsi, University of Miami/Jackson Memorial Hospital, Miami, FL*

Background: The cell-surface transferrin receptor TFR1 imports iron-bound transferrin into cells via clathrin-mediated endocytosis. Tumors require constitutive iron import to drive proliferation, and several studies establish TFR1 as a target able to facilitate intracellular delivery of cytotoxic therapeutic molecules. Our own work previously revealed association between high expression of *TFRC*, the gene encoding TFR1, and high risk for poor outcome in diffuse large B-cell lymphoma (DLBCL). We showed therapetuic targeting of TFR1 in DLBCL results in significant anti-tumor benefit. Systematic analysis of *TFRC* expression as a prognostic marker across tumor types, however, has not been investigated. **Methods:** Tissue samples underwent comprehensive molecular profiling at Caris Life Sciences. Analyses included next generation sequencing of DNA (592 Gene Panel, NextSeq, or whole exome sequencing, NovaSeq), RNA (NovaSeq, whole transcriptome sequencing, WTS) and immunohistochemistry. Overall survival (OS) was calculated from date of tissue collection to last contact from insurance claims data and employed Kaplan-Meier analysis by Wilcoxon statistics, with $p < 0.05$ defined as significant. **Results:** Amongst 47 cancer types included, colorectal cancer (CRC) displayed the highest level of *TFRC* mRNA, followed by gastric cancer. In an all-tumor cohort (n = 93248), patients with higher *TFRC* expression (cutoff = median) had significantly worse OS (HR = 1.348, 95% CI [1.317-1.38] , $p < 0.00001$). This was statistically significant in 23 individual tumor types. Drilling down further, *TFRC* adverse prognostic value was mainly driven by cohorts with larger number of samples in the database, including non-small cell lung cancer (n = 17309), CRC (n = 12860), breast cancer (n = 8632), ovarian carcinoma (n = 7998), uterine neoplasms (n = 6097), prostate adenocarcinoma (n = 3411), glioblastoma (n = 2821), gastric cancer (n = 1579), and others. Surprisingly, *TFRC* overexpression correlated with improved outcome in vulvar squamous cell carcinoma (VSCC, n = 297). *TFRC* was found to be most prognostic in prostate adenocarcinoma with median OS 1139 days in pts with high vs 3230 days in pts with low *TFRC* (HR = 2.556, 95% CI [2.213-2.951], $p < 0.00001$). **Conclusions:** Our study is the first to combine modern molecular profiling with a large cohort of clinical tissue samples to reveal a prognostic role for *TFRC* expression in a variety of solid tumor types. We found *TFRC* overexpression to be prognostic in a large proportion of histologies, though surprisingly association with improved OS in VSCC. Highest expression occured in CRC and gastric cancer, diseases with needs for new therapies. A number of TFR1-targeting therapeutics are currently at various stages of development, and warrant further investigation in disease cohorts identified from our study. Research Sponsor: None.

3121 **Poster Session**

Molecular characterization of cancers with *ALK* gene fusions in nonlung tumors. *First Author: Jin Zhang, Department of Thoracic Surgery, China-Japan Friendship Hospital, Beinjing, China*

Background: *ALK* gene rearrangement is known as "diamond mutation". Targeted tyrosine kinase inhibitors have perfect therapeutic effects on *ALK* fusion lung cancer patients (pts), but the molecular characteristics of *ALK* fusions in other cancers have not been systematically elucidated. **Methods:** We retrospectively analyzed the NGS data of *ALK* fusion-positive Chinese tumor pts (n = 1068) to characterize *ALK* fusions in pan-cancer (excluding lung cancer) pts. **Results:** A total of 66 *ALK* fusion-positive pts with 13 types of cancer (excluding lung cancer) were screened, including 0.4% (24/5800) of brain tumor pts, 0.1% (11/7725) of gastrointestinal cancer pts, 0.4% (7/1741) of thyroid cancer pts, 0.5% (8/1732) of sarcoma pts, 0.2% (4/2031) of liver cancer pts, 0.6% (3/540) of melanoma pts, 9% (2/22) of inflammatory myofibroblastic tumor pts, 2.5% (2/79) of embryonal tumor pts, 0.4% (1/282) of lymphoma pts, 3.2% (1/31) of parotid carcinoma pts, 0.1% (1/985) of breast cancer pts, 0.4% (1/241) of prostatic cancer pts and 0.3% (1/320) of ovarian cancer pts. Herein, we reported 28 *ALK* fusion patterns, of which the most common partners were *EML4* (n = 24) and *STRN* (n = 8), and mainly occurred in brain tumors (14/24, 58.8%) and thyroid cancers (6/8, 75%), respectively. In addition, there were 8 *ALK* fusion modes that were never reported before. Of the *ALK* fusion patterns described above, 92.4% (61/66) of fusions were located at the most canonical site of *ALK* (exon20), preserving the intact kinase domain. Meanwhile, rare fusion positions in the *ALK* gene were also found, such as *PPP1CB-ALK*(ex2:ex4), *NUP107-ALK*(ex20:ex3), *COL14A1-ALK*(ex8:ex4), *BRAF-ALK*(ex9:ex4), which preserve the extracellular and transmembrane domains, as well as *RASD2-ALK*(ex2:ex24), of which the breakpoint in *ALK* gene may disrupt the formation of kinase domain. **Conclusions:** We demonstrated the rarity of *ALK* gene fusions in nonlung cancers. Analyzing the *ALK* fusion characteristics of these cancer may help to clarify their pathogenesis and provide ideas for new drug treatment. Research Sponsor: None.

Partners of *ALK* gene fusions.

	Partners	Counts	Partners	Counts	Partners	Counts	Partners	Counts
Known fusions	*EML4*	24	*KIF5B*	2	*FN1*	1	*TIMP3*	1
	STRN	8	*PPP1CB*	2	*KLC1*	1	*TPM3*	1
	DCTN1	3	*TPM4*	2	*PLEKHH2*	1	*LCLAT1*	1
	NPM1	3	*CLIP2*	1	*PRKAR2A*	1	*PABPC1*	1
	ATIC	2	*CLTC*	1	*RANBP2*	1	*HMBOX1*	1
Unreported fusions	*AMN*	1	*GTF2I*	1	*RASD2*	1		
	BRAF	1	*NUP107*	1	*TBC1D16*	1		
	COL14A1	1	*ZKSCAN1*	1				

3122 **Poster Session**

Results of a phase II trial of the PARP inhibitor, niraparib, in BAP1 and other DNA damage response pathway deficient neoplasms. *First Author: Thomas J. George, The University of Florida Health Cancer Center, Gainesville, FL*

Background: BRCA1-Associated Protein 1 (BAP1) acts as a tumor suppressor and critical regulator of the cell cycle and DNA damage response (DDR). PARP inhibitors (PARPi) demonstrate synthetic lethality in BAP1 mutant (mBAP1) preclinical models, independent of underlying germline BRCA status. mBAP1 leads to a loss of functional protein in several solid tumors. This study aimed to explore the clinical activity of niraparib in patients (pts) with advanced tumors likely to harbor mBAP1. **Methods:** Eligible adult pts with measurable metastatic solid tumors having exhausted approved therapies, adequate organ function, and ECOG PS 0-1 were assigned to Cohort A (histology-specific): tumors likely to harbor mBAP1 (i.e., cholangiocarcinoma, uveal melanoma, mesothelioma, or clear cell renal cell carcinoma) with tissue available for mBAP1 confirmation; or Cohort B (histology-agnostic): tumors with other known non-BRCA confirmed DDR mutations. Known BRCA1 or 2 mutations or prior PARPi exposure were excluded. All pts received niraparib 200-300mg daily, depending on weight and/or platelet count. Radiographic response was assessed by RECIST v1.1 measured every 8 weeks while on treatment. The primary endpoint was ORR with secondary endpoints of PFS, OS, clinical benefit (CR+PR+SD), toxicity, and exploratory biomarker determinations. Cohort A employed Simon's optimal two-stage design to assess a 30% ORR increase ($a = 0.05$; power = 90%). Cohort B aimed to assess a 40% ORR increase for this molecularly selected/enriched patient population. **Results:** From 08/13/2018 to 12/21/2021, 37 pts enrolled from two different centers, with 32 evaluable for response (Cohort A n = 18; Cohort B n = 14). In Cohort A, best ORR was 1 PR (6%), 8 SD (44%; median 5.7 mo; range 2 - 9.4 mo), and 9 PD (50%). Cohort A was stopped at the first stage following the pre-specified Simon's design. mBAP1 was confirmed in 7/9 pts (78%) with PR or SD but in only 2/9 (22%) in those with PD. In Cohort B, best ORR was 6 SD (43%; median 7.5 mo; range 3.3 - 8.6 mo) and 8 PD (57%). Mutations in those with SD included ATM, CHEK2, PTEN, RAD50, and ARID1A. Common grade 3/4 AEs observed were anemia (16%), thrombocytopenia (16%), nausea (11%), and vomiting (8%). There were no unexpected nor grade 5 toxicities. **Conclusions:** The use of niraparib was well tolerated in pts with advanced treatment refractory solid tumors but failed to meet pre-specified efficacy threshold of ORR. However, clinical benefit was identified in 78% of patients in cohort A who had a confirmed mBAP1 tumor. Further correlative analyses are ongoing and additional clinical development restricted to mBAP1 tumors may be justified. Clinical trial information: NCT03207347. Research Sponsor: University of Florida Health Cancer Center and GlaxoSmithKlein.

3123 **Poster Session**

Inference of sample-specific genetic interactions to increase accuracy of indication prioritization in oncology clinical trials and facilitate exploration of combined therapy opportunities. *First Author: Sarah Jenna, My Intelligent Machines Inc., Montreal, QC, Canada*

Background: Precision oncology is growing rapidly in parallel with advances in high throughput sequencing. Development of new anti-cancer therapies is, however, still associated with low efficacy issues, leading to phase II and III clinical trial failures. Improved methodologies are required to identify clinical and molecular patient profiles associated with good drug response to inform decisions on indication prioritization. **Methods:** We used a sample-specific Genetic Interaction Graph Inference ($ssGI^2$) algorithm, integrating bulk tumor transcriptomic data as well as data collected from 120 public databases and scientific literature in oncology, to infer genetic interactions (GI). More than 10,000 genes from 17,000 samples, covering 195 oncology ICD10 codes, were used to infer GIs for each individual sample. GIs involving a given drug target are selected from a compendium of 17,000 networks of 2M GIs each, and ranked based on their prevalence in the patient cohort and data-support. The mean Z-scored expression of genes from the top ranked GIs were subsequently used to predict drug response for each patient and to calculate the response rate for each indication. Detailed information on each drug target's genetic interactors was used to characterize the drug's mechanisms of action and explore opportunities for combined therapies. We investigated our method's ability to predict good responders using four FDA approved immune and targeted therapies (pembrolizumab, nivolumab, ipilimumab and sorafenib) across seven clinical studies. Importantly this methodology is suitable for drugs with no clinical studies available. **Results:** Our results show that the prediction of good responders can be achieved with Precision-Recall AUC on average 13% higher than predictions based on drug target expression level solely, in five out of seven studies. Also, for each drug target, between 30 to 140 genetic interactors with good performance (Precision=0.92; Recall=0.61) were identified, suggesting potential synergistic effects of drugs, some of which have already been confirmed by clinical studies on combined therapies. **Conclusions:** Our $ssGI^2$-derived signatures are powerful predictors of good response to a drug even without available clinical data. Applying this methodology at a pre-clinical stage will significantly de-risk clinical trials, particularly for novel therapies, and could also support investigation of new combined therapies. Research Sponsor: My Intelligent Machines Inc.

3124 **Poster Session**

Comprehensive genomic profiling to identify gene alterations in DNA repair pathway across solid tumors. *First Author: Kevin J. McDonnell, City of Hope, Duarte, CA*

Background: Deleterious events in DNA damage response (DDR) are hallmarks of cancer associated with sensitivity to PARP inhibitors (PARPi) and immune checkpoint inhibitors (CPI). This study investigated DDR pathway alterations across solid tumors. **Methods:** Samples were sequenced with the Oncomap ExTra assay using tumor-normal paired whole-exome DNA sequencing to detect single base substitutions, indels, and copy number alterations that were clinically actionable, defined as associated with FDA approved drugs or clinical trial enrollment. Here, we report the frequency of MSI-high and TMB-high (>10 mutations/Mb), and clinically-actionable alterations for the following 49 DDR genes: *ARID1A, ATM, ATR, ATRX, BAP1, BARD1, BLM, BRCA1/2, BRIP1, CDK12, CHEK1/2, EPCAM, ERCC1/2/3/4/5, FANCA/C/D2/E/F/G/I/L/M, MLH1, MRE11A, MSH2/6, MUTYH, NBN, PALB2, PMS2, PPP2R2A, PTEN, RAD21/50/51/51B/51C/51D/52/54L, XRCC1/2/3*. **Results:** Of the 6055 patient samples profiled, 1633 (27.0%) had clinically actionable alterations in DDR genes; DDR alterations varied from 0-64.3% across tumor types. For the 5657 samples with TMB/MSI data, 429 (7.6%) had high TMB and 193 (3.4%) were MSI-high; MSI-high samples were usually TMB-high (n = 180; 93.2%). The percent of cancers that were TMB-high or MSI-high varied from 0-64.8% and 0-20.8% respectively. Actionable *BRCA1/2* gene alterations were present in 319 patients (5.3%, range 0-15.3%). Three cancers (biliary, brain and liver) had *BRCA1/2* alterations in less than 2% of patients but across the 49 DDR genes alterations were present in more than 20% of patients, representing a greater than 10-fold difference. Across solid tumors, this analysis identifies a group of 1314 patients (21.7%) who harbor a DDR gene alteration other than *BRCA1/2*. **Conclusions:** Defective DNA repair as detected by deleterious alterations in DDR genes along with TMB/MSI status has the potential to guide clinicians to FDA-approved therapy or clinical trial enrollment in a large percentage of patients across solid tumor types. Research Sponsor: Exact Sciences Corporation.

Number (percent) of patients with alterations in DDR, TMB-High and MSI-High.

Tumor Type	Total	All DDR genes	BRCA1/2	TMB-high	MSI-High
ALL	6055	1633 (27.0%)	319 (5.3%)	429 (7.6%)	193 (3.4%)
Biliary	89	28 (31.5%)	1 (1.1%)	0	0
Brain	264	102 (38.6%)	5 (1.9%)	3 (1.6%)	2 (1.1%)
Breast	1103	246 (22.3%)	69 (6.3%)	16 (1.5%)	2 (0.2%)
Endometrial	184	115 (62.5%)	13 (7.1%)	41 (23.0%)	37 (20.8%)
Epithelial Ovarian	275	90 (32.7%)	42 (15.3%)	5 (2.0%)	4 (1.6%)
Melanoma	188	65 (34.6%)	4 (2.1%)	69 (37.7%)	1 (0.5%)
Prostate	313	91 (29.1%)	22 (7.0%)	9 (2.9%)	8 (2.6%)
Stomach	156	51 (32.7%)	8 (5.1%)	21 (14.4%)	21 (14.4%)

3125 **Poster Session**

Molecular and immune landscape of *FH*-mutated cancers. *First Author: Bayan A Al-Share, Barbara Anna Karmanos Cancer Institute, Livonia, MI*

Background: Fumarate Hydratase (FH) encodes an essential enzyme in the TCA cycle. Inactivating germline mutations in FH lead to hereditary leiomyomatosis and renal cell cancer syndrome with risk of development of certain cancers. Sporadic FH mutations have been described in different cancers but implications of somatic mutations on cancer outcomes and survival are not well described. Here, we characterize the molecular landscape of FH-mutant cancers. **Methods:** Tumors analyzed using NGS (NextSeq, 592 genes; NovaSeq, WES), IHC, and WTS (NovaSeq) (Caris Life Sciences, Phoenix, AZ). PD-L1 tested by 22c3, 28-8 (Agilent) and SP-142 (Spring Biosciences) IHC (>1%). MSI tested by FA, IHC, and NGS. TMB measured by totaling somatic mutations per tumor (TMB-h > 10 mutations/MB). Real-world overall survival was extracted from insurance claims data and calculated from first treatment to last contact using K-M survival curves for molecularly defined cohorts. Statistical significance was determined using chi-square and Wilcoxon rank-sum test, adjusted for multiple comparisons ($q<0.05$). **Results:** 3239 *FH* mutations were seen in 45 tumor types in 3149 FH-mutated tumors. NSCLC, colorectal and endometrial cancers harbored the most mutations. There were 839 pathogenic (P) or likely pathogenic (LP) and 2400 variants of unknown significance (VUS). Some tumors had multiple mutations. The most common mutations: R233H (P; 37), K477dup (LP; 555), and A41V (VUS; 70). VUS had increased TMB-H (40.4% vs 29.8%, q=0.004) and *CREBBP* mutations (5.1% vs 1.6%, q=0.012) compared to P+LP. A41V-mt tumors had significantly lower TMB-H than other VUS (8.8% vs 41.5%, q=0.002) and lower MSI-H (3.13% vs 3.69% vs 29.4%, q=0.003) and *DICER1*, *PRKDC*, *FBXW7* mutations ($q<0.05$) compared to K477dup and R233. The A41V-mt patients had worse survival compared to patients with P+LP (HR: 1.4, 95% CI: 1.0-2.0, p = 0.049) and a trend toward worse survival compared to K477dup and R233H. In patients treated with chemotherapy, A41 was associated with worse survival compared to P+LP (HR: 4.6, 95% CI: 2.0-10.3, $p<0.0001$) and compared to K477dup and R233 ($p<0.01$). There was a trend towards worse survival after IO of A41-mt compared to P+LP (HR: 1.99, 95% CI: 0.88-4.5, p = 0.093). **Conclusions:** FH alterations are found in multiple cancers. A41V was the most common VUS mutation and is associated with a distinct molecular profile compared to K477dup-mt and R233-mt tumors; it was associated with worse survival in all-comers and after chemotherapy compared to P+LP mutations. This highlights the significance of this mutation and the need for further investigation into how this specific and other FH mutations contribute to cancer progression and treatment outcomes. Research Sponsor: None.

3126 **Poster Session**

Insights of clinical significance from solid tumor profiles with FoundationOne CDx. *First Author: Andreas M. Heilmann, Foundation Medicine, Inc., Cambridge, MA*

Background: FoundationOne CDx (F1CDx) is a US FDA-approved companion diagnostic test to identify patients who may benefit from treatment in accordance with the approved therapeutic product labeling for 28 drug therapies. Tumor profiling with F1CDx detects genomic findings with evidence of additional clinical significance. This study analyzes the breadth and impact of clinical decision insights from F1CDx clinical reports across solid tumors. **Methods:** F1CDx consecutive reports (n = 109,695) were retrospectively analyzed for the type and frequency of clinically significant predictive, prognostic, and diagnostic genomic alterations and signatures in common cancer types and across solid tumors. Predictive markers were defined as therapeutically relevant markers in drug labels or NCCN guidelines or targets of ESCAT evidence Tier I/II (Mateo et al., 2018; PMID: 30137196). Prognostic and diagnostic markers were determined in accordance with NCCN, ESMO, or WHO guidelines. We also describe the frequency and targets of interventional clinical trials with targeted therapies or immune checkpoint inhibitors that were matched to tumor profiles based on clinical or strong preclinical evidence. **Results:** Predictive genomic findings of clinical significance were identified in more than half of non-small cell lung cancer (NSCLC), colorectal cancer (CRC), breast cancer (BC), and melanoma (MEL) tissue samples; over a third of ovarian cancer (OC), urothelial carcinoma (UC), and head and neck squamous cell carcinoma (HNSCC); approximately a fourth of prostate cancer (PC), gastro-esophageal adenocarcinoma (GEA), cholangiocarcinoma (CA), and glioma (GL) samples; and one in 18 pancreatic adenocarcinoma (PA) samples (Table). Prognostic markers were reported for patients with NSCLC (18%), CRC (10%), BC (16%), PC (25%), CA (8.1%), MEL (24%), GL (74%), or HNSCC (7.1%). Diagnostic markers were frequently detected for patients with GL and noted for patients with BC, GEA, or MEL (Table). Interventional clinical trials were evidence-matched to most F1CDx tumor profiles (89%, range 82% in PC to 99% in PA), with the targets of approved therapies accounting for a small subset of targets in clinical development. **Conclusions:** F1CDx reports support clinical decision making by interpreting predictive, prognostic, and diagnostic markers according to professional guidelines as well as investigational markers for the enrollment in clinical trials. Research Sponsor: Foundation Medicine, Inc.

Frequency of predictive, prognostic, and diagnostic markers of clinical significance by cancer type in F1CDx reports (N total reports, na not applicable).

Cancer Type	N	Predictive	Prognostic	Diagnostic
NSCLC	22152	59.8%	18.4%	na
CRC	13193	64.7%	10.3%	na
BC	11016	54.2%	16.3%	14.4%
OC	6999	36.2%	na	na
PC	6513	27.3%	24.7%	na
PA	6168	5.5%	na	na
GEA	4762	22.8%	na	6.2%
UC	3236	46.7%	na	na
CA	2901	24.0%	8.1%	na
MEL	2743	79.7%	24.1%	3.6%
GL	2350	24.1%	74.0%	80.6%
HNSCC	1787	38.4%	7.1%	na

3127 **Poster Session**

Molecular reflex testing in non-small cell lung cancer: An optimal approach? *First Author: Kari Hooper, AmeriPath, Oklahoma City, OK*

Background: Molecular testing of non-squamous non-small cell lung cancer (NSCLC) tumors can guide appropriate treatment decisions and improve patient outcomes, but guideline complexity and frequent revision may negatively affect adherence. To assist oncologists in making timelier informed treatment decisions, we implemented a pathologist-directed molecular reflex pathway for non-squamous NSCLC at our clinical laboratory. Testing patterns and adherence to NCCN testing guidelines before and after implementation were reviewed. **Methods:** This retrospective cohort analysis included patients with diagnosed NSCLC who had molecular testing performed without a molecular reflex testing pathway in place (April 2016-March 2018, cohort A) and after the pathway was implemented (April 2018-March 2020, cohort B) at our clinical laboratory. TATs were calculated using dates of biopsy specimen submission and of molecular testing completion. Molecular testing methods (e.g., polymerase chain reaction, next-generation sequencing [NGS]), genetic alterations tested for and identified, PD-L1 by immunohistochemistry, and specimen quantity not sufficient (QNS) for testing were obtained from patients' clinical laboratory reports. NSCLC diagnosis and cancer stage were obtained from electronic medical records, and adherence to NCCN guidelines (i.e., under-tested, over-tested genetic alterations) was evaluated according to specimen submission. **Results:** The mean TAT was 35.1 days for cohort A (n = 123) and 15.8 days for cohort B (n = 168), though the median in both was 14 with a range of 6 – 674 days in cohort A and 9 – 44 in cohort B (Table).Targetable genetic alterations were identified in 12.4% of patients in cohort A and 61.3% in cohort B; 46.3% in cohort A and 60.1% in cohort B had ≥1% positive *PD-L1* staining. QNS results declined from 16.7% (n = 20) in cohort A to 12.5% (n = 21) in cohort B. Non-NCCN guideline testing was observed in 86.7% of patients in cohort A and 25.6% in cohort B, with those in cohort A being primarily under-tested (70%) and those in cohort B being over-tested. Only 13.3% of cohort A had alignment with NCCN guidelines for appropriate time of testing. **Conclusions:** Implementation of a pathology-driven molecular reflex pathway for non-squamous NSCLC was associated with increased identification of potentially targetable genetic alterations and improved adherence to NCCN NSCLC testing guidelines, along with reduction in QNS results. Though the TAT mean decreased after pathway implementation, the median did not change, offsetting the often increased lab TAT for NGS methodology vs. PCR and FISH alone. Research Sponsor: Quest Diagnostics.

	TAT (mean)	Targetable mutations identified	Non-NCCN guideline testing
Total N reviewed (data missing)	291 (3)	291 (6)	291 (3)
2016-2018 cohort A	35.1 days (n = 120)	12.4% (n = 120)	86.7% (n = 120)
2018-2020 cohort B (reflex testing panel)	15.8 days (n = 168)	61.3% (n = 165)	25.6% (n = 168)
Change for cohort B vs cohort A	*-55.1%*	*+48.9%*	*-61.1%*

3128 **Poster Session**

Molecular correlates of *MAEA* expression in colorectal cancer (CRC). *First Author: Shivani Soni, Division of Medical Oncology, USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA*

Background: Macrophage Erythroblast Attacher (MAEA) plays an important role in actin cytoskeleton rearrangement in macrophages and erythroid cells. We previously reported that MAEA suppresses migration, invasion and enhances chemosensitivity in CRC cell lines. Here we aimed to characterize the molecular features associated with *MAEA* gene expression in CRC. **Methods:** 14416 CRC were tested at Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing on DNA (592 genes or WES) and RNA (WTS). Top quartile transcripts per million (TPM) for *MAEA* expression were considered high (Q4) while bottom quartile low (Q1). Consensus molecular subtypes (CMS) were assessed using RNAseq. Cell infiltration (CI) in the tumor microenvironment (TME) was estimated by QuantiSEQ. X^2 and Fisher-Exact tests were used and significance was determined as *P*-value adjusted for multiple comparisons ($Q < 0.05$). **Results:** *MAEA* expression was highest in rectal tumors (13.6 median TPM) followed by transverse and right-sided tumors (13.0 and 12.8, respectively) and lowest in left-sided tumors (12.5). Overall, *MAEA* TPM were associated with higher tumor mutational burden (≥ 10 Mut/Mb) (11.8% vs. 8.2%) and dMMR/MSI-H (8.7% vs. 5.1%) ($Q < 0.0001$); however, the association with TMB was not observed in MSS tumors. In the MSS cohort, *MAEA* expression was the highest in CMS4 (14.9 median TPM) followed by CMS1 (12.5), CMS2 (11.9), and the lowest in CMS3 (10.3, all intergroup $Q < 0.05$). *MAEA* high was associated with lower mutation rates of *APC* and amplification of *FLT1*/*FLT3* while higher mutation rates of *ASXL1*, *KMT2A/C/D*, *SMARCA4*, *FBXW7*, *PTEN*, *RNF43*, *BRCA2*, *HNF1A* in the overall cohort ($Q < 0.05$). In the MSS cohort, *FBXW7* mutation significance with *MAEA* high expression held true ($Q < 0.05$) while *MAEA* high expression trended to associate with higher mutation rates of *KMT2D*, *SMARCA4*, *PTEN*, *BRCA2* mutations, and a lower frequency of *FLT1*/*FLT3* CNA ($P < 0.05$ but $Q > 0.05$). High *MAEA* was associated with higher immune CI in the TME, including B cells, macrophages (M1 and M2), neutrophils, NK cells, Tregs, CD4+ T cells and myeloid dendritic cells both in the overall cohort and in MSS tumors (fold change: 1.11-1.33, all $Q < 0.001$). **Conclusions:** Our data show a strong association between *MAEA* gene expression and distinct molecular features (including CMS and immune biomarkers) and TME cell infiltration in CRC. These findings suggest that targeting MAEA may have relevant clinical applications in selected CRC subgroups and MAEA may be an important player in determining the composition of the TME. Research Sponsor: Partly supported by NCI P30CA014089, Gloria Borges WunderGlo Foundation, Dhont Family Foundation, Ming Hsieh research fund, San Pedro Peninsula Cancer Guild, V foundation for cancer research, Fong research project.

3129 **Poster Session**

Comprehensive profiling of clock genes expression in colorectal cancer (CRC). *First Author: Francesca Battaglin, Division of Medical Oncology, USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA*

Background: Disruption of the circadian clock has been linked to cancer risk, development and progression. Core clock proteins are emerging as novel therapeutic targets in cancer. We previously showed that polymorphisms in clock genes were associated with anti-VEGF treatment outcome in metastatic CRC. Here we further evaluated the molecular landscape of clock pathway alterations in CRC. **Methods:** 7591 CRC tested at Caris Life Sciences (Phoenix, AZ) with WTS (Illumina NovaSeq) and NextGen DNA sequencing (NextSeq, 592 Genes and NovaSEQ, WES) were analyzed. Clock gene Score (CS) was determined using expression of core clock genes Z scores (positives of *CLOCK*, *ARNTL*, *RORA/B/C* and negatives of repressors *CRY1/2*, *PER1/2/3*, *REVERBA/B*) stratified by quartiles. xCell was used to quantify cell infiltration in the tumor microenvironment (TME). Consensus molecular subtypes (CMS) were assessed by RNAseq. Significance was determined as *P*-values adjusted for multiple testing (*q*) of < .05. Real world survival was obtained from insurance claims data and Kaplan-Meier estimates were calculated for comparison. **Results:** CS was higher in primary tumors than metastases and in right- than left-sided CRC ($P < .001$). Liver metastases were associated with lower CS (23% Q1 vs 19% Q4, $P < .001$). CS was positively associated with CMS1 and 3 (21 vs 11% and 23 vs 9%, respectively, Q4 vs Q1) and negatively correlated with CMS2 and 4 (22 vs 32% and 34 vs 48%) (all $P < .001$). These associations were confirmed in mismatch repair proficient (pMMR) tumors. Overall, TMB-H and dMMR/MSI-H were positively associated with CS (11 vs 6% and 8 vs 4%, Q4 vs Q1, $q < .0001$) and PD-L1 showed a similar trend ($P < .01$, $q = .06$); the association with TMB-H was not significant in pMMR. High CS was associated with alterations of genes in WNT signaling, RAS, PI3K, TGF-*β*, and NOTCH pathways, while negatively associated with *TP53* mutations, *HER2* expression and *CDX2* copy numbers, confirmed in pMMR (all $q < .05$). CS negatively correlated with the angiogenesis pathway signature (Q1 vs Q4 Z score: 6.6 vs -4.6, $P < .001$). B cells, M1 and M2 macrophages, neutrophils, NK, Tregs, CD4+ and CD8+ T cells, and myeloid dendritic cells were more abundant in the TME of tumors with high CS while cancer associated fibroblasts were lower, regardless of MMR status (all $q < .001$). Individually, *ARNTL* tumor expression below median was associated with better OS (overall: HR 0.88, 95% CI [0.82-0.94]; pMMR: HR 0.88 [0.81-0.94]) and longer time on treatment of bevacizumab (overall: HR 0.91 [0.83-0.99]; pMMR: HR 0.91 [0.83-0.99]). **Conclusions:** This is the most extensive profiling study to investigate the expression of clock genes in CRC. Our data show that clock genes expression is strongly associated with distinct molecular features, immune cell infiltration, angiogenesis pathway enrichment and patient outcomes. These findings support the clock pathway as a therapeutic target in CRC, with a major role in CRC biology and TME modulation. Research Sponsor: Partly supported by NCI P30CA014089, Gloria Borges WunderGlo Foundation, Dhont Family Foundation, Ming Hsieh research fund, Daniel Butler Research Fund, Victoria and Philip Wilson Research Fund.

3130 **Poster Session**

Increasing targeted therapy options for patients with relapsed cancer with broader somatic gene panel analysis from the primary tumor: The Profiler02 randomized phase II trial. *First Author: Olivier Tredan, Medical Oncology Department, Centre Léon Bérard, Lyon, France*

Background: PROFILER-02 is a multicenter randomized prospective study comparing the proportion of metastatic cancer patients (pts) with Targeted Agent (TA) recommendation provided by large NGS panel (FOne panel, 324 genes) *vs* home 87-gene NGS panel (CTRL) (PMID 30865223). **Methods:** Adult pts with advanced/metastatic cancer during 1st or 2nd line of therapy without known targetable gene alteration were eligible and randomized (1:1) to FOne *vs* CTRL panel. Both panels were performed for each patient. The randomization arm defined the first panel reviewed by dedicated Molecular Tumor Board (MTB) at disease progression while the 2nd panel remained blinded. The primary objective was the pts rate with at least one TA recommendation by the MTB using either FOne or CTRL panel. The study was designed in order to detect difference in proportions of 10% between the two panels. A sample size of 289 pts with both panels were requested to show this difference with an expected proportion of discordant pairs of 20% using a McNemar's test with 98% power and 5% two-sided significance level. Secondary endpoints included number of pts receiving at least one TA, progression free survival (PFS) and overall survival (OS). **Results**: From June 2017 to June 2019, among the 339 included pts 171 and 168 pts were randomized in FOne or CTRL panels' first use, respectively. Median age was 57 years [19.0 - 85.0]; 54.9% were female. The median time from randomization to first MTB was 7.62 months [range 0.80 - 48.1]. Among the 339 pts, 147 pts (43.4%) had no TA recommendation, 108 pts (31.9%) had at least one TA recommendation according to both panels, 67 pts (19.8%) had one or more TA recommendation according to FOne panel only and 17 pts (5%) according to CTRL panel only (McNemar $p < 0.001$). At the time of the analysis, 51/339 (15%) pts started recommended treatment: 27 pts (8%) with TA recommendation from both panels, 21 pts (6.2%) from FOne only and 3 pts (0.3%) from CTRL only. Main initiated TA were PARP inh. (FOne n = 12; CTRL n = 9), PI3K/AKT/mTOR inh. (FOne n = 10; CTRL n = 9) and immunotherapy (ICI) (FOne n = 7; CTRL n = 0). Median PFS following first MTB were 3.2 months (95% CI 2.5-3.8) and 2.6 months (95% CI 2.0-3.8), median OS were 8.7 months (95% CI 6.6-10.8) and 8.4 months (95% CI 6.4-9.7), in the FOne and CTRL arm, respectively. **Conclusions**: Larger NGS panel including Tumor Mutational Burden increased the number of recommended options (TA and ICI), as well as the number of treatment initiation. Clinical trial information: NCT03163732. Research Sponsor: Roche, Other Foundation, Other Government Agency.

3131 **Poster Session**

Primary results from JUPITER, a phase 2 basket trial of combination therapy with trastuzumab and pertuzumab in patients with HER2-amplified solid tumors. *First Author: Sadakatsu Ikeda, Tokyo Medical and Dental University, Tokyo, Japan*

Background: Human epidermal growth factor receptor 2 (HER2) gene amplification or mutations have emerged as oncogenic drivers and therapeutic targets not limited to breast and gastric cancers, but also in a variety of cancers. Despite its considerable therapeutic potential, the evidence has not been established. To address this unmet need, we conducted an organ-agnostic basket trial targeting HER2-amplified solid tumors. **Methods:** JUPITER is a multicenter, single-arm, phase 2 basket trial for solid tumor patients (pts) with HER2 amplification determined by next-generation sequencing (NGS). Both tissue and liquid NGS results were allowed. HER2 amplification by ISH or HER2 overexpression by IHC were not used for inclusion. Pts had treatment-refractory metastatic tumors, or rare cancers without established standard of care. Breast, gastric, and colorectal cancers were excluded. Pts were treated with intravenous trastuzumab (8 mg/kg loading dose followed by 6 mg/kg) and pertuzumab (840 mg loading dose followed by 420 mg) every 3 weeks until disease progression or any other reason for discontinuation. Tumor response was assessed using RECIST v1.1. Primary endpoint was ORR by blinded independent central review (BICR), and secondary endpoints were ORR assessed by the investigators, progression-free survival (PFS), overall survival (OS), duration of response (DOR), and safety. We set the ORR threshold 5% and expected ORR was 20%. Estimated sample size was 38 patients with one-sided alpha 2.5% and power 80%. **Results:** Between April 2019 and June 2020, 42 pts were consented, and 40 pts were treated. Median age was 62 (range, 21-86) and 60% were females. The most common diagnosis was biliary tract cancer (20%), followed by salivary ductal carcinoma (12.5%) and endometrial cancer (12.5%). At data cutoff (1 Sep 2021), ORR by BICR was 22.5% (95%CI: 10.8%-38.5%). ORR assessed by the investigator was 25% (95%CI: 12.7%-41.2%). PFS, OS and DOR were not reached at data cutoff; 3 responders remained on treatment. Of 40 pts, 32.5% had grade ≥ 3 adverse events; 10% were treatment-related, including neutropenia, hypertension, peripheral sensory neuropathy and lymphoedema (all grade 3). No treatment-related death was observed. Exploratory biomarker analysis of response and resistance is in progress. **Conclusions:** Combination therapy with trastuzumab and pertuzumab was well tolerated and showed promising efficacy for the patients with HER2-amplified solid tumors determined by NGS. Clinical trial information: jRCT2031180150. Research Sponsor: AMED (Japan Agency for Medical Research and Development).

3132 **Poster Session**

Reversion mutations in *BRCA1* or *BRCA2* genes: Resistant mechanism(s) in patients treated with platinum-based agents or poly (ADP-ribose) polymerase(PARP) inhibitors. *First Author: Sourat Darabi, Hoag Family Cancer Institute, Newport Beach, CA*

Background: Reversion mutations (RM) in homologous recombination pathway genes including *BRCA1/2* have been identified in patients with ovarian, breast, and prostate cancers whose tumors have become refractory to platinum chemotherapy or PARP inhibition. Utilizing a multi-institutional molecular database, we report the prevalence of *BRCA1/2* RM in a large cohort across various tumor types. **Methods:** Primary and/or metastatic tumor samples underwent DNA (underwent NextSeq, 592 genes; NovaSeq, whole-exome) and RNA (NovaSeq, whole transcriptome) sequencing (Caris Life Sciences, Phoenix, AZ). RM were identified by a board-certified molecular geneticist and called only if the patient had been treated with a PARPi or a platinum agent. Baseline clinical and outcomes data were obtained through linked insurance claims data. **Results:** Among 118,000 solid tumors profiled, RM were observed in 54 tumors samples. RMs were seen most commonly in ovarian cancer (OC), 1.5% (23/1500) of tumors with *BRCA1/2* pathogenic mutations (mut), followed by breast cancer (BC) (2.4%, 17/700), endometrial cancer (1.0%, 4/400), pancreatic cancer (1.0%, 2/210), cholangiocarcinoma (2.5%, 2/80), prostate cancer (1.3%, 3/230), cervical cancer (1.4%, 1/70), cancer of unknown primary (1.0%, 1/100), and a neuroendocrine tumor of prostate (1 RM of 9 *BRCA* mut). Among all RM, we detected 17 in *BRCA1* and 6 in *BRCA2* in OC. In BC, we identified 7 RM in *BRCA1* and 10 in *BRCA2*. Frameshift mut that restored the reading frame in *BRCA1/2* were the most common type of RM. Molecular profiles of 14 high-grade serous ovarian cancers (HGSOC) with RM were compared to 87 control HGSOC with pathogenic *BRCA1/2* mut without RM. Tumors with RM had lower ER expression (25% vs. 64%, $p = 0.024$) and higher *KDM6A* mut rate (15% vs. 0, $p = 0.016$). Additionally, *TP53* mut rates were similar in RM and control (100% vs. 95%), seen in HGSOC. In patients with RM, 7 of the 14 (50%) *TP53* mut were gain-of-function (GOF) while only 19 of 84 (23%) *TP53* mut in the control group were GOF ($p = 0.048$). More detailed clinical data were available for 29 patients with RM (17 *BRCA1* & 12 *BRCA2*). Among these patients, 7 had received prior platinum-based chemotherapy (carboplatin or cisplatin), 7 patients were treated with PARP inhibitors (olaparib or rucaparib), or both ($n = 7$). Notably, 5 patients had been treated with carboplatin ($n = 2$, ovarian), olaparib ($n = 1$, breast), or both agents ($n = 2$, ovarian and prostate) after the detection of RM. **Conclusions**: This dataset is one of the largest reporting on the prevalence of *BRCA1/2* RM across various tumor types. We demonstrate that the rate of RM was low among *BRCA1/2* mutated tumors; this may be because some patients may not have repeat profiling post-treatment. Repeating tumor profiling at times of treatment resistance can help inform therapy selection in the refractory disease setting. Research Sponsor: None.

3133 **Poster Session**

Pan-cancer landscape of *CD274* (PD-L1) and *PDCD1LG2* (PD-L2) structural variations. *First Author: Emily L. Hoskins, Ohio State University, Columbus, OH*

Background: PD-1 receptor and PD-L1 ligand interactions are the target of immunotherapies across multiple tumor types. Established biomarkers that predict response to immunotherapy are microsatellite instability, tumor mutational burden, and PD-L1 immunohistochemistry. Structural variations in *CD274* (PD-L1) and *PDCD1LG2* (PD-L2) have been observed in cancer, but the comprehensive landscape is unknown. Here we describe the genomic landscape of *CD274* and *PDCD1LG2* structural variations, their potential impact on the tumor microenvironment, and evidence that patients with these alterations can benefit from immunotherapy. **Methods:** We analyzed sequencing data from 514 cancer cases with *CD274* and *PDCD1LG2* structural variations across 25 publications and data sources, including large pan-cancer sources: Foundation Medicine, Inc (FMI), The Cancer Genome Atlas (TCGA), and Oncology Research Information Exchange Network. To evaluate immune signature enrichment, we ran the software ImSig on gene expression data. We curated literature reporting clinical outcomes of patients harboring structural variations in *CD274* and *PDCD1LG2*. **Results:** From 25 studies and datasets, we curated 514 cancer cases with structural variations in *PD-L1* and *PD-L2*, including 158 duplications, 126 deletions, 97 inversions, 178 translocations, and 96 unclassified structural variations, totaling to 655 events. We observed breakpoint 'hotspots' in the 3'-untranslated regions (UTRs) of *PD-L1* and *PD-L2*. Leveraging TCGA data, we observed, in *CD274*-rearranged tumors, significant upregulation in PD-L1 and PD-L2 expression and signatures for interferon signaling, macrophages, monocytes, T cells, and immune cell proliferation (each $p < 0.001$, compared to *CD274* non-rearranged, copy neutral tumors). Furthermore, retrospective review of 12 studies that included patients with structural variations in *CD274* or *PDCD1LG2*, including duplications, inversions and copy number amplifications, revealed a 73% (52/71) response rate to PD-1 immunotherapy with durable responses. **Conclusions:** Our evaluation of *CD274* and *PDCD1LG2* structural variations shows that the 3'-UTR is frequently affected and is associated with increased expression of ligands and immune signatures. Enriched interferon signaling in *CD274*-rearranged tumors is of particular interest, as interferon exposure is known to drive PD-L1 and PD-L2 expression. Retrospective evidence from curated studies suggests that these genomic alterations could identify candidates for PD-1 or PD-L1 immunotherapy. We expect that these findings will better define *CD274* and *PDCD1LG2* structural variations in cancer and support our pan-cancer prospective clinical trial to target these alterations. Research Sponsor: U.S. National Institutes of Health.

3134 **Poster Session**

Defining transcriptomic profiles of early-stage mucinous breast cancers: A FLEX sub study. *First Author: Abirami Sivapiragasam, SUNY Upstate Medical University, Syracuse, NY*

Background: Mucinous breast cancer (MuBC) is a rare subtype of invasive ductal carcinoma (IDC) that accounts for less than 2% of all breast cancers and is associated with a favorable prognosis. Since MuBCs are rare in clinical trials, current treatment guidelines are extrapolated from IDC-no special type (IDC-NST). To provide better understanding of MuBCs and factors contributing to their clinical behavior, we examined the transcriptomic profiles of MuBCs in our FLEX study. **Methods:** The prospective, observational FLEX Study (NCT03053193) includes stage I-III breast cancer patients who receive MammaPrint (MP)/BluePrint (BP) testing and consent to full transcriptome and clinical data collection. For this study, histologically confirmed MuBCs ($n = 102$) in the FLEX database were included. All patients examined were ER+/HER2- by immunohistochemistry and Luminal by BP. MuBC was compared with IDC matched for Age, MP, and BP index ($n = 97$). Differential gene expression analyses (DGEA) were performed with R package 'limma' and differentially expressed genes (DEGs) were considered significant if they had an adjusted $p < 0.05$ and fold change ≥ 2. **Results:** DGEA comparing MuBC ($n = 102$) with IDC ($n = 97$) revealed 60 DEGs, regardless of the genomic risk, of which 42 genes were upregulated and 18 were downregulated in MuBC relative to IDC. Genes associated with MuBC, such as MUC2, TFF1, CARTPT were among the upregulated genes. Of the 102 MuBC patients, 56 were Luminal A (MP Low Risk-LR) and 46 were Luminal B (MP High Risk-HR) by MammaPrint and BluePrint. Comparison of LR MuBC with LR IDC revealed 111 DEGs. Functional enrichment showed upregulation of pathways involved in estrogen response (early & late) and androgen response and a downregulation of the epithelial to mesenchymal transition (EMT) and E2F pathways in LR MuBC compared to LR IDC. DGEA between HR MuBC and HR IDC revealed only 22 DEGs with immune pathways being downregulated in HR MuBC. DGEA comparing LR MuBC with HR MuBC resulted in 63 DEGs, indicating LR and HR MuBC are biologically distinct types. Interestingly in LR MuBC, the tumor suppressor marker SCUBE2 is upregulated. Over expression of SCUBE2 is associated with better prognosis. **Conclusions:** Although MuBCs are often expected to have low clinical risk, MP revealed that half of the MuBCs examined in this study were MP High Risk (Luminal B). MP low risk MuBC is biologically different from MP low risk IDC, and downregulation of E2F and EMT pathways might lead to favorable prognoses in MP low risk MuBC. MP high risk MuBC showed limited DEGs compared to high-risk IDCs indicating these tumor types are highly genomically similar and likely to benefit from chemotherapy. The downregulation of immune pathways in MP high risk MuBC may lead to immune surveillance escape resulting in metastasis and further investigation is needed. Clinical trial information: NCT03053193. Research Sponsor: None.

3135 **Poster Session**

Clinicopathologic characterization of ERK2 E322K mutation in solid tumors: Implications for treatment and drug development. *First Author: Dazhi Liu, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: *MAPK1* encodes ERK2, a kinase component of the mitogen activated signaling (MAPK) pathway. *ERK2 E322K* is a known activating mutation that leads to increased phosphorylation and ERK signaling. In vitro studies found this mutation to be associated with resistance to dabrafenib, trametinib, but potential sensitivity to ERK inhibitors. Despite its potential as a drug target, little is known about the clinicopathologic characteristics of this hotspot mutation across solid tumors. **Methods:** Patients with solid tumors underwent tumor next-generation sequencing at Memorial Sloan Kettering Cancer Center between Jan 2015 and Sep 2020 using the MSK-IMPACT assay. Using the cBioPortal database and clinical charts, we analyzed tumors harboring MAPK1/ERK2 E322K mutations, assessed their clinicopathologic characteristics, co-mutational status and overall survival (OS). OS was measured from time of tumor sequencing to date of death or last follow-up. **Results:** A total of 37 tumor samples from 35 patients were identified in 59,822 tumors sequenced (0.06%) to harbor an ERK2 E322K mutation. The distribution across tumor types was as follows: head and neck squamous cell carcinoma (29%), bladder cancer (20%), lymphomas (9%), colorectal cancers (9%), gastric cancers (9%), cholangiocarcinoma (6%), cervical cancers (6%), lung cancers (6%), germ cell tumor (3%), Merkel cell carcinoma (3%), and breast cancers (3%). The OS in patients with metastatic disease and ERK2 E322K was 22.29 months (95%CI: 7.56-NA) months. Other mutations in RAS pathway frequently co-occurred with ERK2 E322K mutation (17/37, 46%). Concurrent mutations are also involved in pathways of cell cycle (71%), PI3K (71%), TP53 (66%), NOTCH (57%), RTK (51%), HIPPO (29%), TGF-beta (29%), WNT (26%), NRF2 (20%), MYC (14%). The median TMB score of samples from solid malignancies was 12.3 (range:0-101, quartiles: 6.9-33.0) mutation/Mb. Two patients (2/35, 6%) had microsatellite-instability high (MSI-H) tumors. The most frequent concurrent activating mutations include ARID1A (29%), FBXW7 (26%), PI3KCA (22%), PI3KR1/2/3 (20%), CDKN2A (11%), PTEN (8%), BRCA1/2(8%), FGFR3 (8%), BRAF (6%), Only one of these 35 patients received treatment targeting BRAF/MEK/ERK pathway and achieved partial response. One patient with NSCLC harboring a concurrent EGFR L858R mutation did not respond to erlotinib. One patient with PI3KCA mutated head and neck cancer did not respond to PI3K inhibitor. Two patients had TMB score of 100.9 and 12.9 mutation/Mb had partial response to pembrolizumab. **Conclusions:** ERK2 E322K mutation is a rare oncogenic mutation across diverse solid tumor types, associated with a high co-occurrence of other activating mutations and a high TMB. The lack of response to other targeted therapies suggests ERK2 E322K is a potential driver mutation. These findings may inform treatment and further development of ERK inhibitors. Research Sponsor: U.S. National Institutes of Health.

3136 **Poster Session**

Using CDKN2A loss in the context of wildtype TP53 to predict sensitivity for the MDM2 inhibitor milademetan. *First Author: Vijaya G Tirunagaru, Rain Therapeutics, Newark, CA*

Background: MDM2 is an E3 ubiquitin ligase that plays a critical role in the degradation of the tumor suppressor p53. Milademetan (RAIN-32) is an orally available, small molecule inhibitor of MDM2 that disrupts the MDM2-p53 complex thereby restoring p53 activity. Approximately 50% of tumors harbor wildtype (WT) *TP53* and thus may be susceptible to strategies that reactivate p53. The *CDKN2A* gene is altered in more than 15% of all tumors (TCGA PanCancer Atlas) and encodes two proteins, $p14^{ARF}$ and p16, which are inhibitors of p53 and cyclin dependent kinases, respectively. Given the role of $p14^{ARF}$ in regulating the MDM2-p53 pathway, we investigated the use of *CDKN2A* loss in the context of WT *TP53* as a strategy for selection of patients who might benefit from milademetan. **Methods:** N/A. **Results:** We evaluated the sensitivity of 215 cancer cell lines to milademetan treatment (Ishizawa et al., 2018) by *CDKN2A* and *TP53* status. The median IC_{50} of *CDKN2A* homozygous (HZ) loss vs. non-HZ loss was 8,620 vs. 10,000 nM. However, when we assessed *CDKN2A* HZ loss with WT *TP53* versus mutant *TP53* the median IC_{50} was 79.5 vs. 10,000 nM demonstrating that the use of both *CDKN2A* and *TP53* was better able to discriminate sensitive vs. resistant cell lines. To validate these *in vitro* findings, we tested milademetan in 5 xenograft models with *CDKN2A* HZ loss and WT *TP53*, all of which demonstrated tumor growth inhibition with milademetan. As suppression of p53 activity by *MDM2* amplification (Kato et al. 2017) or *CDKN2A* loss (Adib et al. 2021) has been associated with resistance to immune checkpoint inhibitors (ICI), we also tested the combination of anti-PD1 with milademetan in the colon-26 syngeneic model (*CDKN2A* HZ loss) and observed a significant enhancement in tumor growth inhibition compared to milademetan or anti-PD1 alone. Based on the differential sensitivity to milademetan using both *CDKN2A* loss and WT *TP53* status we evaluated TCGA Pan-Cancer Atlas data to estimate the frequency of these genetic co-alterations. Among solid tumors types the most frequent percentage of these co-alterations included glioblastoma, mesothelioma, melanoma, bladder, sarcoma, pancreatic and NSCLC. Overall, the percentage of all tumors with co-alteration of *CDKN2A* HZ loss and WT *TP53* was 6.2%. Patients with *CDKN2A* HZ loss had a significantly worse overall survival than those without CDKN2A HZ loss (median OS of 29.7 vs. 97.4 months, $p < 0.0001$), and this was maintained when accounting for tumor type in multivariate analysis ($p < 0.0001$). **Conclusions:** Milademetan showed evidence of preclinical anti-tumor activity across multiple tumor types with *CDKN2A loss* and WT *TP53*. In vivo data supported potential synergy of milademetan with an ICI in this genetic subset. A clinical trial evaluating the safety and efficacy of milademetan plus atezolizumab in advanced solid tumors with *CDKN2A HZ* loss and WT *TP53* (MANTRA-4) is planned. Research Sponsor: Rain Therapeutics.

3137 **Poster Session**

Identification of homologous recombination deficiency (HRD) by RAD51 in a tumor molecular profiling program for precision medicine. *First Author: Alba Llop-Guevara, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain*

Background: Tumor molecular profiling by panel sequencing helps to identify candidate patients for precision oncology. Mutations in genes of the homologous recombination repair (HRR) pathway confer DNA repair deficiency and sensitivity to DNA damaging agents, such as PARP inhibitors (PARPi) or platinum-based drugs. RAD51 nuclear foci is a biomarker of functional HRR deficiency (HRD). We aimed to incorporate the RAD51 test in an academic molecular profiling program to identify HRD tumors beyond genetic testing. **Methods:** We included patients with metastatic breast cancer (TNBC, ER+ <60y, 3rd line HER2+ BC), newly diagnosed high-grade epithelial ovarian cancer (HGOC) and metastatic and/or castration-resistant prostate adenocarcinoma (PC) undergoing tumor/germline genetic testing. A customized capture-based targeted sequencing of 450 genes was performed in FFPE tumor samples. RAD51 was manually stained by immunofluorescence and functional HRD was defined as RAD51 score ≤10%. **Results:** Between January 2021 and January 2022, tumor panel sequencing was performed in 279 tumors. Panel sequencing was informative in 264/279 (95%) samples and the RAD51 test was evaluable in 81/90 (90%). In total, 77 samples were evaluable for both tumor/germline sequencing and RAD51, namely 42 BC, 16 HGOC and 19 PC (Table 1). Functional HRD by RAD51 was observed in 15/77 (20%) cases. Panel sequencing identified 17/77 (22%) cases carrying HRR gene alterations, of which nine were confirmed as HRD by RAD51. In BC, 2/6 tumors with HRD by RAD51 did not carry a germline or tumor mutation in HRR genes. HRD tumor profiling triggered the germline analysis of one hereditary *BRCA2* BC patient. Four g*BRCA1/2* BC with HRD by RAD51 became HRR proficient (HRP) at PARPi progression. In addition, the RAD51 test identified 2/5 HGOC and 2/4 PC tumors as HRD despite not carrying a tumor HRR gene mutation. **Conclusions:** RAD51 testing is feasible in an established molecular profiling program and complements gene panel sequencing results by providing evidence of functional HRR status. In particular, the RAD51 test extends the identification of HRD tumors beyond those with HRR gene mutations and captures HRR restoration after PARPi treatment. We aim to expand the analysis of RAD51 to other tumor types. Research Sponsor: Asociación Española Contra el Cáncer (AECC), LaCaixa Foundation (CaixaImpulse grant), Generalitat de Catalunya (AGAUR-Producte and PERIS), Instituto de Salud Carlos III (ISCIII), Fondo Europeo de Desarrollo Regional (FEDER).

Number of samples with both functional HRR status by RAD51 and HRR gene mutation status by panel sequencing in breast, high-grade ovarian and prostate cancers.

Number of cases	Tumor/germline sequencing (HRR genes)	HRD by RAD51	HRP by RAD51
BC (n = 42)	mutated	4	6
	non-mutated	2	30
HGOC (n = 16)	mutated	3	1
	non-mutated	2	10
PC (n = 19)	mutated	2	1
	non-mutated	2	14
All tumor types(n = 77)	*mutated*	***9 (12%)***	***8 (10%)***
	non-mutated	***6 (8%)***	***54 (70%)***

3138 **Poster Session**

Paired tumor/normal sequencing to overcome racial differences in tumor mutational burden (TMB). *First Author: Kenneth Robert Carson, Tempus Labs, Inc., Chicago, IL*

Background: TMB is routinely reported in cancer patients tested with broad-panel next generation sequencing and has become a predictive biomarker associated with response to checkpoint inhibitor (CPI) therapy. Sequencing of paired tumor and normal specimens allows correction of TMB estimates with patient-specific germline variants. When a paired normal specimen is unavailable, TMB estimates are corrected using germline variant annotations derived from population-scale germline variant surveys. Germline variants do not generate neoantigens, which is the putative target of the immune response in CPI treated patients. To evaluate TMB differences in paired sequencing (PS) and tumor-only sequencing (TOS), we compared TMB assessments—stratified by race—in two common malignancies**. Methods:** Using de identified records from the Tempus clinico-genomic database, cohorts of patients with non-small cell lung cancer (NSCLC) and breast cancer sequenced using the Tempus xT NGS platform (DNA-seq of 595-648 genes at 500x coverage, whole exome capture RNA-seq) and noted to not have microsatellite instability, were identified for analyses. The Kruskall-Wallis test was used to compare TMB distributions. **Results:** Among 4,817 NSCLC patients with race information (13% Black (B), 5% Asian (A), 82% White (W), 3,052 had PS, and 1,765 had TOS performed. Median TMB for B, A, and W patients was 5.8, 2.6, and 4.7 (within group $p < 0.0001$), respectively in patients with PS, and 9.5, 6, and 7.4 (within group $p < 0.0001$), in patients with TOS. Comparisons across PS and TOS were highly significant ($p < 0.0001$). The absolute difference in median TMB was 3.7, 3.4, and 2.5, respectively. Among 3,191 patients with breast cancer (17% B, 4% A, 78% W), 2,220 had PS, and 971 had TOS. Median TMB for B, A, and W patients was 2.6, 2.1, and 2.6 (within group $p = 0.11$), respectively, in patients with PS, and 6.3, 5.8, and 4.7 (within group $p < 0.0001$) in patients with TOS. Comparisons across PS and TOS were highly significant ($p < 0.0001$). The absolute difference in median TMB was 3.7, 3.7, and 2.1, respectively. **Conclusions:** PS reduces estimated TMB compared to TOS across all racial groups with a pronounced difference in Black and Asian racial groups. This is expected as population databases of germline variation are based on cohorts predominantly from individuals of European ancestry, leading to artifactually high TMB in minorities tested with TOS. As a result, artifactually elevated TMB estimates from TOS may promote treatment with CPI in patients with a low probability of response which could exacerbate known race-based outcome disparities. PS provides a more accurate estimate of TMB regardless of race and could reduce the use of CPI in patients with a low likelihood of response. Research Sponsor: Tempus Labs, Inc.

3139 **Poster Session**

Next-generation sequencing (NGS) for identifying actionable molecular alterations in patients with newly diagnosed and recurrent IDHwt-glioblastoma (GBM): A large mono-institutional experience. *First Author: Marta Padovan, Department of Oncology, Oncology 1, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy*

Background: NGS panels allow the identification of alterations within hundreds of cancer-related genes and can guide a personalized strategy in glioma treatment. **Methods:** From Nov 2019 to Jan 2022 at Veneto Institute of Oncology, Padua, Italy, a large cohort of IDHwt-GBM tissues was analyzed by NGS (FoundationOneCDx). We identified all potential actionable molecular alterations at diagnosis and/or at recurrence. High tumor mutational burden (TMB) was defined as ≥10 mutations/megabase. **Results:** We analyzed 429 IDHwt-GBM samples: NGS profile was available for 419 samples (97.7%); sample failures in 10 cases (2.3%). 351 (84%) and 68 (16%) GBM samples derived from surgery at diagnosis and recurrence, respectively. All patients received radiotherapy and/or temozolomide as first line therapy. Among all the analyzed samples, the most frequent actionable molecular alterations were: CDKN2A (57%), CDKN2B (53%), EGFR amplification (39%), EGFR mutation (24%), PTEN loss (27%), RB1 (23%), NF1 (18%), PIK3CA (18%), CDK4 (15%), MDM2 (10%), PDGFRA (8%), BRCA1-2 (7%), FGFR1-3 (7%), Myc (6%), JAK (6%), ROS1 (5%), METmut (2%), METampl (2%), BRAF V600E (2%). No NTRK1/2/3 druggable alterations were observed. High TMB was found in 18 samples. Incidence of actionable molecular alterations in newly diagnosed and relapsed GBM samples is described in the Table. The incidence of alteration of EGFR (ampl/mut), RB1, PIK3CA was statistically different between the two subgroups of samples (Fisher test). To date, 10% of patients received a personalized treatment as compassionate use, off-label use or in clinical trials (9 Dabrafenib/Trametinib, 8 Alpelisib, 3 Erdafitinib, 2 Ipatasertib, 1 Alectinib, 1 Capmatinib, 1 Palbociclib, 1 Entrectinib, 1 Pamiparib). Activity analysis is still ongoing. **Conclusions:** NGS is feasible in GBM samples. Potentially, a high rate of patients could receive a personalized treatment. The activity analysis is ongoing. However, the incidence of actionable molecular alterations may differ between diagnosis and recurrent GBM samples. Research Sponsor: None.

Gene alteration	All cases (out of 419 cases)	%	At Diagnosis (out of 351 cases)	%	At Recurrent (out of 68 cases)	%	p
CDKN2A	240	57,3	195	55,6	45	66,2	0,1
CDKN2B	221	52,7	180	51,3	41	60,3	0,1
EGFR ampl	163	38,9	129	36,8	34	50,0	**0,04**
PTEN loss	113	27,0	99	28,2	14	20,6	0,2
EGFR mut	102	24,3	78	22,2	24	35,3	**0,02**
RB1	98	23,4	47	13,4	51	75,0	**0,0001**
NF1	76	18,1	64	18,2	12	17,6	0,9
PIK3CA	75	17,9	55	15,7	20	29,4	**0,009**
CDK4	64	15,3	58	16,5	6	8,8	0,1
MDM2	45	10,7	42	12,0	3	4,4	0,08
BRCA1-2	44	10,5	33	9,4	11	16,2	0,1
POLE	34	8,1	29	8,3	5	7,4	0,9
PDGFRA	33	7,9	29	8,3	4	5,9	0,6
FGFR1-3	28	6,7	22	6,3	6	8,8	0,4
MYC	27	6,4	22	6,3	5	7,4	0,7
JAK	24	5,7	18	5,1	6	8,8	0,2
ROS1	21	5,0	19	5,4	2	2,9	0,5
MET mut	10	2,4	8	2,3	2	2,9	0,6
MET ampl	9	2,1	7	2,0	2	2,9	0,6
BRAF V600E	9	2,1	6	1,7	3	4,4	0,1
NTRK1-3	0	0,0	0	0,0	0	0,0	NA
H-TMB	18	4,3	12	3,4	6	8,8	0,09

3140 **Poster Session**

Combining autophagy and immune characterizations to predict prognosis and therapeutic response in lung adenocarcinoma. *First Author: Qiaxuan Li, Department of Thoracic Surgery, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China*

Background: As a key regulator of programmed cell death, autophagy is critical for maintaining the stability of the intracellular environment. Increasing evidences have found that the clinical importance of the interaction between autophagy and immune status in LUAD. Reliable prognostic signatures based on combination of autophagy and immune status have not been well-established. We aimed to explore the potential autophagy-immune-derived biomarkers to predict prognosis and therapeutic response in lung adenocarcinoma. **Methods:** Patients from GSE72094 dataset were randomized 7:3 to a training set or an internal validation set. Three independent cohorts, TCGA, GSE31210 and GSE37745, were used as the external verification. Unsupervised hierarchical clustering was used to identify the autophagy-associated and immune-associated molecular patterns for LUAD based on autophagy-genes and immune-genes. The LASSO analysis, univariate and multivariate cox regression analysis were performed to filtrate significant prognostic autophagy-immune-based genes, followed with model construction and patient stratification. Tumor immune microenvironment and functional pathways were investigated. The potential therapeutic responses were explored by GDSC database, TIDE algorithm, and immunotherapy clinical cohorts. **Results:** We found that autophagy cluster A had the better survival prognosis ($p < 0.001$) and high immune status ($p < 0.001$) was identified as favorable factors for patients' overall survival. We merged autophagy and immune subtype into a two-dimensional index to characterize the combined prognostic classifier 535 genes were defined as autophagy-immune-related DEGs. Four genes (C4BPA, CD300LG, CD96, and S100P) were identified to construct the autophagy-immune-related prognostic risk model. Survival analysis and receiver operating characteristic curve showed significant prognostic efficacy. Through ssGSEA and CIBERSORT analysis, the majority of immune infiltrating cells were shown to be enriched in the low-risk group. What's more, the expression of crucial immune checkpoint molecules, such as PD-1, PD-L1 and CTLA-4, was observed highest in low-risk group ($p < 0.001$). TIDE and immunotherapy clinical cohorts' analysis showed that low-risk group was predicted with more potential responders to immunotherapy. In addition, there are different patterns of autophagy between low- and high- risk patients. GO, KEGG and GSEA function analysis focus on cell cycle, MAPK, apoptosis, MTORC1 and selective autophagy pathway. Docetaxel, rapamycin and sorafenib may be the potential drugs candidate in high-risk group ($p < 0.01$). **Conclusions:** In summary, the autophagy-immune-based gene signature represents a promising tool for risk stratification tool in lung adenocarcinoma, which can regard individualized treatment and follow-up scheduling for patients. Research Sponsor: Natural Science Foundation of Guangdong Province, China.

3141 **Poster Session**

The distribution of genetic mutations correlated with resistance to $KRAS^{G12C}$ inhibitors in Chinese patients with lung cancer. *First Author: Shengcheng Lin, Cancer Hospital Chinese Academy of Medical Sciences, Shenzhen, China*

Background: In lung cancer, p.G12C is the most frequent variant in Kirsten rat sarcoma viral oncogene homologue (KRAS) gene. $KRAS^{G12C}$ inhibitors have shown promising efficacy in lung cancer in recent clinical trials, acquired resistance, however, eventually occurred in most patients. Preliminary studies revealed that a number of genetic mutations were correlated with resistance to this type of drugs, including *KRAS* secondary mutations, *KRAS* activating mutations, mutations in RTK-RAS-MAPK signaling pathways members, oncogene rearrangements and copy number gain. To clarify the potential clinical application of $KRAS^{G12C}$ inhibitors, herein we analyzed the distribution of reported resistance gene alterations in a large and natural group of Chinese lung cancer, as well as the gene mutation landscape of the subset of patients with suspected resistant mutations. **Methods:** A total of 32878 Chinese lung cancer including early-stage, late-stage without treatment or late-stage with previously treated were analyzed in this study. Wide NGS panel testing was used to detected single nucleotide variants (SNV), copy number variants (CNV) and oncogenic gene rearrangements. **Results:** *KRAS* mutations were detected in 2767 (8.4%) cases, of which *KRAS* G12C was the most common variant (30.86%). Among 854 patients (2.6%) harbored *KRAS* G12C, 75 (10%) carried the above resistance mutations, such as G12D/R/V (n = 7). Fusions (20%) which previously observed only in coloretal cancer were unexpectedly detected in this corhort, including *EML4-ALK* (n = 1), *FGFR1-MECOM* (n = 1), *EWSR1-CHEK2* (n = 2), *SPEN-KAZN* (n = 2), *MET-KCNB2* (n = 1), *NOTCH2-NOTCH2NLA* (n = 5), *SMARCA4-DNAH8* (n = 1), and *LIPM-FAS* (n = 1). Furthermore, *KRAS* (46.7%), *MYC* (25.3%) and *MET* (10.7%) were amplified. Among this subset of patients with resistant mutations, *TP53* (66%), *LRP1B* (25%), and *STK11* (22%) were the most frequently mutated genes. It is noteworthy that *STK11/KEAP1 /NFE2L2* gene mutation was detected in nearly 30% in this group of patients. **Conclusions:** The results of our analysis suggested that about 10% *KRAS* G12C-mutated Chinese lung cancer patients would be resistant to *KRAS* G12C inhibitors. Moreover, a small number patients have co-mutated genes which were negatively related to immunotherapy in NSCLC, indicating they were also inappropriate for immunotherapy. Research Sponsor: None.

3142 **Poster Session**

A digital imaging analysis (DIA) platform for identifying tertiary lymphoid structures (TLS) in lung adenocarcinoma (LUAD). *First Author: Vladimir Kushnarev, BostonGene Corporation, Waltham, MA*

Background: Previous studies of non-small cell lung cancer (NSCLC) have shown that TLS can be predictive of therapy response and a positive prognostic factor for survival. Currently, TLS identification is manually performed by pathologists with limited morphological criteria. Standardizing TLS detection with an automated DIA workflow could guide clinical trials in precision medicine by improving patient stratification. Here, we investigate the reproducibility and sensitivity of our DIA platform for evaluating TLS in LUAD using digital histopathology and machine learning. **Methods:** TLS were assessed by 3 pathologists on whole slide images (WSI) in a validation cohort of 22 LUAD samples using current TLS characterization criteria of dense lymphoid structures, the presence/absence of a germinal center, and high endothelial venules (HEVs). The intraclass correlation coefficient (ICC) was used to measure reproducibility between pathologists. The BostonGene DIA platform was used to train models for automated TLS detection. Quantitative measurements of area, lymphocyte number, and density of each TLS were obtained. A prospective cohort of 8 samples was used to compare pathologist and DIA identification of TLS. Normalized numbers of TLS in the tumor area were used for cohort stratification for overall survival (OS) analysis using the Kaplan-Meier method in an independent clinical cohort of 104 TCGA-LUAD patients. **Results:** A panel of 3 pathologists identified 326 unique TLS from 22 samples. Between-pathologist detection of TLS, independent of germinal center or HEV criteria, resulted in good reproducibility with an ICC of 0.77. Our DIA platform exhibited excellent reproducibility with an ICC of 0.94 when compared to validated prospective cohort annotation. In total, 155 and 189 TLS were identified by pathologists and our DIA platform, respectively. The DIA platform demonstrated a markedly improved sensitivity of 0.91 for TLS identification. Furthermore, OS analysis revealed that a TLS density greater than 0.94 TLS per mm^2 of tumor assessed by DIA is a statistically significant independent biomarker of better OS in the LUAD cohort from TCGA. **Conclusions:** These results demonstrate the BostonGene DIA platform detects TLS in LUAD, with improved reproducibility and sensitivity over previous methods. Additionally, the DIA platform showed a TLS density greater than 0.94 TLS per mm^2 of tumor is a positive prognostic marker for OS in LUAD. Standardized TLS DIA identification can be exploited in digital pathology applications for future clinical trials, informing clinicians of predictive and prognostic information during the decision-making process. Research Sponsor: BostonGene Corporation.

3143 **Poster Session**

Rapid access to biomarker data in a community setting: Integration of next-generation sequencing into routine pathologic workflow. *First Author: Kirstin Perdrizet, University of Toronto, Toronto, ON, Canada*

Background: Biomarker data in the form of next generation sequencing (NGS) are critical to the delivery of precision cancer care. Onsite testing is often limited to large academic centers, requiring smaller community centers to rely on samples send outs. Turnaround time for biomarkers can be lengthy and can adversely affect the delivery of optimal therapy in many tumor types. This study aims to evaluate the feasibility of rapidly delivered comprehensive NGS in a community center using a novel workflow in the laboratory by integrating NGS into the routine immunohistochemistry (IHC) service. **Methods:** An automated NGS workflow utilizing the Genexus integrated sequencer with the Oncomine precision assay GX (OPA, Thermofisher Scientific), was validated for clinical use and integrated into the routine diagnostic IHC service. During the study period (Oct 2020 – Oct 2021), NGS biomarker data was generated and reported alongside IHC biomarkers where applicable. A retrospective chart review was performed to assess the early experience and performance characteristics of this novel approach to biomarker testing. **Results:** A total of 578 solid tumor samples underwent genomic profiling. Median turnaround time for biomarker results was 3 business days (IQR 2-5). The majority (n = 481, 83%) of cases were resulted in fewer than 5 business days. Tumor types included lung cancer (n = 310, 54%), melanoma (n = 97, 17%), and colorectal cancer (n = 68, 12%). Specimen types included surgical resections (n = 104, 18%), core biopsies (n = 411, 71%), and cytology specimens (n = 63, 11%). NGS testing detected key driver alterations at expected prevalence rates in respective tumor types; lung *EGFR* (16%), *ALK* (3%), *RET* (1%), melanoma *BRAF* (43%), colorectal *RAS/RAF*wild-type (33%), among others. **Conclusions:** This is the first study demonstrating the clinical feasibility and turnaround time statistics of automated comprehensive NGS performed and interpreted in parallel with diagnostic histopathology and immunohistochemistry in a community setting. This novel approach of integrating biomarkers, IHC, and morphology offers rapid turnaround by removing the need for outsourcing biomarker data. This model could be adopted by other community centers to improve rapid access to biomarker data and therapeutic decision making. Research Sponsor: Pfizer Canada, Pharmaceutical/Biotech Company.

3145 **Poster Session**

Impact of clonal hematopoiesis on tumor control following radiation therapy. *First Author: Jacqueline Tao, Department of Medicine, New York-Presbyterian Weill Cornell, New York, NY*

Background: Clonal hematopoiesis (CH) has well established associations with adverse clinical outcomes including all-cause mortality, cardiovascular disease, and progression to hematologic malignancy. The presence of CH has also been demonstrated to adversely impact survival from non-hematologic cancers, however whether CH may modulate response to radiation therapy (RT) in solid tumors is not known. Here we investigate the potential impact of CH mutations on radiation outcomes. **Methods:** We analyzed data from two previously well annotated cohorts of patients with tumors harboring somatic *ATM* mutations (n = 358) and *FAT1* mutations (n = 365) who received RT and underwent prospective tumor and matched WBC sequencing utilizing the MSK-IMPACT assay. CH variants were detected in the blood samples utilizing a well-validated variant detection and filtration pipeline. Given that pathogenic mutations in ATM have been shown to be strongly associated with improved response to RT, these patients were excluded to avoid confounding. Additionally, patients with blood sampling for CH assessment that occurred more than 6 months after RT were excluded to address the possibility of therapy-related CH. We compared outcomes including irradiated tumor progression in patients with and without CH. **Results:** The final analysis consisted of 412 patients who underwent 811 total courses of radiation. A wide spectrum of solid tumor types were represented, most commonly non-small cell lung cancer (32.5%) and breast cancer (11.9%). A total of 161 patients (39.0%) had CH, with the most commonly mutated genes being *DNMT3A* (25.6%), *PPM1D* (6.2%), *TET2* (5.8%), and *TP53* (5.0%), consistent with prior studies of CH. Patients with CH were older at blood sample collection (67.6 vs 60.2 years, $p < 0.001$), reflecting an expected increase in CH burden with age. Fine Gray competing risks analysis, with death treated as a competing event and with clustering around patient identifier, showed no difference in irradiated tumor progression between patients with and without CH (HR 1.03, 95% CI 0.69 – 1.53, $p = 0.896$). Similarly, subanalyses by CH variant allele frequency and putative CH-driver mutations did not reveal an association between CH and response to RT. A hypothesis generating subgroup analysis by common cancer types, however, suggested that CH was associated with increased risk of progression post-radiation in prostate (HR 4.68, 1.14 – 19.1) and thyroid (HR 3.13, 1.55 – 6.34) cancer cohorts, warranting further investigation. **Conclusions:** We found no difference in irradiated tumor progression among patients who did and did not have CH. There may be an association between CH and poor radiation outcomes in certain cancer types, and further studies are needed to clarify the specific clinical and genomic factors that may influence radiation response. Research Sponsor: None.

3146 **Poster Session**

De novo EGFR T790M mutations in a community-based oncology practice. *First Author: Marilyn E. Holt, Sarah Cannon Research Institute, Nashville, TN*

Background: With the 2018 FDA approval of osimertinib for first-line treatment in EGFR-mutated lung cancers, the prevalence of acquired EGFR T790M mutations is expected to decrease, heightening the significance of de novo T790M mutations. Previous studies have reported a wide range of de novo T790M prevalence, and smaller retrospective studies have indicated that germline T790M may comprise the majority of de novo T790M mutations. Here, we assess the frequency of de novo T790M mutations in a community-based setting and report on germline T790M mutations occurring within this population. **Methods:** Patients with T790M-positive lung cancer were identified using Sarah Cannon's clinicogenomics database containing information for patients treated within the Sarah Cannon research network. All T790M mutations were detected on tissue- and plasma-based NGS tests delivered as part of routine care. De novo and germline EGFR T790M status was determined via manual electronic health record chart review. When available, allele fraction and %cfDNA values were extracted from the structured NGS report and analyzed separately. **Results:** Of T790M-positive lung cancers with available pretreatment testing results, 36% (16/44) were confirmed to be T790M+ prior to EGFR TKI exposure; five of these patients received germline testing, and all five were confirmed to have originated in the germline. Two patients with germline T790M mutations detected on testing ordered by external providers were added to our de novo T790M+ patient analysis after chart review. Co-occurring EGFR mutations, including L858R, were detected in pre-TKI samples for 78% (14/18) of de novo T790M+ patients (Table). Co-occurring mutations in TP53, KRAS, PTEN, or RB1 were detected in pre-TKI samples of all patients without co-occurring EGFR mutations. EGFR C797S was observed after osimertinib treatment in one of four patients with post-TKI testing results. Of confirmed germline T790M+ cases with available allele frequencies, 100% (4/4) had allele fractions >0.5 (tissue) and/or %cfDNA values >50% (plasma). Average allele fraction and %cfDNA values were higher for de novo T790M mutations (allele fraction: 0.5 ± 0.2; %cfDNA: 40% ± 20%) than for acquired T790M mutations (allele fraction: 0.3 ± 0.2; %cfDNA: 2% ± 2%). **Conclusions:** Roughly one-third of T790M mutations detected in real-world settings occur before EGFR TKI exposure and may be associated with germline inheritance. Allele frequency may be a potential indicator of de novo T790M mutations in scenarios where pre-treatment data is not available. Future studies will investigate the impact of de novo T790M mutations on treatment response and evolution of resistance mechanisms in osimertinib-treated patients. Research Sponsor: None.

Co-occurring EGFR mutations in pre-TKI samples.

EGFR Variant	N (%)
L858R	6 (33)
Exon 19 Deletion	2 (11)
G719S	3 (17)
L861Q	2 (11)
H835L	1 (6)
None	4 (22)

N: number of de novo T790M+ patients.

3147 **Poster Session**

Construction of a near-term predictive model for irAEs induced by PD-1 inhibitors. *First Author: Ying Zhang, Changzhi People's Hospital Affiliated to Changzhi Medical College, Changzhi, China*

Background: Immune checkpoint inhibitors have opened a new chapter in cancer therapy, but the incidence of irAEs caused by them is high, and severe irAEs can be fatal. The current research on irAEs is almost focused on early predictions, and there is a lack of near-term predictions (the cycle before the occurrence of irAEs). Absolute eosinophil count (EO#) has been reported to be associated with immune-related pneumonia, but its association with other systemic irAEs requires further exploration. The aim of this study was to explore the near-term predictive value of neutrophil/lymphocyte (NLR), platelet/lymphocyte (PLR), and EO# for PD-1 inhibitor-induced irAEs. **Methods:** The data are from tumor patients who received PD-1 inhibitor therapy in our department from July 2019 to May 2021. A total of 146 cases were included, of which 56 had irAEs. The data of NLR, PLR and EO# in the cycle before the occurrence of irAEs (the median number of cycles was the second cycle) were collected, and the data of the second cycle was used as the control for patients without irAEs group. Logistic method was used to analyze the correlation between NLR, PLR and EO# and irAEs, and a predictive model was constructed. The sensitivity and specificity of the model were evaluated by ROC curve. This study was registered on Chinese Clinical Trail Registry (ChiCTR2100049849). **Results:** A total of 146 tumor patients were included, of which 56 developed at least one irAEs. Grade 1-2 irAEs occurred in 39 cases, grade 3-4 in 12 cases (including cardiac, liver, lung and skin toxicity), grade 5 in 2 cases(including cardiac and lung toxicity), and ungraded in 3 cases. The data of the cycle before the occurrence of irAEs were analyzed. Univariate analysis showed that NLR (odds ratio [OR], 1.4, $p< 0.05$) and EO# (OR, 12.6, $p< 0.05$) were associated with irAEs, and multivariate analysis suggested NLR (OR, 1.7, $p< 0.001$) and EO# (OR, 20.4, $p< 0.05$) were independent risk factors for irAEs. The prediction model composed of NLR, PLR and EO# had a correct rate of 76.7% (AUC = 0.752) in predicting the occurrence of irAEs in the near-term cycle, with a sensitivity of 51.8% and a specificity of 92.2%; the correct rate of predicting irAEs of grade 3 and above was as high as 91.9% (AUC = 0.778), the sensitivity was 14.3% and the specificity was 99.2%. **Conclusions:** The model composed of NLR, PLR and EO# may predict the occurrence of irAEs in the near-term cycle, especially the prediction of irAEs above grade 3, which can provide early warning for the occurrence of irAEs. Clinical trial information: ChiCTR2100049849. Research Sponsor: None.

3148 **Poster Session**

Landscape of endocytosis pathway in colorectal cancer (CRC). *First Author: Hiroyuki Arai, Division of Medical Oncology, USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA*

Background: Recent proteogenomic analyses of CRC revealed that driver gene alterations are enriched in the endocytosis pathway (Vasaikar S, et al. Cell 2019;177:1035-49). Endocytosis is a cellular system involving post-translational modification of plasma membrane proteins through internalization, intracellular trafficking, degradation, and recycling. Clathrin-mediated endocytosis (CME) is the main endocytic portal, and endosomal sorting complexes required for transport (ESCRT) play a critical role in the lysosomal degradation pathway. Besides the well-known function of endocytosis attenuating signaling pathways through receptor clearance from the cell surface, the opposite function contributing to signal maintenance has also been reported. However, the clinical implications of the endocytosis pathway alterations in CRC are largely unclear. **Methods:** We retrospectively reviewed CRC patient samples (n = 15025) submitted to a commercial CLIA-certified laboratory (Caris Life Sciences, Phoenix AZ). Next-generation sequencing of DNA and RNA (whole-transcriptome sequencing) and immunohistochemistry (IHC) were performed. CME-related (47 genes) and ESCRT-related (35 genes) expression signatures were calculated as composite z-scores and compared between subgroups stratified by *RAS*/*BRAF* mutation status, MSS/MSI status, tumor sidedness, and consensus molecular subtype (CMS). *VPS4A*/*VPS4B* expression correlation with major oncogenic pathway signatures (composite z-scores) and *CMTM6*/*CMTM4*/*HIP1R* expression association with PD-L1+ IHC were also assessed. **Results:** Among 17 endocytosis-related genes, no pathogenic/likely pathogenic mutations were identified. The CME-related signature was increased in *RAS*/*BRAF* wild type vs. mutant (0.93 z-score difference, $p= 0.04$) and MSS vs. MSI-high (6.0 z-score difference, $p< 0.01$), while the ESCRT-related signature was higher in MSS compared to MSI-high (2.7 z-score difference; $p< 0.01$). No differences between tumor sidedness were observed in both CME- and ESCRT-related signatures (0.81 and 1.17 z-score differences, respectively). CMS4 had the highest expression of both signatures, while CMS3 had the lowest, of both CME- and ESCRT-related genes (each > 20 z-score difference, $p< 0.01$). *VPS4A* and *VPS4B* expression had a strong positive correlation with WNT, EGFR/MAPK, TGF-beta, and Notch pathway signatures (0.65-0.83 Spearman, all $p< 0.01$). *CMTM6* expression was positively associated with PD-L1+ IHC (1.2-fold increase vs PD-L1-negative, $p< 0.01$), while *CMTM4* and *HIP1R* expression showed a negative association (0.7- and 0.9-fold decrease, respectively, $p< 0.01$). **Conclusions:** This large study indicates endocytosis pathway expression is positively associated with oncogenic pathway signaling in CRC. Further analysis of *RAS*/*BRAF* wild type, MSS, and CMS4 patient subgroups are warranted to determine the efficacy of targeting endocytosis pathways in CRC. Research Sponsor: This work was supported by the National Cancer Institute [P30CA 014089 to HJL], Gloria Borges WunderGlo Foundation, Dhont Family Foundation, Daniel Butler Memorial Fund, Victoria and Philip Wilson Research Fund, and San Pedro Peninsula Cancer Guild.

3149 **Poster Session**

BRAF-targeted therapy for locally advanced ameloblastoma of the mandible: A potential neoadjuvant strategy. *First Author: Shirly Grynberg, Ella Lemelbaum Institute for Immuno Oncology and Melanoma, Sheba Medical Center, Ramat-Gan, Israel*

Background: Ameloblastoma is a rare benign but locally aggressive odontogenic neoplasm, with 2% of cases representing ameloblastic carcinoma or metastatic ameloblastoma. It affects young adults with high recurrence rates after surgery. The standard therapy is radical bone resection with subsequent functional, aesthetic & psychological impairments. Therefore, other therapeutic options, including neoadjuvant approach, should be considered. Sixty to 70% of mandible Ameloblastoma carry a BRAF mutation, usually V600E, and previous case reports have shown durable responses to treatment with BRAF inhibitors in these patients. We sought to explore the possibility of neoadjuvant BRAF or BRAF+MEK inhibition as neoadjuvant treatment in mandible Ameloblastoma. Here we present results of 12 patients with locally advanced disease who were treated with BRAF with or without MEK inhibitors. **Methods:** Patients who were unable to undergo jaw preservation surgery for locally advanced Ameloblastoma with a BRAF V600E mutation were treated with Dabrafenib or Dabrafenib-Tratmetinib in an EAP form. Patient records were analyzed for baseline parameters, treatment regimen, toxicity, response to therapy and the ability to convert to a mandible preservation surgery. Data were collected and analyzed in accordance with Sheba Medical Center IRB approval. Statistical analyses were done with STATA v.17. **Results:** Twelve patients were treated with Dabrafenib/ Dabrafenib-Tratmetinib between 2017-2021. Five patients received BRAF-MEK inhibitors and 7 BRAF inhibitor alone. Median age was 21. Ten patients(83%) showed excellent response to therapy and have successfully converted from planned radical bone resection to mandible preservation surgery. The other 2 patients are still on therapy and have also showed deep responses that enable conversion to mandible preservation. Median time to surgery was 10 months. With median follow up of 18 months, no cases of recurrence were documented. Rate of adverse events was as expected with only 1 case of G3-4 (hepatitis). **Conclusions:** Targeted therapy with BRAF with or without MEK inhibition may serve as an important therapeutic tool for locally advanced Ameloblastoma with the potential of organ preservation treatment, and is an important example of oncological therapy assisting in non-cancerous tumors. Research Sponsor: None.

3150 **Poster Session**

Updated survival follow-up for phase I study of abexinostat with pazopanib in patients with solid tumor malignancies. *First Author: Erica S Tsang, University of California San Francisco, San Francisco, CA*

Background: Histone deacetylase (HDAC) inhibition downregulates HIF-1a, which may be effective in overcoming resistance to VEGF-targeting tyrosine kinase inhibitors. We report the updated survival follow-up for patients treated with abexinostat and pazopanib in a phase Ib trial. **Methods:** Patients with solid tumor malignancies were enrolled in this phase Ib, open-label trial (NCT01543763) of abexinostat in combination with pazopanib (3+3 design), with a dose expansion restricted to renal cell carcinoma (RCC). Patients received a 1-week run-in period with abexinostat alone, and then combination abexinostat with pazopanib during a 28-day treatment cycle until disease progression, unacceptable toxicity or study withdrawal. Plasma samples from 29 patients were sent for metabolomics analysis. **Results:** 51 patients were enrolled: N = 36 patients in dose escalation, N = 15 in dose expansion. At the time of last report in 2017, 5 patients remained on study treatment: N = 4 with RCC, and N = 1 with thymic neuroendocrine carcinoma. 4 of these patients have now had disease progression. Median duration of therapy measured 44.9 months (range 39.8-102.2). One patient with metastatic RCC (patient 1) remains on study treatment, after progression on 5 prior lines of systemic therapy. With updated survival follow-up, median OS measured 12.4 months in the dose escalation arm and 27.65 months in the RCC dose expansion cohort. Overall median duration of therapy in all 51 patients measured 5.6 months (range 1-103 months). Progression-free survival among patients with high PBMC HDAC2 expression (> 0.4) remains longer compared to those with low expression (median 6.3 vs. 3.7 months, p = 0.0041). Metabolomics analysis demonstrated a negative correlation between HDAC2 and N6-acetyllysine, suggesting that baseline HDAC2 may impact efficacy of HDAC inhibition. **Conclusions:** The combination of abexinostat with pazopanib appears promising, with the potential for long-term responses particularly in patients with metastatic RCC. This has led to an ongoing phase III trial examining this combination in RCC. Clinical trial information: NCT01543763. Research Sponsor: GlaxoSmithKline, Pharmacyclics.

Patient	Pazopanib dose (mg/ daily)	Abexinostat Dose (mg/m^2 twice daily)	Histology	Age at Study Entry	Number of Prior Systemic Therapies	Duration of Therapy (months)	Best Response
1	400	30	RCC	71.1	5	102.2	Partial response
2	800	45	Thymic neuroendocrine carcinoma	66.5	1	57.7	Stable disease
3	800	45	RCC	52	2	43.4	Partial response
4	800	45	RCC	60	None	39.8	Partial response
5	800	45	RCC	73	None	44.9	Partial Response

3151 **Poster Session**

Combination treatment of radiofrequency ablation and peptide neoantigen vaccination: Promising modality for future cancer immunotherapy. *First Author: Yong Fang, Internal Medicine-Oncology, Sir Run Run Shaw Hospital ZheJiang University School Of Medicine, Hangzhou, China*

Background: We previously reported the safety and immunogenicity of a personalized neoantigen-based peptide vaccine, iNeo-Vac-P01, in patients with a variety of cancer types. The current study investigated the synergistic effects between radiofrequency ablation (RFA) and neoantigen vaccination in cancer patients and tumor-bearing mice. **Methods:** 28 cancer patients were enrolled in this study, including 10 patients who had received RFA treatment within 6 months before scheduled for vaccination, and 18 patients who had not. Individualized neoantigen peptide vaccines were designed, manufactured, and delivered for all patients, followed by subcutaneous administration of GM-CSF as an adjuvant. Mouse models were used to validate the synergistic efficacy of combination treatment of RFA and neoantigen vaccination. **Results:** Longer median progression free survival (mPFS) and median overall survival (mOS) were observed in patients receiving RFA prior to vaccines compared to patients only receiving vaccines (4.42 and 20.18 months vs. 2.82 and 10.94 months). *Ex vivo* ELISpot assay showed that patients who received both had stronger IFN-γ responses against patient-specific neoantigens at baseline and post vaccination. Mice receiving RFA together with vaccine displayed higher antitumor immune responses than mice receiving single modality; addition of anti-PD-1 further enhanced the antitumor response. **Conclusions:** Neoantigen vaccination after RFA treatment led to an overall increase in clinical response and immune response among patients of different cancer types. Combination treatment of both modalities in mice further validated their synergistic antitumor potentials, which could be further enhanced by the addition of anti-PD-1. The mechanisms of their synergies require further investigation. Clinical trial information: NCT03662815. Research Sponsor: National Natural Science Foundation of China; Medical Science and Technology Project of Zhejiang Province; National Natural Science Foundation of China; Natural Science Foundation of Zhejiang Province; Health Commission of Zhejiang Province.

3152 **Poster Session**

Do early phase trials predict clinical efficacy in subsequent phase III biomarker-enriched randomized trials? *First Author: Suji Udayakumar, Sunnybrook Research Institute, Toronto, ON, Canada*

Background: Efficacy endpoints of randomized controlled trials (RCT) are commonly used as the basis of regulatory drug approvals. Recently, promising results in early phase trials have resulted in approval of biomarker-targeted therapies. We examined if early phase trial results were associated with efficacy in subsequent biomarker-enriched RCTs. **Methods:** All cancer drug RCTs conducted between January 2006 and March 2021 were identified through Clinicaltrials.gov. Trials were eligible if a biomarker was used to select a patient population for treatment with a targeted agent. Associated early phase trials were included if they matched the RCT in treatment setting and patient population. Trials pairs were compared using objective response rate (ORR) and progression-free survival (PFS). We assessed difference in endpoints using summary measures (e.g., average, range). We examined whether early phase trials results were associated with RCT results using logistic regression. **Results:** The search yielded 2,157 unique phase III RCTs and 27 RCTs met eligibility criteria pairing with associated early phase trials, where 17 RCTs met their primary endpoint. The most common biomarkers were EGFR+ (n = 8), HER2+ (n = 5) and PD-L1 (n = 5). Based on average difference of trial pairs, ORR was similar between trials (1.59%, 95% CI = -2.5-5.6, p = 0.50) and median PFS was slightly higher in early phase trials (1.95 months, 95% CI = 0.91-2.99, p < 0.05). On an individual pair basis, there was large range of variability in the difference between early phase trials and RCTs for ORR (range = -23.9-20.2%) and median PFS (range = -0.8-7.4 months). The probability of the RCT meeting its primary endpoint is 50% or 95%, when the early phase trial ORR is 41.2% (95% CI = 35.2-47.1%) or 77.7% (95% CI = 71.7-83.6%), respectively. **Conclusions:** Through comparison of early phase trials and subsequent phase III RCT, we found that, overall, ORR has minimal bias in early phase trials, and median PFS appears to be slightly overestimated. Substantial variability in results for trial pairs suggests that, on an individual basis, results in early phase trial can be inconsistent with results in subsequent RCT. Early phase trial results may be associated with RCTs meeting their primary endpoint when ORR is very high; however, caution must be exercised when using early phase trials as representative of RCTs for decision-making as the predictive ability of early phase trials is limited. Research Sponsor: None.

TPS3153 **Poster Session**

First-in-human study of the B7-H4 antibody-drug conjugate (ADC) AZD8205 in patients with advanced/metastatic solid tumors. *First Author: Funda Meric-Bernstam, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: ADCs are a class of anti-cancer agents that leverage the selectivity of monoclonal antibodies to preferentially target and deliver chemotherapeutic agents to cancer cells. AZD8205 is an ADC, administered by IV infusion, that consists of a human anti-B7-H4 antibody conjugated via a cleavable linker to a topoisomerase I inhibitor (TOP1i) warhead. B7-H4 is a transmembrane protein that binds to an unknown receptor on activated T cells, inhibiting their function. It is highly expressed by a wide variety of tumors including cholangiocarcinoma (CCA) and breast, ovarian and endometrial cancers, and is associated with poor prognosis. AZD8205 specifically binds to B7-H4 expressing tumor cells and is internalized. The TOP1i warhead is released, interfering with TOP1 during DNA replication leading to transcription-mediated DNA damage and cell death. TOP1i ADCs have shown clinical activity in several tumor types including breast cancer. In preclinical studies, AZD8205 has shown promising antitumor activity in various patient-derived xenograft models and an acceptable toxicity profile. This first-in-human study (NCT05123482) is evaluating AZD8205 for the treatment of selected advanced/metastatic tumors. **Methods:** This phase I/IIa, open-label, dose-escalation and dose-expansion study is currently investigating AZD8205 monotherapy in patients ≥18 years old (≥20 years for Japan) with CCA, breast, ovarian or endometrial cancers. Eligibility criteria include relapsed/metastatic disease following standard of care treatment, measurable disease per RECIST v1.1, and ECOG PS 0–1. Key exclusion criteria include spinal cord compression or leptomeningeal carcinomatosis, symptomatic brain metastases, and history of interstitial lung disease/pneumonitis. Expression of B7-H4 will be evaluated using a validated central laboratory immunohistochemistry assay on tumor samples collected before, during, and when feasible, after AZD8205 treatment. In the escalation phase, patients will receive AZD8205 followed by 21 days of observation for dose-limiting toxicities. Patients will be enrolled in escalating dose cohorts using the modified toxicity probability interval-2 model with at least 3 evaluable patients per dose level. Patients will continue on study treatment until disease progression, initiation of alternate anticancer therapy, unacceptable toxicity, or withdrawal of consent. Primary objectives are to determine the safety and tolerability of AZD8205 and identify the maximum tolerated dose and/or recommended phase 2 dose. Secondary objectives include assessing initial activity (objective response and progression-free survival by RECIST v1.1, and overall survival), pharmacodynamics, pharmacokinetics, and immunogenicity. The trial is currently recruiting and will enroll patients globally. Clinical trial information: NCT05123482. Research Sponsor: AstraZeneca.

TPS3154 **Poster Session**

Phase 1 study of SGN-PDL1V, a novel, investigational vedotin antibody–drug conjugate directed to PD-L1, in patients with advanced solid tumors (SGNPDL1V-001, trial in progress). *First Author: Amita Patnaik, START San Antonio, San Antonio, TX*

Background: Programmed cell death ligand 1 (PD-L1) is a cell-surface protein involved in the programmed cell death protein 1 (PD-1)/PD-L1 immune checkpoint, which inhibits T-cell activation. Elevated PD-L1 expression is observed across a broad spectrum of solid tumor types. Expression of PD-L1 in tumors can signal through PD-1 on T cells to inhibit T-cell effector function. Blockade of the PD-1/PD-L1 signaling axis may restore antitumor immunity by reactivating T-cell effector function in the tumor microenvironment. SGN-PDL1V is a novel, investigational vedotin antibody–drug conjugate directed to PD-L1 with multiple proposed mechanisms of action including monomethyl auristatin E (MMAE)-directed cytotoxicity, bystander effect, and immunogenic cell death (ICD). Even in xenograft models with low, heterogeneous PD-L1 expression, SGN-PDL1V demonstrated antitumor activity via direct cytotoxicity and the bystander effect. Cytotoxicity mediated by SGN-PDL1V also led to immune activation due to MMAE-induced ICD (Kwan et al 2021). These preclinical findings provide a rationale for evaluating SGN-PDL1V in patients (pts) with advanced solid tumors. **Methods:** SGNPDL1V-001 (NCT05208762) is a phase 1, first-in-human, multicenter, open-label trial designed to evaluate the safety, tolerability, pharmacokinetics (PK), and antitumor activity of SGN-PDL1V in pts with advanced solid tumors. This study includes 3 parts: dose escalation (Part A), dose and schedule optimization cohorts (Part B), and dose expansion in disease-specific cohorts and a biology cohort (Part C). Adult pts (≥18 years) with histologically/cytologically confirmed metastatic/unresectable solid tumors, including non-small cell lung cancer, head and neck squamous cell carcinoma, esophageal squamous cell carcinoma, melanoma, or ovarian cancer, will be eligible. Pts must have ECOG PS 0–1 and have failed or are unable to tolerate standard therapies. Pts must have PD-L1 expression ≥1 by tumor proportion score or combined positive score based on historical testing. Prior treatment with an MMAE-containing agent or an anti–PD-L1 agent (within 6 months) is not permitted. Primary endpoints include adverse events, laboratory abnormalities, dose-limiting toxicities, and cumulative dose-level safety. Secondary endpoints include rate and duration of objective response, progression-free survival, overall survival, PK, and incidence of antidrug antibodies. Exploratory endpoints include pharmacodynamics (PD), PK/PD relationships, and patient-reported outcomes. Safety and antitumor activity endpoints will be assessed using descriptive statistics. Objective response rate will be analyzed by tumor type, dose levels, and schedules. Enrollment for Part A is ongoing at sites in North America and is planned in Europe. Clinical trial information: NCT05208762. Research Sponsor: Seagen Inc.

TPS3155 **Poster Session**

Phase 1 study of SGN-B7H4V, a novel, investigational vedotin antibody–drug conjugate directed to B7-H4, in patients with advanced solid tumors (SGNB7H4V-001, trial in progress). *First Author: Amita Patnaik, START San Antonio, San Antonio, TX*

Background: B7-H4, a B7 immune checkpoint ligand, is expressed at low levels in normal tissue and negatively regulates T-cell function by inhibiting T-cell proliferation and cytokine production. B7-H4 expression is elevated in solid tumors, including breast, ovarian, and endometrial cancers. Targeting B7-H4–expressing tumor cells may relieve B7-H4–mediated T-cell inhibition. SGN-B7H4V is a novel, investigational vedotin antibody–drug conjugate directed to B7-H4 with proposed mechanisms of action including monomethyl auristatin E (MMAE)-directed cytotoxicity, bystander effect, antibody-dependent cellular cytotoxicity, and antibody-dependent cellular phagocytosis. SGN-B7H4V elicited antitumor activity in cell line-derived xenograft models of triple-negative breast cancer (TNBC) and patient-derived xenograft models of TNBC and ovarian cancer (Gray et al 2021), providing a rationale to evaluate SGN-B7H4V in patients (pts) with advanced solid tumors. **Methods:** SGNB7H4V-001 (NCT05194072) is a phase 1, first-in-human, multicenter, open-label trial evaluating the safety, tolerability, pharmacokinetics (PK), and antitumor activity of SGN-B7H4V in pts with advanced solid tumors. This study includes 3 parts: dose escalation (Part A), dose and schedule optimization (Part B), and dose expansion in disease-specific cohorts and a biology cohort (Part C). Adult pts (≥18 years) with histologically/cytologically confirmed locally advanced unresectable or metastatic solid tumors including high-grade serous epithelial ovarian cancer, primary peritoneal cancer, fallopian tube cancer, human epidermal growth factor receptor 2-negative and hormone receptor-positive breast cancer, TNBC, endometrial carcinoma, squamous non-small cell lung cancer, cholangiocarcinoma, or gallbladder carcinoma, are eligible. Pts must have ECOG PS 0–1 and relapsed/refractory disease or be intolerant to standard-of-care therapies. Prior treatment with an MMAE-containing agent or a B7-H4–targeted agent is not permitted. Primary endpoints include the rate of adverse events, laboratory abnormalities, dose-limiting toxicities, and cumulative dose-level safety. Secondary endpoints are objective response rate (ORR), complete response rate, duration of objective response (DOR), progression-free survival (PFS), overall survival (OS), PK, and incidence of antidrug antibodies. Exploratory endpoints include pharmacodynamic (PD) analyses, PD and PK exposure measurements, B7-H4 characterization on malignant cells, and biomarker analyses. Safety and antitumor activity endpoints will be assessed using descriptive statistics. ORR will be analyzed by tumor type and dose. DOR, PFS, and OS will be estimated using the Kaplan–Meier method. Enrollment for Part A is ongoing in North America and is planned in Europe. Clinical trial information: NCT05194072. Research Sponsor: Seagen Inc.

TPS3156 **Poster Session**

TIP: A phase I/II study of MGTA-117, an anti-CD117 antibody-drug conjugate, in patients with adult acute myeloid leukemia (AML) and myelodysplasia with excess blasts (MDS-EB). *First Author: Andrew S. Artz, City of Hope, Duarte, CA*

Background: Hematopoietic stem cell transplantation (HSCT) is used with curative intent for AML and MDS-EB. MGTA-117 is a novel Ab-drug conjugate (ADC) in development for conditioning prior to HSCT. MGTA-117 selectively targets CD117 (c-Kit) with a human monoclonal Ab to CD117 conjugated to an amanitin payload that depletes CD117-expressing cells by inhibiting RNA polymerase II. Human hematopoietic stem cells and AML tumor cells express high levels of CD117, and MGTA-117 potently depletes these target cells, with an IC50 of <10pM in vitro. MGTA-117 has demonstrated in vitro and in vivo stability, confirming its characterization as a highly potent and selective agent. In a primate GLP toxicology study, MGTA-117 maximally depleted bone marrow stem cells at a dose not associated with evidence of toxicity in other tissues. Dose-dependent reduction of peripheral reticulocytes, produced from CD117+ erythroid precursors in the bone marrow, was an early and time sensitive biomarker of bone marrow CD117+ cell depletion. Higher doses were associated with the elevation of transaminases and histopathology that were asymptomatic and transient. Highest Non- Severely Toxic Dose (HNSTD) was used to establish the starting dose in this First-in-Human study. Based upon dose exposure and allometric scaling, it is expected that the clinical exposures after a 0.02 mg/kg dose in the first human cohort will provide an optimal > 100-fold safety margin over exposures observed after the 0.3 mg/kg dose that was the HNSTD in the primate GLP toxicology study. **Methods:** This phase I/II, multicenter, open-label, dose-escalation study will investigate the safety, tolerability, PK profile, PD activity, and blast depletion activity of MGTA 117 given intravenously as a single dose in adults with R/R AML or MDS-EB. Patients must be 18-75 yrs, have a WHO-defined diagnosis of CD117+ R/R AML or MDS-EB with ≥5% marrow myeloblasts. Patients must have ECOG PS ≤2, and adequate hepatic, renal, and cardiac function. The primary objective is to establish a minimum safe and biologically effective (MSBE) dose of MGTA-117 in R/R AML and MDS-EB patients based on safety and CD117 receptor occupancy (RO) in circulating leukemic blasts after dosing. The observation period for dose limiting toxicities is 21 days. Patients will be followed for changes in reticulocyte, neutrophil, and platelet counts in PB and percent change from baseline in leukemic blasts or stem/progenitor cells in PB and/or BM. CD117 receptor occupancy by MGTA-117 will be measured and MSBE dose will be based on safety and receptor occupancy. The study is designed with the possibility that subjects would proceed to HSCT >28 days after MGTA-117 administration, if eligible per the local transplant practices. Clinical trial information: NCT05223699. Research Sponsor: Magenta Therapeutics.

TPS3157 **Poster Session**

First-in-human, phase 1, open-label, dose-escalation, dose-expansion study of ADCT-901 as monotherapy in patients with select advanced solid tumors. *First Author: R. Donald Donald Harvey, Winship Cancer Institute, Atlanta, GA*

Background: Kidney associated antigen 1 (KAAG1) is highly and selectively expressed on tumor cell surface, such as ovarian, prostate, and triple negative breast cancers (TNBC), and is rapidly internalized and co-localized with a lysosomal marker, making an ideal candidate for an antibody-drug conjugate (ADC) target. ADCT-901 is an ADC composed of a humanized monoclonal antibody IgG1 against KAAG1, conjugated through a cathepsin-cleavable linker to SG3199, a pyrrolobenzodiazepine (PBD) dimer cytotoxin. In mouse xenograft models of human-derived TNBC, ovarian, and renal cancers significant tumor reduction was observed after a single dose of ADCT-901, providing the rationale for clinical development of a PBD-based ADC to treat KAAG1 expressing tumors (Zammarchi et al, AACR 2019). This study aims to identify the recommended dose and schedule for expansion and to characterize safety and tolerability of ADCT-901 in patients (pts) with selected advanced solid tumors that generally express KAAG1. **Methods:** ADCT-901-101 is a phase 1, multicenter, 2-part, open-label study that will enroll ~70 pts (NCT04972981). Part 1: pts will receive escalating doses of ADCT-901 guided by a 3+3 design (1st dose: 15 μg/kg every 3 weeks [Q3W]; highest dose: 290 μg/kg Q3W). Dose escalation will be evaluated by administering the lowest dose to first 3 pts, then increasing/decreasing the dose based on dose-limiting toxicity (DLT) experienced by pts. The dose and schedule of ADCT-901 identified in part 1 will be tested in part 2 to characterize safety, tolerability, and preliminary efficacy of ADCT-901. Primary endpoints include incidence of DLTs (part 1 only), frequency/severity of adverse events (AE) and serious AE, clinically significant changes in vitals, laboratory values, overall tolerability, and frequency of dose interruptions and reductions. Secondary endpoints include overall response rate, duration of response, progression-free and overall survival, pharmacokinetic parameters of ADCT-901 total antibody, PBD-conjugated antibody, unconjugated SG3199 in serum, and frequency of confirmed positive antidrug antibody responses. Exploratory endpoints include tumor modulation and potential pharmacodynamic changes. Key inclusion criteria: pathologic diagnosis of selected solid tumor (cholangiocarcinoma, renal cell carcinoma, ovarian/fallopian tube and prostate cancers, TNBC) locally advanced or metastatic at time of screening, pts refractory or intolerant to existing therapy, tissue biopsy or available tissue sample, ECOG of 0-2, and adequate organ function based on predefined laboratory parameters. Pts with symptomatic CNS metastases and clinically significant third space fluid accumulation will be excluded. The study opened for recruitment in September 2021; enrollment is ongoing. Funding: ADC Therapeutics; medical writing: CiTRUS Health Group. Clinical trial information: NCT04972981. Research Sponsor: ADC Therapeutics.

TPS3158 **Poster Session**

ELU-FRα-1: A study to evaluate ELU001 in patients with solid tumors that overexpress folate receptor alpha (FRα). *First Author: Wen Wee Ma, Division of Medical Oncology, Mayo Clinic, Rochester, MN*

Background: ELU001 is a novel, first-in-class, new molecular entity described as a C'Dot Drug Conjugate (CDC). ELU001 consists of ~12 folic acid targeting moieties and ~22 exatecan topoisomerase-1 inhibitor payloads on Cathepsin-B cleavable linkers covalently bound to the surface of each silicon core/polyethylene glycol C'Dot nanoparticle. CDCs are small in size (~6 nm) , have a greater ability to penetrate into and through tumors as compared to ADCs, and are rapidly eliminated by the kidneys. The rapid systemic elimination is expected to lead to less toxicity than is observed with targeting platforms like ADCs that have a longer half-life in circulation. ELU001's high avidity is believed to promote internalization into FRα overexpressing cancer cells, selectively delivering it's ~22 molecules of payload. The first-in-human clinical trial, ELU-FRα-1, is currently recruiting patients that have advanced, recurrent or refractory FRα overexpressing tumors considered to be topoisomerase 1 inhibitor-sensitive based on the literature, and, in the opinion of the Investigator, have no satisfactory therapeutic options available. **Methods:** This is a Phase 1 / 2 multicenter, open label clinical trial with two parts: Part 1 Dose Escalation and Part 2 Tumor Group Expansion Cohort(s). In Part 1, patients with cancer types with a high likelihood of having FRα overexpressing tumors based on historical data, (specifically, ovarian, endometrial, colorectal, gastric, gastroesophageal junction, triple negative breast, or non-small cell lung cancers, or cholangiocarcinoma), will be enrolled to the study. Patients will receive ELU001 on a weekly dose regimen (QW) (once a week for 3 weeks, 1 week rest) or every other week dose regimen (Q2W, with no rest between cycles). Retrospective analysis of FRα expression will be determined. Part 2 uses a Simon's Two-Stage design to evaluate 4-6 tumor group expansion cohorts, each consisting of patients with specific tumor types (to be identified based on emerging data) that overexpress FRα (prospectively determined prior to enrollment). The primary objective for Part 1 is to identify the MTD/RP2D and for Part 2 is ORR. Dose Escalation will recruit about 25 patients per dose regimen (QW or Q2W). Dose Expansion will recruit about 15 patients per tumor group expansion cohort. Secondary objectives are anti-tumor activity (DOR, PFS, TFST, PFS2, OS), frequency, severity and tolerability of adverse events, PK, ADA, and FRα expression assessments. The study is actively enrolling in the US – Cohorts 1-2 have been completed without DLT. Enrollment to Cohort 3 began in December 2021. Clinical trial information: NCT05001282. Research Sponsor: Elucida Oncology.

TPS3159 **Poster Session**

Phase 1 study of SGN-ALPV, a novel, investigational vedotin antibody–drug conjugate directed to ALPP/ALPPL2 in advanced solid tumors (SGNALPV-001, trial in progress). *First Author: Nehal Lakhani, START Midwest, Grand Rapids, MI*

Background: Alkaline phosphatase placental (ALPP) and ALPP-like 2 (ALPPL2) are proteins with 98% sequence similarity that are highly expressed in ovarian, endometrial, gastric, and testicular cancers. Restricted normal tissue expression and efficient lysosomal trafficking of ALPP and ALPPL2 highlight their potential as anticancer targets. SGN-ALPV is a novel investigational vedotin antibody–drug conjugate composed of a humanized anti-ALPP/ALPPL2 monoclonal antibody, a protease-cleavable linker, and the microtubule disrupting agent monomethyl auristatin E (MMAE). The proposed mechanism of action of SGN-ALPV is binding to ALPP/ALPPL2 on the cell surface, where it is internalized and trafficked to the lysosome. Lysosomal proteases cleave the linker to release MMAE into the cytoplasm, where it binds and disrupts the microtubule network, causing cell cycle arrest and apoptosis. Additional mechanisms of action of SGN-ALPV include immunogenic cell death and apoptosis of neighboring cells via the bystander effect. Promising preclinical data support the evaluation of SGN-ALPV in a clinical trial. **Methods:** SGNALPV-001 (NCT05229900) is a phase 1, open-label, multicenter study designed to evaluate the safety, tolerability, pharmacokinetics (PK), and antitumor activity of SGN-ALPV in patients (pts) with select advanced solid tumors. This study consists of 3 parts: dose escalation (Part A), dose and schedule optimization (Part B), and dose-expansion in disease-specific cohorts and a biology cohort (Part C). Adult pts (≥18 years) with confirmed ovarian, endometrial, non-small cell lung, gastric, cervical cancer, or testicular germ-cell tumors, relapsed or refractory to approved therapies, with measurable disease per RECIST v1.1 and an ECOG PS 0–1 are eligible. Primary endpoints include incidence of adverse events, laboratory abnormalities, dose-limiting toxicities, and cumulative safety. Secondary endpoints include estimates of antidrug antibodies, PK parameters, objective response rate, duration of response, progression-free survival, and overall survival. Exploratory endpoints are pharmacodynamic and biomarker measurements. Safety and antitumor activity endpoints will be summarized using descriptive statistics. Enrollment for Part A is ongoing in sites in North America and Europe. Enrollment for Parts B and C will be opened upon completion of Part A. Clinical trial information: NCT05229900. Research Sponsor: Seagen.

TPS3161 **Poster Session**

Phase 1 study of patritumab deruxtecan (HER3-DXd; U3-1402) in combination with osimertinib in patients with advanced *EGFR*-mutated NSCLC. *First Author: Pasi A. Janne, Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, MA*

Background: Although first-line treatment with the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor osimertinib improved survival in patients (pts) with advanced/metastatic *EGFR*-mutated (*EGFRm*) non-small cell lung cancer (NSCLC), therapy after acquired resistance to osimertinib remains an unmet need. HER3 is expressed in the majority of *EGFRm* NSCLCs. HER3-DXd is a novel, investigational, HER3-directed antibody-drug conjugate that demonstrated preliminary single-agent clinical activity in *EGFRm* NSCLC. In preclinical models of *EGFRm* NSCLC, osimertinib increased membrane HER3 expression, improved the internalization rate of HER3-DXd, and enhanced tumor growth inhibition by HER3-DXd. Therefore, HER3-DXd with osimertinib might improve outcomes in pts with disease that progressed with osimertinib therapy. This phase 1 study (NCT04676477; U31402-A-U103) evaluates HER3-DXd in combination with osimertinib in pts with advanced *EGFRm* NSCLC that has progressed with first-line osimertinib therapy. **Methods:** This is an open-label, 2-part study of HER3-DXd in combination with osimertinib. Pts are enrolling in North America, Europe, and Asia. Dose escalation enrolls pts with locally advanced/metastatic NSCLC with an *EGFR*-activating mutation (exon 19 del or L858R) and progression during or after osimertinib therapy. Pts receive HER3-DXd 1.6, 3.2, 4.8, or 5.6 mg/kg intravenously (IV) every 3 weeks (Q3W) in combination with osimertinib 40 or 80 mg orally (PO) once daily (QD). Pts are enrolled in each cohort guided by safety (dose-limiting toxicities) using a Bayesian logistic regression model. Primary objectives of dose escalation are to assess safety and tolerability of the combination and identify a recommended combination dose (RCD). In dose expansion, pts will be randomized 1:1 to receive either HER3-DXd and osimertinib at the RCD (arm 1, [≈60 pts]) or HER3-DXd 5.6 mg/kg IV Q3W (arm 2, [≈60 pts]). A third arm (arm 1b, [≈60 pts]) may be added to evaluate 2 provisional RCDs of HER3-DXd + osimertinib. The primary objective of dose expansion (arms 1, 2, and 1b) is to evaluate efficacy of the combination vs that of monotherapy. The primary endpoint is objective response rate (ORR) as assessed by blinded independent central review. Other efficacy endpoints include ORR by investigator and duration of response, disease control rate, time to response, progression-free survival, and overall survival. If the RCD includes an osimertinib dose of 80 mg PO QD, ≈30 pts with advanced *EGFRm* NSCLC without prior treatment will be enrolled and treated at the RCD in a separate cohort; the primary objective is to assess safety and tolerability. A tumor sample after progression with osimertinib (or prior to entry) is required for pts enrolled in dose expansion for retrospective evaluation of HER3 and biomarker analyses. Clinical trial information: NCT04676477. Research Sponsor: Daiichi Sankyo Inc.

TPS3162 **Poster Session**

Datopotamab deruxtecan (Dato-DXd) plus pembrolizumab in treatment-naive advanced/metastatic (adv/met) non–small cell lung cancer (NSCLC) with PD-L1 ≥ 50% and without actionable genomic alterations. *First Author: Benjamin Philip Levy, Johns Hopkins Sidney Kimmel Cancer Center, Washington, DC*

Background: First-line treatment with immunotherapy has significantly improved survival in patients with adv/met NSCLC. Pembrolizumab (pembro) as monotherapy has shown superior efficacy compared with chemotherapy in treatment-naive patients with advanced NSCLC and PD-L1 expression ≥50%, but most patients will ultimately experience progression. Dato-DXd is an antibody-drug conjugate (ADC) consisting of a humanized anti-TROP2 IgG1 monoclonal antibody attached to a topoisomerase I inhibitor payload via a stable tetrapeptide-based cleavable linker. In the ongoing phase 1 TROPION-PanTumor01 study (NCT03401385; DS1062-A-J101), Dato-DXd 6 mg/kg monotherapy demonstrated an objective response rate (ORR) of 28% and a manageable safety profile in pretreated patients with NSCLC. In addition, preclinical studies showed that DXd ADCs combined with an anti–PD-1 antibody was more effective than monotherapy with either agent alone. The tolerability of Dato-DXd 6 mg/kg in combination with pembrolizumab was confirmed in the phase 1b TROPION-Lung02 trial (NCT04526691; DS1062-A-U102). Here we describe the phase 3 TROPION-Lung08 trial evaluating Dato-DXd combined with pembro in treatment-naive patients with adv/met NSCLC. **Methods:** TROPION-Lung08 (NCT05215340; DS1062-A-U304) is a global, randomized, open-label, phase 3 trial of Dato-DXd plus pembro vs pembro alone in treatment-naive patients with adv/met non-actionable oncogenic driven NSCLC with PD-L1 ≥50% (as determined by PD-L1 IHC 22C3 pharmDx assay). Approximately 740 patients will be randomized to receive pembro 200 mg plus Dato-DXd 6 mg/kg or pembro 200 mg alone every 21 days until discontinuation or 35 cycles of pembro. Randomization will be stratified by Eastern Cooperative Oncology Group performance status (0 vs 1), histology (squamous vs nonsquamous), geographic region (East Asia vs rest of world), and smoking status (former/current vs never). Patients must have stage IIIB/IIIC NSCLC ineligible for curative treatment or stage IV disease. Patients must not have received prior systemic therapy; if patients received neoadjuvant/adjuvant systemic therapy without immune checkpoint inhibitors, it must have been given ≥6 months before the diagnosis of adv/met disease. The primary endpoints are progression-free survival (assessed by blinded independent central review per Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1) and overall survival, with target hazard ratios of 0.65 and 0.75, respectively. Secondary endpoints include ORR, duration of response, time to response, disease control rate, safety, and antidrug antibody prevalence. Pharmacokinetic parameters, biomarkers, and patient-reported outcomes will also be explored. Clinical trial information: NCT05215340. Research Sponsor: Daiichi Sankyo Inc.

TPS3163 **Poster Session**

TARGET National: A U.K.-wide liquid-based molecular profiling program to enhance recruitment to early-phase trials. *First Author: Ana Ortega-Franco, The Christie NHS Foundation Trust, Manchester, United Kingdom*

Background: Precision medicine programs have largely focused on tissue-based assays to screen patients for genomic variants amenable to experimental targeted therapies. Challenges faced in such studies include time taken to acquire archival biopsies and limitation in capturing tumor heterogeneity and clonal evolution. The TARGET study (Rothwell, Nature Medicine 2019) previously demonstrated feasibility of using ctDNA to match patients to early phase trials with the benefit of rapid turnaround of results. With an ever-increasing number of novel therapies in development targeting rare genomic alterations across different tumor types, ctDNA holds great promise in enhancing recruitment to studies with rapid and efficient comprehensive genomic profiling assays covering a broad range of variants. There is need to perform profiling at scale to identify rare alterations and to utilise networks for identification of suitable clinical trials across the country. ctDNA is not detectable in all patients (owing to differences across disease types/ burden), thus tissue analysis still plays an important role. **Methods:** TARGET National is an investigator-initiated multi-centre molecular profiling study. The primary endpoints are to establish a national framework to offer profiling from blood samples (or tissue if appropriate) for patients being considered for early phase clinical trials across the UK Experimental Cancer Medicine Centre (ECMC) Network, and to measure the number of patients receiving matched therapy (MT). Secondary endpoints include curating the genomic landscape of the early phase population in the UK, and outcomes for patients receiving MT versus unmatched. Enrolment began in July 2021 and >250 patients have been recruited across 9 ECMCs with plans to expand to 20 centres by Q3 2022. Planned enrolment is 6000 patients over 5 years. Patients must be ≥ 16 years old, provide written consent, have histologically confirmed advanced solid cancer, progressing disease and be considered fit enough to receive an experimental therapy. ctDNA is analysed with Foundation Medicine Liquid CDx with option for other providers. A multi-disciplinary national Molecular Tumor Board enables interpretation of genomic reports and identifies suitable clinical trials, supported by eTARGET; a bespoke clinical-genomic data capture solution including trial finding software. The study provides broad access to genomic profiling throughout the UK, increasing experience with ctDNA assays, and will improve opportunities for patients to participate in early phase research. The UK database will provide means for identification of rare genomic patient groups for new first-in-human studies, and the program provides a national infrastructure to collect additional samples for translational research and pre-clinical models to progress understanding of biological predictors of response and resistance. Clinical trial information: NCT04723316. Research Sponsor: The Christie Charity, Other Foundation, Pharmaceutical/Biotech Company.

TPS3164 **Poster Session**

DELFI-L101: Development of a blood-based assay that evaluates cell-free DNA fragmentation patterns to detect lung cancer. *First Author: Peter J. Mazzone, Cleveland Clinic, Cleveland, OH*

Background: Despite longstanding national recommendations, uptake of lung cancer screening in the US remains low. Barriers include access to lung cancer screening, costs, and concerns over potential harms like false-positives and radiation exposure. The DELFI technology evaluates fragmentation patterns of cfDNA using supervised machine learning to distinguish cancer from non-cancer [PMID30943338; 34417454; 31142840]. **Methods:** The DELFI-L101 is a case-control observational study (NCT04825834) prospectively enrolling at academic and community sites. Eligible participants (≥50 years of age) are individuals who currently smoke or previously smoked, with smoking histories of ≥20 pack-years. Individuals are ineligible if they had cancer treatment in the prior year or a history of hematologic malignancies or myelodysplasia. Cases are individuals with pathologically confirmed cancers (group A – lung, group C – non-lung). Controls are those without cancer (group B) as determined by low-dose computed tomography screening completed within 6 weeks of enrollment. Cases and controls are identified among enrollees from all participating sites. Total enrollment is estimated to be ~2500 participants across all groups. Blood samples are collected at enrollment for DELFI analyses, which involves cfDNA isolation from plasma, low-coverage, whole-genome, next-generation sequencing, and machine learning methods. Clinical data (medical history, demographics, and diagnostic, surgery, imaging, and pathology reports, and/or other diagnostic information) are collected at enrollment and at 12 months post-enrollment. The primary objective is to train and test a classifier for the detection of lung cancer using the DELFI technology with other biomarkers and clinical features. Secondary objectives include the evaluation of classifiers to distinguish lung cancer from other cancers, modeling benefits and harms using performance estimates of these classifiers, and description of the analytical performance (eg, repeatability and reproducibility) of the DELFI technology and classifiers. The primary endpoint is the accuracy of lung cancer detection as measured by sensitivity, specificity, and the area under the receiver operating characteristic curve. Secondary endpoints include accuracy of tissue of origin classification, and adverse events associated with blood sample collection. The training and performance characterization of a DELFI classifier will further the development of an affordable, accessible, blood-based cancer detection tool with potential to overcome barriers to lung cancer screening. Clinical trial information: NCT04825834. Research Sponsor: Delfi Diagnostics, Inc.

TPS3165 **Poster Session**

A phase 2 study of the MDM2 inhibitor milademetan in patients with *TP53*-wild type and *MDM2*-amplified advanced or metastatic solid tumors (MANTRA-2). *First Author: Ecaterina Elena Dumbrava, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Murine double minute 2 (MDM2) is a potent negative regulator of the tumor suppressor p53. MDM2 induces degradation of p53 and promotes tumorigenesis in solid tumors, and preclinical models have shown that inhibition of MDM2 can restore p53 tumor suppressor activity in *TP53*-wild type (WT), *MDM2*-amplified tumors. We performed a mutual exclusivity analysis of patients with solid tumors (n = 42,125; AACR Project GENIE) and found that the frequency of co-occurring *TP53* mutations decreased with increasing *MDM2* copy number. An *MDM2* copy number of 12 was chosen as the threshold. An estimated 1.1% of solid tumors meet this molecular criteria, excluding glioblastomas, dedifferentiated liposarcomas, and intimal sarcomas where this signature is enriched. Milademetan (RAIN-32), an oral, selective MDM2 inhibitor, inhibits growth of *TP53*-WT/*MDM2*-amplified cell lines and patient-derived xenograft models from varying tumor types. Furthermore, tumor regression was observed in 3/3 non-liposarcoma patients with *MDM2* copy number > 12 in a phase 1 trial of milademetan. MANTRA-2 (RAIN-3202) is a phase 2, multicenter, single-arm, open-label, basket trial designed to evaluate the efficacy or clinical benefit of milademetan in *TP53*-WT solid tumors with *MDM2* amplification (copy number ≥ 12). **Methods:** Eligible patients must be ≥ 18 years of age with histologically and/or cytologically confirmed locally advanced, incurable or metastatic solid tumors refractory to standard therapy. Local testing demonstrating *TP53* WT and *MDM2* amplification is required, defined as a *MDM2* copy number ≥ 12 or 6-fold increase. Patients with well-differentiated/de-differentiated liposarcomas, intimal sarcomas, or primary central nervous system tumors are excluded. Prior treatment with an MDM2 inhibitor is not permitted. Patients receive milademetan 260 mg orally once daily on Days 1–3 and 15–17 of a 28-day cycle. Tumor response is evaluated by RECIST v1.1 at Weeks 8, 16, 24, and 32, and then every 12 weeks. Primary endpoint: objective response rate. Secondary endpoints include: duration of response; progression-free survival; growth modulation index; disease control rate; overall survival; safety; health-related quality of life scores. Exploratory endpoints include: biomarkers in blood and/or tumor tissue; pharmacodynamics; pharmacokinetics. Enrollment of 65 patients is planned to ensure that 57 patients have centrally confirmed *TP53* WT and *MDM2* copy number ≥ 12. The trial opened in November 2021 and is actively enrolling patients. Clinical trial information: NCT05012397. Research Sponsor: Rain Therapeutics, Inc.

TPS3166 **Poster Session**

Rationale and design of phase 1 FTIH study of FOXP3 antisense oligonucleotide AZD8701 in patients with selected advanced solid tumors. *First Author: Michele Petruzzelli, AstraZeneca, Cambridge, MD, United Kingdom*

Background: The forkhead box family transcription factor FOXP3 is essential for T regulatory cells (Tregs) development and immune suppressive function. Tregs are an integral component of the adaptive immune system and contribute to maintaining tolerance to self-antigens and preventing autoimmune diseases. In the context of cancer, however, Tregs contribute to tumor progression by suppressing antitumor immunity. To date inhibition of Treg-mediated immunosuppression tested in the clinic has lacked specificity. Targeting FOXP3 provides a selective approach to impair the immunosuppressive function of Tregs but targeting transcription factors has been a challenge using conventional drug modalities. AZD8701 employs next-generation antisense oligonucleotide (ASO) technology (Ionis Pharmaceuticals) to bind mRNA with high affinity and selectively reduce human Foxp3 mRNA expression levels. Foxp3-specific ASOs promote potent dose-dependent reductions in Foxp3 mRNA and protein in vitro. In preclinical models, AZD8701 induced Foxp3 knockdown results in Tregs with a reduced immunosuppressive capacity, loss of immunosuppressive markers, and increased markers of activation on $CD8^+$ T-cells. AZD8701 reduces tumor growth as monotherapy in preclinical models and increased tumor inhibition is obtained by combining AZD8701 with a PD-L1 inhibitor. **Methods:** This is a Phase I multicenter study of AZD8701 alone or in combination with durvalumab in participants with selected advanced solid tumors. Eligible patients must have ECOG performance status 0 or 1, measurable target lesion per RECIST v1.1 and be diagnosed with selected tumor types as described below. Monotherapy and combination dose escalation phase is open for participants with head and neck squamous cell carcinoma (HNSCC), triple-negative breast cancer (TNBC), non-small-cell lung cancer (NSCLC), clear cell renal cell carcinoma (ccRCC), gastroesophageal cancer, melanoma, cervical cancer, small-cell lung cancer (SCLC), and/or solid tumors that have demonstrated a response to prior programmed death-ligand-1 (PD-[L]1) treatment (as defined by duration of response > 18 weeks). Participants with NSCLC, HNSCC, TNBC, and ccRCC will be included in the pharmacodynamic cohort at the selected monotherapy dose and/or disease expansion cohorts. The primary objectives are to assess safety and tolerability and to determine the preliminary antitumor activity of AZD8701 (objective response rate) when administered as monotherapy or in combination with durvalumab. Secondary endpoints include, disease control rate, duration of response, progression free survival and overall survival, pharmacokinetics and pharmacodynamics (including changes in Foxp3 mRNA in paired tumor samples). The trial is currently recruiting. Clinical trial information: NCT04504669. Research Sponsor: AstraZeneca.

TPS3167 **Poster Session**

Design and rationale of a phase 1 dose-escalation study of AMG 193, a methylthioadenosine (MTA)-cooperative PRMT5 inhibitor, in patients with advanced methylthioadenosine phosphorylase (MTAP)-null solid tumors. *First Author: Miguel Angel Villalona-Calero, City of Hope National Medical Center, Duarte, CA*

Background: Protein arginine methyltransferase 5 (PRMT5) is an emerging target for cancer treatment. MTAP homozygous deletion occurs in 15% of cancers and often coincides with deletion of the tumor suppressor gene CDKN2A, leading to buildup of its substrate MTA. MTA shares close structural similarity to S-adenosyl methionine (SAM), the substrate methyl donor for PRMT5. By competing with SAM, MTA partially inhibits PRMT5. Thus, MTAP-null cancers are susceptible to further PRMT5 inhibition (Kryukov *Science* 2016). Current direct/indirect PRMT5 inhibitors (PRMT5i) showed preliminary anticancer activity, albeit with considerable toxicities due to their indiscriminate activities. AMG 193 is an MTA-cooperative PRMT5i that preferentially targets the MTA-bound state of PRMT5 that is enriched in MTAP-null tumors and represents a novel strategy to increase the therapeutic margin of this class of inhibitors. AMG 193 potently inhibits MTAP-null cancer cell lines and patient-derived xenografts. **Methods:** NCT05094336 is a first-in-human (FIH), multicenter, open-label, phase 1/1b/2 trial evaluating the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and efficacy of AMG 193 in patients with advanced MTAP-null solid tumors. Eligible patients (≥ 18 years) with histologically confirmed locally advanced/metastatic solid tumors not amenable to curative treatment with surgery and/or radiation, homozygous MTAP and/or CDKN2A deletion (by local next generation sequencing), or MTAP protein loss in tumors (by central immunohistochemistry), measurable disease, ECOG PS 0–1, adequate hematopoietic, renal, liver, pulmonary, cardiac, coagulation function and glucose control will be included. The study will be conducted in 3 parts, each with subparts. Here, we describe Part 1a/b (dose exploration). Five dose levels are planned. Treatment continues until progression or withdrawal. The primary objectives are to evaluate the safety and tolerability of AMG 193 monotherapy; endpoints include dose-limiting toxicities, treatment-emergent adverse events, serious adverse events, electrocardiograms, laboratory abnormalities, and vital signs. Secondary objectives include the characterization of the PK parameters of AMG 193 including C_{max}, T_{max}, and AUC after single or multiple doses. This study is expected to enroll approximately 30 patients in Part 1a/b. This is the first FIH trial open for enrollment for this new class of PRMT5i and enrollment is ongoing. Clinical trial information: NCT05094336. Research Sponsor: Amgen Inc.

TPS3168 **Poster Session**

A phase 1, first-in-human study of IK-930, an oral TEAD inhibitor targeting the Hippo pathway in subjects with advanced solid tumors. *First Author: Anthony W. Tolcher, NEXT Oncology and Texas Oncology, San Antonio, TX*

Background: The transcriptional enhanced associate domain (TEAD) family of proteins are key transcription factors in the Hippo signaling pathway and play a critical role in cell proliferation, migration, angiogenesis, and apoptosis. Published literature demonstrates that approximately 10% of all solid tumors present with a dysregulated Hippo pathway and subsequent constitutive activation of TEAD, which drives gene expression involved in cell growth and pro-survival signaling. Deficiencies in neurofibromin 2 (NF2), a key regulator of the Hippo pathway, can be found in over 40% of cases of malignant pleural mesothelioma (MPM). *NF2* deficiency also occurs at high incidence in meningiomas, cholangiocarcinomas, thymoma, and schwannoma. Gene fusions in in Yes1 associated transcriptional regulator (YAP1) or WW domain containing transcription regulator 1 (TAZ/WWTR1) are also indicative of high TEAD activation and can be seen in solid tumors including epithelioid hemangioendothelioma (EHE) where >90% of cases are associated with TAZ-CAMTA1 gene fusion and the other 10% of cases have YAP1/TFE3 gene fusion. IK-930 is a novel, selective, small molecule inhibitor of TEAD that prevents palmitate binding and thereby disrupts aberrant TEAD-dependent transcription. In preclinical models, IK-930 demonstrates antitumor activity in mouse xenograft models with Hippo pathway genetic alterations. IK-930 is under clinical investigation as an oral agent in patients with advanced solid tumors. **Methods:** This is a phase 1, first-in-human, open-label, multicenter dose escalation and dose expansion study to evaluate the safety and tolerability of IK-930 as monotherapy, and to determine the recommended phase 2 dose (RP2D) and/or maximum tolerated dose (MTD) using the Bayesian Optimal Interval Design (BOIN). Eligible participants in dose escalation include adult patients with advanced or metastatic solid tumors for whom there is no available therapy known to confer clinical benefit. Patients will receive escalating doses of IK-930 starting at 25mg daily. IK-930 will be administered initially in a 28-day cycle and will progress to a 21-day cycle when evaluated as safe and well-tolerated. A dose expansion phase will follow with four genetically defined cohorts of solid tumors, including: *NF2*-deficient MPM (Cohort 1), other *NF2*-deficient solid tumors agnostic to tumor type (Cohort 2), EHE with *TAZ-CAMTA1* or *YAP1-TFE3* gene fusions (Cohort3), and solid tumors with *YAP1/TAZ* gene fusions agnostic to tumor type (Cohort 4). Primary endpoints include evaluation of dose-limiting toxicities and treatment-emergent adverse events and determination of RP2D and/or MTD. Secondary objectives include evaluation of preliminary antitumor activity by RECIST 1.1 and pharmacokinetic (PK) parameters. The study began in January 2022 and is currently enrolling. Clinical trial information: NCT05228015. Research Sponsor: Ikena Oncology.

TPS3169 **Poster Session**

Phase 1a/b open-label study of IK-175, an oral AHR inhibitor, alone and in combination with nivolumab in patients with locally advanced or metastatic solid tumors and urothelial carcinoma. *First Author: Meredith McKean, Sarah Cannon Research Institute, Tennessee Oncology, PLLC, Nashville, TN*

Background: Aryl Hydrocarbon Receptor (AHR) is a ligand-activated transcription factor that regulates the activity of multiple innate and adaptive immune cells. Kynurenine, generated from tryptophan by IDO1 and TDO2, is a ligand that binds AHR and leads to a net immunosuppressive tumor microenvironment, making AHR an attractive therapeutic target in multiple cancer types. IK-175 is a selective, small molecule inhibitor of AHR being developed as an oral agent. In preclinical mouse tumor models, IK-175 demonstrates antitumor activity as a single agent or in combination with checkpoint inhibitors. AHR immunohistochemistry (IHC) tumor microarray analysis across 15 different tumor types revealed that bladder cancer has the highest level of AHR protein expression and nuclear localization indicative of ligand-bound and active AHR signaling. Therefore, nuclear AHR in urothelial carcinoma tumors is being investigated for potential predictive clinical benefit with IK-175. **Methods:** This is a first-in-human, phase 1a/b, open-label, multicenter, dose-escalation and expansion study of IK-175 as a single agent and in combination with nivolumab. The primary objectives are to determine the maximum tolerated dose (MTD) and/or maximum administered dose (MAD), identify the recommended phase 2 dose (RP2D), and evaluate the safety and tolerability of IK-175 alone and in combination with nivolumab. Secondary objectives are to evaluate the pharmacokinetics (PK) of IK-175, evaluate pharmacodynamic (PD) immune effects, and assess preliminary antitumor activity. Key exploratory objectives are to evaluate the PD effects on peripheral immune cells and target gene expression, to assess candidate baseline biomarkers, and correlative analyses of tumor AHR nuclear localization with clinical response. The study is exploring tumor AHR nuclear localization by IHC as a predictive biomarker in patients with urothelial carcinoma. A minimum of 10 patients with a positive AHR nuclear localization test (cutoff for positive AHR is 65% tumor cells positive for 2+/3+ nuclear AHR by a validated IHC assay) will be enrolled in the combination arm. IK-175 is administered daily in 21 or 28 day-cycles as a single agent, and in combination with nivolumab (480 mg q4w on Day 1 of every cycle), in adult patients with advanced solid tumors (dose escalation) and urothelial carcinoma (dose expansion). Key eligibility criteria include patients with histologically confirmed solid tumors (including urothelial carcinoma) who have locally recurrent or metastatic disease that have progressed on or following all standard of care therapies deemed appropriate by the treating physician including prior checkpoint inhibitors. Estimated enrollment is 93 patients; the study began in January 2020 and is ongoing. Clinical trial information: NCT04200963. Research Sponsor: Ikena Oncology.

TPS3170 **Poster Session**

Phase 1 study of KT-413, a targeted protein degrader, in adult patients with relapsed or refractory B-cell non-Hodgkin lymphoma. *First Author: Don A. Stevens, Louisville Onc, Louisville, KY*

Background: Oncogenic mutations in myeloid differentiation primary response 88 (MYD88) occur in approximately 25% of diffuse large B-cell lymphoma (DLBCL) cases, including approximately 30% of activated B-cell DLBCL and up to 70% of primary extranodal DLBCL, and are associated with poor survival following 1st line therapy. MYD88 mutations result in activation of the NF-κB pathway which drive a range of protumor activities including upregulation of proinflammatory cytokines and genes involved in tumor cell proliferation and survival. Activation of this pathway results in upregulation of IRF4 through the transcription factors Ikaros and Aiolos, which in turn further augments NF-kB activation while simultaneously downregulating Type I IFN signaling, thereby preventing oncogene-induced cell death. Constitutive NF-kB pathway activation resulting from MYD88 mutations is dependent on the interleukin-1 receptor associated kinase 4 (IRAK4), a key component of the myddosome complex which normally stimulates NF-kB signaling following TLR or IL-1R engagement and MYD88 activation. KT-413 is a potent and selective heterobifunctional small molecule protein degrader mediating the degradation of both IRAK4 and the IMiD substrates Ikaros and Aiolos via the ubiquitin-proteasome system. The therapeutic hypothesis is that degradation of IRAK4 and IMiD substrates will maximize NF-κB inhibition while simultaneously upregulating the Type I Interferon response, thus restoring the apoptotic response and enabling oncogene-mediated cell death, resulting in robust antitumor response in MYD88-mutant DLBCL. KT-413 induced strong antitumor activity, including complete or partial regressions, in cell line- and patient-derived xenograft models of $MYD88^{MT}$ DLBCL (Mayo 2021). **Methods:** KT-413 is being evaluated in an open label, dose escalation (Phase 1a) study in patients with relapsed/refractory (R/R) B-cell non-Hodgkin lymphoma (NHL), followed by dose expansion (Phase 1b) in patients with R/R DLBCL with documented tumor MYD88 mutation status. All patients must be ineligible or refused auto-SCT or CAR-T therapy. The Phase 1a (n = 40) utilizes an accelerated titration followed by a 3+3 design in ascending doses of IV administered KT-413 in once every 21-day cycles to identify the maximum tolerated dose (MTD)/recommended Phase 2 dose (RP2D) (primary endpoint). Secondary endpoints include pharmacokinetics (PK) and preliminary pharmacodynamic effects (PD) using blood and tumor tissue. Once MTD/RP2D is determined in 3-6 patients, it will be confirmed by enrolling additional patients with B-cell NHL, for a total of nine. In Phase 1b, up to 40 R/R DLBCL patients will be enrolled into one of two cohorts (n = 20): $MYD88^{MT}$ or $MYD88^{WT}$ to further characterize tolerability, PK, PD and evaluate the clinical activity of KT-413. KT413-DL-101 began enrollment in February 2022. Clinical trial information: NCT05233033. Research Sponsor: Kymera Therapeutics.

TPS3171 **Poster Session**

Phase 1 study of KT-333, a targeted protein degrader, in patients with relapsed or refractory lymphomas, large granular lymphocytic leukemia, and solid tumors. *First Author: Alexander Starodub, The Christ Hospital, Cincinnati, OH*

Background: The signal transducer and activator of transcription 3 (STAT3) protein is activated by cytokines and growth factors resulting in tumor growth and promotion and hindering antitumor immunity. Approximately 70% of human cancers including both hematological malignancies and solid tumors exhibit increased levels of phosphorylated STAT3 (pSTAT3). There is evidence of constitutive activation of STAT3 through genetic mutations or aberrant cellular signaling pathways in tumors such as large granular lymphocytic leukemia (LGL-L), peripheral T-cell lymphoma (PTCL), and cutaneous T-cell lymphomas (CTCL). Hyperactivation of STAT3 has been reported in a variety of solid tumors. In several of these cancers, the levels of pSTAT3 and/or activated STAT3 have been shown to correlate with poor clinical prognosis. As with other transcription factors, selective inhibition of STAT3 has been proven to be difficult with conventional therapeutic approaches. KT-333 is a potent highly selective, heterobifunctional small molecule degrader of STAT3. In preclinical studies, durable tumor regressions were seen with weekly KT-333 administration in STAT3-dependent T cell lymphomas, and antitumor activity was seen in solid tumors in combination with anti-PD1 (ASH 2021, SITC 2021). **Methods**: KT-333 is being evaluated in an open-label, dose escalation (Phase 1a, n = 40) study in patients with lymphomas relapsed or refractory (R/R) to at least two prior systemic treatments or for whom standard therapies are unavailable. Dose escalation will be conducted by accelerated titration followed by a 3+3 design in ascending doses of intravenous KT-333 administered once weekly in 28-day cycles to evaluate safety and define the maximum tolerated dose (MTD)/recommended Phase 2 dose (RP2D) (primary endpoint). Secondary endpoints include pharmacokinetics (PK) in plasma and urine and preliminary pharmacodynamic effects (PD) of KT-333 using blood (peripheral blood mononuclear cells [PBMCs], plasma/serum) and tumor tissue. After confirming the MTD/RP2D in patients with lymphoma, patients with advanced solid tumors will be enrolled in a separate Phase 1a cohort at the MTD/RP2D. In Phase 1b (n = 80), patients with PTCL, CTCL, LGL-L (T-cell LGL-L or chronic lymphoproliferative disorder of natural killer-cells), or solid tumors R/R to at least one prior systemic standard of care treatment or for whom standard therapies are not available, will be enrolled in separate 20 patient cohorts. This will further characterize safety, PK, PD and evaluate the clinical activity of KT-333. Treatment with KT-333 will continue until disease progression, unacceptable toxicity, or patient refusal. KT333-TL-101 began enrolling in January 2022. Clinical trial information: NCT05225584. Research Sponsor: Kymera Therapeutics.

TPS3172 **Poster Session**

A two-part, phase II, multi-center study of the ERK inhibitor ulixertinib (BVD-523) for patients with advanced malignancies harboring MEK or atypical BRAF alterations (BVD-523-ABC). *First Author: Mark E. Burkard, University of Wisconsin Carbone Cancer Center, Madison, WI*

Background: Ulixertinib (BVD-523) is a small molecule inhibitor of extracellular signal-regulated kinases 1/2 (ERK1/2) in development as a novel anti-cancer drug. Early clinical data demonstrated anti-tumor activity, especially for patients with tumors harboring atypical BRAF or MEK1/2 alterations (Sullivan et al., Cancer Discov. 2018;8(2):184-195). Atypical BRAF (non-V600) alterations can be categorized according to characteristics of molecular signaling (Class II or III), are seen in approximately 3% of all human cancers, and there are currently no approved therapies for this indication. Similar to atypical BRAF alterations, the incidence of MEK1/2 alterations are rare in human tumors (< 1 %). Preclinical data have demonstrated activity of ulixertinib in MEK mutant models. Ulixertinib has FDA fast-track designation for patients with solid tumors, other than CRC, with specific BRAF mutations (G469A, L485W, or L597Q). Designed with intent to register, the BVD-523-ABC clinical trial will continue evaluation of ulixertinib in patients with tumors harboring any atypical BRAF or MEK1/2 alteration (NCT04488003). **Methods:** This multi-center, phase II study, will be conducted in two parts and assess the clinical benefit, safety, pharmacokinetics, and pharmacodynamics of ulixertinib in patients with advanced malignancies. Ulixertinib will be administered at the RP2D of 600 mg BID for 28-day treatment cycles. Eligible patients will have locally advanced or metastatic cancer which progressed following standard systemic therapies, or for which the patient is not a candidate or refused systemic therapy. Planned correlative analyses include reverse phase protein array and transcriptomics of tumor tissue. Part A is open-label and tumor agnostic, except for group 4 and 6 (CRC patients only). Patients will enroll into one of six groups based on BRAF (groups 1-4) or MEK1/2 (groups 5-6) tumor alteration (38 patients per group). Overall response rate (ORR) is the primary endpoint for Part A, with secondary endpoints including duration of response (DOR), progression-free survival (PFS), and overall survival (OS). Part B is tumor histology specific. Patients will be randomized to receive either ulixertinib or physician's choice of treatment in a 2:1 ratio. Up to three specified tumor histologies will be defined, guided by available Part A data (n = 80-100 per histology). The primary endpoint of Part B is PFS, and secondary endpoints include OS, ORR, and DOR. This study has enrolled 43 patients of the planned 228 in Part A at the time of abstract submission. Clinical trial information: NCT04488003. Research Sponsor: BioMed Valley Discoveries.

TPS3173 **Poster Session**

Phase 1/2 dose escalation study of NUV-422, a potent inhibitor of cyclin-dependent kinases 2, 4, and 6, in recurrent or refractory (r/r) high-grade gliomas (HGG) and solid tumors. *First Author: Patrick Y. Wen, Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Boston, MA*

Background: CDKs that govern the G1-S transition of the cell cycle (CDK2, CDK4 and CDK6) are deregulated in many cancers. CDK2 expression, in particular, is associated with worse overall survival in glioblastoma (GB), disease-free recurrence in prostate cancer, and resistance to approved CDK4/6 inhibitors (CDK4/6i) in breast cancer. These provide rationale for inhibition of CDK2/4/6 as a potential novel therapeutic strategy in these cancers. NUV-422 is a potent (low nM) small molecule CDK2/4/6i with limited activity against CDK1, a target potentially associated with toxicities in other CDKi. Preclinical studies have shown that NUV-422 has favorable blood-brain barrier penetration, inhibited growth of multiple glioma cell lines in vitro, and exhibited antitumor activity in GB xenograft models. NUV-422 also exhibited antitumor activity in multiple patient-derived xenograft (PDX) models of HR+ HER2- mBC resistant to CDK4/6i, and PDX models of prostate cancer resistant to anti-androgens. **Methods:** NUV-422-02 (NCT04541225) is a phase 1/2, first in human, open label, multicenter study to evaluate single-agent NUV-422 (given orally) in patients with advanced solid tumors (r/r HGG, r/r HR+ HER2- mBC, or r/r mCRPC). The Ph 1 dose escalation will use a 3+3 design to evaluate safety, tolerability, and PK of NUV-422 and establish the recommended phase 2 dose (RP2D). Ph 1 also includes a randomized surgical substudy to characterize PK and pharmacodynamics (PD) of preoperative NUV-422 in resected GB tumor tissue. After the RP2D is identified, parallel enrollment into phase 2 expansion cohorts will begin. Cohort 1 will evaluate isocitrate dehydrogenase wild type (IDH-WT) GB. Cohort 2 will evaluate HR+ HER2- mBC (without active brain metastases); Cohort 3 will evaluate mCRPC; and Cohort 4 will evaluate HR+ HER2- mBC with active brain metastases. The Ph 2 primary endpoint is objective response rate. Secondary efficacy endpoints include clinical benefit rate, duration of response, progression-free survival, and overall survival. Response assessments will be based on response criteria appropriate to the tumor type (HGG [RANO]; HR+HER2- mBC [RECIST 1.1 or RANO-Brain Metastases]; mCRPC [RECIST 1.1, PCWG3, prostate-specific antigen decrease]). Blood, urine, or tumor tissue will be obtained to assess safety, PK, PD, and for additional exploratory analyses to characterize NUV-422 mechanism of action. Enrollment was initiated in December 2020, and dose escalation is ongoing. The NUV-422 program will also be expanded in 2022 to include additional studies in mBC and mCRPC in combination with standard of care treatments. Clinical trial information: NCT04541225. Research Sponsor: Nuvation Bio.

TPS3174 **Poster Session**

A phase I trial of elimusertib in combination with cisplatin or with cisplatin plus gemcitabine in advanced solid tumors with an emphasis on urothelial carcinoma. *First Author: Ryan Leibrandt, UC Davis Comprehensive Cancer Center, Sacramento, CA*

Background: Cisplatin, a well-established backbone of combination therapy of various advanced solid tumors, inhibits DNA synthesis by forming DNA cross-links and adducts. Despite the activity of cisplatin, tumor cells can either be refractory or develop resistance to treatment. Cisplatin has been demonstrated to cause cell cycle G2/M arrest, which may allow for DNA damage response (DDR) and repair. Ataxia telangiectasia mutated (ATM) and ataxia telangiectasia and Rad 3-related (ATR) protein kinases are key regulators of DDR, and contribute to maintaining genomic integrity in response to various exogenous and endogenous genotoxic insults like cytotoxic chemotherapy. In fact, cisplatin has been shown to transiently increase ATR expression. Inhibitors of ATR have been studied in combination with cisplatin both *in vitro* and *in vivo*, demonstrating enhanced activity. The oral small molecule ATR inhibitor elimusertib, which has been studied as a single agent in a Phase I study, has also demonstrated enhanced activity with cisplatin *in vitro* in lung cancer and bladder cancer cell lines. We sought to conduct a Phase I study evaluating the combination of elimusertib with cisplatin or with cisplatin and gemcitabine. **Methods:** In the first cohort, patients with histologically confirmed advanced solid tumors for which cisplatin-based therapy would be considered appropriate, who exhibit adequate organ function, and have received < 300 mg/m^2 of cisplatin previously are treated with cisplatin on Day (D) 1 and with elimusertib on D2 & 9 of each 21-day cycle. The study follows a phase I queue (IQ) 3+3 dose escalation design, following standard practices for dose-limiting toxicity (DLT) impact on escalation, and when the maximum tolerated dose (MTD) is established with cisplatin alone, this will inform the first dose level of the next cohort, in which patients will be treated with cisplatin on D1, gemcitabine on D1 & 8, and elimusertib on D2 & 9 of each 21-day cycle. An expansion cohort will enroll urothelial carcinoma patients when the second MTD is established. The primary objective of the study is to evaluate the safety and MTD of elimusertib in combination with cisplatin, as well as in combination with cisplatin and gemcitabine. Secondary study objectives include evaluation of pharmacokinetics of elimusertib in these combinations, preliminary efficacy, and evaluating the association between ATM expression and responses to therapy. Currently, 6 patients have been enrolled to the first cohort of the study. Clinical trial information: NCT04491942. Research Sponsor: U.S. National Institutes of Health.

TPS3175 **Poster Session**

A first-in-human phase I dose-escalation trial of the B7-H6/CD3 T-cell engager BI 765049 ± ezabenlimab (BI 754091) in patients with advanced solid tumors expressing B7-H6. *First Author: Gerald Steven Falchook, Sarah Cannon Research Institute at HealthONE, Denver, CO*

Background: B7-H6 is a member of the B7 family of immune receptors, which is expressed in several solid tumors, but with little to no expression detected in normal tissues[Brandt et al. J Exp Med 2009;206.1495–503; Boehringer Ingelheim. Data on file]. BI 765049 is a novel IgG-like bispecific T-cell engager (TcE) designed to bind simultaneously to B7-H6 on tumor cells and CD3 on T cells, resulting in cytolytic synapse formation and tumor lysis. Preclinical studies have demonstrated that BI 765049 monotherapy induced dose-dependent antitumor activity in humanized *in vivo* CRC tumor models. Consistent with the mode of action, treatment with BI 765049 led to profound infiltration of T cells into the tumor tissue, which correlated with apoptosis and tumor shrinkage. The inflammatory tumor microenvironment created by treatment with the B7-H6/CD3 TcE also led to an increase of PD-1 on T cells and PD-L1 on the tumor cells [Hipp et al. AACR Annual Meeting 2021]. This upregulation of PD-(L)1 provides the rationale for combining BI 765049 with a PD1 inhibitor. **Methods:** NCT04752215 is a first-in-human, open-label, dose-escalation trial of BI 765049 ± the PD-1 inhibitor, ezabenlimab. Adults with advanced, unresectable and/or metastatic CRC, NSCLC, HNSCC, hepatocellular, gastric or pancreatic carcinoma are eligible. Patients must have progressed on, or be ineligible for, standard therapies. B7-H6 positivity must be confirmed at screening by central review (immunohistochemistry assay) in archived tissues/fresh biopsies (except CRC). Patients must have ≥1 evaluable lesion (modified RECIST 1.1) outside of the central nervous system and adequate organ function. The primary objective is to determine the maximum tolerated dose (MTD) or recommended dose for expansion of BI 765049 ± ezabenlimab, based on dose-limiting toxicities during the MTD evaluation period. Further objectives are to evaluate safety, tolerability, PK/PD, and preliminary efficacy of BI 765049 ± ezabenlimab. The trial will assess up to four intravenous dosing regimens: A (BI 765049 once every 3 weeks [q3w]); B1 (BI 765049 qw); B2 (BI 765049 qw with step-in dosing); C (BI 765049 + ezabenlimab q3w). Dose escalation will be guided by a Bayesian Logistic Regression Model with overdose control that will be fitted to binary toxicity outcomes using a hierarchical modelling approach to jointly model all dosing regimens. Treatment will be allowed to continue until confirmed progressive disease, unacceptable toxicity, other withdrawal criteria, or for a maximum duration of 36 months, whichever occurs first. Approximately 150–175 patients will be screened and ~120 patients enrolled. As of January 2022, eight patients have been recruited in early dose-escalation cohorts. Clinical trial information: NCT04752215. Research Sponsor: Boehringer Ingelheim.

TPS3176 **Poster Session**

A phase 1 dose-escalation and expansion-cohort study of the oral CDK7 inhibitor XL102 as a single-agent and in combination therapy in patients (pts) with advanced solid tumors. *First Author: Geoffrey Shapiro, Dana-Farber Cancer Institute, Boston, MA*

Background: XL102 is an orally bioavailable, selective, and covalent small-molecule inhibitor of cyclin-dependent kinase 7 (CDK7). CDK7 is a serine/threonine kinase that is overexpressed in multiple tumor types. CDK7 controls cell cycle progression via the phosphorylation of CDKs (1, 2, 4, and 6) and regulates transcription through phosphorylation of RNA polymerase II. XL102 induced cell death in various cancer cell lines and caused tumor regression in multiple human tumor cell line to mouse xenograft tumor models. Here, we present the study design of an ongoing phase 1 trial in pts with advanced solid tumors, including hormone receptor-positive breast cancer (HR+BC), triple-negative breast cancer (TNBC), epithelial ovarian cancer (EOC), and metastatic castration-resistant prostate cancer (mCRPC). **Methods:** This first-in-human, open-label, phase 1 trial (NCT04726332) consists of a dose-escalation stage and a disease-specific cohort expansion stage. In the dose-escalation stage (modified interval 3+3 design), a maximum tolerated dose and/or recommended dose (MTD/RD) of XL102 will be established (primary endpoint) for use alone (solid tumors) and then for use in combination with standard dose fulvestrant (HR+BC) or abiraterone/prednisone (mCRPC); dose escalation will require ~36 pts for the single-agent cohort and ~15 pts for each combination cohort. Pts enrolled in the dose-escalation stage must have an unresectable or metastatic tumor for which available therapies are intolerable, ineffective, or do not exist. Upon determining the MTD/RD for each regimen, the cohort-expansion stage will enroll according to Simon's Two-Stage Minimax design, assuming a power of 80% and one-sided α of 15%, for single-agent XL102 (HR+BC, TNBC, EOC, and mCRPC) and XL102 in combination therapy (HR+BC and mCRPC); the expansions will enroll ~36 pts for each single-agent cohort and ~44 pts for each combination cohort. Pts enrolled in the expansion stage must have measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), adequate organ function, and exposure to prior therapy, with specific therapy requirements based on the disease cohort. The primary endpoint of the expansion stage is objective response rate (ORR) of XL102 alone and in combination therapy as assessed by investigator per RECIST v1.1. Secondary endpoints are safety, tolerability, and pharmacokinetics. Exploratory endpoints include duration of response (DOR) and progression-free survival (PFS) as assessed by the investigator per RECIST v1.1, overall survival, and correlation of tumor and blood biomarkers with response. ORR, DOR, and PFS may also be assessed by blinded independent radiology committee in selected expansion cohorts. The study began enrolling pts in February 2021 and is ongoing. Total enrollment is estimated to be up to 298 pts. Clinical trial information: NCT04726332. Research Sponsor: Exelixis, Inc.

TPS3177 **Poster Session**

Phase 1 study of C019199, an oral CSF-1R/DDRs/VEGFR2 multiple kinase inhibitor, to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics in patients with advanced solid tumors, including tenosynovial giant cell tumor. *First Author: Lin Shen, Department of Gastrointestinal Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital & Institute, Beijing, China*

Background: C019199 was designed to be a tumor immune microenvironment (TME) modulator in order to improve the efficacy against tumor growth when combined with immune checkpoint inhibitors, like anti-PD1 or anti-PD-L1. It was shown to have a specific inhibition profile against CSF-1R, DDR1 and VEGFR2 with IC_{50} of 14nM, 40nM and 79nM, respectively. CSF-1R's inhibition may deplete Tumor-associated macrophages (TAMs) in TME, help the infiltration of T cells and enhance T cell responses. But a single modulating mechanism may not be strong enough or may be vulnerable and easily overcome by tumors. C019199 can reshape the TME by additionally inhibiting DDRs and VEGFR2, which may remove the "physical barrier" of tumor extracellular matrix and further increase T cell infiltration on top of inducing tumor blood vessels normalization. As a single agent with the appropriate combination of multiple modulation effects, it will potentially turn "cold" tumors into "hot" tumors. Preclinical studies have shown that C019199 inhibits tumor growth in multiple animal tumor models and has better antitumor efficacy when combined with immune checkpoint blockades. **Methods:** A first-in-human, open label, multicenter, dose-escalation/expansion study of C019199 is currently enrolling. Eligible subjects (age ≥ 18 years and <76 years) with histologically or cytologically confirmed relapsed, refractory, or progressive metastatic solid tumors will be enrolled in. In Part A, the safety and tolerability of C019199 will be assessed in about 25 subjects to identify the maximum tolerated dose and recommended phase II dose (PR2D). In Part B, the safety and antitumor activity of the RP2D will be assessed in about 60 subjects in disease-specific expansion cohorts. Primary endpoints are adverse events, laboratory abnormalities, dose-limiting toxicities. Secondary endpoints will include pharmacokinetics, objective response rate, progression-free survival, and disease control rate. Exploratory biomarker analyses include CSF-1 and VEGF. Clinical trial information: CTR20202045. Research Sponsor: Fujian Haixi Pharmaceuticals Co., Ltd.

TPS3178 **Poster Session**

A phase 1/2 study of DCC-3116 as a single agent and in combination with trametinib in patients with advanced or metastatic solid tumors with RAS or RAF mutations. *First Author: Anthony W. Tolcher, Texas Oncology-San Antonio Babcock NEXT Oncology, San Antonio, TX*

Background: Autophagy, a catabolic process to resupply nutrients and recycle damaged organelles, is activated by cancer cells to survive hypoxia, limited nutrients, or chemotherapy. The RAS family of oncoproteins are the most commonly mutated oncoproteins in human cancer and require autophagy for tumor growth and survival. RAS activates signaling through the mitogen-activated protein kinase (MAPK) pathway that is responsible for regulating cell survival. ULK1/2 are kinases that receive and process input from nutrient and stress sensors to initiate autophagy. Inhibition of the MAPK pathway releases tonic inhibition of ULK1/2 and triggers autophagy as a survival mechanism, suggesting that ULK1/2 may provide a promising therapeutic target. DCC-3116 is a potent and selective ULK inhibitor that showed preclinical antitumor activity in combination with the MAPK kinase inhibitor trametinib (Smith et al. 2019 AACR-NCI-EORTC Poster). Here, we describe the Phase 1 study of DCC-3116 monotherapy and combination therapy with trametinib in patients with RAS or RAF mutant advanced or metastatic solid tumors. **Methods:** This is a Phase 1/2, multicenter, open-label, first-in-human study evaluating safety, tolerability, clinical activity, pharmacokinetics, and pharmacodynamics of DCC-3116 as a single agent and in combination with trametinib (NCT04892017). The study consists of single agent and combination dose escalation cohorts and expansion of combinations with demonstrated safety. Single-agent oral DCC-3116 will be administered twice daily (BID) in escalating cohorts in 28-day cycles until the recommended Phase 2 dose (RP2D) is determined. Subsequently, the single-agent RP2D or one level below the maximum tolerated dose (MTD) will be administered in combination with trametinib. Participants in the dose escalation phase must be ≥18 years with a histologically confirmed diagnosis of advanced or metastatic solid tumor with a documented RAS or RAF mutation, have progressed despite standard therapies, and have received ≥1 prior anticancer therapy. In the dose expansion phase, DCC-3116 will be given BID with trametinib in 28-day cycles to participants with pancreatic ductal adenocarcinoma, non-small cell lung cancer, colorectal cancer, or melanoma (Cohorts 1–4, respectively). Primary outcomes are incidence of adverse events, identification of MTD, and objective response rate per RECIST v1.1. Secondary outcomes include duration of response, clinical benefit rate, time to response, progression-free survival, and pharmacokinetic/pharmacodynamic attributes. Participants in dose expansion cohorts must be ≥18 years and meet cohort-specific criteria including histologically confirmed diagnoses, documented mutation status, and number of prior lines of systemic therapy. This study is recruiting and plans to enroll up to 130 participants. Clinical trial information: NCT04892017. Research Sponsor: Deciphera Pharmaceuticals, LLC.

TPS3179 **Poster Session**

A multicenter, open-label, phase 1a/b study of HC-7366, a modulator of integrated stress response (ISR) kinase GCN2 in subjects with advanced solid tumors. *First Author: Meredith Pelster, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: To survive harsh tumor microenvironments, cancer cells actively utilize ISR as an adaptive stress response and survival mechanism. General control nonderepressible 2 (GCN2), a serine-threonine kinase is essential for maintaining cellular homeostasis in amino acid stress conditions. HC-7366 is a novel, highly selective, and potent GCN2 kinase modulator. Single agent HC-7366 has demonstrated potent anti-tumor activity resulting in regression and complete responses in several pre-clinical tumor models. **Methods:** This is a first in human, multicenter, open label, Phase 1a/b dose escalation and expansion study to establish the maximum tolerated dose, evaluate safety and tolerability, and determine the recommended Phase 2 dose of daily oral dosing of HC-7366 in patients (pts) with advanced solid tumors. Up to 36 pts with squamous cell carcinoma of the head and neck (SCCHN), colorectal cancer (CRC), non-small cell lung cancer (NSCLC), or transitional cell carcinoma of the bladder (TCC) will be enrolled into Phase 1a; other solid tumors are eligible if selection criteria are met (capped at 50%). A 3+3 design will be employed and dose escalation determined by occurrence of dose limiting toxicities (DLT) within Cycle 1 (21 days). A Safety Monitoring Committee will review each cohort when the planned number of pts complete the DLT period. Six dose levels (10, 20, 40, 75, 125, 150 mg) of HC-7366 will be evaluated. Phase 1b will be an expansion of up to two Phase 1a dose levels and enroll 15 pts per cohort. Secondary endpoints include ORR, DOR, TTF, PFS, and OS. Pharmacokinetic data will be profiled. Exploratory objectives include evaluation of pharmacodynamic markers in tumor biopsies and immunophenotyping in blood samples. Main inclusion criteria include: SCCHN, CRC, NSCLC, TCC or other solid tumors; >1 radiologically measurable lesion per RECISTv1.1; >1 biopsiable lesion at baseline; no immune checkpoint inhibitor within 4 weeks (wks) of 1st dose; ECOG 0 or 1; <10% body weight loss in 4 wks before 1st dose & serum albumin >3 g/dL; and normal/adequately controlled pan-endocrine function. Main exclusion criteria include: autoimmune disease, organ transplant, retinitis or photosensitive skin disorders; history of interstitial lung disease or pneumonitis within 1yr; and overt or latent disorders of the exocrine pancreas. Formal hypothesis testing will not be performed. Descriptive statistics of parameters of interest will be presented by dose level and safety parameters will be summarized. The trial is sponsored by HiberCell, Inc. Approximately 9 US sites will participate. Clinical trial information: NCT05121948. Research Sponsor: HiberCell, Inc.

TPS3180 **Poster Session**

Efficacy of afatinib in patients with advanced/metastatic solid tumors harboring *NRG1* gene fusions: A novel, prospective real-world outcomes study based on single-patient protocol data. *First Author: Stephen V. Liu, Georgetown University Medical Center, Washington, DC*

Background: Oncogenic neuregulin 1 (*NRG1)* gene fusions occur in ~0.2% of solid tumors overall and in up to 31% of cases of invasive mucinous lung adenocarcinoma [Laskin et al. *Ann Oncol.* 2020;31(12):1693–1703; Cadranel et al. *Oncologist.* 2021;26(1):7–16]. NRG1 fusion proteins provide an extracellular anchor for the epidermal growth factor (EGF) domain of NRG1 to bind to ErbB3 (HER3), leading to HER3 heterodimerization and activation of downstream signaling pathways, resulting in oncogenesis. Afatinib, an irreversible pan-ErbB tyrosine kinase inhibitor, represents a potential treatment for *NRG1*-fusion positive (*NRG1+*) tumors. This study aims to examine the safety and efficacy of afatinib in patients with *NRG1+* solid tumors, for which no authorized targeted therapy exists. **Methods:** This prospective, decentralized, US study (NCT05107193) will include 40 evaluable patients aged ≥18 years. Participating molecular test providers across the USA will identify eligible fusions in the course of routine diagnostic assays. When a patient with an *NRG1* fusion is identified, participating test providers will notify the treating physician of the study as a treatment option for the patient. Patients' primary oncologists will then contact the trial sponsor to confirm patient eligibility. Once approved by the central Institutional Review Board, patients will receive afatinib on a single-patient protocol basis, until disease progression or treatment is no longer tolerated. The recommended dosage per SmPC is 40 mg orally QD. Patients will be screened and enrolled into the study at their existing point-of-care setting. Inclusion criteria include a histologically or cytologically confirmed diagnosis of an advanced, unresectable/metastatic, non-hematologic malignancy with an *NRG1* fusion, evaluable per RECIST 1.1. Any coding gene as the *NRG1* fusion partner is permitted. Fusion status will be confirmed prospectively by a contracted molecular test provider. Exclusion criteria include prior systemic anti-cancer therapy or investigational drug within 14 days or 5 half-lives (whichever is shorter) of the start of afatinib treatment; an actionable driver mutation other than *NRG1* fusion for which FDA-approved targeted therapy is available; and prior treatment with an ErbB-targeted therapy. The primary endpoint of the study is confirmed objective response (OR) by independent central review per RECIST 1.1, defined as best overall response of either complete response or partial response and analysed as the proportion of patients with an OR. The key secondary endpoint is duration of response, defined as the time from the first documented OR to progression or death. Secondary endpoints include time to OR and disease control per investigator assessment. Safety will also be assessed. The study is open for recruitment. Clinical trial information: NCT05107193. Research Sponsor: Boehringer Ingelheim.

3500 **Oral Abstract Session**

Perioperative chemotherapy with mFOLFOX6 or CAPOX for patients with locally advanced colon cancer (OPTICAL): A multicenter, randomized, phase 3 trial. *First Author: Huabin Hu, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China*

Background: Adjuvant chemotherapy is the recommended standard treatment for resected stage III and high-risk stage II colon cancer, but disease recurrence remain common. Perioperative chemotherapy has proved effective in several tumors, but not in colon cancer. We aimed to assess whether perioperative chemotherapy could improve outcomes in patients with locally advanced colon cancer. **Methods:** In this multicenter, randomized, phase 3 trial, participants were recruited from 28 hospitals in China. Eligible patients were aged 18-75 years, had a colon adenocarcinoma, with radiologically staged locally advanced (T3 with ≥5 mm invasion beyond the muscularis propria or T4 assessed by CT). Patients were randomly assigned (1:1) to either the experimental group or standard of care group, stratified by center, cT stage, and cN stage. The experimental group received 3 months of neoadjuvant chemotherapy with mFOLFOX6 or CAPOX, then surgery, then 3 months of adjuvant chemotherapy. The standard of care group received immediate surgery, and optional adjuvant chemotherapy (per physician's discretion according to pathological stage). The primary endpoint was disease-free survival assessed in the intention-to-treat population at 3 years. **Results:** Between January 6, 2016, and April 3, 2021, 752 patients were enrolled and randomly assigned to a treatment, of whom 744 were eligible (371 in the experimental group; 373 in the standard of care group). At a median follow-up of 32.5 months (IQR 19.2-45.7), 3-year disease-free survival rates were 78.7% (95%CI 73.8-83.5) in the experimental group and 76.6% (95%CI 71.8-81.4) in the standard of care group (stratified HR 0.83, 95%CI 0.60-1.15; p = 0.138). A pathological complete response was achieved in 26 (7%) of 371 patients in the experimental group. 69 (19%) patients in the experimental group had low pathological disease stage (pT0-2N0) compared with 16 (4%) of 373 in the standard of care group (p < 0.0001). 3-year overall survival rates were 94.9% (95%CI 92.1-97.7) in the experimental group and 88.6% (95%CI 84.6-92.5) in the standard of care group (stratified HR 0.47, 95%CI 0.25-0.87; p = 0.012). The post hoc subgroup analyses revealed perioperative chemotherapy induced an increase in disease-free survival in female patients (HR 0.54, 95%CI 0.31-0.83; p = 0.025). **Conclusions:** In patients with locally advanced colon cancer, perioperative chemotherapy with mFOLFOX6/CAPOX increased chance of pathological downstaging, but did not improve disease-free survival compared with standard of care. Clinical trial information: NCT02572141. Research Sponsor: Sun Yat-sen University Clinical Research 5010 Program.

	Experimental group N(%) (n = 371)	Standard of care group N(%) (n = 373)	P
Median age, years (range)	56 (19-75)	56 (22-73)	
Male	215 (58)	223 (60)	
Pathological disease stage			< 0.0001
pT0N0M0/ pTisN0M0-stage 0	27 (7)	0 (0)	
Stage I	42 (11)	16 (4)	
Stage II	181 (49)	180 (48)	
Stage III	106 (29)	164 (44)	
Stage IV	7 (2)	13 (4)	
No surgery or missing data	8 (2)	0 (0)	

3501 **Oral Abstract Session**

Noninferiority multicenter prospective randomized controlled study of rectal cancer T2–T3s (superficial) N0, M0 (T2T3sN0M0) undergoing neoadjuvant treatment and local excision (TEM) versus total mesorectal excision (TME): Preoperative, surgical, and pathological outcomes—The TAUTEM-study. *First Author: Xavier Serra-Aracil, Corporacion Sanitaria Parc Tauli, Sabadell, Spain*

Background: The standard surgical treatment of rectal adenocarcinoma above T1 is total mesorectal excision (TME), but it is associated with high morbidity and quality of life disorders. Transanal endoscopic microsurgery (TEM) achieves minimal postoperative morbidity rates. The treatment of T2, T3 superficial, N0, M0 rectal cancers is TME due to local excision achieving high recurrence rates. Initial reports of preoperative chemoradiotherapy (CRT) in association with TEM shows reduction in local recurrence. The TAU-TEM study aims to demonstrate the non-inferiority of the oncological outcomes and the improvement in morbidity and quality of life achieved with CRT-TEM compared with TME. **Methods:** Prospective, multicenter, randomized controlled non-inferiority trial including patients with rectal adenocarcinoma less than 10 cm from the anal verge and up to 4 cm in size, staged as T2T3sN0M0. Patients were randomized to: CRT-TEM (Arm A) or TME (Arm B). Postoperative morbidity and mortality were recorded and patients in both arms completed quality of life questionnaires when starting treatment and 6 months after surgery. Patients attended follow-up controls for local and systemic relapse. Trial registration: ClinicalTrials.gov Identifier: NCT01308190. **Results:** From July/2010 to October/2021, 173 patients from 17 Spanish hospitals were included (Arm A: 86, Arm B: 87). Ten were excluded after randomization (Arm A: 4, [3 re-staged > T2T3sN0M0, 1 refused follow-up study]; Arm B: 6 [4 refused the arm, 2 re-staged > T2T3sN0M0]). Therefore, the patients with modified intention to treat analysis were: TME, 81 and CRT-TEM, 82. There was no mortality after CRT. In this group, 2 patients abandoned neoadjuvant therapy; thus 80/82 (97.6%) completed CRT. The CRT-morbidity was low (25/82, 30%) and of low grade (95% G1-2). In the CRT-TEM group, MRI showed disease progression in 3 patients who were treated with TME. Finally, 77 patients underwent TEM surgery. One patient died in each arm (1.2%). Postoperative morbidity was 41/81 (50.6%) (Arm B) and 17/82 (20.7%) (Arm A) (p < 0.001, 95 CI% 43.9 to 15.9). Median Comprehensive Complication Index was 8.7 (IQR 20.9) Arm B and 0 (IQR 0) Arm A (p < 0.001). Median hospital stay was 7 days (IQR 7) Arm B and 2 days (IQR 2) Arm A (p < 0.001). Complete response in Arm A was 45.3% (34/75 patients) with 5.3% ypT3 (4/75 patients) and in Arm B: pT1 (12.3%; 10/81patients), deep-pT3 (4.95; 4/81patients), pN1 (21%; 17/81). **Conclusions:** CRT-TEM treatment obtains high pathological complete response rates (45.3%), with a high CRT compliance rate (97.6%) and low morbidity. Postoperative complications and hospitalization are significantly lower in the CRT-TEM group. We await the results of the follow-up. Clinical trial information: NCT01308190. Research Sponsor: Olga Torres Foundation Grant, Other Foundation.

3502 **Oral Abstract Session**

STAR-TREC phase II: Can we save the rectum by watchful waiting or transanal surgery following (chemo)radiotherapy versus total mesorectal excision for early rectal cancer? *First Author: Simon Parkinson Bach, University of Birmingham, Birmingham, United Kingdom*

Background: No randomised trials have compared non-operative organ preservation (OP) therapy for early-stage rectal cancer versus standard of care (SoC) using total mesorectal excision (TME) alone. STAR-TREC evaluated the feasibility of recruiting to a study comparing contrasting OP therapies, optimised for treatment of early tumours, versus SoC. **Methods:** STAR-TREC was a prospective, randomised, open-label, feasibility study in the UK, Netherlands and Denmark. Patients with biopsy proven adenocarcinoma of the rectum, staged ≤mrT3b N0 M0, ≤40mm diameter, ECOG 0-1 were randomised in a 1:1:1 ratio to TME, OP via mesorectal short-course radiotherapy (5x5 Gy), or OP via mesorectal chemo-radiotherapy (25x2 Gy + capecitabine) (Peters FP et al. Mesorectal radiotherapy for early stage rectal cancer: A novel target volume. *Clin Transl Radiat Oncol* 2020; 21: 104-11). Standardised response assessment classified OP cases as complete response for no further treatment, partial response for transanal endoscopic microsurgery or poor response for TME by 20 weeks. Surveillance following OP consisted of 3-monthly endoscopy/MRI. All cases had CT thorax/abdomen/pelvis at 24 months (m). The primary outcome was recruitment rate over 2 years, with randomisation of 120 international cases calculated as sufficient to support a phase III trial. Secondary outcomes included acute toxicity, stoma and OP rates at 12m, disease free survival (DFS) and non-regrowth DFS (NRDFS) at 24m and EORTC QLQ-C30 summary score at 12 and 24m. Phase II analysis was pre-specified, approved by the data monitoring committee conditional upon grouping of OP arms to inform phase III design, without prejudicing the outcome (STAR-TREC Phase III protocol. *Colorectal Disease* 2022). **Results:** Recruitment endpoints were met on 28 Oct 2019. Key secondary outcomes are tabulated by intention to treat. No 6-month mortality occurred. **Conclusions:** OP pathways optimised for early tumours reduce acute surgical morbidity without introducing substantial radiation toxicity to achieve OP in 60% with no increase in NRDFS at 24m compared to SoC. Overall quality of life was evenly matched. STAR-TREC phase III will determine the optimal strategy for achieving OP (STAR-TREC Phase III protocol. *Colorectal Disease* 2022). Clinical trial information: NCT02945566. Research Sponsor: Cancer Research UK, Dutch Cancer Society, Danish Cancer Society.

		OP N = 80	SoC N = 40	Posterior probability OP superior to SoC (%)
Acute toxicity ≤ 4 wk†	Radiation ≥G3	3 (3.75)	0	
	Major surgical	8 (10)	7 (17.5)	87.3
12 m stoma†		14 (17.5)	11 (27.5)	89.6
12 m organ preservation†		48 (60)	0	
24 m NRDFS*		90.1 (83.4, 97.4)	85.9 (75.1, 98.2)	46.1
24 m DFS*		75.1 (66.0, 85.5)	91.2 (82.2, 100.0)	2.5
QLQ C30	Baseline	88.6 (1.3; 77)	93.2 (1.4; 29)	
	12 m	90.1 (1.6; 49)	89.5 (1.9; 24)	40.9
	24 m	89.8 (1.6; 47)	86.3 (3.5; 22)	70.5

†n (%) *% (95% CI) ‡Summary score: mean (SD; n).

3503 **Oral Abstract Session**

Randomized intermittent or continuous panitumumab plus FOLFIRI (FOLFIRI/PANI) for first-line treatment of patients (pts) with RAS/BRAF wild-type (wt) metastatic colorectal cancer (mCRC): The IMPROVE study. *First Author: Antonio Avallone, Istituto Nazionale Tumori Fondazione G. Pascale, Naples, Italy*

Background: Continuous anti-EGFR-based FOLFIRI is a first-line standard of care in pts with RAS/BRAF wt mCRC. The emergence of resistance and treatment-related toxicity limit the efficacy of continuous treatment. Thus, an intermittent strategy could reduce both toxicity and resistance. **Methods:** This is a prospective, randomized, non-comparative, open-label, multicenter phase II study. Unresectable, previously untreated RAS/BRAF wt mCRC pts, were randomized to a control arm (A) receiving FOLFIRI/PANI continuously until progression or to the experimental arm (B), receiving 8 cycles of the same regimen followed by a treatment free interval. This lasted until progressive disease, when another treatment period of up to 8 cycles was restarted. This intermittent strategy was continued until progression occurred on treatment. Tumor assessment was always done every 8 weeks in both arms. Pts were stratified for center, ECOG PS (0-1 vs 2), previous adjuvant therapy (yes or no), sidedness (right vs left) and metastatic sites (1 vs ≥ 2). The primary endpoint was the progression-free survival on treatment (PFSOT) at 1 year. Assuming p1=43% PFSOT at 1 year, corresponding to an expected median PFSOT time ≥ 10 months in the experimental arm, and a 5% drop-out rate, a sample size of 68 pts in each arm granted the study a power of 80%, with a type I error of 10% (binomial test) for rejecting the null hypothesis, p0=30%, corresponding to a median PFSOT time of ≤ 7 months. Secondary endpoints were safety, quality of life, OS and response rate (ORR); ctDNA samples were also collected. No formal comparison between the two arms was planned. **Results:** From May 2018 to June 2021, 137 pts were randomized (69 arm A/68 arm B). Main pts' characteristics were (arm A/B): males 59/61%; median age 62/66yrs; PS 0 84/72%; right colon 17/15%; previous adjuvant therapy 22/29%; single metastatic site 33/26%. At a median follow-up of 18 months (IQR: 10-26), median PFS OT was 12.6 months (95% CI: 9.0-16.1) in arm A and 17.6 months (95% CI: 7.5-27.8) in arm B with a 1 year PFSOT rate of 51.7% and 61.3%, respectively. ORR (arm A/B) was 64/56%. Median number of FOLFIRI/PANI cycles administered per patient were (arm A/B) 13/12. Main grade 3-4 toxicities were (arm A/B): skin 27/13%, neutropenia 23/22%; diarrhea 13/15%. **Conclusions:** The primary endpoint of the study was met with the intermittent FOLFIRI-PANI strategy producing a long PFS with a reduced skin toxicity. These data deserve further investigations in a phase III trial. Clinical trial information: NCT04425239. Research Sponsor: AMGEN (partially funded).

3504 **Oral Abstract Session**

STRATEGIC-1: Multi-line therapy trial in unresectable wild-type KRAS/NRAS/BRAF metastatic colorectal cancer—A GERCOR-PRODIGE randomized open-label phase III study. *First Author: Benoist Chibaudel, Department of Medical Oncology, Franco-British Institute, Levallois-Perret, France*

Background: The management of unresectable metastatic colorectal cancer (mCRC) is a comprehensive treatment strategy involving several lines of therapy, maintenance, salvage surgery, and treatment-free intervals. Besides chemotherapy (fluoropyrimidine, oxaliplatin, irinotecan), anti-angiogenic and anti-epidermal growth factor receptor (EGFR) agents have become available. Ultimately, strategy trials are needed to define the optimal use and the best sequencing of these agents. **Methods:** Patients with previously untreated RAS/BRAF wild-type unresectable mCRC were randomly assigned (1:1 ratio) to receive either FOLFIRI-cetuximab followed by mFOLFOX6-bevacizumab (arm A) or OPTIMOX-bevacizumab followed by FOLFIRI-bevacizumab followed by EGFR mab +/- irinotecan (arm B). This trial was designed as a superiority study (hypothesis arm B > arm A) with Duration of Disease Control (DDC) as primary endpoint, defined as the sum of PFS of each active sequence of treatment (Chibaudel B, J Clin Oncol, 2011). Secondary endpoints were overall survival (OS), Time to Failure of Strategy (TFS), Progression-free survival (PFS) and response rate (RECIST version 1.1) per sequence, salvage surgery rate, safety, and Quality of life (QoL). **Results:** Between October 2013 and May 2019, 263 eligible patients were randomized (arm A, n = 131; arm B, N = 132). After a median follow-up of 51.2 months (95% CI 43.3-57.4), 188 events for DDC were observed. Efficacy outcomes are presented in table. Median DDC was similar in both arms (HR 0.97, 95% CI 0.72-1.29; P = 0.805). Salvage surgery for metastasis (+/- radiofrequency ablation) was done in 36 (27.5%) patients in arm A and 28 (21.2%) in arm B. Median time until definitive deterioration of QoL (global health status) were 18.3 and 18.0 months (P = 0.628). The safety profiles were consistent with the established safety profiles of each treatment regimen. **Conclusions:** STRATEGIC-1 is the first randomized phase III study comparing multi-line standard treatment strategies in patients with KRAS/NRAS/BRAF wild-type mCRC. This study did not meet its primary endpoint of DDC. The treatment strategy starting with FOLFIRI-cetuximab followed by mFOLFOX6-bevacizumab led to higher response rates and to a trend for better median OS exceeding 3 years. These findings may add to our understanding of treatment sequencing in mCRC. Clinical trial information: NCT01910610. Research Sponsor: ROCHE, GERCOR.

	Arm A	Arm B	HR (95%CI)	*P*-value
Whole strategy	**N = 131**	**N = 132**		
DDC, months (95%CI)	22.5 (20.1-27.1)	23.5 (17.9-26.2)	0.97 (0.72-1.3)	0.805
OS, months (95%CI)	37.8 (32.2-47.7)	34.4 (27.6-42.2)	1.26 (0.94-1.7)	0.121
First-line (L1)	**N = 131**	**N = 132**		
PFS_{L1}, months	11.7 (10.5-13.8)	11.9 (10.2-12.6)	1.07 (0.82-1.4)	0.631
ORR_{L1}, %	82.4 (103/125)	65.9 (85/129)		0.003
Second-line (L2)	**N = 82**	**N = 67**		
PFS_{L2}, months	7.3 (5.7-7.8)	6.2 (4.6-7.4)	1.01 (0.72-1.4)	0.945
ORR_{L2}, %	21.2 (17/80)	17.2 (11/64)		0.541

LBA3505 **Oral Abstract Session**

Modified FOLFOXIRI plus panitumumab (mFOLFOXIRI/PAN) versus mFOLFOX6/PAN as initial treatment of patients with unresectable *RAS* and *BRAF* wild-type metastatic colorectal cancer (mCRC): Results of the phase III randomized TRIPLETE study by GONO. *First Author: Chiara Cremolini, Department of Translational Research and New Technologies in Medicine and Surgery-Unit of Medical Oncology 2, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

LBA3506 **Oral Abstract Session**

FOLFOXIRI + bevacizumab versus FOLFOX/FOLFIRI + bevacizumab in patients with initially unresectable colorectal liver metastases (CRLM) and right-sided and/or *RAS*/*BRAFV600E*-mutated primary tumor: Phase III CAIRO5 study of the Dutch Colorectal Cancer Group. *First Author: Cornelis J. A. Punt, University Medical Center Utrecht, Utrecht, Netherlands*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

LBA3507 **Oral Abstract Session**

Randomized clinical trial on resection of the primary tumor versus no resection prior to systemic therapy in patients with colon cancer and synchronous unresectable metastases. *First Author: Nuh N. Rahbari, Universityhospital Mannheim, University of Heidelberg, Medical Faculty Mannheim, Mannheim, Germany*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

3508 **Oral Abstract Session**

Atezolizumab plus modified DCF (docetaxel, cisplatin, and 5-fluorouracil) as first-line treatment for metastatic or locally advanced squamous cell anal carcinoma: A SCARCE-PRODIGE 60 randomized phase II study.

First Author: Stefano Kim, Bourgogne-Franche Comté University, Department of Medical Oncology, Besançon University Hospital, Besançon, France

Background: Modified docetaxel, cisplatin, and 5-fluorouracil (mDCF) regimen is one of the first-line standard regimens for the treatment of metastatic or unresectable locally advanced recurrent squamous cell carcinoma of the anus (SCCA) after demonstrating an improved efficacy (12-month PFS of 47%) in the Epitopes-HPV02 trial. Antibodies targeting the checkpoint inhibitor (CKI) programmed cell death protein-1 have been shown to be effective as monotherapy in advanced SCCA, refractory to chemotherapy. The aim of this study was to evaluate the combination of atezolizumab and mDCF as first-line treatment. **Methods:** This is a 2:1 randomized, non-comparative, multicenter, phase II study (NCT03519295) with an experimental arm (Arm A, mDCF plus atezolizumab) and standard arm (Arm B, mDCF). Patients with chemo-naive SCCA, metastatic or unresectable locally advanced recurrence were eligible. In Arm A, survival probabilities for null and alternative hypotheses for the primary endpoint 12-months PFS rate were 35 and 50%, respectively. Using one-arm non-parametric survival with unilateral alpha type I error of 5% and a statistical power of 81%, 64 patients in 2 years with 1 year of follow-up need to be randomized in Arm A. The lowest expected critical value would be a PFS rate of 46% to reject H0. In both arms, 8 cycles of mDCF were administered. In Arm A, patients received a fixed dose of atezolizumab (800 mg every 2 weeks) before each mDCF cycle and were followed up to 1 year. **Results:** Ninety-sevenevaluable patients were enrolled, 64 in Arm A and 33 in Arm B. The median age was 64.1 years, 73.2% were women, and 78,3% had a metastatic disease. More patients in Arm A had an ECOG-PS 1 (42.2% vs 27.3%), liver involvement (56.9% vs 48%), and an extensive local recurrence (23.5% vs 8%). The median follow-up was 22.3 months (95% CI 20.8-24.8).The 12-month PFS rate was 44.2% (90% CI 33.7-54.2) and 43.2% (90% CI 28.5-57.0) in Arm A and Arm B, respectively, and the 12-month OS rate was 77.7% (95% CI 68.1-88.7) and 80.8% (95% CI 68.1-95.9).The objective response rate was 74.6% and 78.1% in Arm A and Arm B, respectively. A high dose-intensity and a good safety profile were observed in both arms. Grade ≥3 toxicities were observed in 59.0% and 36.4% of patients in Arm A and Arm B, respectively, with no toxic death. **Conclusions:** The results of SCARCE trial are consistent with previous results of mDCF, with high efficacy and safety at first-line in patients with advanced SCCA. However, the concomitant addition of CKI did not make a significant clinical impact at 12 months. Updated results will be presented. Clinical trial information: NCT03519295. Research Sponsor: ROCHE, GERCOR.

3509 **Poster Discussion Session**

Phase II study of nivolumab in combination with FOLFOXIRI/bevacizumab as first-line treatment in patients with advanced colorectal cancer RAS/BRAF mutated (mut): NIVACOR trial (GOIRC-03-2018).

First Author: Angela Damato, Medical Oncology Unit, Azienda USL-IRCCS Reggio Emilia, Reggio Emilia, Italy

Background: FOLFOXIRI plus bevacizumab (BEV) represents standard chemotherapy in first-line treatment of patients (pts) with metastatic colorectal cancer (mCRC). The NIVACOR study evaluates the addition of nivolumab (NIV) to FOLFOXIRI/BEV as first-line therapy in mCRC RAS/BRAF mut pts regardless of MSS/MSI status. **Methods:** This is a single-arm, multicenter, open-label, phase II trial in first-line treatment of pts with mCRC RAS/BRAF mut. Pts received NIV at a flat dose of 240 mg q14 days, FOLFOXIRI (irinotecan 165 mg/m^2, oxaliplatin 85 mg/m^2, leucovorin 200 mg/m^2, and 5-fluorouracil CI 3,200 mg/m^2 for 48 hours) in combination with BEV at the dose of 5 mg/kg IV q14 days for eight cycles and then, the maintenance with BEV/NIV until PD or unacceptable toxicities. The primary endpoint was the ORR according to RECIST 1.1 Criteria. All images are reviewed by Independent Data Monitoring Committee. According to Fleming's design with alpha and beta levels of 0.05 and 0.2 respectively, in a sample size of 73 pts (comprehensive of a 10% drop-out rate), at least 56 responses were necessary to not reject the alternative hypothesis of an ORR=0.80. **Results:** From October 2019 to March 2021, 73 pts were enrolled in 9 Italian centers. The median age was 60 (51-65) years and 50.7% were male; the main primary tumor side was right (50.7%). The molecular characterization was: 87.7% RAS mut, 16.2% BRAF mut, and 4.5% both RAS and BRAF mut; 10/62 were MSI (16.1%), 52/62 (83.9%) MSS, and 11 pts not assessed. Liver metastases were present in 56.2% pts. The median follow-up was 14.3 (IQR 11.5-16.5) months on December 31, 2021. The median (m) duration of treatment was 12 (8-17) cycles. The ORR was 76.7%, with 7(9.6%) CR and 49(67.1%) PR. SD were 15(20.6%) with a DCR of 97.3%; 2(2.7%) pts were not evaluable. The mDOR was 8.4 (95%CI, 7-NE) months. The mPFS was 10.1 months (95%CI, 9.4-NE) and 12-months PFS was 53.4%. At data cut-off, 65 (89.1%) pts are still alive. In subgroups analysis of MSS pts the ORR was 78.9% with a mDOR of 7.59 (95% CI 6.21 -11.43) months, DCR of 96.2%, and mPFS of 9.8 (95%CI 8.18-15.24) months. The surgery of the primary tumor, metastases, or both was performed in 6(8.2%), 9(9.6%), and 5(6.9%) of pts, respectively. The main grade (G) 3 -4 toxicities were: neutropenia (G3 21.9%, G4 15.1%), diarrhea (G3 17.8%, G4 1.4%), hypertension G3 (6.8%), fatigue G3 (6.8%), and febrile neutropenia G4 (4.1%). **Conclusions:** The primary endpoint ORR was met. These results show the preliminary efficacy and safety of NIV in combination with FOLOXIRI/BEV as first-line therapy in pts with mCRC RAS/BRAF mut. Also, promising activity was observed in MSS subgroup pts. These data support the conduction of phase III randomized-controlled study. Research Sponsor: Bayer, Bristol Myers-Squibb. Clinical trial information: NCT04072198.

3510 **Poster Discussion Session**

Nivolumab (NIVO) ± ipilimumab (IPI) in patients (pts) with microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): Five-year follow-up from CheckMate 142.

First Author: Michael J. Overman, University of Texas MD Anderson Cancer Center and SWOG, Houston, TX

Background: NIVO ± IPI is approved in previously treated pts with MSI-H/dMMR mCRC in the US, EU, and Japan, based on findings from the phase 2 CheckMate 142 study (NCT02060188). NCCN guidelines include NIVO + IPI as an initial therapy option for pts with MSI-H/dMMR mCRC. Results from a ~ 5-year follow-up from CheckMate 142 cohorts 1–3 (C1–3) are reported here. **Methods:** In this non-randomized, multicohort study, pts with MSI-H/dMMR mCRC were treated as follows: C1 (2L+; NIVO 3 mg/kg Q2W), C2 (2L+; NIVO 3 mg/kg + IPI 1 mg/kg Q3W [4 doses], followed by NIVO 3 mg/kg Q2W) and C3 (1L; NIVO 3 mg/kg Q2W + IPI 1 mg/kg Q6W), until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR) by investigator assessment (INV) per RECIST v1.1. Other key endpoints were disease control rate (DCR), duration of response (DOR), progression-free survival (PFS), all by INV and blinded independent central review; overall survival (OS), and safety. **Results:** In C1 (N = 74), C2 (N = 119), and C3 (N = 45), median (range) follow-up (time from first dose to data cutoff) was 70.0 (66.2–88.7), 64.0 (60.0–75.8), and 52.4 (47.6–57.1) months (mo), respectively. ORR (95% CI) by INV was 39% (28–51), 65% (55–73), and 71% (56–84; Table) and progressive disease (PD) rates were 26%, 12%, and 16% in C1, C2, and C3, respectively. Median DOR was not reached in the 3 cohorts. The 48-mo PFS rates were 36%, 54%, and 51% and 48-mo OS rates were 49%, 71%, and 72% in C1, C2, and C3, respectively (Table). PFS and OS rates with up to 60 mo of follow-up will be presented. Safety data are shown in the table. **Conclusions:** With extended follow-up of ~ 5 years, NIVO ± IPI continued to demonstrate durable OS and PFS benefit, with no new safety signals. These updated data further support current treatment recommendations for 2L+ NIVO ± IPI and 1L NIVO + IPI for pts with MSI-H/dMMR mCRC. Clinical trial information: NCT02060188. Research Sponsor: Bristol Myers Squibb.

Efficacy	C1[a] N = 74	C2[a] N = 119	C3[a] N = 45
ORR,[b,c] n (%) [95% CI]	29 (39) [28–51]	77 (65) [55–73]	32 (71) [56–84]
DCR,[b,d] % (95% CI)	69 (57–79)	81 (72–87)	84 (71–94)
PFS,[b] median, mo (95% CI)	13.8 (4.7–38.2)	NR (32.8–NE)	NR (28.8–NE)
48-mo PFS rate, % (95% CI)	36 (25–47)	54 (44–63)	51 (34–66)
OS, median, mo (95% CI)	44.2 (20.9–75.1)	NR (NE)	NR (NE)
48-mo OS rate, % (95% CI)	49 (37–59)	71 (62–78)	72 (57–83)
Safety, n (%)			
Any-grade/grade 3–4 TRAEs	58 (78)[e]/20 (27)	101 (85)/38 (32)	36 (80)/9 (20)
Any-grade TRAEs leading to discontinuation	7 (9)	16 (13)	7 (16)

[a]Study cohorts were neither randomized nor designed for a formal comparison; [b]INV; [c]Pts with CR or PR divided by the number of treated pts; [d]Pts with CR, PR, or SD (for ≥ 12 weeks) divided by the number of treated pts; [e]One grade 5 event (sudden death). CR, complete response; NE, not estimable; PR, partial response; SD, stable disease.

3511 **Poster Discussion Session**

Neoadjuvant nivolumab, ipilimumab, and celecoxib in MMR-proficient and MMR-deficient colon cancers: Final clinical analysis of the NICHE study.

First Author: Yara L. Verschoor, Netherlands Cancer Institute, Amsterdam, Netherlands

Background: The combination of PD-1 and CTLA4 blockade has changed the treatment landscape for several cancer types. Although this treatment is highly effective in metastatic mismatch-repair deficient (dMMR) colorectal cancers, metastatic MMR-proficient (pMMR) tumors do not respond. The NICHE study was the first neoadjuvant immunotherapy study in colon cancer (CC) to show impressive responses in 100% of dMMR (n= 20) and 27% of pMMR (n= 15) CC. In contrast, pathologic response to neoadjuvant chemotherapy using standard of care folfox is approximately 5% in dMMR tumors. Here we present the final efficacy data for the original NICHE study cohorts. **Methods:** Patients with non-metastatic, resectable dMMR or pMMR CC were treated with a single dose of ipilimumab 1mg/kg and two doses of nivolumab 3mg/kg and underwent surgery within 6 weeks. In addition, patients with pMMR tumors were randomized to receive celecoxib. The primary endpoints were safety and feasibility, and secondary endpoints included pathologic response rate and disease-free survival in 30 patients with dMMR and 30 with pMMR tumors. Pathologic response was defined as 50% or less viable tumor rest (VTR), and major pathologic response (MPR) as <10% VTR. **Results:** Thirty patients with pMMR and 32 with dMMR tumors were evaluable for the efficacy analyses. In the pMMR cohort, pathologic response was observed in 9/30 (30%, 95% CI 14-46%) patients, consisting of 7 MPR (including 3 pathologic complete responses {pCR}) and 2 partial responses. Four out of 9 pMMR responders had received celecoxib. Five patients received adjuvant chemotherapy. At a median follow-up of 25 months (IQR 12-35 months), 3 patients (all non-responders) in the pMMR group had disease recurrence. In the 32 patients with dMMR tumors, pathologic response was observed in 100% of patients, with 31/32 MPR (97%, 95% CI 91-100%) and one partial response. Pathologic complete response was observed in 22/32 (69%, 95% CI 53-85%) patients. None of the patients in the dMMR cohort had disease recurrence. Surgery was delayed in one patient with a pMMR tumor due to myositis. Grade 3 immune-related adverse events were observed in 12% of patients, consistent with our previous report on the primary endpoint. There were no grade 4 immune-related AEs nor unexpected surgical complications. **Conclusions:** These data confirm our previously published results of the NICHE study, with responses to neoadjuvant nivolumab plus ipilimumab in 30% of pMMR and 100% of dMMR CC in the completed original cohorts. Validation of the dMMR responses in a large group of dMMR patients is ongoing and has the potential to change current practice. Clinical trial information: NCT03026140. Research Sponsor: BMS.

3512 **Poster Discussion Session**

Contact x-ray brachytherapy (Papillon) in addition to chemoradiotherapy to improve organ preservation in early cT2-T3 rectal adenocarcinoma: The 3-year results of OPERA randomized trial (NCT02505750). *First Author: Jean-Pierre Gerard, Department of Radiation Oncology, Centre Antoine Lacassagne, Côte d'Azur University, Nice, France*

Background: The OPERA trial was testing the hypothesis that Contact x-ray brachytherapy (CXB) 50 kV boost will increase the rectal preservation rate in early T2-T3ab rectal adenocarcinoma. We present the 3 years clinical results. **Methods:** Inclusion criteria were: Age > 18 years, PS: 0-1, adenocarcinoma, distal - middle rectum, cT2-T3ab cN0-N1 < 8mm staged using MRI, M0. Stratification: T < vs ≥ 3 cm diameter. Control arm (A) was chemoradiotherapy (CRT) 45Gy/ 5 weeks with concurrent chemotherapy (Capecitabine 825 mg / m^2) and external beam radiotherapy boost (9Gy/ 5 fr/ 1 week). Experimental arm used the same CRT (Cape 45) but the boost used CXB (90 Gy/ 3 fr/ 4 weeks). CXB was given first (B1) for tumor < 3 cm and after cap 45 (B2) for tumor ≥ 3 cm. Response assessment was made at week 14 after treatment start using palpation, endoscopy and MRI. A new assessment could be made at week 20 and 24 with a second MRI.TME was recommended in case of Partial response, Watch& Wait in case of clinical complete response (cCR). Bowel function measurement used LARS score. Main end- point was: Rate of organ preservation at 3 years. The hypothesis (in 2014) was 20% arm A vs 40% arm B (HR:0.53). **Results:** Between 5-2015 and 6-2020, 144 patients were included (France 96, UK 44, Switzerland 4). The analysis was made in 01-2022 with a median Follow-up time of 34 months. Treatment compliance was good in ≥ 90% of patients. Table gives main patients characteristics and clinical outcome. At three years the OP rate (Kaplan Meier estimate) was respectively arm A vs B: 60% vs 81% (HR 0.34 [95% CI 0.19 – 0.73]; *p*= 0.005). At three years OP for group A1 and B1 were: 65% vs 97% (HR 0.081 [95% CI 0.01-0.64]; *p*= 0.02). **Conclusions:** A CXB boost, when combined with chemoradiotherapy, increases the rate of organ preservation in early rectal adenocarcinoma. Starting with CXB in T < 3 cm appears as an attractive option. A B A1*(T < 3cm)* B1 *(T < 3cm)* N° patient 71 73 30 32 Median age 68 69 69 70 Gender M/F 45/26 43/30 18/12 18/14 T2/T3 45/26 47/26 25/5 29/3 Distal/middle 53/18 53/20 21/9 27/5 cCR (W 14-24) 61% 90% p < 0.001 70% 94% p = 0.027 TME 26 12 8 1 Death 2 2 1 0 LARS < 30 80% 83% 87% 86%. Research Sponsor: PHRC FRANCE, Charity fund.

LBA3513 **Poster Discussion Session**

A phase II study of capecitabine plus concomitant radiation therapy followed by durvalumab (MEDI4736) as preoperative treatment in rectal cancer: PANDORA study final results. *First Author: Stefano Tamberi, UOC Oncologia Ravenna, AUSL Romagna, Ravenna, Italy*

LBA3514 **Poster Discussion Session**

Curative chemoradiation for low rectal cancer: Primary clinical outcomes from a multicenter phase II trial. *First Author: Lars Henrik Jensen, Danish Colorectal Cancer Center South, Vejle University Hospital, Vejle, Denmark*

3515 **Poster Discussion Session**

Primary surgery followed by selective radiochemotherapy versus conventional preoperative radiochemotherapy for patients with locally advanced rectal cancer with MRI-negative circumferential margin (PSSR): A multicenter, randomized, open-label, noninferiority, phase 3 trial. *First Author: Ke-Feng Ding, Department of Colorectal Surgery and Oncology, Key Laboratory of Cancer Prevention and Intervention, Ministry of Education, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China*

Background: Neoadjuvant radiochemotherapy is the standard treatment for locally advanced rectal cancer. However, radiation therapy can lead to bowel, urinary and sexual dysfunction. The study aims to clarify whether locally advanced rectal cancer with a distance of 6 to 12 cm from the anus with negative circumferential margins (CRM) predicted by MRI can be exempted from preoperative radiotherapy. **Methods:** PSSR (NCT02121405), a multicentre, randomized, open-label, non-inferiority, phase 3 trial, was done across 10 hospitals in China. Patients aged from 18 to 75 years with locally advanced rectal cancer (including all cT3/4 and/or Nany) with negative MRI-predicted CRM and tumor distance of 6 to 12 cm from anus were randomly assigned (1:1), by central randomization, to intervention group (surgery directly, in which positive CRM was supplemented with chemoradiotherapy, negative CRM received adjuvant chemotherapy according to surgical pathologic staging), or control group (neoadjuvant chemoradiotherapy then underwent surgery and adjuvant chemotherapy). The primary endpoint is the rate of 3-year disease-free survival (DFS). A sample size of 350 was set according to the original non-inferiority margin of 15% for the difference of rates for 3-year DFS, which was changed to 5% under the Data Safety Monitoring Board (DSMB) suggestion after an interim analysis. The efficacy analysis followed the per-protocol (PP) principle. **Results:** From December 2015 to February 2021, 299 patients were recruited. DSMB stopped this trial due to the difference of 3-year DFS's rate between two groups more than 5% at the interim analysis in July 2021. A total of 275 were included for the final analysis. Based on the PP dataset, 238 patients followed the original protocol (135 patients in the intervention group and 103 patients in the control group). Patients who had positive CRM were 2(1.5%) and 1(1.0%) in two groups, respectively (*P*= 1.00). After a median follow-up of 34.6 (IQR: 18.2-45.7) months, a total of 42 patients had positive events (30 patients in the intervention group and 12 patients in the control group). There were 5 (3.7%) patients with local recurrence in the intervention group (*P*= 0.062). Patients with pathological complete response (pCR) and near pCR were 19 (18.4%) and 21 (20.4%) in the control group. The rate of 3-year DFS was 81.1% (77.3%-84.9%) (HR = 2.02, 95%CI: 1.01-4.06, *P*= 0.048) in the intervention group and 86.6% (82.7%-90.5%) in the control group, with difference of 5.4% (5.3%-5.6%), which did not meet the criteria for non-inferiority. **Conclusions:** In terms of DFS, initial surgery was inferior to conventional preoperative radiochemotherapy for locally advanced middle rectal cancer with MRI negative circumferential margin. Clinical trial information: NCT02121405. Research Sponsor: Grant Number: RCT-2019-005A.

3516 **Poster Discussion Session**

Short-term outcomes of laparoscopy-assisted versus open surgery for low rectal cancer (LASRE): A multicenter, randomized, controlled trial. *First Author: Pan Chi, Fujian Medical University Union Hospital, Fuzhou, China*

Background: The efficacy of laparoscopic versus open surgery for low rectal cancer has not yet been established. We aimed to evaluate whether laparoscopic surgery is non-inferior to open surgery for low rectal cancer in terms of oncologic outcomes. **Methods:** LASRE trial (NCT01899547) is a multicenter, noninferiority, randomized controlled trial being conducted in 22 tertiary hospitals across China. Patients with low rectal cancer and without evidence of pelvic lateral lymph nodes or distant metastasis were randomly assigned (2:1) to laparoscopic or open surgery. The primary outcome was 3-year disease-free survival (DFS). Secondary outcomes included pathological outcomes, 30-day postoperative complications, 30-day mortality, overall survival (OS), and quality of life. The target sample size was 1065 patients. The short-term pathological, surgical, and postoperative recovery outcomes, analyzed in a modified intention-to-treat population (mITT). **Results:** Between November 12, 2013, and June 6, 2018, 1070 patients were randomized into laparoscopic (n = 712) or open surgery (n = 358) groups; 1039 were included in the mITT analysis (685 in laparoscopic and 354 in open group). Seventeen patients (2.5%) in the laparoscopic group required conversion to open surgery. There were no significant between-group differences in the rates of complete mesorectal excision (85.3% vs. 85.8%; p = 0.777), negative circumferential resection margins (98.2% vs. 99.7%; p = 0.085), negative distal resection margins (99.4% vs. 100%; p = 0.362), and numbers of retrieved lymph nodes (13.0 vs. 12.0; p = 0.394). The laparoscopic surgery group exhibited a shorter time to first flatus (40.4 vs. 44.8 hours; p = 0.006), time to first defecation (61.2 vs. 66.3 hours; p = 0.031), duration of analgesic use (45.0 vs. 48.0 hours; p = 0.001), and duration of hospitalization (8.0 vs. 9.0 days; p = 0.008) compared to the open surgery group. The postoperative complication rates were 13.0% and 17.2% in the laparoscopic and open surgery groups, respectively (p = 0.065). There was no incidence of 30-day mortality. **Conclusions:** In patients with low rectal cancer, laparoscopic surgery performed by experienced surgeons can provide pathological outcomes comparable with those of open surgery in terms of complete mesorectal excision and negative resection margins, rapid postoperative recovery, and fewer postoperative complications. Clinical trial information: NCT01899547. Research Sponsor: Key Clinical Specialty Discipline Construction Program from the National Health and Family Planning Commission of China (2012-649), the Minimally Invasive Medical Center Construction Program from the Fujian Province of China ([2017]171), and Joint Funds.

3517 **Poster Discussion Session**

International validation of the Immunoscore-biopsy (IS_B) to guide selection and monitoring of patients treated with watch-and-wait (WW) strategy for rectal cancer. *First Author: Franck Pages, Department of Immunology, Hôpital Européen Georges Pompidou, University of Paris, Paris, France*

Background: The WW strategy for patients with rectal cancer who achieved a clinical complete response (cCR) after neoadjuvant therapy (nT) allows to avoid major resection and the associated morbidity and mortality. Standardized criteria to select and monitor WW patients, including biomarkers predicting recurrence after nT, are lacking. The prognostic impact of the immune infiltrate in colorectal cancers is now demonstrated and has been implemented into clinics through the Immunoscore, the first standardized digital-pathology-based assay, recommended by academic institutions. We evidenced that an Immunoscore adapted to biopsies (IS_B) performed at diagnosis, predicts the response to nT and the risk of recurrence after nT. Its clinical utility was suggested in a test cohort of WW patients (El Sissy et al., Clin Cancer Res 2020). The aim of this study was to confirm the ability of the IS_B to predict clinical outcomes, improve patients' eligibility for the WW strategy, and optimize a follow-up schedule. **Methods:** A total of 304 WW patients from 10 centers across 7 countries were included. Tumor biopsies before treatment were immunostained for CD3+ and CD8+ T-cells and converted to IS_B using the predefined cut-off. The primary endpoint was time-to-recurrence (TTR). Secondary endpoint was disease-free-survival (DFS). As immune response originates in draining lymph nodes, signs of immune activation were carried out in lymph nodes of additional patients managed by radical surgery with complete pathological response (pCR; n = 12) or non-pCR (n = 12) by 3' RNA-Seq and immunofluorescence technologies. **Results:** High-IS_B patients presented with the lowest risk of recurrence after WW. 5-year recurrence-free rates were 97% (92%-100%), 61% (49%-76%), and 56% (44%-73%) with IS_B High, Intermediate, and Low, respectively (HR [Low-vs-High] = 14.3, 95% CI 1.8-100). In patients with cCR after nT (n = 209), High-IS_B showed a significant association with prolonged TTR and DFS (Logrank P = 0.005 and P = 0.006, respectively). When IS_B was evaluated as a continuous variable, the risk of recurrence was increasing along with decreasing IS_B (Wald tests, all P < 0.005). In multivariate analyses, IS_B was independent of age, sex, location, and cTNM stage and was the single parameter correlated with TTR (HR [IS_B High-vs-Low] = 0.08, 95% CI 0.01-0.6; P = 0.015) and DFS (P = 0.013). Unlike for patients with cCR, no difference according to IS_B was observed for those with incomplete response (n = 41) or treated with brachytherapy (n = 34). Finally, intranodal signs of T-cell and B-cell activation were only evidenced in patients with pCR. **Conclusions:** IS_B provides a reliable biomarker to predict clinical outcomes, improve eligibility, and optimize patients' follow-up. Intranodal T-cell and B-cell activation further supports the immune benefit of both organ and lymph node preservation. Research Sponsor: None.

3518 **Poster Discussion Session**

Plasma *RAS* dynamics and anti-EGFR rechallenge efficacy in patients with *RAS*/*BRAF* wild-type metastatic colorectal cancer: REMARRY and PURSUIT trials. *First Author: Yoshinori Kagawa, Department of Gastroenterological Surgery, Osaka General Medical Center, Osaka, Japan*

Background: Rechallenge with anti-EGFR monoclonal antibody (EGFR mAb) showed certain activities in patients (pts) with *RAS*/*BRAF* V600E wild-type (wt) metastatic colorectal cancer (mCRC), particularly in pts with negative plasma *RAS* (p*RAS*) mutation by circulating-tumor DNA (ctDNA) assay at 'just before' the rechallenge therapy. However, the efficacy is unknown in pts with *RAS*/*BRAF* wt mCRC whose p*RAS* was converted to positive once during or after EGFR mAb. Therefore, we conducted REMARRY, a prospective longitudinal study to investigate the p*RAS* dynamics, and PURSUIT trials, a phase II trial to investigate the efficacy of EGFR mAb rechallenge in pts with p*RAS* wt just before rechallenge therapy. **Methods:** The eligibility criteria of REMARRY trial included *RAS*/*BRAF* V600E wt mCRC; ECOG PS 0-1; CR or PR during EGFR mAb; and a refractory ≤ 2 months from the last administration of EGFR mAb. p*RAS* status by the BEAMing method was prospectively monitored at timepoints of progression on EGFR mAb and each subsequent therapy. The eligibility criteria of PURSUIT trial included enrollment in the REMARRY trial with confirmed p*RAS* wt prior to enrollment in PURSUIT trial; being refractory or intolerant to fluoropyrimidine, oxaliplatin, and irinotecan; and ≥ 4 months of EGFR mAb-free interval. Study treatment was rechallenge with panitumumab + irinotecan (6 mg/kg + 150 mg/m^2 q2wks). Primary endpoint was a confirmed objective response rate (ORR) according to RECIST v1.1. The required number of pts was 45, with a null ORR of 10%, an expected ORR of 25%, power of 85%, and one-sided α of 0.05. **Results:** Between May 2019 and May 2021, 183 pts with 343 timepoints (median, 2) were enrolled in REMARRY trial from 27 institutions, and 50 pts were enrolled in PURSUIT trial; median age, 68 years; left-sided primary, 44 pts; prior EGFR mAb, 1st/2nd/≥3rd lines was 28/6/16 pts; and p*RAS* status at progression on prior EGFR mAb, wt/mutant (mt)/unknown in 31/7/12 pts. Confirmed ORR and disease control rate were 14% (90% CI, 7.8%–23.9%) and 80% (95% CI, 67.0%–88.8%), respectively. In addition, 4 pts showed an unconfirmed PR. With a median follow-up time of 8.7 months, median progression-free survival was 3.6 months (95% CI, 3.0 – 4.7 months). The subgroup analysis showed a significantly higher confirmed ORR in pts with a longer EGFR mAb-free interval than a shorter one (> vs. < 365 days, 44.4% vs. 7.3%, p = 0.0037). Without any unexpected safety signals, 58.5% of pts had ≥ grade 3 adverse events. Of 31 patients with wt p*RAS* at progression on prior EGFR mAb, 5 had a confirmed response (ORR, 16%), whereas no response was observed in patients with 7 p*RAS* mt (ORR, 0%) (p = 0.25). **Conclusions:** The primary endpoint of confirmed ORR was not met; however, pts with p*RAS* wt at progression on prior EGFR mAb may benefit from rechallenge with, implying a lack of or worse response if p*RAS* becomes positive even once during or after EGFR mAb. Clinical trial information: REMARRY: UMIN000036424 PURSUIT: jRCTs031190096. Research Sponsor: REMARRY: Sysmex Corporation PURSUIT: Takeda Pharmaceutical Company Limited.

3519 **Poster Discussion Session**

Randomized study to investigate a switch maintenance concept with 5-FU plus bevacizumab after FOLFIRI plus cetuximab induction treatment versus continued treatment with FOLFIRI plus cetuximab: Report of a secondary endpoint of the phase-III FIRE-4 study (AIO KRK-0114). *First Author: Sebastian Stintzing, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Hematology, Oncology, and Cancer Immunology (CCM), Berlin, Germany*

Background: FIRE-4 (AIO KRK-0114) is performed in RAS-wild-type (wt) mCRC patients. This randomized study tests the efficacy of early switch maintenance during 1st-line therapy (part 1) and re-challenge with cetuximab (part 2) in later-line treatment. In part 1, all patients received first-line induction treatment with FOLFIRI plus cetuximab (FOLFIRI/Cet). In arm A, patients were randomized to continue FOLFIRI/Cet until progression or intolerable toxicity. In arm B, patients received FOLFIRI/Cet for 8-12 cycles, after which maintenance therapy with Fluoropyrimidin plus bevacizumab was applied. The first randomization evaluates the question if an early switch from cetuximab to bevacizumab during maintenance therapy may prolong PFS. **Methods:** Within this randomized, controlled, open-label phase-III study, patients received FOLFIRI (irinotecan plus 5-FU/FA) plus cetuximab every two weeks at the standard dosing schedule. In arm A, FOLFIRI plus cetuximab was continued every 2 weeks until progression or intolerable toxicity. De- and re-escalation was allowed according to the local standard of care. In arm B, patients received 8 cycles of FOLFIRI plus cetuximab (in case of tumor response) or 12 cycles (in case of stable disease) followed by maintenance with Fluoropyrimidin plus bevacizumab (5mg/kg) every two weeks until disease progression or intolerable toxicity. Overall survival after second randomization (part 2) is evaluated as a primary endpoint. Here, we report PFS in first-line (part 1) as a secondary study endpoint of the study. Other secondary endpoints included ORR, OS, safety, and tolerability. **Results:** From August 2015 to January 2021, 672 patients were randomized and 656 patients were assigned to treatment in 120 German and 10 Austrian centers (327 arm A and 329 in arm B). PFS was comparable between both treatment arms (10.7 vs 11.3 months, HR 0.92 (95% CI: 0.76-1.10), p = 0.36). ORR in evaluable patients was not different and reached 75.7% and 72.3% with a DCR of 94.6% vs. 92.5% in the respective arms. Preliminary OS (≤40% of OS events recorded) was also similar between both arms (HR 1.030; p = 0.81) . Updated results will be presented at the meeting. No new or unexpected toxicities were observed. **Conclusion:** Switch from FOLFIRI cetuximab to maintenance therapy with 5-FU plus bevacizumab did not induce superior efficacy (PFS, ORR, OS) compared to continued application of cetuximab. The results suggest that early switch maintenance from cetuximab to bevacizumab is not effective to postpone disease progression during targeted therapy. FIRE-4 confirms the efficacy of FOLFIRI plus cetuximab as first-line treatment of patients with RAS wild-type mCRC. Clinical trial information: NCT02934529. Research Sponsor: MERCK.

3520 **Poster Discussion Session**

Phase 2 study of anti-EGFR rechallenge therapy with panitumumab with or without trametinib in advanced colorectal cancer. *First Author: Christine Megerdichian Parseghian, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: In *RAS/RAF* WT colorectal cancer (CRC), rechallenge with anti-EGFR therapy (EGFRi) in patients (pts) with prior response leads to clinical benefit, with response rates up to 30% in prior trials. However, secondary MTs in the MAPK signaling pathway have been implicated in resistance to EGFRi. We designed a phase 2 trial to evaluate the efficacy of EGFRi rechallenge +/- a MEK inhibitor (trametinib) based on pre-treatment ctDNA MTs. **Methods:** This trial evaluated the efficacy and safety of EGFRi rechallenge +/- trametinib in pts with *RAS/BRAF* WT, MSS, treatment refractory mCRC who achieved clinical benefit with prior EGFRi based therapy for ≥16 weeks with subsequent progression. Pre study ctDNA was used to enroll in one of 3 arms: Arm A: Pts with an acquired *EGFR* ECD MT but absence of *RAS/BRAF/MAP2K1* or with absence of any acquired resistance MT (Arm C) at time of study initiation received panitumumab 6 mg/kg IV Q2 wks. Arm B: Pts with an acquired *RAS/BRAF/MAP2K1* MT received panitumumab 4.8 mg/kg plus trametinib 1.5 mg PO daily. Pts in Arms A and C were allowed to cross over on progression. The primary endpoint was ORR by RECIST v1.1. **Results:** 54 pts were enrolled, with 52 evaluable for efficacy. Median age is 59 yrs (range, 37-78), and 23 (46%) are female. Median number of prior therapies was 3. Three, 20, and 31 pts were enrolled in Arms A, B, C, respectively. Grade 3 TREAs occurred in 29 (54%) pts (all receiving the doublet regimen) and included acneiform rash in 17 (31%) and others occurring in < 5% of pts. There were no grade 4 TRAEs. In pts with no acquired MTs (Arm C), ORR was 20% (6/30) (95% CI, 0.07-0.37), DCR 67% (20/30) (95% CI, 0.45- 0.81), and median PFS and OS 4.1 mo and 11.2 mo, respectively. The median DOR was 5.5 mo. 22 patients crossed over to add trametinib at time of progression, without any responses. In contrast, in pts with acquired *RAS/RAF/MAP2K1* MTs (Arm B), there were no responses, with DCR of 63% (12/19) (95% CI, 0.36-0.81), and median PFS and OS 2.1 mo and 5.9 mo, respectively. Only 3 pts were identified with *EGFR* ECD MTs (Arm A), and ORR is 0% (0/3) in this cohort, with DCR 67% (2/3) (95% CI, 0.09-0.99). Pts with PR had a longer median interval from prior EGFRi and longer time on prior EGFRi than those with SD+PD (5.5 vs 3.6 mo; p = 0.03, and 9.5 vs. 8.8 mo; p = 0.03, respectively). **Conclusions:** CtDNA guided rechallenge leads to responses in 20% of pts without acquired resistance MTs, with DCR of 67%. This exceeds current third line standard options. While panitumumab has the potential to block EGFR ECD mutations arising from cetuximab, these mutations in isolation were uncommon and there were no signals of efficacy. Although the acneiform rash induced by the combination of MEK and EGFR inhibition was manageable with close dermatologic management, the combination failed to improve outcomes for pts with acquired resistance. Alternative approaches to downstream MAPK blockade should be explored to improve outcomes. Clinical trial information: NCT03087071. Research Sponsor: Amgen and Novartis, U.S. National Institutes of Health.

3521 **Poster Session**

Pembrolizumab (pembro) plus mFOLFOX7 or FOLFIRI for metastatic colorectal cancer (CRC) in KEYNOTE-651: Long-term follow-up of cohorts B and D. *First Author: Richard D. Kim, Moffitt Cancer Center, Tampa, FL*

Background: Response to antiPD-1 monotherapy is poor in patients (pts) with advanced microsatellite stable (MSS)/mismatch-repair proficient (pMMR) CRC. Combination of chemotherapy with antiPD-1 pembro may potentiate the antitumor immune response and provide greater antitumor activity than either agent alone. Combination of pembro and mFOLFOX7 or FOLFIRI in the ongoing phase 1b multicohort KEYNOTE-651 (NCT03374254) study in metastatic MSS/pMMR CRC showed antitumor activity. We present results with approximately 20 mo of additional follow-up. **Methods:** Pts had metastatic MSS/pMMR CRC and were previously untreated (cohort B) or received 1 prior line including a fluoropyrimidine + oxaliplatin (cohort D). Pts received pembro 200 mg Q3W + mFOLFOX7 Q2W (cohort B) or pembro 200 mg Q3W + FOLFIRI Q2W (cohort D). Primary end points were safety (DLT) and RP2D. Secondary end point was ORR per RECIST v1.1 by investigator review. DOR, DCR, and PFS per RECIST v1.1, and OS were exploratory end points. **Results:** Median study follow-up (range) at data cutoff (Oct 15, 2021) was 30.2 mo (25.0-43.6) for cohort B (n = 31) and 33.5 mo (25.2-43.2) for cohort D (n = 32). Treatment was discontinued in 29 pts (94%) in cohort B and 28 pts (88%) in cohort D, mostly because of PD (61% and 66%, respectively). At prior analysis (Feb 10, 2020), RP2D was confirmed as the starting dose in both cohorts; no new DLT had occurred. In cohort B, gr 3/4 TRAEs occurred in 18 pts (58%), most commonly neutropenia and decreased neutrophil count (both n = 5; 16%); 19 pts (61%) discontinued drug because of a TRAE. In cohort D, gr 3/4 TRAEs occurred in 17 pts (53%), most commonly, neutropenia (n = 7; 22%), diarrhea and fatigue (both n = 4; 13%); 3 pts (9%) discontinued drug because of a TRAE. There were no gr 5 TRAEs in either cohort. Efficacy by cohort and *KRAS* mutation status are below (Table). PD-L1 data and DNA/RNA-based biomarker data including GEP, consensus signatures, TMB, and LoF mutations will be included in the presentation. **Conclusions:** After 2.5 y of follow-up, the combination of pembro with either mFOLFOX7 or FOLFIRI continued to demonstrate a manageable safety profile with no new safety signals. Efficacy data from these single-arm cohorts appear comparable to historical data for current SOC. Clinical trial information: NCT03374254. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Patients	n	ORR (95% CI), %	DOR, median (range), mo	PFS, Median (95% CI), mo	OS, Median (95% CI), mo
Cohort B	31	61 (42-78)	12.2 (2.0+-23.5+)	8.6 (7.2-14.1)	28.6 (18.0-36.3)
***KRAS* WT**	14	71 (42-92)	12.2 (2.0+-22.3+)	8.6 (6.3-NR)	29.5 (12.8-NR)
***KRAS* mut**	17	53 (28-77)	18.7 (4.0-23.5+)	9.3 (5.6-20.8)	23.4 (11.2-NR)
Cohort D	32	25 (11-43)	20.2 (9.4-27.0+)	8.3 (2.2-15.6)	25.1 (19.0-NR)
***KRAS* WT**	15	47 (21-73)	20.2 (9.5-27.0+)	16.4 (2.1-22.6)	NR (21.7-NR)
***KRAS* mut**	17	6 (0-29)	9.4 (9.4-9.4)	2.3 (2.1-8.3)	21.6 (6.1-25.1)

"+" indicates there is no PD at last assessment.

3522 **Poster Session**

Mucinous adenocarcinoma of the anal canal: Clinical characteristics and outcomes of 767 patients from National Cancer Database. *First Author: Sam Melamed, The Lundquist Research Institute, Torrance, CA*

Background: Mucinous adenocarcinoma of the anal canal (MAAC) is a relatively rare disease, constituting less than 10% of anal cancers. It carries a relatively poor 5-year survival rate of between 50-60%. MAAC rarity and proximity to rectal mucosa can present a diagnostic challenge as it can be misidentified as adenocarcinoma of the lower rectum. Because of its rarity, the bulk of knowledge of the disease is derived from individual case studies or small institutional reviews. Thus, there remains no clear standard of treatment for AAC. While abdominal perineal resection is the main management approach, the role of systemic therapy and radiation on clinical outcomes remains ill-defined. The lack of national guidelines, variability in institutional approaches and in access to tertiary cancer centers may contribute to differences in patient outcomes and raise the question of healthcare disparities. In this study, we analyzed the data from 767 patients with MAAC from the National Cancer Database (NCDB). **Methods:** We obtained clinicopathological demographic, socioeconomic data and survival outcomes from 767 patients with MAAC that were registered in the NCDB from 2004 to 2017. The treatment patterns and prognostic factors were analyzed. **Results:** The majority of patients, 85%, were older than 50. White patients comprised 75.6%, Black 18.8% and Asians 3.3%. Only 3.9% were Hispanics. Among 647 patients who had survival data, the majority received the following therapies: 311 received surgery and chemoradiation, 131 only surgery and 131 only chemoradiation. White and Black patients had similar survival odds, whereas Asian patients had significantly higher overall survival (OS) (HR 0.42). Patients treated at academic facilities had significantly better OS than patients treated at non-academic facilities (HR 1.41-1.57), and patients with private insurance (HR 0.37) had significantly better survival when compared to patients with other insurance types. Patients with only Stage II exhibited significant survival differences when given both surgery and chemoradiation, compared being given either treatment modality alone (HR 0.56); interestingly, male patients in this group did not benefit from adding chemoradiation to surgery while female patients did (p = 0.1, p = 0.011). **Conclusions:** Surgical resection seems to be the most important treatment modality in MACC, while for patients with stage II addition of chemoradiation statistically significantly improves survival. Access to tertiary cancer centers and therapy costs contribute to differences in survival outcomes, which brings the question of healthcare disparities and the need for national guidelines for MACC management. Research Sponsor: None.

3523 **Poster Session**

***DEFB1* gene expression and the molecular landscape of colorectal cancer (CRC).** *First Author: Jae Ho Lo, Division of Medical Oncology, USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA*

Background: Defensins are antimicrobial peptides that play important roles in innate immune response. Deregulation of beta-defensin-1 (*DEFB1*) gene expression has been implicated in several cancers and we previously showed that single nucleotide polymorphisms in *DEFB1* are associated with clinical outcomes in patients with metastatic CRC. Hence, we aimed to further characterize the molecular features associated with *DEFB1* gene expression in CRC. **Methods:** 14416 CRC tumors tested at Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing on DNA (592 genes or WES), RNA (WTS) and IHC were analyzed. Top quartile transcripts per million (TPM) for *DEFB1* expression were considered high (Q4) while bottom quartile low (Q1). Consensus molecular subtypes (CMS) were assessed using RNAseq. Cell infiltration in the tumor microenvironment (TME) was estimated by QuantiSEQ. X^2/Fisher-Exact were used and significance was determined as *P*-value adjusted for multiple comparison ($Q < .05$). Real-world overall survival information was obtained from insurance claims data and Kaplan-Meier estimates were calculated for molecularly defined patients. **Results:** *DEFB1* expression was highest in left-sided and rectal tumors (median TPM 2.27) and lowest in right-sided tumors (median TPM 1.62). Overall, when compared to low expression, high *DEFB1* was negatively associated with high TMB (≥ 10 Mut/Mb) (4.8% vs 17%), dMMR/MSI-H (2.2% vs 13.1%), and PD-L1 expression (3.1% vs 5.2%) (all $Q < .05$). Additionally, *DEFB1* high was associated with higher expression of immune checkpoint genes *CD274*, *CD80*, *CD86*, *HAVCR2*, *LAG3*, *PDCD1* and *PDCD1LG2* (Fold Change/FC: 1.27-1.56) but lower *IDO1* (FC: 0.89) (all $Q < .05$). Similar results were confirmed in MSS tumors only, but IDO1 was now positively associated with *DEFB1* high (FC: 1.23). In the MSS cohort, *DEFB1* expression was highest in CMS2 and lowest in CMS3 (2.84 vs 1.67 median TPM, $Q < .05$). In the MSS cohort, *APC* mutations were more frequent in *DEFB1* high tumors (79% vs 72%) while *BRAF* (5.8% vs 9.4%), *GNAS* (1.1% vs 4.4%), *FBXW7* (7.8% vs 10.5%), *SMAD4* (12.3% vs 17%), *RNF43* (2.2% vs 3.5%) and *POLE* (0.2% vs 0.7%) mutations as well as *MYC* (1.2% vs 2.6%) and *MYB* amplifications (0.1% vs 0.9%) were less frequent in *DEFB1* high (all $Q < .05$). Higher neutrophils, NK cells, M2 macrophages, CD4+ T cells and myeloid dendritic cells but lower M1 macrophages, Tregs and CD8+ T cells in the TME were significantly associated with high *DEFB1*; both in the overall and MSS cohorts ($Q < .001$). CRC patients with *DEFB1* expression level above the median had worse OS compared to those below the median both in the overall cohort (HR: 1.18, 95% CI: 1.10-1.27) and in MSS tumors (HR: 1.18, 95% CI: 1.10-1.27). **Conclusions:** Our data show a distinct molecular landscape, including mutational profiles, CMS, immune biomarkers, and TME cell infiltration associated with *DEF1B* gene expression in CRC. These findings suggest a key role for DEF1B in modulating anti-tumor immunity and TME. Research Sponsor: Partly supported by NCI P30CA014089, Gloria Borges WunderGlo Foundation, Dhont Family Foundation, Ming Hsieh research fund, Daniel Butler Research Fund, Victoria and Philip Wilson Research Fund.

3524 **Poster Session**

Prognostic role of systemic inflammatory markers in patients with metastatic MSI-h/dMMR colorectal cancer receiving immunotherapy. *First Author: Deepak Bhamidipati, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Markers of systemic inflammation including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (LMR) are prognostic in patients with metastatic colorectal cancer receiving systemic chemotherapy. The presence of liver metastases has also been hypothesized to modulate response to immunotherapy. In this study, we assess the prognostic role of these markers in patients with microsatellite high (MSI-H)/deficient mismatch repair (dMMR) tumors receiving immunotherapy for metastatic or unresectable colorectal cancer (CRC). **Methods:** This was a single-institution retrospective analysis of patients with dMMR/MSI-H CRC who received anti-PD-(L)1 and/or anti-CTLA-4 therapy for metastatic or unresectable disease at between 2015 and 2021 (n = 59). NLR, PLR, and LMR were calculated based on the complete blood count obtained within 1 week prior to treatment. Patient and tumor characteristics were obtained from the clinical record. Patient characteristics were compared using Fisher's exact test and Mann-Whitney U where appropriate. Progression free survival (PFS) and overall survival (OS) were the primary endpoints and log-rank test was used for comparison of survival distribution among groups. **Results:** 59 patients with metastatic dMMR/MSI-H CRC were identified. Median age was 60, 53% (n = 31) had right-sided tumors, 35% (n = 35) of patients with testing available had RAS-mutated tumors, and 37% (n = 22) received prior chemotherapy. Most common sites of metastatic disease were peritoneum (n = 23, 39%) and liver (n = 17, 29%). Patients were divided into NLR-High (NLR ≥ 3, n = 20) and NLR-Low (NLR < 3, n = 39), and both groups had similar baseline characteristics. The rate of progressive disease as best response was not different in NLR-Low versus NLR-High (15% vs 30%, p = 0.3). At a median follow-up of 32 months, neither median PFS nor median OS were reached. 74% (n = 29) remained progression free at 1 year in the NLR-Low group versus 60% (n = 12) in NLR-High group which was not statistically significant (p = 0.37); 90% (n = 35) remained alive at 2 years in the NLR-low versus 80% (n = 16) in the NLR-High group (p = 0.4). Similarly, using a cut-off of 150 and 3 for PLR and LMR respectively, there was no significant difference between PFS at 1 year in the PLR-Low (n = 32) vs PLR-High (n = 27) (66% vs 74%, p = 0.58) and LMR-Low (n = 35) vs LMR-High (n = 24) (60% vs 83%, p = 0.084) groups. The presence of liver metastasis or the presence of a RAS mutation did not influence PFS at 1 year (p = 0.35 and p = 1.00, respectively). **Conclusions:** Markers of systemic inflammation may have a limited prognostic role for patients with dMMR/MSI-H CRC receiving immunotherapy. Research Sponsor: None.

3525 **Poster Session**

Effect of primary tumor sidedness on the association of tumor-infiltrating lymphocytes with survival of patients with stage III colon cancer (NCCTG N0147) [alliance]. *First Author: Bahar Saberzadeh Ardestani, Mayo Clinic, Rochester, MN*

Background: Tumor-infiltrating lymphocytes (TILs) are significantly associated with clinical outcomes in patients with colon cancer. However, the potential for a differential effect of TILs on prognosis based on primary tumor sidedness has not been studied. We determined the interaction between TILs and tumor sidedness in relationship to disease-free survival (DFS). **Methods:** We analyzed data on TIL densities by primary tumor sidedness in 1532 stage III colon carcinomas from participants in a phase III trial of FOLFOX-based adjuvant chemotherapy (NCCTG N0147). TIL densities were dichotomized as low or high (≤3 /HPF) based on an optimized cut-off previously identified for DFS in this cohort. Right-sided tumors were defined as proximal to the splenic flexure. Analysis of TILs and sidedness with DFS were examined using Kaplan-Meier methodology and multivariable Cox regression. **Results:** Overall, tumors with high vs low TILs had the best DFS [HR_{adj}: 0.58 (95%CI: 0.45-0.74); P_{adj} <0.0001]. The association of TIL densities with 5-yr DFS differed significantly by primary tumor sidedness ($P_{interaction\ (adj)}$ = 0.045). Among right-sided tumors, high vs low TILs were significantly associated with improved DFS (P_{adj} <0.0001)[Table]. Among left-sided tumors, however, DFS did not differ significantly for high vs low TILs (P_{adj} =0.173)[Table]. Similar results for TILs and DFS by sidedness were found for pMMR cancers. We then analyzed our data in low risk (T_{1-3}, N_1) and high risk (T_4 and/or N_2) tumors. Among low risk tumors, high vs low TILs was significantly associated with improved 5-yr DFS only in right-sided tumors (P_{adj} =0.006) [Table]. Among high risk tumors, high vs low TILs were significantly associated with better DFS in both right-sided (P_{adj}<0.001) and left-sided (P_{adj} =0.024) tumors. **Conclusions:** Overall, tumors with high TIL densities had significantly better DFS in right-sided but not left-sided cancers. Among low risk patients, the association of high TILs with better DFS was limited to right-sided tumors. These findings suggest that TILs should be interpreted by sidedness for prognostication. ClinicalTrials.gov Identifier: NCT00079274. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company, U.S. National Institutes of Health, U10CA180821, U10CA180882, U24CA196171.

Disease-free survival for patients with colon cancer stratified by TILs and sidedness among overall population, high-risk patients, and low-risk cases.

Population	Tumor sidedness	5-year Free	Disease Survival	HR (95%CI)	P-value
		High TILs	Low TILs		
Overall	Right	77%	57%	0.50 (0.36-0.69)	<0.0001
	Left	76%	69%	0.77 (0.52-1.13)	0.173
Low risk	Right	84%	70%	0.48 (0.28-0.83)	0.006
	Left	79%	78%	0.97 (0.57-1.66)	0.914
High risk	Right	68%	44%	0.49 (0.32-0.75)	0.0004
	Left	71%	60%	0.54 (0.30-0.96)	0.024

3526 **Poster Session**

Estimating the impact of reducing the age of colorectal cancer screening on cancer incidence, mortality, and costs in Canada using OncoSim. *First Author: Anastasia Kalyta, University of British Columbia Faculty of Medicine, Vancouver, BC, Canada*

Background: Organized colorectal cancer (CRC) screening programs currently cover Canadians aged ≥50 at average-risk of developing CRC and have contributed to declining CRC incidence. Rising incidence of early-onset CRC in individuals < 50 has led to lowering of the recommended screening start age to 45 rather than 50 in some jurisdictions. We used OncoSim, a publicly-available simulation tool, to model the effects of earlier screening initiation on Canadian CRC incidence, mortality and healthcare costs. **Methods:** OncoSim uses Canadian population and cancer registry data to simulate a representative sample of individuals from birth to death. We modeled four scenarios: no screening in average-risk individuals, screening initiation at age 50, initiation age lowered to 45 in 2022, and initiation age lowered to 40 in 2022. Each includes 32 million simulated participants. In the model, average-risk screening involves biennial FIT, available to all simulated participants regardless of family history with participation of 60% at the first recruitment attempt and 80% for repeat screening. Participants with a family history in all 4 scenarios were eligible for additional screening by colonoscopy every 5 years. **Results:** In our model, earlier screening yields reduced CRC incidence and mortality with increasing benefit over time. By 2051, screening initiation at age 45 or 40 reduces age-standardized incidence by 3.4% and 4.8% respectively, and age-standardized mortality by 3.3% and 4.6% respectively, compared to initiation at age 50. Screening initiation at age 45 yields 3,848 additional quality-adjusted life-years (QALYs) in 2051 at a cost of $9,350 per QALY gained and a 5% increase in colonoscopies performed. Initiation at age 40 yields 6,255 additional QALYs at $16,350 per QALY gained and a 9% increase in colonoscopies. The difference in screening costs compared to screening from age 50 is consistent year-to-year after 2024. In 2051 screening costs increase by $75mil and $155mil per year with initiation at ages 45 and 40 respectively, while costs of cancer management (including diagnosis, treatment, recurrence, palliative and end of life care) decrease by $42mil and $57mil respectively. **Conclusions:** Our model predicts that lowering the CRC screening initiation age for average-risk Canadians to 45 or 40 could reduce CRC incidence and mortality. Costs per QALY gained are high in the first few decades but decrease over time. Costs are modest after 30 years of screening compared to other life-preserving interventions such as dialysis. Our results suggest that lowering the screening age in Canada may be warranted, but further investigation is needed to assess capacity for increased colonoscopy demand. Research Sponsor: None.

3527 **Poster Session**

Race, age, and sex differences on the influence of obesity on colorectal cancer (CRC) sidedness and mortality: A national cross-sectional study. *First Author: Mark Bilinyi Ulanja, CHRISTUS Ochsner St. Patrick Hospital, Lake Charles, LA*

Background: CRC sidedness has recently been recognized as a significant prognostic factor for survival; left-sided colorectal cancer (LCRC) is associated with superior outcomes as compared to right-sided colon cancer (rCC). Although obesity has long been recognized as a risk factor for CRC, the influence of obesity on CRC sidedness remains to be elucidated. To evaluate the effect of obesity on CRC sidedness and determine how race, age, and sex affect mortality among individuals with obesity and CRC. **Methods:** A survey-weighted analysis was conducted using data obtained from the National Inpatient Sample (NIS) between 2016 and 2019. **Results:** Of the 24,549 patient discharges included in the cohort with a diagnosis of CRC and a reported body mass index (BMI), 52.6% were LCRC and 47.5% were rCC. The race distribution was 67.7% White, 17.6% Black, 10.0% Hispanic, and 4.8% Other (American Indian, Asian, Pacific Islander, or Alaskan Native). Overweight and obese individuals were more likely to have rCC as compared to normal weight patient discharges [adjusted OR (aOR) = 1.28; 95% CI:1.17 – 1.39 and aOR = 1.45; 95% CI:1.37 –1.54, respectively). In addition, among the obese population, Blacks were more likely to have rCC as compared to Whites (aOR = 1.23; 95% CI: 1.09 – 1.38). Normal weight, overweight, and obese individuals in the "Other" race category had increased odds of death as compared to all other races (aOR=1.18; 95% CI:1.13-1.22; aOR=1.09 95% CI: 0.99-1.19; and aOR=1.19; 95% CI: 1.13-1.25, respectively). Overweight and obese patient discharges over the age of 65 years were more likely than their younger counterparts to present with rCC. As compared to males, females had a higher likelihood of presenting with rCC irrespective of weight, but lower mortality across all weight categories (Table). **Conclusions:** Obesity is associated with an increased risk of rCC. Racial disparities in CC sidedness and outcomes are particularly pronounced among the overweight and obese population. Investigation into causes of these disparities may help improve outcomes among all individuals with CRC. Research Sponsor: None.

Race, age, and sex effect on obesity and sidedness of colon cancer (right vs. left).

Variable	Normal weight		Overweight		Obese	
Race	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
White (ref)						
Black	0.92 (0.80-1.04)	0.189	1.14 (0.90-1.44)	0.277	1.23 (1.09-1.38)	0.001
Hispanic	0.93 (0.78-1.11)	0.413	0.93 (0.72-1.20)	0.573	0.82 (0.71-0.94)	0.006
APINA/other	0.72 (0.61-0.86)	<0.001	0.67 (0.47-0.95)	0.025	0.82 (0.67-1.01)	0.061
Age						
<50 (ref)						
50-64	1.16 (0.97-1.37)	0.100	1.35 (1.02-1.79)	0.037	1.54 (1.36-1.74)	<0.001
65-90	2.11 (1.74-2.55)	<0.001	1.99 (1.43-2.77)	<0.001	2.86 (2.46-3.33)	<0.001
Sex						
Male (ref)						
Female	1.47 (1.34-1.61)	<0.001	1.40 (1.20-1.63)	<0.001	1.18 (1.09-1.28)	<0.001

Ref = reference.

3528 **Poster Session**

Clinical impact of DNA methylation status on first-line antiepidermal growth factor receptor treatment in patients with metastatic colorectal cancer. *First Author: Hiroki Osumi, Department of Gastroenterology, The Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan*

Background: The CpG island methylator phenotype (CIMP), important for carcinogenesis, is a predictor of prognosis and chemotherapy sensitivity in colorectal cancer. However, there is a lack of consensus of CIMP markers, and thus, more comprehensive methylation markers are required to reliably predict the clinical outcomes. Previously, we reported that genome-wide DNAmethylation statuscould predict the effect of epidermal growth factor receptor (EGFR) inhibitors more accurately than previously reported methylation classifications (Ouchi et al. Cancer Sci 2015). Moreover, we had developed a DNA methylation assay based on MethyLight to reflect genome-wide DNA methylation status and reported its usefulness in predicting prognosis in patients with metastatic colorectal cancer (mCRC) treated with EGFR inhibitors as a third-line chemotherapy (Ouchi et al. Cancer Sci 2022). This study aimed to clarify the effects of genome-wide DNA methylation status on clinical outcomes in patients with mCRC treated with first-line EGFR inhibitors. **Methods:** We enrolled 241 patients with mCRC, who received chemotherapy plus EGFR inhibitors as a first-line treatment, and analyzed the associations between genome-wide DNA methylation status using a novel comprehensive methylation marker panel and clinical outcomes and evaluated the predictive power and value of the methylation status. **Results:** Total 169 patients were included in the final analyses. The frequency of highly methylated CRC (HMCC) was 8.9% (15/169). The characteristics of patients with HMCC included right-sided primary tumor location (P = 0.042), undifferentiated histology (P = 0.047), and *BRAF*V600E mutation (P < 0.001). Patients with HMCC showed worse clinical outcomes than those with low methylated CRC in terms of response rate (P = 0.017), progression-free survival (PFS; P = 0.004), and overall survival (P = 0.019). In the multivariate analysis, peritoneal metastasis (Hazard ratio (HR): 2.24, P = 0.017), methylation status (HR: 3.04, P = 0.037), and *BRAF*V600E mutations (HR: 5.83, P = 0.0001) were independent factors for shorter PFS. **Conclusions:** Genome-wide DNA methylation status may be an independent predictor of first-line EGFR inhibitors in patients with mCRC. Research Sponsor: Project for Development of Innovative Research on Cancer Therapeutics, Project for Cancer Research and Therapeutic Evolution.

3529 **Poster Session**

A secondary data analysis of colorectal cancer screening among males assigned at birth: Differences by sexual orientation and race/ethnicity. *First Author: Hui Xie, Zilber School of Public Health, University of Wisconsin-Milwaukee, Milwaukee, WI*

Background: We have limited information on CRC screening disparities in people of color (POC) with sexual minority identity. **Methods:** We analyzed the Behavioral Risk Factor Surveillance Survey (BRFSS) data of males assigned at birth age 50-75 years for up-to-date CRC screening. Descriptive analyses in demographics, socioeconomics, healthy behaviors, and CRC screening were conducted by race/ethnicity, followed by multivariable regressions to identify predictors of CRC screening stratified by race/ethnicity. **Results:** About 67.70% of eligible males reported having an up-to-date CRC screening that met the USPSTF guideline, with the highest rate among gay men (74.92%) and the lowest among bisexual men (65.35%; p = 0.0024). Non-Hispanic Whites had the higher rates of receiving CRC screening across all groups (p < 0.010). In the adjusted multivariable logistic models for NH-White males, gay men (1.52, 95% CI: 1.20-1.91), non-current smokers (1.56, 95% CI: 1.44-1.69), being overweight/obese (1.15, 95%CI: 1.07-1.23), and being physically active (1.08, 95%CI: 1.00-1.16) had greater odds of having CRC screening. Similar patterns were not found in Hispanic and non-Hispanic Black males. Gay men (3.88, 95% CI: 1.51-9.98) had greater odds of CRC screening in Hispanics, whereas being a non-current smoker (1.42, 95%CI: 1.13-1.79) was a significant factor in NH-Blacks. Health insurance coverage was a significant factor across all racial/ethnic groups. **Conclusions:** CRC screening disparities were most pronounced among racial/ethnic minority males. Future work on developing tailored CRC screening programs for racial/ethnic subgroups using an intersectional framework is warranted to elucidate observed heterogeneity across race/ethnicity and sexual orientation. Research Sponsor: None.

3530 **Poster Session**

Analysis of plasma angiogenesis factors on the efficacy of first-line (1L) chemotherapy (chemo) combined with biologics in *RAS* wild-type metastatic colorectal cancer (mCRC): Results from GI-SCREEN CRC Ukit study. *First Author: Satoshi Yuki, Department of Gastroenterology and Hepatology, Hokkaido University Hospital, Sapporo, Japan*

Background: Angiogenesis factors have been reported as prognostic and predictive biomarkers of angiogenesis inhibitors for mCRC (Weickhardt AJ. Br J Cancer 2015. Tabernero J. Ann Oncol 2018). We investigated whether plasma angiogenesis factors could predict the efficacy of biologics combined with chemo in 1L treatment in patients (pts) with *RAS* wild-type mCRC. **Methods:** Serial plasma samples were prospectively collected at the time points of pre- and post-treatments in mCRC pts receiving biologics in either 1L or 2nd-line (2L) chemo. From Sep 2017 to Dec 2020, 497 pts were enrolled [1L chemo plus bevacizumab (1L BEV, n=102), 1L chemo plus anti-EGFR antibody (1L aEGFR, n=100), 2L chemo plus bevacizumab (n=100), 2L FOLFIRI plus RAM (n=99), 2L FOLFIRI plus aflibercept (n=85) and other treatment (n=11)]. Total of 17 plasma angiogenesis factors (HGF, PlGF, VEGF-A, VEGF-D, Angiopoietin-2, IFN-γ, IL-6, IL-8, sNeuropilin-1, TSP-2, OPN, sVEGFR1, sVEGFR2, sVEGFR3, sICAM-1, sVCAM-1, and TIMP-1) were analyzed by the multiplex assay with Luminex® technology. Interactions of their pre-treatment measurements with treatment groups on PFS and OS were assessed via Cox proportional hazards model. The strength of interactions was estimated using a propensity score weighting analysis, and the continuous plasma angiogenesis variables were categorized according to the median. The significance level in the interaction was defined as p≤0.1. **Results:** 133 pts were included in adjusted *RAS* wild-type 1L cohort (1L BEV: n=33, 1L aEGFR [reference]: n=100). Baseline characteristics of adjusted *RAS* wild-type 1L cohort were as follows; median age 64 years; male 62.4%; left-sided tumor 88.7%; triplet chemo 15.0%. Propensity-score weighted Cox model for OS showed significant interactions in IL-8 (median 8.03 pg/mL, high: HR 1.738, p=0.0838, Low: HR 0.479, p=0.2624, interaction p=0.0283), sVEGFR-1 (median 1,350 pg/mL, high: HR 0.333, p=0.1770, Low: HR 1.311, p=0.3004, interaction p=0.0777), and sVCAM-1 (median 1,020,000 pg/mL, high: HR 0.100, p=0.0558, Low: HR 1.616, p=0.1765, interaction p=0.0011). In terms of PFS, there were significant interactions in IL-8 (high: HR 1.322, p=0.0418, Low: HR 0.517, p=0.0528, interaction p=0.0752) and sVCAM-1 (high: HR 0.285, p=0.0414, Low: HR 1.200, p=0.7725, interaction p=0.0156). **Conclusions:** Pre-treatment plasma IL-8 and sVCAM-1 could be predictive biomarkers for efficacy of biologics combined with chemo in 1L treatment of *RAS* wild-type mCRC. Clinical trial information: UMIN000028616. Research Sponsor: Japan Agency for Medical Research and Development.

		Below median	Below median	Above median	Above median	Interaction p-value*
	Median	1L BEV	1L aEGFR	1L BEV	1L aEGFR	Below vs. above median
IL-8	OS	NE	NE	21.9 m	29.7 m	0.0283
	PFS	37.1 m	10.9 m	8.3 m	14.1 m	0.0752
sVCAM-1	OS	21.9 m	29.7 m	NE	NE	0.0011
	PFS	11.5 m	12.6 m	NE	14.5 m	0.0156

Note: NE, not estimable: *defined as p≤0.1.

3531 **Poster Session**

Microbial translocation, toll-like and vitamin D receptor polymorphisms in blood and risk of recurrence in stage III colorectal cancer. *First Author: Ippokratis Messaritakis, Laboratory of Translational Oncology, School of Medicine, University of Crete, Heraklion, Greece*

Background: Microbial translocation from the intestinal lumen into the blood circulation is significantly linked to intestinal dysbiosis; thus, leading to colorectal cancer (CRC), disease progression and decreased survival. Toll-like (TLRs) and vitamin D receptors (VDRs) play essential role in immunity and gut microbiome determination. Polymorphisms in such receptors have been associated with increased CRC incidence risk and mortality. The aim was to evaluate the microbial translocation in the blood of stage III CRC patients and correlate the presence of TLR and VDR genetic variants with microbial DNA fragments at risk of CRC development and progression. **Methods:** A total of 132 stage III CRC patients and 100 healthy donors were enrolled in the study. Peripheral blood DNA was analyzed using PCR for the amplification of microbial DNA encoding 16S rRNA, β-galactosidase gene of *Escherichia coli*, glutamine synthase of *Bacteroides fragilis*, and *5*.8S rRNA of *Candida albicans*. Moreover, DNA from patients and controls was analyzed using PCR and PCR-RFLP for genotyping functional polymorphisms of both *TLR* (TLR2, TLR4, TLR9) and *VDR* (*Taq*I, *Apa*I, *Fok*I and *Bsm*I) genes. **Results:** Median age of patients was 62 years, 59.8% were males, 92.7% had a colon/sigmoid tumor, 24.4% had a right colon tumor and 99.2% had a good performance status. Microbial DNA fragments from 16S rRNA, *E. coli*, *B. fragilis,* and *C. albicans* were detected in 43.2%, 20.5%, 31.8% and 36.4% of patients, respectively. Significantly higher rates of all microbial fragments, but *E. coli*, were detected in the group of patients in comparison to healthy donors ($p < 0.001$). Similarly, higher rates of both TLR and VDR genetic variants were detected in CRC patients compared to healthy donors ($p < 0.001$). Moreover, individuals with homozygous mutant alleles of either TLR or VDR polymorphisms had significantly higher detection rates of microbial DNA fragments. *KRAS*, *BRAF* and MSI status were significantly correlated with TLR9 genetic variants ($p= 0.001$, $p= 0.013$ and $p= 0.011$, respectively) and MSI status was significantly correlated with all four VDR polymorphisms (*Taq*I, $p= 0.044$; *Apa*I, $p= 0.037$; *Fok*I, $p= 0.002$ and *Bsm*I, $p< 0.001$). Cox regression analysis revealed that *BRAF* mutations, histology type and *Apa*I genetic variants are significantly associated with shorter disease-free survival (DFS). *C. albicans* detection is significantly associated with shorter overall survival, and *B. fragilis* is an independent poor prognostic factor for decreased DFS (HR = 33.85; $p = 0.018$). **Conclusions:** The detection of higher frequencies of the *TLR*/*VDR* genetic variants was correlated with significantly higher detection rates of microbial DNA fragments. The detection of these TLR/VDR polymorphisms and microbial DNA fragments in CRC patients highlighted their role in cancer development, progression, and patients' survival. Research Sponsor: None.

3532 **Poster Session**

Metagenomic analysis of the fecal microbiome in patients with colorectal cancer compared to healthy controls as a function of age. *First Author: Jordan Kharofa, University of Cincinnati Cancer Center, Cincinnati, OH*

Background: Colorectal cancer (CRC) incidence is increasing in young patients (< 50 years old) without a clear etiology. Emerging data has implicated the fecal microbiome in CRC carcinogenesis. However, its impact on young onset CRC (YO-CRC) is poorly defined. Colibactin producing *E. Coli* and fadA producing *Fusobacterium nucleatum* can drive CRC carcinogenesis, however their effects across the age spectrum are unknown. **Methods:** We performed a meta-analysis of fecal metagenomics sequencing from n = 692 patients with CRC and n = 602 healthy controls from eleven studies to evaluate species and known microbial derived factors (colibactin and FadA) associated with CRC as a function of age. Generalized linear mixed effects regression was used to model the predicted prevalence of gene families and taxa as a non-linear function of age. Two-stage individual patient data meta-analysis (IPDMA) with adjustment for gender, CRC status, and body mass index was also used to estimate summary odds ratios for colibactin, *F. nucleatum,* and *E. Coli*. Interaction ORs were obtained to assess the difference in the effect of each gene or taxa on CRC case status in YO-CRC. Shannon Diversity index and metabolic pathway differences in the fecal metagenome for YO-CRC patients were assessed using phyloseq and MetaCyc respectively using an IPDMA approach. **Results:** Summary odds ratios (OR) for CRC were increased relative to controls with the presence of colibactin (OR 1.92 95%CI 1.08-3.38), fadA (OR 4.57 95%CI 1.63-12.85), and *F. nucleatum* (OR 6.93 95%CI 3.01-15.96) in models of all patients adjusted for age, gender, and body mass index. The OR for CRC for the presence of *E.coli* was 2.02 (0.92-4.45). An increase in the prevalence of *F. nucleatum* (OR = 1.40 [1.18; 1.65] and *Escherichia coli* (OR = 1.14 [1.02; 1.28]) per 10-year increase *in age* was observed in models including samples from both CRC and healthy controls. No difference was observed for Shannon Diversity (OR 1.36 95%CI 0.68-2.72) or MetaCyc pathways in YO-CRC patients. Species relative abundance was differentially enriched in YO-CRC relative to old CRC patients and controls for five species-*Intestinimonas butyriciproducens, Holdemania filiformis, Firimicutues bacterium CAG 83, Bilophilia wadsworthia, and Alistipes putredinis.* **Conclusions:** Strong associations with CRC status were observed for colibactin, fadA, and *F. nucleatum* with *increased F. nucleatum* in older patients. Several species were enriched in YO-CRC patients including *B. wadsworthia* which can produce carcinogenic sulfur metabolites and is increased with adherence to a sulfur microbial diet-low in vegetables and legumes. A sulfur microbial diet has also been associated with higher incidence of YO-CRC in population studies (Nguyen *Gastroenterology* 2021). Additional study is warranted to understand causal mechanisms of enriched species observed in YO-CRC patients. Research Sponsor: None.

3533 **Poster Session**

Clinical and genomic distinction of class 1/2/3 *BRAF*-mutant colorectal cancer and differential prognosis. *First Author: Yungchang Chen, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China*

Background: Mutations occurring at the V600 amino acid of *BRAF* is the most common *BRAF* mutations in colorectal cancer (CRC), which lead to RAS-independent active monomers (Class 1) and are the targets of BRAF inhibitors. *BRAF* non-V600 mutants can be further classified as RAS-independent active dimers (Class 2) and RAS-dependent impaired kinase (Class 3). The clinical and genetic distinction of CRC patients carrying different subtypes of *BRAF* mutations remain to be revealed. **Methods:** A multicenter retrospective study investigated the mutational profiles of 2,118 CRC patients whose baseline tumor samples were analyzed between June 2015 and June 2020 using capture-based hybrid NGS targeting 400+ cancer-related genes. Clinical characteristics including age, sex, stage, and tumor location were analyzed. A public cBioPortal cohort of 471 metastatic CRC patients was used for survival analysis. **Results:** A total of 473 patients were identified to contain *BRAF* mutations and can be sub-grouped into Class 1 (N = 246), Class 2 (N = 29), Class 3 (N = 53), and others (N = 145). All Class 1 *BRAF* mutations were V600E, while the Class 2 and Class 3 mutations were predominantly G469 (52%) and D594 (56%), respectively. No difference in patient's age, sex, and stage was observed among *BRAF* Class 1-3 subgroups, but the anatomical location of the tumor differed among subgroups, particularly between Class 1 and Class 3 *BRAF*-mutant patients significantly (p = 0.027). Specifically, 39% of tumors carrying Class 1 mutations occurred at the right colon, while the most frequent location of tumors with Class 3 mutations was rectum (58%). Mutational profiling revealed that *KRAS* and *APC* mutations were enriched in Class 2/3 compared to Class 1 *BRAF*-mutant patients, while *RNF43* and *SMAD4* mutations were more frequently observed in Class 1 patients. Mutations causing the activation of the Wnt or RTK/RAS signaling pathways were also more common in Class 2/3 subgroups comparing to Class 1 patients. Furthermore, based on the analysis of mutation allele frequency, Class 1 *BRAF* mutations tended to be drivers while Class 2/3 *BRAF* mutations were more likely to be passengers. In addition, mutational signature profiling showed that the NER signature was enriched in Class 1 *BRAF*-mutant patients but the APOBEC signature in Class2/3 classes. The tumor mutational burden of Class 2 *BRAF* tumors was higher than the other two subgroups (median: 10.4 vs 7.6 and 8.4), and microsatellite instability-high tumors were more common in Class 1 (11% vs 7% and 4%). In the cBioPortal cohort, Class 1 *BRAF*-mutant patients had the worst overall survival whereas Class 3 patients demonstrated the best prognosis. **Conclusions:** The clinical and genetic features of CRC patients harboring Class 2 and 3 *BRAF* mutations were different from those carrying Class 1 *BRAF* mutations in aspects including tumor location, concurrent mutations, mutational signatures, as well as survival outcomes. Research Sponsor: None.

3534 **Poster Session**

Clinical outcomes of immune checkpoint inhibitor (ICI) therapy among Veterans Affairs patients with colorectal cancer and discordant dMMR/MSI-H status. *First Author: James Isaacs, Duke University, Durham, NC*

Background: Clinical trials have demonstrated improvements in survival with immune checkpoint inhibitors (ICIs) for advanced colorectal cancer patients with MSI-H/dMMR detected using PCR-based assays (PCR) or immunohistochemistry (IHC), respectively. MSI-H can also be assessed by next-generation sequencing (NGS). Evaluation of real-world outcomes among MSI-H patients by NGS treated with ICIs are warranted, particularly when results are discordant between these tests. **Methods:** The VA National Precision Oncology Program Database was accessed to select veterans with colorectal cancer and an MSI-H biomarker by NGS. Baseline patient variables, disease characteristics, and duration of ICI treatment were obtained from the VA's Corporate Data Warehouse. Concordance between NGS and IHC or PCR testing was computed, and the response rate and duration of ICI treatment in patients with discordant test results were recorded from chart review. **Results:** Among 1,276 colorectal cancer patients, 71 (5.6%) were found to have MSI-H by NGS. Of these, 22 (30.1%) received ICI. Among 49 patients who did not receive ICI, 36 had stage I-III disease, 5 had limited performance status, 5 were actively being treated with chemotherapy and 3 had completely resected stage IV disease. Of the 71 patients, 29 had dMMR IHC testing, 8 had MSI-H PCR testing, 1 had both IHC and PCR testing, and 34 patients had only NGS testing. No PCR tests were discordant with NGS but 8 of 29 IHC tests were discordant. Among these 8 patients with discordant IHC MMR and MSI-H by NGS, 5 received pembrolizumab. There were 3 partial responses, 1 stable disease and 1 progressive disease. Durable responses were seen with 3 of 5 patients remaining on therapy without progression at the time of this analysis at a median follow up of 8.5 months. **Conclusions:** In a cohort of NGS MSI-H colorectal cancer patients, there was a high rate of discordant IHC results. Clinical benefit is seen in patients treated with ICI with discordant testing results, suggesting that NGS testing identifies patients with false negative dMMR IHC testing in the real-world clinical setting. Research Sponsor: U.S. National Institutes of Health.

3535 **Poster Session**

Molecular characteristics of advanced colorectal cancer and multi-hit *PIK3CA* mutations. *First Author: Michael Cecchini, Yale Cancer Center, New Haven, CT*

Background: Approximately 20% of colorectal cancer (CRC) has an activating mutation in the *PIK3CA* oncogene. *PIK3CA* codes for the catalytic subunit of phosphoinositide 3-kinase alpha (PI3Kα), which ultimately activates the AKT and mammalian target of rapamycin (mTOR) pathway. The PI3Kα inhibitor alpelisib has been approved for breast cancer where a single *PIK3CA* activating mutation is sufficient for response. However, two activating mutations (multi-hit) in the *PIK3CA* allele substantially increases PI3Kα signaling compared to single hot spot mutations and results in exceptional response to PI3Kα inhibition. We aimed to identify the prevalence of *PIK3CA* multi-hit mutations in CRC to identify patients potentially susceptible to PI3K inhibitors. **Methods:** Tissue-based comprehensive genomic profiling (CGP) was performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified, CAP (College of American Pathologists)-accredited laboratory (Foundation Medicine Inc., Cambridge, MA, USA) on all-comers during the course of routine clinical care from 2013-2021. Approval was obtained from the Western Institutional Review Board (Protocol No. 20152817). Hybrid capture was carried out for at least 324 cancer-related genes, including *PIK3CA*. **Results:** We identified 48,836 patients with advanced CRC who underwent Foundation Medicine testing and 846 (1.7%) patients with multi-hit *PIK3CA* mutations. Additional clinical and molecular data was available for 41,154 of these patients of which 710 (1.7%) had multi-hit *PIK3CA* and 7627 (19%) had any deleterious *PIK3CA* mutation. The local colon tumor was used for sequencing in 70% of cases and a separate site in 30% of cases. Patients with *PIK3CA* multi-hit mutations were 53% male with a median age of 60 (interquartile range 50-70). The microsatellite status was available for 697 of 710 patients with multi-hit *PIK3CA* and 123/697 (18%) were microsatellite instability-high. The Table outlines the genes with cooccurring mutations of >10% prevalence for multi-hit *PIK3CA* CRC, including the clinically relevant mutations in KRAS (65%) and BRAF (13%). The four most common *PIK3CA* variants were H1047R (9.8%), E545K (9.2%), E542K (9.0%) and R88Q (7.1%). The most common variant pair was E542K with E545K in 4.7% of multi-hit cases. **Conclusions:** Double-hit mutations in *PIK3CA* are seen in 1.7% of advanced CRC patients and may represent a subset of patients that may have enhanced sensitivity to PI3K inhibitors. Given the high prevalence of CRC in the United States and worldwide this represents a clinically meaningful prevalence of multi-hit *PIK3CA*. Future investigation on the clinical utility of PI3K inhibitors may be warranted in multi-hit *PIK3CA* CRC. Research Sponsor: Foundation Medicine.

Co-occurring variants with > 10% prevalence in multi-hit *PIK3CA* CRC.

Gene	Variant Frequency (n=709)
APC	81%
KRAS	65%
TP53	42%
FBXW7	23%
SOX9	21%
SMAD4	20%
ARID1A	19%
PTEN	17%
AMER1	15%
BRAF	13%
ASXL1	13%
ATM	12%
KMT2D	12%
CTNNB1	12%
MSH3	12%

3536 **Poster Session**

Negative hyperselection for mutations associated with anti-EGFR antibody resistance in *RAS* wildtype metastatic colorectal cancer (mCRC): Evaluation of the PANAMA trial (AIO-KRK-0212, maintenance therapy with 5-FU, folinic acid (FU/FA) with or without panitumumab). *First Author: Andreas Kind, Department of Hematology, Oncology and Cancer Immunology (CCM), Charité-Universitätsmedizin Berlin, Freie Universität Berlin, Humboldt-Universität zu Berlin and Berlin Institute of Health, Berlin, Germany*

Background: We evaluated the prognostic and predictive impact of DNA mutations related to anti-EGFR antibody resistance in patients of the PANAMA trial, which compared Panitumumab (Pmab) and FU/FA versus FU/FA maintenance therapy after Pmab-FOLFOX induction therapy in *RAS* wild-type (wt) mCRC. **Methods:** Next generation panel sequencing was conducted on 201 of 248 tumors obtained prior to study inclusion from the full analysis set using the Cancer Hotspot Panel v2 on an Illumina MiSeq system. Hyperselection covered mutations of the following genes: *KRAS, NRAS, BRAF, HER2, PTEN, AKT1, PIK3CA.* Median progression-free (PFS) and overall survival (OS) since start of maintenance were estimated by Kaplan-Meier and Cox-regression (log rank test). Objective response rates (ORR) of maintenance therapy were compared by Chi-square-test. **Results:** From 201 tumors, 41 (20.4 %) carried at least one mutation: *KRAS:* 7 (3.5%), *BRAF:* 23 (11.4%), *PTEN:* 4 (2.0%), *AKT1:* 2 (1.0%), *PIK3CA:* 12 (6.0%), with 6 tumors harboring co-occuring mutations. No mutations were found in NRAS and HER2. Negative hyperselection (wt for all genes) was associated with (numerically) favourable prognosis in terms of PFS (HR 0.79 (95% CI 0.55 – 1.12), p=0.184), OS (HR 0.61 (95% CI 0.40 – 0.95), p=0.028) and ORR (39.4% vs. 29.3%, p=0.279). The benefit of adding Pmab to FU/FA during maintenance was limited to the hyperselection wt subgroup, with significantly longer PFS (9.9 vs. 6.0 months, 0.64 (95% CI 0,46 – 0.90), p = 0.011), numerically longer OS and significantly higher ORR (49.4% vs 26.6%, p=0.009) compared to FU/FA (Table). **Conclusions:** Mutations related to resistance concerning anti-EGFR antibodies were detected in 41 of 201 (20.4%) of analysed tumors and associated with a worse prognosis compared to hyperselected wt tumors. Negative hyperselection may aid in the identification of patients with relevant benefit from maintenance therapy including Pmab. Research Sponsor: Arbeitsgemeinschaft Internistische Onkologie (AIO) Studien gGmbH, Berlin, Germany, Pharmaceutical/Biotech Company.

Hyperselection of EGFR resistance mutations in patients of the PANAMA trial.

	All patients n = 201		Hyperselection wt n = 160		Hyperselection mut n = 41	
	FU/FA + Pmab n = 102	FU/FA n = 99	FU/FA + Pmab n = 83	FU/FA n = 77	FU/FA + Pmab n = 19	FU/FA n = 22
PFS (months)	8.8	5.8	9.9	6.0	7.4	5.4
HR (95% CI)	0.70 (95% CI 0.52 – 0.95)		0.64 (95% CI 0,46 – 0.90)		0.97 (0.52 – 1.81)	
p (log-rank)	p = 0.020		p = 0.011		p = 0.926	
OS (months)	32.3	25.6	37.6	26.4	24.8	23.4
HR (95% CI)	HR 0.84 (95% CI 0.57 – 1.24)		0.81 (95% CI 0.51 – 1.27)		0.94 (0.45 – 1.99)	
p (log-rank)	p =0.378		p = 0.356		p = 0.876	
ORR, %	47.1%	25.3%	49.4%	28.6%	36.8	22.7
p (Chi-square)	p = 0.005		p = 0.009		p = 0.493	

Legend: wt = wild-type; mut = mutation; Pmab = panitumumab; FU/FA = fluorouracil/folinic acid; PFS = progression-free survival; OS = overall survival; HR = hazard ratio; CI = confidence interval; ORR = objective response rate.

3537 **Poster Session**

Consensus molecular subtypes (CMS) as prognostic and predictive biomarkers of panitumumab (Pmab), fluorouracil and folinic acid (FU/FA) or FU/FA maintenance therapy following Pmab-FOLFOX induction in *RAS* wildtype metastatic colorectal cancer (mCRC): PANAMA trial (AIO-KRK-0212). *First Author: Beeke Hoppe, Charité - Universitaetsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Hematology, Oncology and Tumor Immunology, Berlin, Germany*

Background: Consensus molecular subtypes (CMS1-4) of colorectal cancer were evaluated as prognostic and predictive biomarkers in the PANAMA trial. PANAMA compared maintenance therapy with panitumumab (Pmab) and fluorouracil/folinic acid (FU/FA) vs. FU/FA alone after Pmab-FOLFOX induction therapy in RAS wildtype mCRC. **Methods:** Gene expression was measured after mRNA isolation in 179 of 248 patients of the full analysis set. The analysis was conducted using a customized Nanostring PanCancer Progression Panel. The original CMS classifier was re-derived for Nanostring data using a multinomial regression analysis.Median progression-free (PFS) and overall survival (OS) since start of maintenance were estimated by Kaplan-Meier-method and Cox-regression, using the log rank test. Objective response rates (ORR) of maintenance therapy were compared by Chi-square-test. **Results:** Prevalence of CMS was: CMS1, n = 15 (8.4 %); CMS2, n = 82 (45.8 %); CMS3, n = 20 (11.2 %) and CMS4, n = 62 (34.6 %). A prognostic impact of CMS regardless of treatment was not evident for PFS (p = 0.245) and OS (p = 0.169), but for ORR (p = 0.022), with CMS1 and CMS3 being associated with unfavourable efficacy during maintenance therapy. Potential predictive effects of CMS were observed in patients with CMS2 and CMS4 tumours. In CMS2 and CMS4 tumours, ORR was significantly higher when treated with Pmab-FU/FA in maintenance therapy (CMS2: 56.5% vs 30.6%, p = 0.026; CMS4: 55.6% vs. 28.6%, p = 0.040). In patients with CMS2 mCRC, this translated into a significant effect on PFS (Hazard ratio: 0.61 (95% CI 0.38 – 0.99) p = 0.046 (Table). **Conclusions:** CMS have limited prognostic impact for pmab-based maintenance therapy. However, CMS2 and CMS4 are positively associated with Pmab efficacy during maintenance therapy in the PANAMA trial. Further trials are necessary to confirm these results. Research Sponsor: AIO Studien gGmbH, Berlin, Germany, Pharmaceutical/Biotech Company.

CMS classification of the PANAMA trial.

	CMS1 n = 15		CMS2 n = 82		CMS3 n = 20		CMS4 n = 62	
	Pmab-FU/FA n = 8	FU/FA n = 7	Pmab-FU/FA n = 46	FU/FA n = 36	Pmab-FU/FA n = 8	FU/FA n = 12	Pmab-FU/FA n = 27	FU/FA n = 35
PFS (months)	5.3	4.1	9.2	6.0	5.8	5.6	8.8	6.0
HR (95%CI)	0.86 (0.29 – 2.51)		0.61 (0.38 – 0.99)		0.84 (0.33 – 2.13)		0.77 (0.45 – 1.32)	
p (log-rank)	p = 0.783		p = 0.046		p = 0.708		p = 0.343	
OS (months)	10.6	15.4	28.7	26.7	22.2	26.0	42.7	23.9
HR (95%CI)	0.77 (0.22 – 2.77)		0.93 (0.50 – 1.74)		0.83 (0.23 – 2.96)		0.62 (0.31 – 1.25)	
p (log-rank)	p = 0.693		p = 0.823		p = 0.772		p = 0.181	
ORR, %	0.0	14.3	56.5	30.6	0.0	41.6	55.6	28.6
p (Chi-square)	p = 0.467		p = 0.026		p = 0.109		p = 0.040	

Legend: CMS = consensus molecular subtypes; Pmab = panitumumab; FU/FA = fluorouracil/folinic acid; PFS = progression-free survival; OS = overall survival; HR = hazard ratio; CI = confidence interval; ORR = objective response rate.

3538 **Poster Session**

Comprehensive characterization of *PTPRT* expression in colorectal cancer (CRC). *First Author: Francesca Battaglin, Division of Medical Oncology, USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA*

Background: *PTPRT* is a protein coding gene involved in signal transduction and cellular adhesion. It acts as a tumor suppressor gene and mutated *PTPRT* has been implicated in the early metastasis of CRC. *PTPRT* mutations have been reported as independent potential biomarkers for bevacizumab resistance in metastatic CRC and linked to improved response and survival of patients treated with checkpoint inhibitors in several tumors. Here we characterized the molecular features and clinical outcomes associated with *PTPRT* gene expression in CRC. **Methods:** 15025 CRC tested with NextGen Sequencing on DNA (592 genes or WES) and RNA (WTS) by Caris Life Sciences (Phoenix, AZ) were analyzed. Top quartile transcripts per million for *PTPRT* expression were considered high (H) and bottom quartile low (L). Cell infiltration in the tumor microenvironment (TME) was estimated by QuantiSEQ. X^2, Fisher-Exact, Mann-Whitney tests were used and significance determined as *P*-value adjusted for multiple comparisons ($Q < .05$). Real world survival was obtained from insurance claims data and Kaplan-Meier estimates were calculated for molecularly defined patients. **Results:** *PTPRT* expression was higher in left- than right-sided CRC and in metastases than primary/local tumors; it was highest in CMS4 and lowest in CMS1 (all $Q < .05$). *PTPRT* mutants had lower expression than wild type (0.037 vs 0.064, Q < .05). Overall, *PTPRT*-H had a lower rate of TMB-H (5% vs 17%), deficient mismatch repair (dMMR) (3% vs 13%) and PD-L1 (2% vs 6%) (H vs L, all $Q < .05$). In the proficient MMR (pMMR) cohort, *PTPRT*-H remained inversely correlated with TMB and PD-L1, was negatively associated with rates of mutated *KRAS*, *PIK3CA*, *SMAD4*, *FBXW7*, and positively associated with mutated *TP53* and *CDX2* amplification (all $Q < .05$). Expression of immune related genes was higher in *PTPRT*-H CRC, including *CD274*, *CD80*, *CD86*, *CTLA4*, *HAVCR2*, *IDO1*, *IFNG*, *LAG3*, *PDCD1*, and *PDCD1LG2*, regardless of MMR status (all $Q < .05$). *PTPRT*-H was associated with higher immune cell infiltration in the TME including B cells, M2 macrophages, neutrophils, NK, Tregs, CD4+ and CD8+ T cells, and myeloid dendritic cells (fold change/FC: 1.21-7.1), but lower M1 macrophages (FC: 0.76), regardless of MMR status (all $Q < .05$) with the only exception of CD8+ T cells in dMMR. *PTPRT* expression above median was associated with better OS (overall: HR 0.69, 95% CI [0.64-0.74]; pMMR: HR 0.67 [0.63-0.73]), longer time on treatment of bevacizumab (overall: HR 0.80 [0.74-0.87], pMMR: HR 0.80 [0.74-0.87]), and shorter time on immunotherapy treatment in the dMMR cohort (HR 2.13 [1.33-3.45]). **Conclusions:** Our data show a strong association between *PTPRT* expression and distinct molecular features (including CMS and immune biomarkers), TME cell infiltration and targeted treatment outcomes in CRC. These findings support *PTPRT* as a candidate prognostic and predictive biomarker for bevacizumab and immunotherapy treatment, and as a potential target in CRC. Research Sponsor: Partly supported by NCI P30CA014089, Gloria Borges WunderGlo Foundation, Dhont Family Foundation, Ming Hsieh research fund, San Pedro Peninsula Cancer Guild, V foundation for cancer research, Fong research project.

3539 **Poster Session**

Discovering colorectal cancer biomarkers with individual fragments analysis of cell-free DNA using attention-based deep multi-instance learning. *First Author: Eunsaem Lee, Amsquare, Pohang-si, Gyeongsangbuk-do, South Korea*

Background: Cell-free DNA(cfDNA) are DNA fragments circulating in blood stream. Among these fragments, there are tumor-derived DNA(ctDNA) fragments which can be a significant biomarker for cancer diagnostics. Recently, there are evidences that reveals methylation patterns of ctDNAs facilitate statistical models to diagnose cancers with plausible accuracy than mutation patterns. Despite of such promising facts, an early detection of cancers with methylation patterns of ctDNAs is still statistically difficult since proportion of ctDNAs to cfDNAs is marginal. As a result, it is difficult to set differential threshold on ctDNA proportion to successfully classify early cancer patients. For such a reason, we develop a high-throughput classifier whose classification resolution is per-fragment unlike per-batch approach in existing models. **Methods:** Targeted methylation sequencing was performed with DNA extracted from plasma cfDNA of 141 colon adenocarcinoma (COAD) patients and 200 healthy individuals. To extract DNA fragment-level methylation status, we profiled the methylation status using Bismark software and home-built python scripts were used to recover methylation status of DNA fragments. We implement an attention based multi-instance learning model which is permutation-invariant with fragments to analyze the impact of individual fragments on COAD prediction. Our models were trained using k-fold cross-validation and to assess generalization performance. **Results:** We first trained on local differentially methylated regions (DMRs) that contain 80 to 200 CpG sites using our deep learning model. With a single local region, we achieved a mean sensitivity of 87.2% (mean 95% CI 75.8–93.2%) at 97.7% (mean 95% CI 88.3–99.1%) specificity. By analyzing attention weights, we scored on each fragment according to the model contribution to predicting cancers. To find biomarkers, we added up scores according to methylation of each CpG site. Top 10 high scored CpG sites were validated with tissue sample DNA and almost all of them are overlapped with the 10 CpG sites with the highest statistical differences between cancer and normal tissue in the region. For the global region analysis, we combined local DMRs to confirm collaboration between distant regions and other chromosomes in the colorectal cancer prediction. We achieved a mean sensitivity of 93.4% (95% CI 80.1–98.1%) at 98.3% (95% CI 90.4–99.3%) specificity for the global region prediction. **Conclusions:** Our study shows a potential of targeted sequencing cell-free DNA as a cancer biomarker. An attention based deep learning model allowed for the analysis of individual fragments and showed the potential for biomarker discovery. The model uses only cell-free DNA and excludes tissue sample DNA, which makes our model less sensitive to the tumor heterogeneity. Research Sponsor: AMSquare, Pharmaceutical/Biotech Company.

3540 **Poster Session**

The clinical relevance of tumor RAS/TP53 dual mutation in early and metastatic colorectal cancer (CRC). *First Author: Jenny F. Seligmann, University of Leeds, Leeds, United Kingdom*

Background: The relevance of individual RAS (KRAS and NRAS) and TP53 mutations in CRC is well described, but the impact of the combination of both mutations together is less understood. RAS/TP53-mutant (mut) patients (pts) were selected in FOCUS 4-C for treatment with Adavosertib (Wee1 inhibitor) due to hypothesised sensitivity due to replication stress and loss of cell cycle checkpoint control. Initial analyses in CRC suggest that RAS/TP53-mut pts may be prognostically distinct from either mutation alone. Here we examine the impact of RAS/TP53-mut status in both early stage and metastatic CRC (mCRC). **Methods:** RAS and TP53 mutational status were assessed by whole gene targeted NGS or PCR in hotspot regions. Pts with RAS/TP53 status in the following studies were included after exclusion of BRAF-V600E mutants and MSI-H cases: for early-stage, QUASAR2 trial (N = 408) and an Australian community cohort (N = 654); for mCRC, FOCUS (N = 373) and FOCUS4 (N = 721). Biomarker prevalence, clinical characteristics and outcome data in the RAS/TP53-mut group were compared to pts not showing dual RAS/TP53-mut. **Results:** The prevalence of RAS/TP53-mut was greater in mCRC compared to early CRC (43.9% vs 25.4% respectively, $p < 0.001$). In early-stage (II & III) cohorts combined, RAS/TP53-mut pts were more likely to be female, have a right-sided primary tumour, and involved lymph nodes. In early CRC RAS/TP53-mut pts had worse outcome: DFS HR = 1.49[1.19-1.88], p = 0.001, and OS HR = 1.48[1.16-1.89], p = 0.001. In FOCUS, RAS/TP53-mut mCRC pts had inferior PFS with 1st line chemotherapy than not dual RAS/TP53-mut: 6.9 vs 8.6 months (HR = 1.44[1.17-1.79], p = 0.001), and also shorter post-progression survival (HR = 1.49, p = 0.001), and overall survival (14.9 vs 18.9 mths [HR = 1.60, $p < 0.0005$]). Consistently, during 16 weeks of induction chemotherapy for mCRC pts in FOCUS4, 27.4% of RAS/TP53-mut pts had progressive disease, compared with 18.4% in not dual RAS/TP53-mut; PFS from study registration was reduced in RAS/TP53-mut (5.3 vs 6.1 mths;HR = 1.53[1.22-1.94],$p < 0.001$), but no statistically significant difference in OS (13.6 vs 17.6 mths;HR = 1.27,p = 0.23). Outcomes by each of the four biomarker groups (RAS/TP53 dual mut; RASwt/TP53mut; RASmut/TP53 wt; RAS/TP53 dual wt) will be presented but in all cases the dual mut subgroup had the worst outcomes compared to the other three groups, marginally better than BRAF-V600E CRC. **Conclusions:** RAS/TP53 dual mutation status provides useful and readily available prognostic information in both early and mCRC, independent of MSI and BRAF status. It is associated with increased risk of recurrence in early CRC, and a higher risk of chemotherapy resistance and inferior outcomes in mCRC. Evaluation of treatment strategies in this sizeable patient group and further understanding of the underlying mechanism of poor outcomes are urgently required. Research Sponsor: None.

3541 **Poster Session**

Cell-free DNA (cfDNA) fragmentomes predict tumor burden in metastatic colorectal cancer (mCRC). *First Author: Alessandro Leal, Delfi Diagnostics, Inc., Baltimore, MD*

Background: Measurement of plasma mutant allele fraction (MAF) in patients with cancer provides prognostic information, but this approach typically relies on prior tumor tissue analyses or knowledge of specific mutations. There is a clinical need to develop rapid and accurate noninvasive plasma-only approaches to estimate disease burden dynamics. Comprehensive genome-wide analyses of cfDNA fragmentomes has become a useful tool for noninvasive cancer characterization. Here we present a novel application to predict MAF from genome-wide fragmentation-related profiles (fMAF) as a prognostic marker in mCRC patients with initially unresectable liver-only metastases enrolled in the phase III CAIRO5 study (NCT02162563). **Methods:** 693 longitudinal plasma cfDNA samples were obtained from patients with RAS/BRAF-mutant mCRC (training arm, N = 78) and patients with RAS/BRAF wild-type mCRC (validation arm, N = 75) treated with first-line fluoropyrimidine-based chemotherapy were collected. MAFs as measured by digital droplet PCR (ddPCR) were obtained for patients in the training arm. We trained an initial regression model to predict MAFs with genome-wide fragmentation features using subject-level random intercepts. Out of sample predictions for participants in the RAS/BRAF-mutant mCRC arm were obtained through cross-validation. Cox proportional hazards models were used to evaluate the association between fMAF and PFS and overall survival (OS) at pre- and first post-treatment blood draws. Standardized hazard ratios (sHR) and 95% confidence intervals (CI) are reported. **Results:** There were 68 and 61 evaluable participants with median (range) age of 62 y (41-79 y) and 58 y (27-76 y), and 38% and 36% female in the training and testing arms, respectively. Median time between pre- and post-treatment blood draw was 8 weeks. In the training cohort, median fMAFs dropped from pre- to post-treatment initiation (17.8% to 1.8%). Median PFS was 9 months. For both fMAFs and RAS/BRAF MAFs, the association with PFS was stronger for the pre-treatment than the post-treatment timepoint (Table). Post-treatment fMAFs were not associated with PFS in the training cohort and similar trends were observed for OS. **Conclusions:** Initial modeling demonstrates the ability of cfDNA fragmentomes to estimate cell-free DNA tumor burden with performance comparable to standard approaches. Ongoing modeling efforts will result in evaluation of a final model in the testing arm. The development of a noninvasive tissue-independent diagnostic approach that does not rely on mutation detection in the circulation has the potential to expand the use of liquid biopsies for advanced disease monitoring. Clinical trial information: NCT02162563. Research Sponsor: Roche.

		fMAF (Training Arm)	MAF (Training Arm)
		sHR (95% CI)	sHR (95% CI)
Pre-treatment	PFS	1.23 (0.96 to 1.58)	1.51 (1.16 to 1.97)
	OS	1.40 (1.06 to 1.85)	1.63 (1.22 to 2.18)
Post-treatment	PFS	0.98 (0.77 to 1.24)	1.19 (0.92 to 1.54)
	OS	1.10 (0.89 to 1.36)	1.54 (1.16 to 2.06)

3542 **Poster Session**

Development of a highly sensitive multicancer, targeted, cell-free DNA epigenomic assay for integrated screening of lung and colorectal cancer. *First Author: Anton Valouev, Guardant Health, Palo Alto, CA*

Background: Cancer screening in asymptomatic individuals who meet guideline criteria has yielded reductions in cancer death rates. However, adherence to screening guidelines remains below targets set forth by leading health-care organizations. A blood-based multi-cancer screening assay with clinically meaningful sensitivity and specificity, in cancer types where early detection and intervention can save lives, that is integrated with existing clinical pathways may increase access to and adherence with guideline recommendations, ensuring more individuals benefit from these proven interventions. We evaluated the performance of a blood-based multi-cancer screening assay that interrogates cell-free DNA (cfDNA) methylation signatures for cancer detection and tissue of origin prediction in a set of tumor types where cancer screening can save lives. **Methods:** Whole blood from 1,607 individuals with and 3,298 individuals without cancer was obtained from multiple unique cohorts. Plasma-derived cfDNA was profiled using a custom assay that enriches fragments with dense CpG methylation and further depletes uninformative background molecules containing unmethylated CpGs. We utilized a broad genomic panel (16 Mb) targeting regions with low rates of methylation in individuals without cancer. The panel captures tumor-associated molecules and allows for high sensitivity of detection at low sequencing costs. A cross-validated analysis was used to estimate the performance of the predictive model upon the sample set. Classification thresholds corresponding to 90%, 95%, and 98% specificities were established using samples from individuals without a cancer diagnosis. **Results:** At 90% specificity, overall sensitivity for lung cancer detection was 92.1% (95% CI: 80-100%; 90.2% in Stage I/II disease (N = 82) and 93.1% in Stage III/IV disease (N = 159)) and 93.1% (CI: 88-98%) for CRC detection (92% in Stage I/II disease (N = 743) and 94.5% in Stage III/IV disease (N = 623)). Tissue of origin prediction evaluated at 98% specificity yielded accurate identification in 99% of CRC and 98% of lung cancers. Lung cancer histology was known for approximately 74% of the cohort. Across Stage I – IV cancers, at 90% specificity, sensitivity was 97.3% in lung squamous cancer (N = 73) and 86.8% in lung adenocarcinoma (N = 106). At 95% and 98% specificity thresholds, overall sensitivity was 86.3% (CI: 75-98%) and 66.4% (CI: 56-77%) for lung cancer and 85.7% (CI:81-91%) and 71.6% (CI: 67-76%) for CRC, respectively. **Conclusions:** This blood-based multi-cancer screening assay yields clinically meaningful sensitivity and specificity for early-stage cancers. This assay is undergoing further development to expand detection capabilities to additional cancer types where screening can save lives. Clinical evaluation in registrational screening trials is ongoing (SHIELD; NCT05117840). Research Sponsor: Guardant Health.

3543 **Poster Session**

A tumor immune microenvironment-related lncRNA signature for the prognosis and immunotherapeutic sensitivity prediction in colorectal cancer. *First Author: Chuling Hu, Department of Colorectal Surgery, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China*

Background: As important molecules in the CRC tumor microenvironment (TME), long non-coding RNAs (lncRNAs) regulate the functions of tumor infiltrating immune cells and sculpt the tumor immune microenvironment (TIME), resulting in difference in survival and response to immunotherapy among CRC patients. However, challenges remain in selecting TIME related lncRNAs (TIME-lncRNAs) of prognosis value and stratifying CRC patients for immunotherapy. Here, the aim of our study was to develop a CRC TIME-lncRNAs signature to provide survival and immunotherapy response predictions. **Methods:** Gene expression profiles and clinical information of CRC cases (n = 1807) were collected from 7 datasets and divided into training cohort (n = 519) and two testing cohorts (n = 595 and 693, respectively). Utilizing gene expression data of 97 immune cell lines and 61 CRC cell lines, differential expression analysis was used to identify TIME-lncRNAs. Univariate Cox regression and LASSO regression analysis were used to establish a TIME-lncRNAs signature to predict the prognosis of CRC patients. To further investigate the model, multivariate Cox regression, lncRNA-mRNA regulation analysis, gene enrichment analysis and immune infiltration analysis were carried out. The immunotherapy response predicting ability of the model was verified with an independent immunotherapy dataset. **Results:** Integrating the expression profiles of 10 TIME-lncRNAs, the model stratified CRC patients into low and high-score groups. Patients of the low score group had significantly prolonged survival in both training (hazard ratio (HR) = 2.63, 95% confidence interval (CI) = 1.9-3.63, $P < 0.001$) and testing cohorts (testing cohort 1: HR = 1.6, 95% CI = 1.19-2.16, $P = 0.002$; testing cohort 2: HR = 1.64, 95% CI = 1.19-2.26, $P = 0.002$), while higher tumor purity and less pro-tumor immune cells infiltration were also observed in the low score group. Further investigation showed that both genes differentially expressed between different groups and mRNAs regulated by 10 lncRNAs of the signature were enriched in immune-related and immunotherapy-related pathways. Multivariate Cox regression indicated that the TIME-lncRNAs signature was an independent prognosis factor. Validated with external immunotherapy dataset, the signature provided distinct predictions for patients' responses to PD-L1 inhibitor therapy, suggesting cases of high score group could benefit more from immunotherapy. **Conclusions:** Based on the expression of 10 lncRNAs in the TIME, the signature makes predictions for patients' survival and immunotherapy responses, which could help in stratifying CRC patients for immunotherapy at the bedside. Research Sponsor: National Natural Science Foundation of China (No. 82002221, FG), The Sixth Affiliated Hospital of Sun Yat sen University Start-up Fund for Returnees (No. R20210217202501975, FG), Guangzhou Basic and Applied Basic Research Fund (No. 202102020820, FG), Sun Yat-sen University 100 Top Talent Scholars Program – China (No. P20190217202203617, FG), National Natural Science Foundation of China (No. 81972212, XW), Natural Science Foundation of Guangdong Province, China (No. 2019A1515010063, XW).

3544 **Poster Session**

Survival outcomes following colorectal cancer surgery in low- and middle-income countries: A systematic review. *First Author: Tom M. Diehl, University of Wisconsin Hospitals and Clinics, Madison, WI*

Background: Colorectal cancer (CRC) is a surgical disease that ranks among leading causes of global deaths, but little is known about survival outcomes following CRC surgery in low- and middle-income countries (LMICs). In this study, we sought to review all published literature on long-term outcomes following CRC resections in LMICs. **Methods:** We completed a systematic review of original research articles presenting survival outcomes after CRC resection with curative intent in LMICs. Databases searched included PubMed, Web of Science, Embase, and Global Index Medicus. Country income groupings were determined by 2020 World Bank data. We excluded articles involving pediatric populations (<18 years), non-primary colorectal cancers, benign disease, and endoscopic/transanal resection only. Articles published before 2005 or without English full text were also excluded. Abstracts and full texts were assessed for eligibility by two independent reviewers; conflicts were resolved by a third reviewer. Data from China dominated the published literature and were excluded from final analysis. Survival data were extracted for 5-year disease free survival (DFS) and overall survival (OS). **Results:** Our search returned 29,134 articles. After automated and manual deduplication, 18,849 abstracts were assessed for eligibility. Following abstract and full-text review, 583 articles met the inclusion criteria for the study. Table 1 shows the most-represented countries and their associated income levels. In total, 1/27 low-income countries, 11/55 lower-middle income countries, and 16/55 upper-middle income countries were represented, which accounted for 0.3%, 12.9% and 86.8% of all included articles, respectively. The majority of articles were from China (379/583; 65%). Excluding data from China, 5-year disease DFS and OS varied significantly across included studies: Stage I = 64-100% DFS and 70-100% OS; Stage II = 75-94% DFS and 50-94% OS; Stage III = 34-87% DFS and 20-93% OS; Stages I-III combined = 53-86% DFS and 29-97% OS. **Conclusions:** There is a dearth of data on long-term outcomes following CRC operations in LMICs, especially among low-income countries. OS ranges markedly by country income group highlighting global disparities in cancer care. Our review emphasizes a dire need for cancer research capacity building in LMICs. Research Sponsor: U.S. National Institutes of Health, Fogarty International Center.

Included article count by country.

Country	Article Count *n (%)*	World Bank Income Group	Country (cont.)	Article Count *n (%)*	World Bank Income Group
China	379 (65.0)	UM	**Romania**	7 (1.2)	UM
Turkey	55 (9.4)	UM	**Malaysia**	5 (0.9)	UM
Brazil	25 (4.3)	UM	**Serbia**	5 (0.9)	UM
India	22 (3.8)	LM	**Sri Lanka**	4 (0.7)	LM
Egypt	17 (2.9)	LM	**Morocco**	3 (0.5)	LM
Iran	14 (2.4)	LM	**Argentina**	2 (0.3)	UM
Thailand	10 (1.7)	UM	**Bulgaria**	2 (0.3)	UM
Mexico	8 (1.4)	UM	**Ethiopia**	2 (0.3)	L
Pakistan	7 (1.2)	LM	**Jamaica**	2 (0.3)	UM

*Low income (L), Lower middle income (LM), Upper middle income (UM).

3545 **Poster Session**

Trends in ethnic-specific colorectal cancer mortality in patients with and without diabetes in the United States: A CDC database population-based study 2011-2019. *First Author: Abdul Rahman Al Armashi, St. Vincent Charity Medical Center, Cleveland, OH*

Background: Colorectal cancer (CRC) is the third most frequent type of cancer and the second most lethal in both sexes combined. CRC is strongly associated with both environmental and genetic risk factors. Previous studies reported an increased mortality in CRC patients with diabetes mellitus, however, the interplay between ethnicity and diabetes mellitus was not explored. This study analyzes trends in mortality across ethnic groups and assess the impact of diabetes mellitus. **Methods:** We queried the Multiple Cause of Death database (International Classification of Diseases, 10th revision) between 2011 and 2019, we identified all patients (Hispanic and non-Hispanic origin) who died of a malignant neoplasm of the colon, rectosigmoid junction, and rectum {Codes C18.x to C20.x reported as the underlying cause of death (UCD)}. Then we identified the same group (UCD) among individuals with diabetes (Insulin-dependent diabetes mellitus and non-insulin-dependent diabetes mellitus) (Codes E10.x to E11.x reported as multiple causes of death). Age-adjusted mortality rates per million persons (PMP) were estimated, standardized to US census data from 2000, and stratified by Hispanic origin. **Results:** In the general population, a total of 464,058 deaths from CRC were identified, with an overall age- adjusted mortality rate of 137.9 PMP (Hispanic: 109.3, Non-Hispanic: 141.1). Overall, age-adjusted mortality declined by 13% among Hispanic, from 118.1 PMP in 2011 to 102.9 PMP in 2019, and by 8% among non-Hispanic, from 153.3 PMP in 2011 to 141.1 PMP in 2019. In the diabetic population, a total of 8679 CRC death were identified, with an overall age-adjusted mortality rate of 2.6 PMP (Hispanic: 3.6, Non-Hispanic: 2.5). Age-adjusted mortality increased by 32% in Hispanic from 3.1 PMP in 2011 to 4.1 PMP in 2019 and by 13% in non-Hispanic from 2.4 PMP in 2011 to 2.7 PMP in 2019. **Conclusions:** This study concludes that between 2011 and 2019, the CRC mortality was reduced in both Hispanic and non-Hispanic in the general population. Notably, this tendency was not observed in the diabetic population, where mortality increased, particularly among Hispanic. Additional studies are warranted to determine the causes of the rise among diabetics and strategies for minimizing the disparity between Hispanic and non-Hispanic. Research Sponsor: None.

Colorectal cancer mortality rates between 2011 and 2019.

Population Type	Ethnicity	Deaths	Population	Crude Rate Per 1,000,000	Age-Adjusted Rate Per 1,000,000
General	Hispanic or Latino	33,779	507,985,686	66.5	109.3
	Non-Hispanic or Latino	430,279	2,378,178,634	180.9	141.1
	Total	464,058	2,886,164,320	160.8	137.9
Diabetic	Hispanic or Latino	1,030	507,985,686	2	3.6
	Non-Hispanic or Latino	7,649	2,378,178,634	3.2	2.5
	Total	8,679	2,886,164,320	3	2.6

3546 **Poster Session**

CXCR4 overexpression: An indicator of poor survival and predictor of response to immunotherapy in patients with metastatic colorectal cancer. *First Author: Sepideh Gholami, University of California Davis Comprehensive Cancer Center, Sacramento, CA*

Background: CXC-chemokine receptor 4 (CXCR4) is a ubiquitous chemokine receptor activated by the CXCL12 ligand and is implicated in tumor invasion, metastasis, and immune cell (IC) trafficking. High CXCR4 expression is associated with poor prognosis in colorectal cancer (CRC). < 10% of metastatic CRC cases harbor microsatellite instability (MSI-H) and demonstrate lower tumor mutation burden (TMB), decreased IC infiltration, and lack of response to current immunotherapy regimens. This study aims to interrogate the role of CXCR4 mRNA expression on the the tumor microenvironment (TME) and its prognostic and predictive value to tailor immunotherapeutic treatment strategies in CRC. **Methods:** A total of 15,026 CRC samples were analyzed using whole-exome sequencing, whole-transcriptome sequencing, and immunohistochemistry (Caris Life Sciences, Phoenix, AZ). Study cohort was stratified by CXCR4 mRNA expression levels in quartiles (Q1 (low) vs Q4 (high)). IC fraction was calculated by QuantiSeq, and real-world overall survival information was obtained from insurance claims data and calculated from tissue collection time to last day of contact. Statistical significance was determined using chi-square/Fisher-Exact and adjusted for multiple comparisons ($q < 0.05$). **Results:** Samples obtained from metastatic sites showed higher CXCR4 mRNA expression than those from primary tumors (22.7 vs 18.6 median transcripts per million (TPM), $p < 0.001$). CXCR4 mRNA expression was significantly lower in liver metastases than in non-liver metastases (21.2 vs 24.8 TPM, $p < 0.001$). Median CXCR4 mRNA expression was highest in the consensus molecular subtypes 4 (33.3 TPM) and lowest in 3 (13.0 TPM, $p < 0.05$). CXCR4 mRNA expression was positively associated with TMB-H, MSI-H/dMMR, and positive PD-L1 IHC status. In the TME, high CXCR4 mRNA expression was observed in tumors with a higher IC infiltration including B cells, M1/M2 macrophages, NK cells, $CD8^+$ T cells and T-regs, regardless of MSI status. High CXCR4 mRNA expression in the primary tumor was associated with poor prognosis (HR 0.77, 95% CI 0.70-0.85; $p < 0.001$), regardless of MSI-status. In metastatic tumors, low mRNA expression was correlated with improved survival (HR 0.89, 95% CI 0.80-0.99; $p = 0.34$); however, this did not reach statistical significance in the MSS cohort (HR 0.90, 95% CI 0.80-1.0; $p = 0.06$). Of note, high CXCR4 mRNA expression was associated with improved survival in all patients with CRC who received pembrolizumab (HR 2.12, 95% CI 1.16-3.91; $p = 0.013$). **Conclusions:** This is the largest clinical dataset to date demonstrating high CXCR4 expression as a predictor for poor survival in CRC. Furthermore, high CXCR4 expression was associated with improved outcome after checkpoint inhibition immunotherapy, indicating its strong potential as a predictive biomarker that could inform immunotherapeutic strategies in CRC. Research Sponsor: None.

3547 **Poster Session**

Characterization of TIM3 and its ligands in colorectal cancer. *First Author: Sandra Algaze, Division of Medical Oncology, USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA*

Background: TIM-3 is an inhibitory checkpoint glycoprotein found on innate and adaptive immune cells and is highly expressed on tumor infiltrating lymphocytes. TIM-3 and its ligands, Galectin 9 (Gal9), HMGB1 and CEACAM1 play a critical role in immune regulation and preclinical data suggest a role in the pathogenesis of colorectal cancer (CRC). We aimed to characterize the molecular features and prognostic value of TIM3 and its ligands in CRC. **Methods:** Tumor molecular profiling was performed from 15,026 FFPE samples by NextGen Sequencing on DNA (592 genes or WES) and RNA (WTS) and immunohistochemistry (IHC) at Caris Life Sciences (Phoenix, AZ). Top quartile transcripts per million (TPMs) for *TIM-3, Gal9, HMGB1 and CEACAM1* were considered high (Q4) while bottom quartile low (Q1) expression (exp). X^2/Fisher-exact tests were used for comparison and significance was determined as *P*-value adjusted for multiple comparison and this was found for the results reported here ($Q < 0.05$). Cell infiltration in the tumor microenvironment (TME) was estimated by quanTIseq. Real-world overall survival (OS) information was obtained from insurance claims data and Kaplan-Meier estimates were calculated for molecularly defined pts. **Results:** Gal 9/TIM3-high tumors had higher prevalence (prev) of high tumor mutational burden (TMB ≥ 10 Mut/Mb) (12% vs. 8%; 14% vs. 6%), deficiency in mismatch repair (dMMR) (9% vs. 5%; 10% vs. 4%), PD-L1 exp (5% vs. 3%; 7% vs. 2%), and was highest in transverse (Fold Change; FC: 1.05, 1.12) and right sided tumors (1.04, 1.10) compared to left sided tumors, and CMS4. In contrast, HMGB1 and CEACAM1-high tumors had lower prev of dMMR (5% vs. 8%, 3% vs. 12%), PD-L1 exp (3% vs. 5%, 3% vs. 6%) and TMB-H (8% vs. 11%, 6% vs. 16%), and was highest in CMS2. In MSS tumors, Gal9/TIM3-high tumors were associated (assoc) with lower frequency of *TP53*, amplifications (amp) of FLT1/3, CDX2, FOXO1, and CDK8 while CEACAM1 and HMGB1-high were assoc with higher mutation (mut) rates of *TP53*, *APC*, *NRAS*, amp of FLT1/3, CDX2, CDX8, and lower mut in *GNAS*, *FBXW7* and *RNF43*. High Gal9 and TIM3 exp was assoc with higher infiltration of B cells, M1 and M2 macrophages, NK cells, CD4+ and C8+ T cells, and Tregs, while high HMGB1 and CEACAM1 exp was negatively assoc with Tregs, M1 macrophages, monocytes and CD8+ T cells. High exp of Gal9, TIM3, HMGB1, and CEACAM1 was assoc with worse OS in the entire cohort (HR 0.90, 95%CI, 0.84-0.97, $P = 0.005$, HR 0.81, 95% CI, 0.75-0.87, $P < 0.00001$; HR 0.88, 95% CI, 0.82-0.95, $P < 0.001$; HR 0.80; 95%CI, 0.74-0.86, $P < 0.00003$, respectively). **Conclusions:** Strong assoc were identified between Gal9/TIM3, HMGB1 and CEACAM1 gene exp and IO biomarkers, distinct molecular features, CMS, TME cell infiltration, and patient outcomes in CRC. Significantly different mut frequencies may signify unique subsets of CRC. These findings provide rationale for further evaluation of TIM3 and its ligands in CRC as prognostic biomarkers and potential therapeutic targets modifying the TME. Research Sponsor: None.

3548 **Poster Session**

Association between environmental quality index and young onset colorectal cancer. *First Author: Suleyman Yasin Goksu, University of Texas Southwestern Medical Center, Dallas, TX*

Background: The factors associated with the rise of young-onset colorectal cancer (YOCRC) remain unclear. However, environmental exposures are believed to be associated with YOCRC in addition to hereditary factors. Therefore, we evaluated the association between the national level Environmental Quality Index (EQI) and YOCRC in the US. **Methods:** We queried the SEER database to identify adult colorectal cancer patients diagnosed between 2010-2016. YOCRC was defined as age at diagnosis < 50 years. EQI (2005-2010) is a measure of county-level cumulative environmental exposures that includes 5 domains: sociodemographic, built, air, land, and water. A higher value represents a lower environmental quality. We distributed the total EQI and each EQI domain into five quintiles. Multivariable logistic regression analysis was used to assess the relationship between YOCRC and quintiles (upper-most vs. lowest) of EQI after adjusting by race (White, Black, and Others), gender, and stage at diagnosis. The age-adjusted incidence rate was also calculated using the SEER*Stat, and correlation efficiency was estimated between EQI domains and incidence rate. **Results:** A total of 261,417 CRC patients were included; 11% were YOCRC. In the adjusted multivariable analysis, poor built EQI (OR 1.15 [1.11-1.20]) and water EQI (OR 1.08 [1.03-1.12]) were more likely to be associated with YOCRC. Poor built EQI was more strongly associated with Black YOCRC (OR 1.21 [1.09-1.35]) as compared to White YOCRC (OR 1.14 [1.09-1.19]). Poor sociodemographic EQI was more strongly associated with Others (OR 1.47 [1.25-1.72]) compared to Black YOCRC (OR 1.14 [1.03-1.25]). In addition, poor built EQI (OR 1.19 [1.12-1.27]) and water EQI (OR 1.12 [1.05-1.19]) were more strongly associated with the metastatic disease among YOCRC patients. However, the total poor EQI was not associated with YOCRC (OR 0.99 [0.95-1.03]). On incidence analysis, there was a positive correlation between the incidence rate of YOCRC and sociodemographic EQI (rho = 0.49, $p < 0.001$), air EQI (rho = 0.30, $p < 0.001$), and land EQI (rho = 0.18, $p < 0.001$). **Conclusions:** This study evaluated a population-based ecological approach and showed that YOCRC was associated with lower environmental quality, including built and water domains. EQI domains were also associated with different racial groups among YOCRC. Instead of studying single environmental exposures, the impact of the cumulative environmental index should be recognized and studied further to understand the mechanism of cancer development. Research Sponsor: None.

3549 **Poster Session**

Dietary quality in early-onset gastrointestinal malignancies: NHANES 2005-2018. *First Author: Mir Lim, UT Southwestern Medical Center, Dallas, TX*

Background: The incidence of early-onset colorectal, stomach, esophageal, and pancreatic cancer, which occur in individuals <50 years of age, is rising worldwide. However, little is known about why rates have been up trending. Previous studies have linked poor diet and nutrition to an increased risk of typical-onset gastrointestinal (GI) malignancies. In this study, we aimed to describe dietary quality in individuals with early-onset GI malignancies and compare it to typical-onset GI malignancies. **Methods:** We queried the 2005-2018 National Health and Nutrition Examination Survey (NHANES) database for all survey participants diagnosed with GI malignancies, including colorectal, esophageal, gallbladder, liver, pancreas, rectal, and stomach cancer. We classified early and typical-onset GI cancer based on age of diagnosis of <50 and ≥50 years, respectively. Participants <50 without a history of cancer were classified as controls. We assessed the dietary quality by calculating the healthy eating index score (HEI-2015) from NHANES database for all participants. The primary outcome was mean HEI-2015 score for early onset GI malignancies. We performed propensity score weighted analysis to balance gender, race, income, education level, and BMI between the groups. We used logistic regression analysis to assess the relationship between early-onset GI malignancies and HEI-2015 quintiles. **Results:** Out of 32,235 participants in NHANES database, 330 individuals (1%) reported a diagnosis of GI malignancy. Sixty-eight (20.5%) individuals had early-onset GI malignancies. We identified 17,420 controls who were <50 years old with no reported history of malignancy. Fifty-three percent of early-onset GI cancers were female vs 47% of typical-onset GI cancers; 59% vs 59% were non-Hispanic White; 66% vs 40% had a college degree; 13% vs 7% had high income and 40% vs 36% were obese. The mean HEI-2015 score in early-onset GI cancer was 52.9 (SD 14.7) compared to 53.6 (SD 13.0) in typical-onset GI cancers, which was not significantly different (p=0.72). There was no significant association between poor HEI-2015 scores in individuals with early-onset vs typical-onset GI malignancies on logistic regression analysis (OR 0.84 [0.35-2.03]). In addition, HEI-2015 quintiles were not significantly associated with those with early-onset GI malignancies compared to controls <50 years old (OR 2.06 [0.72-5.9]). **Conclusions:** The diet quality of early-onset GI malignancies does not align with the national Dietary Guidelines. However, in this analysis of the NHANES database, we did not find a significant difference in HEI-2015 scores between early-onset versus typical-onset GI malignancies. Research Sponsor: None.

3550 **Poster Session**

Early detection of colorectal adenocarcinoma by decoding epigenetic and DNA fragmentation fingerprints of plasma cell-free DNA. *First Author: Li Suxing, Genecast Biotechnology Co., Ltd., Wuxi, China*

Background: Cell-free DNA (cfDNA) methylation, fragmentation patterns, chromosome instability, and chromatin accessiblity have been previously shown to be valid plasma biomarkers for non-invasive cancer detection. However, conventional whole-genome bisulfite sequencing (WGBS) is unable to simultaneously profile all these biomarkers due to bisulfite-induced DNA damages. Here we developed a machine learning approach to comprehensively integrate multiple types of cancer genomic markers from enzyme-conversion-based low-pass whole-methylome sequencing (WMS) of plasma cfDNA to non-invasively detect colorectal adenocarcinoma. **Methods:** Plasma cfDNA sampels from 215 colorectal adenocarcinoma patients and 568 healthy individuals were collected and were split into the discovery and independent testing cohort. The discovery cohort includes 150 cancer patients and 398 healthy individuals and the independent testing cohort includes 65 cancer patients and 170 healthy individuals. Whole methylome sequencing (WMS) libraries were generated from enzymatically converted cfDNA and were subsequently paired-end sequenced at ~2X coverage. The genome-wide methylation density, fragmentation fingerprints, chromosome instability, and chromatin accessibility were extracted from the WMS data and individually modelled via machine learning methods such as SVM, LR, GBDT, random forest. The final predictive model is an ensemble model integrating all uni-modal models. All models were trained and fitted on the discovery cohort. **Results:** Data of different modalities provide complementary information in separating the cancer patients from the healthy individuals. Unsupervised clustering of the individuals showed clear separation between cancer patients and healthy individuals. The final predictive model achieved AUC =0.982 in the discovery cohort and AUC =0.9664 in the independent testing cohort. Under a specificity of 94.71% (CI: 90% - 98.82%), sensitivity was 78.46% (CI: 60% - 92.31%) in the independent testing cohort. Separating the cancer patients into different stages, we found that the detection power is usuaul lower for early-stage cancer patients. **Conclusions:** These results demonstrate the first proof of principle on the feasibility of integrating multiple genomic cancer markers to non-invasively detect colorectal adenocarcinoma from WMS plasma cell-free DNA. A large prospective cohort study is planned to further validate its clinical performance. Research Sponsor: None.

3551 **Poster Session**

Impact of consensus molecular subtyping (CMS) on survival in the CO.26 trial of durvalumab plus tremelimumab versus best supportive care (BSC) in metastatic colorectal cancer (mCRC). *First Author: Jonathan M. Loree, BC Cancer, Vancouver, BC, Canada*

Background: CO.26 was a phase 2 trial (2-sided α=0.1 and 80% power) that randomized 180 patients with refractory mCRC 2:1 to durvalumab + tremelimumab vs BSC with improved overall survival (OS) (HR 0.73, 90%CI 0.55-0.97, P=0.07). A Nanostring assay validated for use with FFPE was used to determine CMS for correlation with outcome. **Methods:** Archival FFPE from 163/180 (91%) of patients (pts) underwent RNA extraction and CMS subtyping. Cox proportional hazard models evaluated the prognostic and predictive impact of CMS on overall survival. **Results:** CMS distribution was skewed towards CMS4 (76%), with lower prevalence of CMS1 (2%), CMS2 (16%) and CMS3 (2%). There were 7/163 cases of indeterminate CMS (4%). Subgroup analysis was restricted to CMS2 and CMS4 based on sample size. With BSC alone, CMS2 showed trends to worse OS compared to all other patients pooled (HR 1.93, 90% CI 1.03-3.61, P=0.085), while CMS4 did not (HR 0.86, 90% CI 0.50-1.48, P=0.64). OS but not progression free survival (PFS) was improved with durvalumab + tremelimumab in the overall population. OS was improved with durvalumab + tremelimumab among patients with CMS2 tumors (HR 0.39, 90% CI 0.19-0.82, P=0.035) but not in patients with CMS4 tumors (HR 0.73, 90% CI 0.52-1.02, P=0.12) compared to BSC. Neither CMS2 (P-interaction=0.37) nor CMS4 (P-interaction=0.91) were predictive of OS benefit from durvalumab + tremelimumab compared to BSC. Disease control rate (DCR) trended to being better among CMS4 (24/85) than CMS2 cancers (1/15, OR 5.51, 90% CI 1.10-29.88, P=0.11) or CMS4 vs all non CMS4 cancers (1/21, OR 7.87, 90% CI 1.65-41.98, P=0.023) for patients on durvalumab + tremelimumab. PFS was not improved with durvalumab + tremelimumab in CMS2 (P=0.19) or CMS4 (P=0.29) cancers relative to BSC. **Conclusions:** In this trial of refractory colorectal cancer, we saw a shift in CMS subtype with more CMS4 than expected. Compared to CMS4, CMS2 showed stronger signals towards improved OS with durvalumab + tremelimumab but had a lower disease control rate. Differences in immune signaling by CMS may be important determinants of which component of immune regulation needs to be targeted in mCRC to improve outcomes. Clinical trial information: NCT02870920. Research Sponsor: Canadian Cancer Society, AstraZeneca (trial costs).

Comparison of activity of durvalumab plus tremelimumab vs. best supportive care in treatment refractory metastatic colorectal cancer.

Group	OS HR (90% CI, P)	PFS HR (90% CI, P)	Disease control rate (DCR) (%) Odds Ratio (OR), (90% CI, P)
All Pts	0.73 (0.55-0.97, P=0.07)	1.01 (0.76-1.34, P=0.97)	23 vs 6.6%, OR 4.18 (90% CI 1.39-12.60, P=0.01)
CMS2	0.39 (0.19-0.82, P=0.035)	1.79 (0.86-3.72, P=0.19)	7 vs 0%, OR n/a, (P=0.99)
CMS4	0.73 (0.52-1.02, P=0.12)	0.81 (0.58-1.13, P=0.29)	28 vs 8%, OR 4.46 (90% CI 1.49-10.85, P=0.017)

3552 **Poster Session**

Real-world outcomes of biosimilar bevacizumab-awwb versus reference bevacizumab in patients with metastatic colorectal cancer. *First Author: Catherine Pham, Kaiser Permanente, Downey, CA*

Background: Bevacizumab-awwb was the first biosimilar approved by the U.S. Food and Drug Administration (FDA) for treatment of cancer and became available for use in July 2019. Clinical comparative efficacy and safety of bevacizumab-awwb to bevacizumab was established in a single study of adult patients with advanced non-squamous non-small cell lung cancer. Approval based on extrapolation was granted by the FDA for all other indications, including metastatic colorectal cancer (mCRC). The objective of this study was to evaluate the real-world effectiveness and safety outcomes of patients with mCRC initiated on bevacizumab-awwb versus bevacizumab in an integrated healthcare delivery system. **Methods:** This was an observational cohort study of patients with mCRC in Kaiser Permanente California, Colorado, and Mid-Atlantic States who were initiated on bevacizumab-awwb between July 2019 and March 2020 or reference bevacizumab between July 2015 and June 2018. Patients with history of bevacizumab use in the 6 months prior to the index treatment date were excluded. Patients were followed until 12 months after treatment initiation, end of plan membership, or death, whichever occurred first. The primary outcome of overall survival (OS) was analyzed using a non-inferiority test with lower margin of 10% and Cox proportional-hazards modeling. Secondary outcomes included count of doses received, treatment duration, all-cause hospitalizations, and incidence of serious adverse events. **Results:** A total of 1,445 patients initiated on either bevacizumab-awwb (n=239) or bevacizumab (n=1,206) were included in the analysis. The mean overall age was 60 ± 13 years and 54% of patients were male. The OS rate was 72.8% and 73.1% for patients receiving bevacizumab-awwb and bevacizumab, respectively ($p<0.01$ for non-inferiority). The adjusted hazard ratio for mortality was 1.01 (0.77-1.33, $p=0.93$). There were no statistically significant differences in secondary outcomes between the 2 study groups (Table). **Conclusions:** Bevacizumab-awwb is a safe and effective option when compared to the reference bevacizumab in the treatment of mCRC. Future studies should evaluate outcomes after longer follow-up time and in different cancer types. Research Sponsor: None.

Unadjusted secondary outcomes of patients with mCRC by treatment group (n=1,445).

OUTCOME	BEVACIZUMAB-AWWB (n = 239)	BEVACIZUMAB (n = 1,206)	*p*-value
Count of doses received, *mean ± SD*	11.2 ± 6.7	10.5 ± 6.6	0.14
Treatment duration (months), *mean ± SD*	6.7 ± 4.1	6.5 ± 4.2	0.67
All-cause hospitalizations, *n (%)*	105 (43.9%)	503 (41.7%)	0.52
Serious adverse events, *n (%)*			
Hemorrhage	11 (4.6%)	52 (4.3%)	0.84
GI perforation	5 (2.1%)	26 (2.2%)	0.95
Severe thromboembolism	12 (5.0%)	34 (2.8%)	0.08
Severe hypertension	34 (14.2%)	174 (14.4%)	0.94
Congestive heart failure	3 (1.3%)	10 (0.8%)	0.46

3553 **Poster Session**

Gene expression of vitamin D (VitD) pathway markers and survival in patients (Pts) with metastatic colorectal cancer (mCRC): CALGB/SWOG 80405 (Alliance). *First Author: Christine G Kohn, Beth Israel Deaconess Medical Center, Boston, MA*

Background: Higher levels of plasma 25-hydroxyvitamin D [25(OH)D)] are associated with better outcomes in mCRC, but underlying biologic mechanisms are unknown. Key components of the VitD metabolic pathway include CYP27B1 (encodes 1-α-hydroxylase, converts 25(OH)D to active calcitriol), VitD receptor (VDR), and CYP24A1 (encodes 24-hydroxylase, degrades calcitriol and 25(OH)D into excreted metabolites). Since these factors may affect 25(OH)D levels and potentially mediate VitD activity in mCRC, we examined the relationship between tumoral gene expression (GEx) of CYP27B1, VDR, and CYP24A and pt outcome in a study nested in a randomized phase III trial of first-line chemotherapy plus biologics in mCRC pts, CALGB/SWOG 80405. **Methods:** We determined GEx of CYP27B1, VDR, and CYP24A1 by RNA sequencing (RNA-Seq) of archival tumor samples using the Illumina TruSeq platform. Primary endpoints were overall (OS) and progression-free survival (PFS). Cox proportional hazard models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs), adjusting for prognostic and molecular characteristics. **Results:** 562 pts with RNA-Seq data were included. Pts with higher CYP27B1 expression (>median) were less likely to have BRAF wild type (WT) (79% vs 90%) compared to pts with lower expression (p=0.0007). Pts with higher VDR expression (>quartile 1 [Q1]) were younger (median age 59 vs 62 years; p=0.03), more likely to have left-sided (63% vs 46%; p=0.0005) and BRAF WT tumors (89% vs 70%; p<0.0001), and less likely to have RAS WT tumors (70% vs 80%; p=0.02) compared to pts with lower VDR. Pts with higher CYP24A1 expression (>median) were more likely to have left-sided tumors compared to pts with lower expression (63% vs 54%; p=0.03). On multivariable analysis, pts with higher CYP27B1 expression had significantly improved OS (HR 0.84; 95% CI, 0.75-0.93; p=0.002) and PFS (HR 0.89; 95% CI, 0.80-0.99; p=0.04). Higher VDR expression (up to Q1) was associated with significantly improved PFS (HR 0.69; 95% CI, 0.53-0.91; p=0.007) but not OS (HR 0.85; 95% CI, 0.66-1.09; p=0.20). Above Q1, this improvement attenuated. Higher CYP24A1 GEx was not associated with improved OS (HR 0.98; 95% CI, 0.88-1.08; p=0.66) or PFS (HR 0.98; 95% CI, 0.89-1.08; p=0.68). We found no significant interactions between GEx of CYP27B1, VDR, or CYP24A with baseline plasma 25(OH)D levels (p for interaction ≥0.10 for all). **Conclusions:** Our findings suggest an association between GEx of VitD pathway markers, particularly CYP27B1 and VDR, and survival in pts with mCRC, lending biologic plausibility to a role of VitD in CRC pathogenesis. Future studies are needed to confirm these findings and elucidate underlying mechanisms of action. Clinical trial information: NCT00265850. Research Sponsor: U10CA180821, U10CA180882, U10CA180888; Pfizer, Genentech; https://acknowledgments.alliancefound.org.

3554 **Poster Session**

Resistance mechanisms to anti-EGFR therapy in *RAS*/*RAF* wildtype colorectal cancer varies by regimen and line of therapy. *First Author: Christine Megerdichian Parseghian, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The conventional theory for the development of treatment resistance to anti-EGFR for metastatic colorectal cancer (mCRC) is the selective growth advantage of pre-existing therapy-resistant subclones with genomic mechanisms such as *RAS* mutations, leading to treatment resistance and disease progression. However, the impact of cytotoxic chemotherapy in combination with anti-EGFR on the mechanisms of resistance has not been assessed. **Methods:** We analyzed paired plasma samples from *RAS/BRAF/EGFR* wild-type mCRC patients enrolled in three large randomized phase 3 trials of anti-EGFR rechallenge in whom paired baseline and time of progression plasma samples had been collected for sequencing of ctDNA on a platform optimized for very low allele frequencies. 569 patients had paired baseline and progression ctDNA samples analyzed, including 147 in the first line study of FOLFOX +/- panitumumab, 91 patients in third line with panitumumab vs best supportive care, and 331 patients in the third line study of cetuximab vs. panitumumab. The mutational signature of the alterations acquired with therapy was evaluated. We also established colon cancer cell lines with resistance to cetuximab, FOLFOX, and SN38, and profiled transcriptional changes. **Results:** Using serial plasma samples, we demonstrate that patients whose tumors were treated with and responded to anti-EGFR alone were approximately 5-times more likely to develop acquired mutations at progression compared to those treated with an EGFR inhibitor in combination with cytotoxic chemotherapy (46% vs. 9%, respectively; $p < 0.001$). Consistent with this clinical finding, cell lines with non-genomic acquired resistance to cetuximab were cross-resistant to cytotoxic chemotherapy and vice-versa, with transcriptomic profiles consistent with epithelial to mesenchymal transition. In contrast, common acquired genomic alterations in the MAPK pathway that drive resistance to EGFR monoclonal antibodies do not impact sensitivity to cytotoxic chemotherapy. Further, contrary to the generally accepted hypothesis of clonal expansion of acquired resistance, in our work we demonstrate that baseline resistant subclonal mutations rarely expanded to become clonal at the time of progression (8%), and most remained subclonal (44%) or disappeared (49%). **Conclusions:** Collectively, this work outlines a model of resistance where non-genomic mechanisms of resistance common to both EGFR inhibitors and cytotoxic chemotherapy predominate in patients treated with EGFR and chemotherapy combinations. With EGFR inhibitor monotherapy, genomic acquired resistance mechanisms predominate, although only rarely through expansion of pre-existing subclones. These findings have important implications for strategies of EGFR-inhibitor rechallenge studies. Research Sponsor: Andrew Sabin Family Fellowship, NIH/NCI GI SPORE, Pharmaceutical/Biotech Company.

3555 **Poster Session**

Aflibercept-LV5FU2 as first-line treatment of non-resectable metastatic colorectal cancers: Results of the FOLFA randomized phase II trial. *First Author: Jean-Louis Legoux, Centre Hospitalier Régional, Orléans, France*

Background: Previous trials have demonstrated that bevacizumab and fluoropyrimidine combination is effective and well-tolerated in older patients (pts) with non-aggressive unresectable metastatic colorectal cancer. We evaluated in this trial safety and efficacy of aflibercept and infusional 5-fluorouracil/folinic acid (LV5FU2 regimen) combination versus LV5FU2 alone in older pts, asymptomatic and/or frail, deemed unsuitable for doublet cytotoxic chemotherapy. **Methods:** The main eligibility criteria for this randomized phase II trial were age ≥ 65 and WHO performance status < 2. Randomization was stratified according to thymidylate synthase (TS)-*5'UTR* germline polymorphism. Common (also called simplified) LV5FU2 regimen was preceded or not by aflibercept (4mg/kg). The primary endpoint was the 6-month progression-free survival (PFS) rate, achieved if > 40% in the experimental arm. Secondary objectives were safety, quality of life, overall survival (OS), and the prognostic impact of TS-*5'UTR* polymorphism. **Results:** 117 patients (pts) were included, 59 in arm A (5FU-aflibercept), 58 in arm B (5FU alone), of median age 81 years (range 67-91; > 75 years: 81%). *RAS*/*BRAF* status (available in 112 pts [96%]) was mutated in 49% and 7%, respectively. The 6-month PFS was 54% in both arms (same 90% CI 42-65). The disease control rate was 83% in arm A and 87% in arm B. The median OS was 21.8 months in arm A and 25.1 months in arm B. The toxicities were more common in arm A: at least 1 grade 3-4 toxicity > 2 in 82% versus (vs) 58.2% pts, hypertension grade > 3 in 42% vs 18% pts, proteinuria (any grade) in 51% vs 11% pts, dysphonia (grade < 3) in 19% vs 2%, 1 colic perforation in arm A. Treatment delays for toxicities were required for 4% of the 753 courses in arm A vs 2% of the 780 courses in arm B, 5FU bolus suppression was decided for 29.8% pts vs 20% (arm A vs arm B), median 29 days vs 73 days after the first course (arm A vs B), without difference in the doses of infusional 5FU. A second and third line of treatment were received in 41% and 14% of pts in arm A vs 67% and 29% of pts in arm B, respectively. The TS *5'UTR* polymorphism (3R3R vs 2R2R or 2R3R) had no impact on PFS or OS. Regarding the quality of life (QLQ C30 score), the difference of overall health score was on average -6.39 (SD = 26.68) in arm A vs -4.91 (SD = 27.15) in arm B, and was very similar in all components. The median time to definitive deterioration in quality of life was 15 months (95% CI: 9-22.8) in arm A vs 9.6 (95% CI: 5.1-19.4) in arm B. **Conclusions:** FOLFA trial meets is primary endpoint with 53.6% of 6-month PFS with LV5FU2-aflibercept. Nevertheless, as compared with LV5FU2 alone we observed no increase in PFS or OS and more toxicities. These results do not argue for an evaluation of LV5FU2-aflibercept combination in a randomized phase III trial. Clinical trial information: EudraCT 2014-001837-10. Research Sponsor: Federation Francophone de Cancerologie Digestive, Pharmaceutical/Biotech Company.

3556 **Poster Session**

Has the COVID-19 pandemic lead to an upshift in emergency presentation and stage migration of colorectal cancer in Uruguay? *First Author: Santiago Fontes, Servicios Oncológicos de la Asociación Española Primera de Socorros Mutuos, Montevideo, Uruguay*

Background: Effective Cancer screening is critical in reducing cancer related mortality in CRC by increasing the detection in earlier stages. Worldwide, practically all cancer pathways have been negatively affected by the implications of the COVID-19 pandemic. Oncological care has not escaped the effects of reprioritization of health care services to handle the surge of COVID-19 patients adequately. Cancer screening programs are no exception as many were temporarily halted to alleviate the pressure on overwhelmed health care systems. In Uruguay, the first covid patients were detected in March 2020, and since then, the country's Public Health policies have been marked by the covid-19 public health emergency. The aim of this study is to assess the impact of the COVID-19 pandemic on CRC diagnosis. We further aimed to analyze the effect on the clinical presentation and stage at diagnosis during 2020-2021 compared with previous years. **Methods:** This was a retrospective cohort study performed at a single tertiary center. Patients diagnosed and managed with colorectal adenocarcinoma during the years 2020-2021 were compared with patients from 2018-2019. Those enrolled in 2018-2019 were classified as the "pre-pandemic group", and those enrolled in 2020-2021 were classified as the "pandemic group". The primary outcome was the rate of stage IV disease at the time of diagnosis. Mann-Whitney test was used in the comparison of quantitative variables and Fisher's exact test was used for qualitative variables. **Results:** A total of 370 patients were included in this study. From March 2018 to 2019 (pre-pandemic), 217 patients were considered, and from March 2020 to 2021 (pandemic), 153 patients. Median age of pre-pandemic and pandemic group was 64.4 and 65.6 years, respectively. There was no statistically significant difference in cancer obstruction or perforation at diagnosis. Patient demographics and tumor clinicopathological features were comparable. The percentage of surgical candidates was lower during the pandemic (69% vs 62%). There was a significant difference in TNM tumor distribution between pre-pandemic and pandemic subgroups with a higher incidence of advanced (cT4 or cN+ or M1) tumors. T4 tumors and node positive disease were equivalent in both groups but the incidence of disseminated disease (cM1) was significantly higher in the pandemic group ($P < 0.001$) **Conclusions:** Our study demonstrates how cancer diagnostic variables, mainly stage at diagnosis, have been affected by the impact of the COVID-19 pandemic on cancer screening programs. Therefore, it is of utmost importance that cancer diagnosis and treatment pathways be reinstalled in full to return to and build on pre-pandemic priority to ensure the benefits from earlier diagnosis and treatment. Future studies are needed to verify the tendency in stage migration and to optimize CRC care in the pandemic scenario. Research Sponsor: None.

3557 **Poster Session**

Bcl-xL and association with apoptosis following KRASG12C inhibition in KRASG12C mutant colorectal cancer. *First Author: Hajrah Khawaja, Queen's University Belfast, Belfast, United Kingdom*

Background: Novel covalent inhibitors of $KRAS^{G12C}$ have shown modest response rates in $KRAS^{G12C}$ mutant (MT) colorectal cancer (CRC) patients. Thus, novel $KRAS^{G12C}$ inhibitor combination strategies that can achieve deep and durable responses are needed. **Methods:** The small molecule $KRAS^{G12C}$ inhibitors AZ'1569 and AZ'8037 were employed. To identify novel candidate combination strategies for AZ'1569, we performed RNA sequencing, siRNA and high-throughput drug screening. Top hits were validated in a panel of $KRAS^{G12C}$MT CRC cells and *in vivo* xenograft models. AZ'1569 acquired resistant CRC models were generated and characterised. **Results:** Response to AZ'1569 was heterogeneous across the $KRAS^{G12C}$MT models. AZ'1569 was ineffective at inducing apoptosis when used as a single agent or combined with chemotherapy or agents targeting the EGFR/KRAS/AKT axis. Using a systems biology approach, we identified the anti-apoptotic BH3-family member *BCL2L1*/Bcl-xL as top hit mediating resistance to AZ'1569. Further analyses identified acute increases in the pro-apoptotic protein BIM following AZ'1569 treatment. ABT-263 (Navitoclax), a pharmacological Bcl-2 family-inhibitor that blocks the ability of Bcl-xL to bind and inhibit BIM, led to dramatic and universal apoptosis when combined with AZ'1569 in a panel of $KRAS^{G12C}$ MT CRC cells. Furthermore, this combination also resulted in dramatically attenuated tumour growth in $KRAS^{G12C}$ MT CRC xenografts. Finally, AZ'1569 acquired resistant $KRAS^{G12C}$ MT CRC cells showed amplification of $KRAS^{G12C}$, EphA2/c-MET activation, increased pro-inflammatory chemokine profile and cross-resistance to standard-of-care chemotherapy and several targeted agents. Importantly, the KRAS amplification and AZ'1569-resistance were reversible upon drug withdrawal, arguing strongly for the use of drug holidays in the case of KRAS amplification. **Conclusions:** Combinatorial targeting of Bcl-xL and $KRAS^{G12C}$ is highly effective, suggesting a novel therapeutic strategy for $KRAS^{G12C}$MT CRC patients. The cross-resistance to other targeted therapies and importantly conventional chemotherapy in the AZ'1569 acquired resistant cells poses a challenge, with implications for the optimal use of $KRAS^{G12C}$ inhibitors as a second or third line option. Research Sponsor: Cancer Research UK (C212/A7402), Other Foundation, Pharmaceutical/Biotech Company, MErCuRIC, funded by the European Commission's Framework Programme 7, under contract #602901.

3558 **Poster Session**

Patient-reported outcomes from the GARNET trial in patients with advanced or recurrent mismatch repair deficient (dMMR) colorectal cancer (CRC): A post hoc subgroup analysis. *First Author: Jennifer Hanlon, GlaxoSmithKline, Waltham, MA*

Background: Dostarlimab is a programmed death 1 (PD-1) inhibitor approved in the US as a monotherapy in patients (pts) with dMMR advanced/recurrent endometrial cancer that has progressed on or after prior treatment with a platinum-containing regimen or in pts with dMMR solid tumors that have progressed on or after prior treatment, with no satisfactory alternative treatment options. Here we report on patient-reported outcomes (PROs) in pts with dMMR CRC, a post hoc subgroup analysis. **Methods**: GARNET is a multicenter, open-label, single-arm phase 1 study. Cohort F enrolled pts with dMMR/microsatellite instabilityhigh or $POL\varepsilon$-mutated non-endometrial solid tumors. Pts with CRC must have received prior fluoropyrimidine, oxaliplatin, and irinotecan. Pts received 500 mg of IV dostarlimab Q3W for 4 cycles, then 1000 mg Q6W until discontinuation. PRO assessment, an exploratory endpoint, was measured using the EORTC-QLQ-C30. PROs were collected at baseline, at each dose cycle, and after discontinuation. Multi-item and item-level analyses were collected and scored; improvement was defined as mean change from baseline (directional change dependent on item). A 10-pt change in mean from baseline was considered clinically significant for the analysis. **Results**: PRO data at baseline were available for 96 pts with CRC who received ≥1 dose of dostarlimab. Improvements from baseline for quality of life (QOL) and most gastrointestinal symptom scales were observed and maintained from cycle 2 through 7 (Table). Stability in diarrhea was seen from cycles 2 through 7. **Conclusions**: PROs from the GARNET trial in pts with dMMR CRC show that QOL and disease-related gastrointestinal symptoms were improved or maintained while on dostarlimab treatment. These data, with the previously reported efficacy and safety profile, support the use of dostarlimab in pts with dMMR CRC. Clinical trial information: NCT02715284. Research Sponsor: GlaxoSmithKline.

	Cycle					
	2	3	4	5	6	7
Patients ongoing in trial, n (%)	91 (94.8)	83 (86.5)	81 (84.4)	76 (79.2)	69 (71.9)	67 (69.8)
Mean change from baseline (95% CI)[a]						
QOL	3.5 (–0.0 to 6.9)	9.0 (5.0 to 13.0)	9.7 (5.3 to 14.2)	11.3 (6.9 to 15.8)	13.9 (9.1 to 18.8)	15.3 (10.0 to 20.7)
Nausea/vomiting	–1.6 (–7.5 to 4.2)	–4.1 (–9.6 to 1.4)	–6.3 (–12.2 to –0.4)	–6.4 (–13.4 to 0.5)	–8.1 (–13.9 to –2.2)	–8.9 (–15.9 to –1.8)
Appetite loss	–1.2 (–7.7 to 5.3)	–11.2 (–17.5 to –4.8)	–14.9 (–23.1 to –6.7)	–18.6 (–26.6 to –10.6)	–20.7 (–30.2 to –11.1)	–23.7 (–33.7 to –13.8)
Constipation	–2.4 (–7.5 to 2.7)	–4.7 (–11.5 to 2.1)	–8.1 (–14.5 to –1.8)	–9.1 (–16.0 to –2.2)	–11.5 (–19.6 to –3.4)	–13.4 (–22.3 to –4.4)
Diarrhea	0.4 (–4.7 to 5.6)	–0.4 (–6.2 to 5.4)	–2.2 (–9.0 to 4.6)	–0.5 (–8.0 to 7.1)	1.2 (–6.4 to 8.8)	3.5 (–6.3 to 13.4)

[a]Trend of improvement in QOL indicated by positive values; trend of improvement in nausea/vomiting, appetite loss, constipation, and diarrhea indicated by negative values.

3559 **Poster Session**

Alternative biweekly dosing schedule of trifluridine-tipiracil (TAS-102) reduces rates of myelosuppression while maintaining therapeutic efficacy in patients (pts) with previously treated metastatic colorectal cancer (mCRC). *First Author: Christopher G Cann, Vanderbilt University Medical Center, Nashville, TN*

Background: Colorectal cancer remains a significant source of morbidity and mortality within the United States, causing nearly 53,000 deaths in 2021. For unresectable pts, the estimated 5-year survival rate is 14%. Given recent advances in treatment, 50% of pts with mCRC will receive third-line therapy or greater, making optimization of therapy in these settings pivotal. Trifluridine-tipiracil (TAS-102) is FDA approved for third-line or greater in mCRC per the RECOURSE Trial. Standard dosing is 35 mg/m^2 twice daily (maximum = 80 mg/day) on Days 1-5 and Days 8-12 of 28-day cycles. This dosing schedule is associated with Grade 3-4 neutropenia (38%), requiring treatment delays (53%), dose reductions (14%) and G-CSF support (9%). To reduce this toxicity while maintaining efficacy, we studied an alternative biweekly dosing (Days 1-5 and Days 15-19 of 28-day cycles). **Methods:** A retrospective analysis was completed (2019-2021) at Vanderbilt-Ingram Cancer Center in pts with refractory mCRC and appendiceal cancer (CA) who completed > 12 days of TAS-102 therapy. Diagnostic imaging was completed every 8-12 weeks. Patient data was evaluated for lines of prior therapy, ECOG performance status (PS), the addition of bevacizumab, and CTCAE grade of treatment-related myelotoxicity. Evaluation of progression-free survival (PFS) was performed only in mCRC pts. **Results:** 24 pts met the criteria, with a mCRC:appendiceal CA ratio of 20:4 and Male:Female 13:11. Median age 61.5 yrs (range 31-80); median number of prior therapies 3; median ECOG PS of 1; and median duration of therapy 73.5 days. Hematologic toxicities: Neutropenia 30% [Grade 3 (13%), Grade 4 (0%)]; anemia 17.4% [Grade 3 (8.7%), Grade 4 (0%)]; thrombocytopenia 4.3% [Grade 3/4 (0%)]. No pts required G-CSF. One patient required a treatment-related dose delay (neutropenia), and 2 pts required dose reductions (fatigue). In mCRC pts, the median PFS was 2.3 months. To date, 7 mCRC pts remain on treatment (range: 38-385). **Conclusions:** In our retrospective cohort analysis, TAS-102 biweekly dosing schedule (35 mg/m^2 twice daily; Days 1-5 and Days 15-19 of 28-day cycles) for pts with refractory mCRC and appendiceal CA reduced Grade 3 myelotoxicity without Grade 4 toxicities, while preserving PFS in pts with mCRC. With an improved toxicity profile, this alternative TAS -102 dosing schedule may be a more favorable option for future combination studies. Additional prospective data are needed to validate these findings. To our knowledge, this is the first analysis of biweekly TAS-102 in a US patient population. Research Sponsor: None.

3560 **Poster Session**

Impact of circulating tumor DNA (ctDNA) mutant allele fraction in response to anti-angiogenic therapy in *RAS*-mutant metastatic colorectal cancer (mCRC): Clinical data in the first-line setting and correlation in patient-derived xenograft (PDX) models. *First Author: Nadia Saoudi Gonzalez, Medical Oncology Department, Vall dHebron University Hospital, Barcelona, Spain*

Background: Currently, there are no well-established biomarkers available to select mCRC patients (pts) who will benefit most from antiangiogenic therapy. *RAS* mutant (mt) allele fraction in plasma (plMAF) is an independent prognostic factor in mCRC. Preliminary data from our group suggests the possible predictive role of plMAF in *RAS* mt pts treated with 1st line chemotherapy (ct) +/- bevacizumab (bev). **Methods:** Data prospectively/retrospectively collected from *RAS*mt mCRC pts who received 1st line ct+/-bev treatment in our center, selecting the subset of pts with plMAF sample evaluable with digital PCR (BEAMing) at baseline. Pts were stratified as high (≥ 5.8%) or low (< 5.8%) plMAF, based on a previously established prognostic cutoff (Elez et al, Mol Onc 2019). We investigated the associations between clinic-pathological variables, overall survival (OS), and progression-free survival (PFS) stratified by plMAF *RAS* levels using Cox regression models. OS and PFS were calculated by Kaplan-Meier method. Murine PDX were developed from mCRC pts including models from patients with *KRASG12/G13* mutations to explore recapitulation of the clinical findings. **Results:** From October '17 to December '21, 102 basal plasma samples were analyzed by BEAMing. 47 pts (46%) were classified as high, 39 pts (38%) as low, and 16 (16%) as no-mt detected by BEAMing (non-shedding). OS was significant longer in low plMAF pts than in high plMAF pts (median OS 15.9 vs 37.1 months (mo); HR 0.43; p = 0.001). In high plMAF pts, a trend towards a better PFS was observed in those pts treated with ct+bev compared to ct alone (median 9.4 vs 6.1 mo; HR 0.6; p = 0.18). No differences were observed in low plMAF pts treated with ct +/- bev (median 14.5 vs 14.9 mo; HR 1.2; p = 0.58). Results were not modified when adjusted by the presence of liver metastases. The multivariate PFS model showed no association between *RAS* plMAF and clinicopathological variables, except for treatment benefit with ct+bev and better outcomes in pts with resectable liver metastases. Interestingly, human ctDNA in one murine PDX model from non-shedding pt was not detectable, whereas human ctDNA was present in another PDX model with a plMAF of 36.2%. **Conclusions:** This study suggests that plMAF could be a promising predictive biomarker of response to bev in 1st line *RAS*mt mCRC, but more pts need to be analyzed to confirm this effect. Our results confirm the prognostic role of *RAS*mt plMAF in mCRC. plMAF could partially depend on tumor cell shedding degree and characteristics on the tumor vasculature architecture, this is being investigated in ongoing imaging studies and PDX models. These models will also help to understand the biology behind tumor response to bev and its connection with ctDNA shedding. Research Sponsor: None.

3561 **Poster Session**

Regorafenib (REGO) plus FOLFIRINOX as frontline treatment in patients (pts) with RAS-mutated metastatic colorectal cancer (mCRC): A phase I/II, dose-escalation and dose-expansion study. *First Author: Antoine Adenis, Institut du Cancer de Montpellier, Montpellier, France*

Background: Standard treatment options for RAS-mutated mCRC pts include the combination of bevacizumab with FOLFIRINOX, a three-drug chemotherapy regimen. Unlike bevacizumab, REGO – an oral multi-tyrosine kinase agent - exhibits not only antiangiogenic properties with cytostatic effects but also true cytotoxic effects. We report the preliminary results of the FOLFIRINOX-R trial (NCT03828799), in which we evaluated the safety and the efficacy of REGO in combination with FOLFIRINOX in pts with RAS-mutated mCRC. **Methods:** FOLFIRINOX-R trial is a prospective, dose-finding, phase I/II study whose dose-escalation part has been completed. Dose escalation was implemented following a 3 + 3 design and included three dose levels (DL). FOLFIRINOX regimen includes oxaliplatin (85 mg/m^2), folinic acid (400 mg/m^2), irinotecan (150–180 mg/m^2), 5-fluorouracil (400 mg/m^2 in bolus then 2400 mg/m^2 over 46h), and was administered every 14 days. REGO (80 to 160 mg per day, as per DL) was administered on days 4 to 10 of each cycle. Treatment was continued up to 12 cycles or until progression or unacceptable toxicity. The primary objectives of the dose-finding part of the study were to determine the maximum tolerated dose (MTD) using as endpoint the incidence of DLTs during the three first cycles of treatment, and to select the recommended phase 2 dose (RP2D). Key eligibility criteria include ECOG PS ≤1 and RAS-mutated mCRC not amenable to surgery with curative intent and not previously treated for metastatic disease. Patients with the 7/7 variant of the UGT1A1*28 polymorphism were not eligible. Prophylactic G-CSF was administered from Day-7 to Day-12. **Results:** Thirteen pts were enrolled across the 3 DL (DL 1: 3 pts, DL 2: 6 pts, DL 3: 4 pts); 46% of pts were female, the median age was 65 yo [range: 40 ; 76]. One pt (at DL 3) was not evaluable for DLT because of poor observance during the first 2 cycles. At data cut-off, median treatment duration and median follow-up were 4.6 mo. (range: 2.3; 10) and 13.4 mo. (range: 3.8; 18.0), respectively. One DLT (a grade 3 hypokalaemia related to grade 2 diarrhoea) occurred at DL 2. MTD was not reached at DL 3 (REGO 160 mg/day). The most common grade ≥3 TRAE per patient were grade 3 neutropenia (n = 1), grade 4 neutropenia (n = 1), grade 3 neuropathy (n = 2) and grade 3 diarrhoea (n = 7). Dose reductions/discontinuations due to grade ≥3 TRAE were necessary in 12/13 (92%) pts. The ORR was 62% (95% CI 32%-86%) and median PFS was 9.1 mo (range: 3.1; 15.4). **Conclusions:** Full-dose FOLFIRINOX plus full-dose REGO (160mg/day, days 4 to 10) can be administered safely. Due to the manageable toxicity profile and the promising efficacy observed in the dose-escalation stage, this regimen deserves to be evaluated in the dose-expansion stage. Clinical trial information: NCT03828799. Research Sponsor: Bayer Pharma.

3562 **Poster Session**

Molecular characterization and subsequent treatments after encorafenib-cetuximab +/- binimetinib in BRAF V600E-mutated colorectal cancer. *First Author: Javier Ros Montañá, Vall d'Hebron Institute of Oncology (VHIO), Medical Oncology, Vall d'Hebron University Hospital (HUVH), Barcelona, Spain*

Background: The *BRAF-V600E* mutation confers poor prognosis in patients with mCRC. E-C+/-B improve clinical outcomes compared with standard of care. Data about subsequent treatment lines and the impact of NGS in the treatment choice after the BRAF targeted treatment are still limited. We have analyzed the global overall survival (OS) and the impact of NGS to guide subsequent treatments (approved targeted therapies (TT) or clinical trials (CT)) after E-C+/-B. **Methods:** Patients who had received E-C+/-B were included. Clinical data was collected prospectively. Tissue NGS was performed prospectively and retrospectively using an in-house NGS panel (VHIO-300). Subsequent treatments' clinical outcomes were described. Percentage of patients who received TT or CT based on NGS results is reported. Clinical outcomes were calculated using survival Kaplan-Meier curves. **Results:** From 2017 to 2021, 59 patients with refractory mCRC received E-C+/-B at our institution. 50 patients have already progressed to the BRAF inhibitor combination and 9 patients remain on BRAF inhibitor treatment. Tumor tissue for NGS testing before BRAF inhibitor treatment was available in 70% of patients (41/59). *BRAF-V600E* mutation was confirmed in tissue using ddPCR in all patients. The most frequent alterations were: *BRAF-V600E* 93%, *TP53* 64%, *RNF43* 30%, *APC* 20%, *PIK3CA* 14%, *NOTCH1/2* 9%, *RANBP2* 8%, *PTEN* 8%, *MET* amplification 5%. MSI incidence was 10%, 2 out of 6 (33%) received subsequent immunotherapy. After the BRAF inhibitor combination, 23 patients (38%) did not receive subsequent treatment (clinical deterioration or death). The 27 remaining patients (62%) received 41 subsequent treatments (37% of them were TT or CT). Median subsequent lines after the BRAF inhibitor combination were 1 (0-3). NGS led to targeted therapy in 20% of the patients: BRAF inhibitors combos (20%), microtubule inhibitors (13%), antiPD1 (13%), NOTCH inhibitors (6%), and MET inhibitor (6%). ORR among patients who received matched TT or CT was 6% and DCR (CR+PR+SD) was 47%. The median OS after the BRAF inhibitor was 3.8 months; 10.1 months vs 3.0 months (HR 0.43 (95%CI 0.2-0.95), p = 0.04) for those patients who received TT or CT vs patients who did not receive TT or CT. When MSI patients were excluded mOS was 5.2 vs 3.0 months (HR 0.61 (95%CI 0.27-1.37), p = 0.23) respectively. There were no differences in terms of OS regarding the number of previous lines (0-1 vs 2-3, HR 0.75 (95%CI 0.4-1.42), p = 0.37) or with the BRAF inhibitor regimen used (E-C vs E-C-B) (HR 0.84, (95%CI 0.44-1.6), p = 0.61) **Conclusions:** This study suggests that patients with *BRAF-V600E* mutant mCRC could have benefit when treated with TT and/or in CT after a BRAF inhibitor-based therapy, including immunotherapy. Genomic analysis might help to guide subsequent treatments. Because of molecular heterogeneity, these patients should be discussed in Molecular Tumor Boards. Research Sponsor: None.

3563 **Poster Session**

A phase 2 trial of sintilimab (IBI 308) in combination with CAPEOX and bevacizumab (BBCAPX) as first-line treatment in patients with RAS-mutant, microsatellite stable, unresectable metastatic colorectal cancer. *First Author: Xuefeng Fang, Department of Medical Oncology, Key Laboratory of Cancer Prevention and Intervention, Ministry of Education, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China*

Background: The prognosis of metastatic colorectal cancer (mCRC) patients with RAS gene mutation and microsatellite stable (MSS) is poor. MSS patients account for 95% of CRC and have a low response rate to immunotherapy. Previous studies have reported that chemotherapy and anti-angiogenesis therapy can promote immunotherapy response. This study aims to assess the safety and antitumor activity of sintilimab (IBI308) combined with CapeOx and bevacizumab in the first-line treatment of patients with RAS-mutant and MSS mCRC. **Methods:** This is an open-label, single-arm, phase II trial. Eligible patients were aged 18 to 75 years with histologically confirmed unresectable metastatic colorectal adenocarcinoma by multidisciplinary team, and had RAS gene mutation and confirmed MSS status. All patients received treatment with sintilimab (200 mg, day 1) plus bevacizumab (7.5mg/kg, day 1) and oxaliplatin (135 mg/m^2, day 1) and capecitabine (1g/m^2, bid, day 1-14) of each 21-day cycle. The primary endpoint included objective response rate (ORR) evaluated via RECIST 1.1 criteria and adverse events according to CTCAE 5.0. Secondary endpoint was progression-free survival (PFS). **Results:** 25 patients were enrolled and received at least two cycle treatment. At baseline, median age was 60 years (range 45-74), 72% of patients were male, ECOG PS 0/1 was 100%, 60% had liver metastases (mets), and the primary tumor site was right-sided colon in 36.0% and left-side colorectum in 64.0%. 25 patients completed at least one efficacy evaluation. 2 (8.0%) patients showed complete response (CR), 19 (76.0%) patients had a partial response (PR) and 4 (16.0%) had stable disease (SD). Patients with liver or lung mets had a higher ORR (93.3% and 100%, respectively) compared to the overall ORR (84.0%). Disease control rate (DCR) reached 100%. Median PFS has not yet reached. No grade 5 adverse events occurred. The most common treatment-related adverse events (TRAEs) in all grades were anemia (19/25, 76.0%), peripheral neurotoxicity (6/25, 24.0%) and neutropenia (17/25, 68.0%). The most frequent grade 3/4 TRAEs were neutropenia (3/25, 12.0%), elevated aspartate transaminase (1/25, 4.0%), elevated alanine transaminase (1/25, 4.0%) and elevated bilirubin (1/25, 4.0%). **Conclusions:** Combination treatment with sintilimab (IBI308) plus CapeOx and bevacizumab demonstrated a high ORR (84.0%; 93.3% in patients with liver mets, and 100% in patients with lung mets) and a manageable safety profile in RAS-mutant and MSS mCRC. Clinical trial information: NCT05171660. Research Sponsor: Innovent Biologics, Inc.

	Liver mets(N = 15)	Lung mets(N = 4)	Other mets(N = 6)	All patients(N = 25)
CR, n (%)	0	0	2 (33.3)	2 (8.0)
PR, n (%)	14 (93.3)	4 (100)	1 (16.7)	19 (76.0)
SD, n (%)	1 (6.7)	0	3 (50.0)	4 (16.0)
Progressive disease, n (%)	0	0	0	0
ORR, n (%)	14 (93.3)	4 (100)	3 (50.0)	21 (84.0)
DCR, n (%)	15 (100)	4 (100)	6 (100)	25 (100)

3564 **Poster Session**

NSABP FC-11: A phase II study of neratinib (N) plus trastuzumab (T) or N plus cetuximab (C) in patients (pts) with "quadruple wild-type" metastatic colorectal cancer (mCRC) based on HER2 status. *First Author: Samuel A. Jacobs, NSABP Foundation, Inc., Pittsburgh, PA*

Background: Patients (pts) with KRAS wild-type (WT) mCRC treated with single agent anti-EGFR therapy (tx) have improved OS compared to BSC but only a 10-15% response rate. Prior EGFR tx may upregulate HER amplification. For pts with quadruple WT mCRC (KRAS, NRAS, BRAF, PIC3KA), data suggest that dual targeting of the MAPK pathway, specifically EGFR and HER2, may be more effective. The purpose of this study was to evaluate the activity of dual MAPK pathway inhibition based on HER2 status: amplified (amp), non-amplified (non-amp), or mutated (mt). **Methods:** This 2-arm phase II trial enrolled pts with quad WT mCRC with ECOG PS 0-2, adequate organ function, prior oxaliplatin- and irinotecan-based regimens, and known HER2 status. Arm 1: HER2 amp (confirmed as >2.14 copy number by Guardant 360) and prior anti-EGFR tx or HER2 mt (with qualifying mt) with or without prior anti-EGFR tx; Arm 2: HER2 non-amp or HER2 amp without prior anti-EGFR tx. Tx included T 4 mg/kg IV loading dose → 2 mg/kg/wk and N 240 mg po daily (Arm 1) or C 400 mg/m^2 IV loading dose → 250 mg/m^2/wk and N 240 mg po daily (Arm 2). Imaging was performed every 8 wks with response per RECIST 1.1. Primary end point (EP) of each arm was 6 mo PFS (PFS_6). Secondary EPs: Response rate (ORR), clinical benefit rate (CBR), toxicity and exploratory assessments of N pharmacokinetics, genetic and molecular analyses, and evaluation of multiple drug combinations in PDX/PDXO models. We tested H_0: PFS_6 <0.13 *v* H_A: PFS_6 >0.47 (α=0.05; power=0.90 to reject H_A). Treating 15 pts in each arm, if ≥5 pts are alive and progression free (PFS_6 0.33), the arm is worth further testing. **Results:** From Jul 2018 - Mar 2021, 25 pts enrolled from 9 different centers. Arm 1 closed due to poor accrual (n=4). Those pts have been excluded from further analysis. Arm 2 enrolled 21 pts. with 15 evaluable for response by imaging. Early discontinuation occurred in 6 of 21 pts: 2 withdrew consent, 3 due to toxicity, and 1 physician withdrawal. Of the 15 evaluable pts, there were 6 PR, 5 of 13 HER2 non-amp, 1 of 2 HER2 amp, (duration 120-171 days; mean 140) and 5 SD (duration 59-231 days; mean 124). The ORR (CR/PR) in all pts who received at least one dose of tx is 33% (6/20). 8 of 15 evaluable pts (53%) were progression free at cycle 6. Common grade 3+ AEs (>5%) included diarrhea (24%), rash (8%), and abdominal pain/distension (8%), without any grade 5 AEs. **Conclusions:** The combination of C+N was reasonably well tolerated with expected toxicities of diarrhea and rash. The ORR, CBR, and PFS compare favorably to pts previously relapsed following oxaliplatin and irinotecan and treated with single-agent anti-EGFR tx. Upon entry, biopsies for PDX implantation had an engraftment success rate of ~80%. We anticipate using these grafts to establish PDXO models for molecular analyses and further drug testing. Support: NSABP Foundation, Puma Biotechnology. Clinical trial information: NCT03457896. Research Sponsor: Puma Biotechnology, Other Foundation.

3565 **Poster Session**

Phase II study of pembrolizumab plus capecitabine and bevacizumab in microsatellite stable (MSS) metastatic colorectal cancer (mCRC). *First Author: Andrea Grace Bocobo, University of California San Francisco, Helen Diller Family Comprehensive Cancer Center, San Francisco, CA*

Background: MSS mCRC rarely responds to pembrolizumab monotherapy, but capecitabine and bevacizumab may induce immune-stimulatory effects. This study evaluates the safety, tolerability and preliminary efficacy of pembrolizumab in combination with capecitabine and bevacizumab in MSS mCRC. **Methods:** Single-center, phase 2 trial with safety lead-in to confirm the recommended phase 2 dose (RP2D) for capecitabine and expansion cohorts (NCT03396926). Key eligibility: MSS mCRC with stable disease (SD) or progressive disease (PD) on prior fluoropyrimidine-based therapy. Treatment: Capecitabine 1000 mg/m2 PO BID D1-14 Q21 days (confirmed RP2D) plus pembrolizumab 200 mg IV D1 Q21 days and bevacizumab 7.5 mg/kg IV D1 Q21 days. Endpoints: Primary: Objective response rate (ORR) by RECIST 1.1. Key secondary: Safety, duration of response (DOR), progression-free survival (PFS), overall survival (OS). **Results:** From 04/2018-10/2021, 44 patients (pts) were enrolled. Overall: Median age 53 years (range 28-79); female 50%; Caucasian 61%. Liver metastases at enrollment 80%. Prior therapies: median prior lines of therapy 2 (range 1-5); PD on fluoropyrimidine-containing regimens 91%; prior exposure to bevacizumab 86%. Complete toxicity data are available for 36 off-treatment pts. Grade ≥ 3 treatment-related (tr)AEs occurred in 10 (28%) pts, including grade 3 immune-related AEs in 4 (11%) pts. All-cause serious (s)AEs occurred in 13 (36%) pts and trSAEs in 5 (14%) pts. (tr)AEs leading to dose interruptions, reductions, or delays occurred in 21 (58%) pts, most commonly palmar-plantar erythrodysesthesia syndrome in 17 (47%) pts. Disposition: of 44 pts enrolled, 35 were removed for PD and 1 was removed for treatment noncompliance; 8 treatment ongoing. ORR in 40 evaluable pts was 5% (95% CI: 0.6,16.9). Best response by RECIST 1.1: partial response (PR) in 2 (5%); SD in 26 (65%); PD in 12 (30%). 2 responders: DOR 12 and 15 months, both with liver metastases. Median follow up was 7 months (range 1-45), with median PFS 4.3 months (95% CI: 3.9, 6.1), PFS at 6 months 31.1% (95% CI: 19.2%, 50.4%), and median OS 9.6 months (95% CI: 6.2, 13). Median time on treatment was 5 months (range 1-26). Single cell RNA sequencing on a subset of paired pre- and on-treatment biopsies demonstrated changes in the frequency of dendritic cells. **Conclusions:** The combination of pembrolizumab with capecitabine and bevacizumab was found to be tolerable with an expected toxicity profile in MSS mCRC pts. The ORR of 5% did not meet the prespecified target of ≥ 15%, however nearly a third of pts had PFS > 6 months. Immune profiling of tumor biopsies and peripheral blood is ongoing. Clinical trial information: NCT03396926. Research Sponsor: Merck.

3566 **Poster Session**

Efficacy and safety of tislelizumab plus cetuximab and irinotecan in patients with previously treated RAS wild-type advanced colorectal cancer: Preliminary findings of a phase II, single-arm study. *First Author: Xiaojing Xu, Department of Oncology, Cancer center, Zhongshan Hospital, Fudan University, Shanghai, China*

Background: For adequately treated patients (pts) with advanced colorectal cancer, the current third-line treatment standard of TKIs or TAS-102 administration has a low clinical objective response rate and its effectiveness seems to be limited. Preclinical studies have suggested that EGFR pathway blockage and immune checkpoint inhibition have synergistic therapeutic effects in these pts. The purpose of this study was to examine the efficacy and safety of tislelizumab (anti-PD-1 antibody) plus cetuximab and irinotecan in pts with previously treated RAS wild-type advanced colorectal cancer. **Methods:** This is an open-label, single-arm, phase II study. RAS wild-type advanced colorectal cancer pts with at least two previous lines of therapy were included in this study and administered with tislelizumab plus cetuximab and irinotecan until disease progression or intolerable toxicity. The primary endpoint was objective response rate (ORR) (RESCIT 1.1). Secondary endpoints included DCR, PFS, OS and safety. **Results:** In total, 35 eligible RAS wild-type advanced colorectal cancer pts were enrolled from March 2021 to September 2021. The median age was 58 years. All 35 pts were identified as BRAF/RAS wild-type, and 33 (94%) had left-sided colon cancer. The percentages of pts with second-line, third-line and ≥fourth-line previous treatments were 37%, 49%, and 14%, respectively. Thirty-four pts (97%) had received targeted therapies previously, including 29 (83%) with anti-EGFR therapy. By December 31, 2021, 2 pts had withdrawn from the study for personal reasons, and the remaining 33 were evaluated for efficacy. Twelve of the 33 (36.4%) pts achieved clinical partial remission and 14 (42.4%) achieved stable disease; disease progression occurred in 6 pts and 1 patient died. The ORR was 36.4% and the DCR was 78.8%. Until December 31, 2021, 23 pts continued treatments, and the median PFS was not reached. Among the 33 treated pts, 32 (97.0%) had treatment-related adverse events (AEs). Common AEs included rash (n = 32), fatigue (n = 29), decreased appetite (n = 24), nausea (n = 24), diarrhea (n = 13), liver dysfunction (n = 10), vomiting (n = 7), leukopenia (n = 7), anemia (n = 6), paronychia (n = 5), oral mucositis (n = 4), and neutropenia (n = 4). Four (12%) of the 33 pts reported grade ≥3 AEs, including rash (n = 1), neutropenia (n = 2) and vomiting (n = 1). **Conclusions:** Tislelizumab plus cetuximab and irinotecan shows an encouraging clinical efficacy and tolerable safety in previously treated pts with RAS wide-type advanced colorectal cancer. Clinical trial information: NCT05143099. Research Sponsor: Special fund for clinical research of Zhongshan Hospital.

3567 **Poster Session**

Impact of age and gender on the efficacy and safety of panitumumab plus fluorouracil and folinic acid versus fluorouracil and folinic acid alone as maintenance therapy in RAS WT metastatic colorectal cancer (mCRC): Subgroup analysis of the PANAMA-study (AIO-KRK-0212). *First Author: Kathrin Heinrich, Department of Medicine III and Comprehensive Cancer Center (CCC Munich LMU), University Hospital, LMU Munich, München, Germany, Munich, Germany*

Background: Clinical trials in mCRC are usually conducted irrespective of gender and mostly also irrespective of age. However, gender- and age-associated differences relating to safety and efficacy in the treatment of mCRC are of presently moving into the focus of interest. We investigated the effect of gender and age on efficacy and safety in the PANAMA trial. **Methods:** PANAMA investigated the efficacy of panitumumab (Pmab) plus fluorouracil and folinic acid (FU/FA) versus FU/FA alone after first-line induction therapy with six cycles of FU/FA and oxaliplatin plus Pmab in patients with *RAS* wild-type metastatic colorectal cancer. In this post-hoc analysis, the study population was stratified for age (≤ 65 years versus > 65 years) and gender (male versus female). Evaluated efficacy endpoints were progression-free survival (PFS), overall survival (OS) of maintenance therapy and objective response rate (ORR) during maintenance therapy. Safety endpoints were rates of any grade and grade 3/4 adverse events (AEs). **Results:** In total, 165 male and 83 female patients were randomized and treated. Male patients had a significant benefit from the addition of Pmab to maintenance treatment with regard to PFS (HR 0.63; 95% CI 0.45-0.88; p = 0.006) and demonstrated a strong trend towards better ORR during maintenance therapy (Odds ratio 1.92; 95%CI 1.02-3.70, p = 0.053). In female patients, no difference regarding PFS was seen between treatment arms (HR 0.85; 95% CI 0.53-1.35, p = 0.491), while a trend towards better ORR with Pmab (Odds ratio 2.50; 95% CI 0.99-6.25; p = 0.063) was observed. Gender had no significant impact on OS, nor did age categories affect survival endpoints. Adverse events grade ≥ 3 occurring during maintenance therapy were comparable between male and female patients (12.9% vs 13.5%; p = 0.791) and in different age categories (p = 0.393). **Conclusions:** In the Panama trial, addition of Pmab to maintenance treatment with FU/FA improved outcome in *RAS* wild-type mCRC. This effect is irrespective of age and is pronounced in male patients. Our results support the relevance of gender in mCRC. Clinical trial information: NCT01991873. Research Sponsor: None.

Population (FAS)	ORR Maintenance		PFS Maintenance		OS Maintenance	
	ORR (%)	Odd's ratio P-value	Months (95%CI)	Hazard ratio P-value	Months (95%CI)	Hazard ratio P-value
Male patients						
FU/FA + Pmab (N = 87)	44.8	1.92 (1.02–3.70)	9.4 (7.2–11.5)	0.63 (0.45–0.88)	27.9 (21.9–33.8)	0.85 (0.55–1.30)
FU/FA (N = 78)	29.5	P = 0.053	5.8 (5.4-6.2)	P = 0.006	26.7 (24.8–28.7)	P = 0.452
Female patients						
FU/FA + Pmab (N = 38)	47.4	2.5 (0.99–6.25)	7.6 (5.1–10.1)	0.85 (0.53–1.35)	29.9 (20.1–39.7)	0.83 (0.47–1.47)
FU/FA (N = 45)	26.7	P = 0.067	5.5 (3.1-7.8)	P = 0.491	22.5 (18.8–26.3)	P = 0.530

3568 **Poster Session**

Trifluridine/tipiracil plus bevacizumab (FTD/TPI + BEV) and trifluridine/tipiracil (FTD/TPI) monotherapy in metastatic colorectal cancer (mCRC): Results of a meta-analysis. *First Author: Takayuki Yoshino, Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan*

Background: FTD/TPI is approved for patients (pts) with refractory mCRC. FTD/TPI + BEV has been evaluated in refractory mCRC in phase 1 and 2 trials and shown efficacy and tolerability, but few head-to-head studies compare FTD/TPI + BEV with FTD/TPI. We therefore conducted this meta-analysis to evaluate outcomes with FTD/TPI + BEV and FTD/TPI monotherapy in mCRC. **Methods:** We searched MEDLINE, Embase, and Cochrane Library databases; ASCO, ESMO, and AACR proceedings (past 3 years); Clinicaltrials.gov and UMIN registries; systematic review bibliographies; gray literature; and guidelines through June 2021 for studies involving pts with mCRC treated with FTD/TPI + BEV or FTD/TPI. Only randomized controlled trials (RCTs), non-RCTs, and prospective observational studies of previously treated pts with mCRC were evaluated. Outcomes included objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), adverse event (AE) rates, and AE-related discontinuation rates. Fixed and random effects models based on inverse-variance weighting were used to estimate relative effects and pooled absolute outcomes for ORR, DCR, AE rates, and AE-related discontinuation rates. PFS and OS were estimated from pooled Kaplan–Meier curves using Guyot's algorithm. **Results:** Twenty-nine of 875 screened publications were selected, which included a total of 10,285 pts and reported on 5 RCTs, 11 non-RCTs, and 10 prospective observational studies. In an RCT (n = 93; Pfeiffer et al. *Lancet Oncol.* 2020), FTD/TPI + BEV was associated with significant reductions in risks for progression and death versus FTD/TPI. Pooled efficacy outcomes were higher with FTD/TPI + BEV than FTD/TPI (Table). Pooled rates for grade ≥3 febrile neutropenia, asthenia/fatigue, diarrhea, nausea, and vomiting were similar with FTD/TPI + BEV and FTD/TPI, although grade ≥3 neutropenia occurred more frequently with FTD/TPI + BEV than FTD/TPI (43% vs 29%). AE-related discontinuation rates were similar (Table). **Conclusions:** This meta-analysis suggests that FTD/TPI + BEV provides benefits over FTD/TPI in pts with refractory mCRC and has a similar safety profile, but it is associated with a higher rate of grade ≥3 neutropenia. Limitations of the analysis include study design heterogeneity. Data from RCTs (eg, phase 3 SUNLIGHT trial [NCT04737187]) are required to confirm these findings. Research Sponsor: Taiho Oncology, Inc.

Pooled absolute outcome	FTD/TPI + BEV	FTD/TPI
ORR, % (no. of studies; sample size)	4 (6; 289)	2 (9; 2784)
DCR, % (no. of studies; sample size)	64 (6; 289)	43 (10; 2809)
Median PFS, mo (no. of studies; sample size)	4.2 (5; 244)	2.6 (6; 1781)
12-mo PFS, % (95% CI)	9 (6–14)	3 (2–4)
Median OS, mo (no. of studies; sample size)	9.8 (5; 244)	8.1 (6; 1814)
12-mo OS, % (95% CI)	38 (32–45)	32 (30–34)
AE-related discontinuations, % (no. of studies; sample size)	8 (5; 244)	7 (10; 3724)

3569 **Poster Session**

NSABP FC-10: A phase Ib study of pembrolizumab (pembro) in combination with pemetrexed (pem) and oxaliplatin (oxali) in patients with chemo-refractory metastatic colorectal cancer (mCRC). *First Author: John C. Krauss, University of Michigan, Ann Arbor, MI*

Background: Most pts with mCRC have microsatellite stable (MSS) disease (95%) which is unresponsive to checkpoint inhibition. Chemotherapy activity is mediated through both cytotoxicity as well as immunological effects including reduced T-regulatory cell activity, enhanced tumor antigen presentation, and induced PD-L1 tumor cell expression. Chemotherapy with checkpoint inhibitors can potentially activate T cells and alter the microenvironment to improve outcomes. Our purpose was to evaluate pembro plus pem in a safety run-in (cohort 1) and the same with dose-escalated oxali (cohort 2). **Methods:** Eligible pts with MSS mCRC had ECOG PS of 0-1, measurable metastatic disease, adequate organ function, and prior treatment with fluoropyrimidine-, oxali-, and irinotecan-based therapies (plus an anti-EGFR agent, if apropos). Cohort 1 treatment was pem 500 mg/m^2 IV plus pembro 200 mg IV every 3 wks. Cohort 2 treatment was the same, plus oxali at an escalating dose of 85-120 mg/m^2 utilizing a 3+3 design with expansion of 6 additional pts at the RP2D. Imaging was performed every 3 cycles; response was determined by RECIST 1.1. Primary endpoint (EP) of each cohort: safety and best ORR with cohort 2 also to establish the RP2D. Secondary EPs: Clinical benefit rate (CBR), PFS, OS at 1 year, and exploratory assessments of circulating immunologic profiles and molecular predictors of response. Descriptive statistics were planned as a signal-seeking study. **Results:** From Jul 2019-Apr 2021, 34 pts enrolled from 4 different centers. In cohort 1 (n=15), one pt was taken off study due to LFT elevation and orchitis attributed to pembro with reduced lymphadenopathy upon withdrawal. There was 1 PR (duration 686 days) and 4 SDs (61, 66, 124, 128 days) among 11 evaluable for response. There were no unexpected nor grade 5 toxicities. In cohort 2 (n=19), 2 pts achieved a PR (127 and 185 days), with SDs in 5 (59, 63, 69, 115, 437), among 13 evaluable for response. At oxali dose of 85 mg/m^2, 1/6 pts had DLT (grade 4 neutropenia ≥7 days); another 1/6 pts had DLT at 120 mg/m^2 (grade 3 AST/ALT). The RP2D was 120 mg/m^2. Common grade 3/4 AEs included: neutropenia (24%), anemia (9%), fatigue (9%), abdominal pain (6%), nausea (6%), and ALT/AST (6%). There was no febrile neutropenia nor any grade 5 events. Combined cohort rates of PR/CBR were 3/24 (12.5%) and 12/24 (50%), respectively. **Conclusions:** In this study of heavily pretreated pts with MSS mCRC, combining pembro plus pem or pem+oxali was well tolerated. Overall CBR was 50%, with objective responses (PRs) in 3/24 (12.5%) evaluable pts. This compares favorably with KEYNOTE 016, in which pembro in MSS mCRC pts had 0/18 objective responses and CBR=11% (2/18). Further studies testing these agents in earlier lines of treatment with robust correlative analyses is supported. Support: NSABP Foundation; Merck; Lilly. Clinical trial information: NCT03626922. Research Sponsor: Merck; Lilly, Other Foundation.

3570 **Poster Session**

Optimal cytoreductive LIVER surgery for unresectable colorectal liver metastases: A prospective observational study. *First Author: Rene Adam, AP-HP, Hôpital Paul Brousse, Univ Paris-Saclay, Villejuif, France*

Background: Patients with multiple colorectal liver metastases (CLM) involving all the hepatic segments are currently not eligible for potentially curative liver surgery. Transplantation is a promising alternative but graft shortage and stringent selection criteria limit its accessibility. Owing to the improving efficacy of chemotherapy, the impossibility to resect all the initial metastatic sites could lead to revisit the role of optimal cytoreductive liver surgery (CLS) aiming to treat by resection ± radiofrequency, all the macroscopic residual tumors after a good response to chemotherapy. Although validated for ovarian cancer and peritoneal carcinomatosis, this strategy remains unexplored in CLM. Our objective was to evaluate the outcome of this strategy in patients with definitively unresectable CLM. **Methods:** Within a prospective monocentric study, we enrolled for debulking surgery, between 2017 and 2021, all consecutive patients with multinodular unresectable CLM involving all segments on initial imaging and consequently ineligible for a curative surgery either after a one or two-stage hepatectomy. These patients should have a strong response to chemotherapy (> 50 % on RECIST criteria) for at least a 3-month period and no or limited extrahepatic disease, to be included. End-points of the analysis were overall and disease-free survival at 3 years. **Results:** Among 26 patients considered for this strategy, optimal CLS could be achieved in 21 patients after a median interval of 10 months from CLM diagnosis. The median number of lesions was 11 (7 - 26) on initial imaging. Four patients (19%) had synchronous lung metastases. Liver-first strategy was undertaken in 19 patients (90%). Postoperative complications (Grade ≥ III) occured in 5 patients (24%). One patient died within 90-day after operation from intra-abdominal hemorrage while on anticoagulation therapy. After a median follow-up of 25 months from hepatectomy, the 3-year OS rates was 85%. Median survival was not reached at the time of the analysis. Of the 4 (19%) patients with complete pathological response on the liver specimen, 3 developed recurrence. A total of 17 patients (81%) developed recurrence after a median time of 10,5 months from hepatectomy. Among them, repeat hepatectomy could be undertaken in four patients. The survival time to surgical failure (recurrence untreatable with curative intent) was 32% and 16% at 2 and 3 years. At last follow-up, seven patients (33%) are alive and recurrence-free. **Conclusions:** The promising results of this prospective series suggest that CLS may be worthy in patients with diffuse CLM non curatively treatable by surgery but responding well to chemotherapy. This strategy should however be reserved to hyperselected patients, super responders, eligible for an optimal resection of all the macroscopic residual tumors, and confimed by other expert centers, to be definitively validated. Research Sponsor: None.

3571 **Poster Session**

Identification of an optimal circulating tumor DNA (ctDNA) shedding threshold to detect actionable driver mutations in colorectal and pancreatic adenocarcinoma. *First Author: Bennett Adam Caughey, Division of Medical Oncology, Duke University School of Medicine, Durham, NC*

Background: In colorectal cancer (CRC), mutations in *KRAS*, *NRAS*, and *BRAF* predict resistance to anti-EGFR therapies. In pancreatic ductal adenocarcinoma (PDAC), ~90% of patients harbor *KRAS* mutations, while *KRAS* wild-type tumors often have clinically actionable fusion alterations. Thus, in both cancers, the accurate ascertainment of *RAS* and *BRAF* driver status is essential. Sequencing of cell-free DNA (cfDNA) from plasma allows convenient assessment of a tumor's molecular profile, but sensitivity can be limited by low ctDNA shedding. We sought to establish a ctDNA shedding threshold at which actionable driver mutations can be reliably detected. **Methods:** Molecular reports and matched clinical data were obtained from the Duke Molecular Registry of Tumors and the SCRUM-Japan GOZILA and GI-SCREEN. CRC or PDAC patients with a pathogenic *KRAS*, *NRAS*, or *BRAF* activating point mutation ("driver") present on tissue next-generation sequencing (NGS) assays and who also had cfDNA assay available were included. Tissue NGS included Foundation One CDx and Oncomine Comprehensive Assay. Guardant 360 (G360) was the sole plasma cfDNA assay. 131 CRC and 24 PDAC cases with 189 total G360 assays met criteria and were included. Samples were analyzed according to detection of the driver mutation and the maximum mutant allele frequency (MAF) of non-driver mutations on G360. An optimal cut-point for max MAF was explored among the CRC and PDAC patients using a maximally selected Wilcoxon rank statistic method. **Results:** 76.8% of driver mutations were in *KRAS*, 22.6% in *BRAF*, and 1.9% in *NRAS* with an overlap of 1 *BRAF* and 1 *NRAS* mutation with a *KRAS* mutation. Overall sensitivity of G360 for drivers was 83.0% for CRC and 54.2% for PDAC. No variants were detected on G360 in 9.1% of CRC and 37.5% of PDAC. Sensitivity for driver mutations increased with higher maximum non-driver MAF, with MAF > 1% predicting sensitivity > 98% (Table). Optimal cut-point analysis identified MAF of > 0.34% ($p < 0.0001$), above which the driver was identified in 97% of patients and below which only 27%. **Conclusions:** In our study, non-driver MAF > 1% on cfDNA NGS predicts high sensitivity for *RAS* and *BRAF* mutations and thus is adequate to guide clinical decisions such as anti-EGFR therapy in CRC, evaluation for fusions in PDAC, and validity in clinical trials. MAF ≤0.34% is a clear threshold to consider an assay inadequate and thus seek alternative testing. Sensitivity rises for MAF between 0.35 and 1% but will require greater patient numbers to establish clinically relevant sensitivity thresholds. These results will be updated with additional data for final presentation. Research Sponsor: Duke University, SCRUM-Japan Funds.

Non-driver max MAF range	Driver detection sensitivity (95% CI)	N
0% (no variants)	7.7% (0.95-25.1)	26
> 0 to ≤0.5%	64.5% (45.4-80.77)	31
> 0.5 to ≤1%	85.7% (57.2-98.2)	14
> 1 to ≤5%	100% (86.8-100)	26
> 5 to ≤10%	95.8% (78.9-99.9)	24
> 10%	98.5% (92.1-99.96)	68

3572 **Poster Session**

Response to epithelial growth factor receptor inhibitor (EGFRi) treatment in patients with early-onset, treatment-naïve metastatic colorectal cancer (mCRC): An ARCAD database analysis. *First Author: Zhaohui Jin, University of Iowa, Iowa City, IA*

Background: Early onset colorectal cancer (eoCRC: disease diagnosed < 50) has been increasing over the past 2 decades. Currently, standard treatment recommendations for eoCRC patients (pts) with metastatic disease does not differ from late-onset CRC (loCRC) pts although outcomes data in eoCRC pts is limited. **Methods:** Individual patient data on 5,761 treatment-naive metastatic eoCRC pts was pooled from 8 phase II and III randomized EGFRi studies (2000 - 2012) from the ARCAD mCRC database. The distribution of demographics, clinicopathological features, and biomarkers were summarized by age groups. Progression-free survival (PFS) was compared between age groups by stratified Cox models, adjusting for potential confounders. Predictive value of age group was evaluated by testing interaction effect between treatment and age variables based on a subset of trials with concurrent randomizations between regimens with and without EGFRi **Results:** eoCRC (n=756) were more evenly distributed between gender, had improved performance status (PS), increased likelihood of metastatic resection, and distant lymph node metastasis, but were less likely to have lung metastasis or KRAS mutation compared to loCRC (n=5,005, table 1). eoCRC and loCRC patients had similar distribution of primary tumor sidedness, primary resection, liver and/or peritoneal involvement, number of metastatic sites involved, and BRAF mutations (MT). No difference in PFS for eoCRC versus loCRC pts was noted (7.8 vs. 7.9 months [M], adjusted hazard ratio [HR_{adj}], 1.02, 95% confidence interval [CI], 0.93-1.11). Among pts with KRAS wild type (WT) and left sided primary tumors, univariable analysis of EGFRi demonstrated improved mPFS in loCRC (9.9 vs 8.5M, HR = 0.74, p<0.001), but this benefit was not seen in eoCRC (8.3 vs 8.9 months, HR 1.20, p=0.36). The same pattern was observed upon multivariable analysis (Table). **Conclusions:** In our pooled analysis,EGFRi + chemotherapy significantly improved PFS in treatment-naïve loCRC patients but not in left sided, KRAS WT, eoCRC patients. Further validation in an independent cohort is warranted. Research Sponsor: None.

Age group	eoCRC	loCRC	HR_{adj} (95% CI)	p-value
Female % (n)	48 (362)	35 (1755)		<0.0001
ECOG Performance score = 0 % (n)	60 (453)	51 (2548)		<0.0001
Prior Metastasectomy % (n)	10 (34)	7 (184)		0.016
Lung metastases % (n)	32 (141)	39 (1240)		0.004
Distant lymph node metastases % (n)	49 (144)	42 (1109)		0.044
KRAS MT % (n)	32 (240)	36 (1794)		0.028
BRAF MT % (n)	8.2 (49)	8.3 (343)		0.92
KRAS and BRAF WT % (n)	63 (374)	60 (2485)		0.55
EGFRi effects on PFS (Difference in months) (n)[1]	–0.6 (162)		1.20 (0.81-1.78)[2]	0.36[2]
		1.4 (1049)	0.74 (0.64-0.85)[2]	<0.0001[2]

[1]Median PFS in EGFRi arm minus that in non-EGFRi arm.

[2]Adjusted for PS, sex, and KRAS status.

3573 **Poster Session**

Pembrolizumab (pembro) plus binimetinib (bini) with or without chemotherapy (chemo) for metastatic colorectal cancer (mCRC): Results from KEYNOTE-651 cohorts A, C, and E. *First Author: Eric Xueyu Chen, Princess Margaret Hospital, Toronto, ON, Canada*

Background: Response to antiPD-1 monotherapy is poor in microsatellite stable (MSS)/mismatch-repair proficient (pMMR) mCRC; the combination of antiPD-1 pembro + anti-MEK bini, with or without chemo, may improve upon this limited response. KEYNOTE-651 (NCT03374254) is an open-label phase 1b multicenter trial of pembro + bini (cohort A) or pembro + bini + chemo (mFOLFOX7 in cohort C, FOLFIRI in cohort E) in MSS/pMMR mCRC. Preliminary results from the dose-finding phase at 2 dose levels (DL) of bini are presented. **Methods:** Patients (pts) had MSS/pMMR mCRC and must have been previously treated with fluoropyrimidine, irinotecan, and oxaliplatin in cohort A, or with fluoropyrimidine + oxaliplatin-based regimen in cohort E; pts were previously untreated in cohort C. Pts received pembro 200 mg Q3W + bini 30 mg BID (cohort A, DL1), pembro 200 mg Q3W+ bini 30 mg BID + mFOLFOX7 Q2W (cohort C, DL1) or pembro 200 mg Q3W + bini 30 mg BID + FOLFIRI Q2W (cohort E, DL1). Bini dose escalation to 45 mg BID (DL2) was planned in cohorts A, C, and E, with a target dose-limiting toxicity (DLT) of 30%. Primary end point was safety (DLT). Secondary end point was ORR. DCR, PFS, and OS were exploratory. ORR, DCR, and PFS were assessed by investigator per RECIST v1.1. **Results:** Median study follow-up at data cutoff (Oct 15, 2021) was 36 mo (range, 32-43) for cohort A, 17 mo (2-24) for cohort C, and 11 mo (2-25) for cohort E. In cohort A, 1/6 pts (17%) had DLT at DL1; no DLT occurred in 14 pts (0%) at DL2. In cohort A, gr 3/4 TRAEs occurred in 3/6 pts (50%) at DL1 and 8/14 pts (57%) at DL2. In cohort C, 3/9 evaluable pts (33%) had DLT at DL1; thus, bini dose was not escalated to DL2. In cohort C, gr 3/4 TRAEs occurred in 9/11 total pts (82%). In cohort E, 1/5 evaluable pts (20%) had DLT at DL1 and 5/10 evaluable pts (50%) had DLT at DL2. Enrollment was stopped in cohort E, DL2 and bini dose was de-escalated to DL1; 2/4 additional pts (50%) had DLT at DL1 (total 3/9 pts [33%] had DLT in cohort E, DL1). In cohort E, gr 3/4 TRAEs occurred in 5/9 pts (56%) at DL1 and 10/11 total pts (91%) at DL2. No gr 5 TRAEs occurred in any cohort. ORR was 0% in cohort A; limited efficacy was seen in cohorts C and E (Table). **Conclusions:** Bini could be safely combined with pembro in cohort A. However, with bini + pembro + chemo, the 45-mg dose of bini was not well tolerated and required dose reduction to 30 mg. Addition of bini to pembro + chemo did not improve efficacy; therefore, enrollment was prematurely closed in cohorts C and E. Efficacy by *KRAS* mutation status will be shown. Clinical trial information: NCT03374254. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Pts	n	ORR, % (95% CI)	DCR, %	PFS, median (95% CI), mo[a]	OS, median (95% CI), mo
Cohort A	20	0 (0-17)	40	2 (2-4)	7 (5-18)
Cohort A: bini DL1	6	0 (0-46)	50	3 (2-NR)	NR (3-NR)
Cohort A: bini DL2	14	0 (0-23)	36	2 (2-4)	7 (3-9)
Cohort C	11	9 (0-41)	100	12 (4-NR)	NR (12-NR)
Cohort E	20	15 (3-38)	70	6 (2-NR)	NR (9-NR)
Cohort E: bini DL1	9	22 (3-60)	78	6 (1-NR)	9 (9-NR)
Cohort E: bini DL2	11	9 (0-41)	64	5 (2-NR)	NR (5-NR)

[a]NR, not reached

3574 **Poster Session**

CPGJ602 plus mFOLFOX6 as first-line treatment for patients with KRAS/NRAS/BRAF wild-type metastatic colorectal cancer: A randomized phase II study. *First Author: Jianming Xu, Department of Gastrointestinal Oncology, The Fifth Medical Center, General Hospital of People's Liberation Army, Beijing, China*

Background: CPGJ602 is a recombinant anti-EGFR human-mouse chimeric monoclonal antibody. CPGJ602 plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) may have efficacy in KRAS/NRAS/BRAF wild-type metastatic colorectal cancer. **Methods:** In this open-label, randomized trial, patients who had received no previous treatment were randomly assigned (2:2:1) to receive CPGJ60 （325mg/m^2, q2w) plus mFOLFOX6 (biweekly group), CPGJ602 (400 mg/m ^{2} initial dose followed by 250 mg/m^2 /week thereafter) plus mFOLFOX6 (weekly group) or cetuximab (400 mg/m^2 initial dose followed by 250 mg/m^2 /week thereafter) plus mFOLFOX6 (cetuximab group). All subjects received treatment up to 16 weeks. The primary endpoint was the best overall response (BOR) at 16 weeks. The second endpoints were DCR, DOR, PFS, safety. **Results:** As of Dec 30, 2021, 76 patients were enrolled (30 in biweekly group, 32 in weekly group and 14 in control group). The best overall response achieved at 16 weeks was 76.7% (23/30, 95% CI 60.3% - 92.0%),78.1% (25/32, 95% CI 62.5% - 92.5%) and 78.6% (11/14, 95% CI 49.2% - 95.3%) in the biweekly group, weekly group and cetuximab group, respectively. The confirmed overall response rate at 16 weeks was 60%(18/30), 71.9%(23/32) and 57.1%(8/14) in the biweekly group, weekly group and cetuximab group, respectively. The PFS rates at 16 weeks were 81.5% (95% CI 57.7% -92.6%), 96.8% (95% CI 79.2%-99.5%), 81.3% (95% CI 41.5%- 95.2%) in the biweekly group, weekly group and cetuximab group, respectively. The most common adverse events were a decreased neutrophil count (60%， 78.1% and 71.4% in the biweekly group, weekly group and cetuximab group respectively), decreased white-cell count (53.3%, 78.1% and 71.4% respectively), decreased platelet count (40.0%, 40.6% and 42.9% respectively), and elevated serum aspartate aminotransferase (43.3%, 37.5% and 35.7% respectively). **Conclusions:** CPGJ602 plus mFOLFOX6 could be an option for KRAS/NRAS/BRAF wild-type metastatic colorectal cancer. Clinical trial information: NCT04466254. Research Sponsor: Sunshine Guojian Pharmaceutical (Shanghai) Co., Ltd.

3575 **Poster Session**

Post-treatment detection of circulating methylated *BCAT1* and *IKZF1* as prognostic indicators for recurrence in patients with colorectal cancer. *First Author: Graeme P. Young, Flinders University, Adelaide, SA, Australia*

Background: Patient risk for recurrence after completion of initial treatment of colorectal cancer (CRC) is difficult to predict. Post-treatment circulating tumor DNA (ctDNA) analysis is a promising approach for stratifying such patients but the value of using tumor-uninformed biomarkers, such as methylated *BCAT1* and *IKZF1*, is unknown. This study aimed to determine whether detection of circulating methylated *BCAT1* and *IKZF1* DNA following completed initial treatment with curative intent, identified patients at elevated risk of CRC recurrence. **Methods:** CRC stage I-III cases were eligible for study inclusion if a *BCAT1/IKZF1* methylation test result was available at least 2 weeks after, but within 12mo, of completing initial treatment, and had had at least 2y follow-up unless recurrence was evident sooner (n = 142). Surveillance included regular clinical assessments and radiographic imaging. Level of methylation was reported as the total methylated *BCAT1/IKZF1* expressed as percent of cell-free DNA; levels ≥0.07% were considered positive. Primary outcome measure was recurrence-free survival. Mantel-Cox (log-rank) method was used to assess the association between *BCAT1/IKZF1* results and recurrence-free survival. Multivariable survival analysis by Cox proportional hazards modelling assessed the impact of covariates, including: *BCAT1/IKZF1* result, age, gender, T-stage (T1-2 vs T3-4), N-stage (N0 vs N1-2), extra- and/or intra-mural vascular invasion (EMVI/IMVI) and nature of treatment. Time to recurrence was measured from the date of treatment completion to first evidence of recurrence and data were censored to last date of follow-up. **Results:** 33/142 (23.2%) cases had recurrence detected at a median 1.6y (IQR: 0.8-2.4). Follow-up time for those who remained recurrence free was 5.3y (IQR: 3.7-6.9). The time between completing treatment and *BCAT1/IKZF1* testing was not different between these groups (median 2.4 vs 3.1mo, p = 0.530). 13 (9.2%) cases were positive for methylated *BCAT1/IKZF1* after completing treatment and a positive result was associated with a significant risk of recurrence (hazard ratio [HR], 10.0 (95%CI 2.6-39.3), p < 0.001). In the multivariable survival analysis, only a positive *BCAT1/IKZF1* methylation result following treatment (HR 2.6, 95%CI: 1.0-6.0, p = 0.041) and evidence of EMVI or IMVI (HR 2.3, 95%CI: 1.0-5.1, p = 0.044) were significant predictors of survival. **Conclusions:** This study shows that post-treatment *BCAT1/IKZF1* methylation testing, which does not need personalization using tumor genotyping, is a promising independent prognostic indicator for CRC recurrence. Such cases are at high risk of recurrence compared to those who had no detectable ctDNA post treatment. These patients warrant enhanced and/or extended surveillance for recurrence. Clinical trial information: 12611000318987. Research Sponsor: Clinical Genomics Inc., Other Foundation.

3576 **Poster Session**

BRAF-mutant metastatic colorectal cancer: Prognostic and predictive value of primary tumor location—A pooled analysis of the AIO studies FIRE-1, CIOX, XELAVIRI, FIRE-3, and VOLFI. *First Author: Annabel Helga Sophie Alig, Charité- Universitaetsmedizin Berlin, corporate member of Freie Universitaet Berlin and Humboldt-Universitaet zu Berlin, Department of Hematology, Oncology, and Cancer Immunology (CCM), Berlin, Germany*

Background: Primary tumor location (PTL: left vs. right) is an established prognostic marker in metastatic colorectal cancer (mCRC) and has predictive impact for anti-EGFR antibody (mAb) efficacy in patients with *RAS* (*KRAS* and *NRAS*) wild-type (WT) mCRC. This analysis of five pooled studies evaluates PTL as a prognostic and - concerning anti-EGFR mAb efficacy - predictive marker in *BRAF* V600E-mutant/*RAS* WT and mCRC. **Methods:** The analysis is based on individual patient data of five pooled 1st-line studies with varying treatment strategies: the pooled population comprises of *BRAF* V600E-mutant/*RAS* WT (*BRAF*mt) mCRC with known PTL. For analysis, treatment was stratified into two groups: treated with or without anti-EGFR mAb. Dichotomous variables (overall response rate, ORR; characteristics) were compared by Chi-Square or Fisher's exact test and time-to event endpoints (progressive-free survival, PFS; overall survival, OS) by Kaplan-Meier method, log rank test and Cox regression. **Results:** Of 102 patients (pts) with *BRAF*mt mCRC, 55 pts (54%) presented with right-sided primary tumors (RPT), 47 (46%) presented with left-sided primary tumors (LPT). Pts with RPT were more likely to be female (p= 0.04). ORR was inferior in RPT compared to LPT (35% vs. 55%; p= 0.04). No difference was seen in PFS (HR 0.8 (95% CI 0.6-1.3; p= 0.32) or OS (HR 0.8; 95% CI 0.8-1.3; p= 0.46). In male pts PTL trended to be associated with longer OS (HR 0.6; 95% CI 0.3-1.0; p= 0.06). 25 pts with RPT (45%) and 21 with LPT (45%) received anti-EGFR mAb. In pts with LPT anti-EGFR mAb based treatment was associated with higher ORR (81% vs. 35%; p< 0.01). No effect was seen in RPT (ORR 35% vs. 36%; p= 0.82). Anti-EGFR mAb treatment resulted in inferior PFS in RPT (HR 2.0; 95% CI 1.1-3.5; p= 0.02) and showed a trend towards improved PFS in LPT (HR 0.6; 95% CI 0.3-1.1; p= 0.11). Pts with RPT had a worse OS when treated with anti-EGFR mAb (HR 1.8; 95% CI 1.0-3.1; p= 0.05), whereas pts with LPT appeared to have a favorable outcome when treated with an anti-EGFR mAb containing regimen (HR 0.4; 95% CI 0.2-0.7; p< 0.01). **Conclusions:** This exploratory analysis of five studies suggests that PTL has limited prognostic impact in *BRAF*mt mCRC but might carry predictive information regarding anti-EGFR mAb efficacy in a 1st-line treatment setting. Further prospective studies are needed to validate these results and to grasp the differences in the heterogeneous group of *BRAF*mt pts. Clinical trial information: FIRE-1 was before mandatory registration, NCT00254137, NCT00433927, NCT01249638, NCT01328171. Research Sponsor: None.

3577 **Poster Session**

Camrelizumab plus famitinib in patients with metastatic colorectal cancer: Results from an open-label, multicenter phase II basket study. *First Author: Tianshu Liu, Department of Medical Oncology, Zhongshan Hospital, Fudan University, Shanghai, China*

Background: Dual blockade of immune checkpoint and angiogenesis is an effective strategy for multiple cancers. We initiated an open-label, multicenter phase II basket study to evaluate the antitumor activity and safety of camrelizumab (an anti-PD-1 antibody) plus famitinib (a receptor tyrosine kinase inhibitor) in patients (pts) with advanced solid tumors. Herein, we report the results from the metastatic colorectal cancer (mCRC) cohort. **Methods:** Pts with histologically confirmed mCRC, who had received previous irinotecan, oxaliplatin, and fluoropyrimidine combination chemotherapy, and progressed after ≥ 2 lines of systemic treatment were enrolled to receive camrelizumab (200 mg i.v. every 3 weeks) and famitinib (20 mg orally once daily). Primary endpoint was objective response rate (ORR) per RECIST version 1.1. **Results:** Between Jul 10, 2020, and Jul 12, 2021, of all the 44 mCRC pts enrolled, 14 (31.8%) pts had colon cancer (CC) and 30 (68.2%) pts had rectal cancer (RC). As of Nov 30, 2021, the median time from enrollment to data cutoff was 10.6 months (range, 4.7-16.7). The ORR was 13.6% (95% CI, 5.2-27.4) and the DCR was 45.5% (95% CI, 30.4-61.2) in all mCRC pts. Of them, no pts with CC achieved response; six pts with RC achieved PR, with the ORR of 20.0% (95% CI, 7.7-38.6) and the DCR of 46.7% (95% CI, 28.3-65.7). Pts with RC showed a median duration of response (DoR) of 7.1 months (95% CI, 2.3-not reached [NR]). The median overall survival (OS) was 15.2 months (95% CI, 7.2-NR) in pts with RC. Of all 44 mCRC pts, 28 (63.6%) had grade 3 or higher treatment related adverse events (TRAEs), mainly hypertension (25.0%), proteinuria (18.2%), decreased platelet count (11.4%), decreased neutrophil count (11.4%) and palmar-plantar erythrodysaesthesia syndrome (11.4%). Three (6.8%) pts discontinued any study treatment due to TRAEs. No grade 5 TRAE was reported. **Conclusions:** Camrelizumab plus famitinib appeared to show encouraging antitumor activity in pts with mCRC, especially in those with RC, and the safety profile of this combination regimen seemed to be manageable and consistent with single agent alone. Clinical trial information: NCT04346381. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Summary of efficacy outcomes in mCRC cohort.

Variables	Colon cancer (n=14)	Rectal cancer (n=30)	All mCRC patients (n=44)
Best overall response, n (%)			
PR	0	6 (20.0)	6 (13.6)
SD	6 (42.9)	8 (26.7)	14 (31.8)
PD	6 (42.9)	12 (40.0)	18 (40.9)
NE	2 (14.3)	4 (13.3)	6 (13.6)
ORR, % (95% CI)	—	20.0 (7.7-38.6)	13.6 (5.2-27.4)
DCR, % (95% CI)	42.9 (17.7-71.1)	46.7 (28.3-65.7)	45.5 (30.4-61.2)
OS, months, median (95% CI)	8.9 (4.8-11.5)	15.2 (7.2-NR)	10.9 (8.0-NR)
DoR, months, median (95% CI)	—	7.1 (2.3-NR)	7.1 (2.3-NR)

3578 **Poster Session**

First-line (L1) therapy targeting EGFR in lung metastases (mets) of colorectal cancer (mCRC): An ARCAD pooled analysis. *First Author: Einat Shacham Shmueli, Cancer center, The Chaim Sheba Medical Center, Ramat Gan, Affiliated with the Sackler School of Medicine, Tel Aviv University, Ramat Gan, Israel*

Background: Monoclonal antibodies (mab) targeting EGFR are recommended in L1 treatment (trt) for mCRC in patients (pts) with RAS wild-type (WT) tumor and primary left CRC. ARCAD database contains individual data of randomized trials that evaluated anti-EGFR mab plus chemotherapy (CT). In this analysis we aimed to evaluate anti-EGFR benefit in mCRC with lung mets, either as single site or multiple sites. **Methods:** Individual pts data from four trials (PRIME, CRYSTAL, COIN, OPUS) comparing CT +/- anti-EGFR were pooled. KRAS status was not required at inclusion to these studies. The primary endpoint, overall survival (OS), was estimated using Kaplan-Meier method, prognostic value of lung mets was evaluated by stratified Cox models in pts groups defined by KRAS status. The predictive value was evaluated by interaction test (Int) between trt and lung mets status in pts group defined by KRAS status and considered as significant with a $P < 0.1$. **Results:** 3681 pts with known KRAS status were included, 2171 WT and 1510 mutant (MT). Pts characteristics were well balanced. Significant median OS benefit of anti-EGFR was observed in the whole KRAS WT population and in the left colon and rectum subgroup but not in the right colon subgroup. In pts with KRAS WT single site mets, a non-significant benefit of anti-EGFR was observed only among pts without lung mets (N = 642). In pts with lung single site mets (N = 129), a significant benefit (P= 0.018) in the KRAS MT population (N = 55) was observed, but Int was non-significant (P =0.157). In pts with KRAS WT and multiple without lung mets sites (N = 673), no benefit of anti-EGFR was observed and Int was significant (P= 0.054). Pts with KRAS MT multiple sites with (N = 656) or without (N = 397) lung mets, had no benefit of anti-EGFR. The same findings were found in the left primary pts and in the two fluoropyrimidine backbone. PFS analyses confirm the OS results. **Conclusions:** In this ARCAD analysis pts with lung mets as a single site appear to benefit from anti-EGFR L1 therapy in case of KRAS MT. This unexpected result based on a limited sample size cannot be explained on the knowledge of anti-EGFR therapy. Furthermore, pts with multiple mets sites have a benefit of anti-EGFR therapy only in the presence of lung mets even in KRAS WT left primary tumor. These findings need further confirmation and may initiate the search for a specific molecular phenotype associated with lung mets in CRC pts. Research Sponsor: A.R.CA.D Foundation.

	Pts with lung mets as single site			Pts without lung mets as multiple sites		
	N/ Event	Median (95% CI)	HR (95% CI) P	N/Event	Median (95% CI)	HR (95% CI) P
KRAS WT – no EGFR-Ab	35/29	20.9 (16.5,27.5)	Ref	345/ 270	17.4 (15.8,19.9)	Ref
KRAS WT – EGFR-Ab	39/37	24.0 (14.4,39.7)	0.75 (0.45,1.25) 0.265	328/ 253	18.3 (16.0,20.3)	1.04 (0.87,1.23) 0.693
KRAS MT – no EGFR-Ab	28/25	25.1 (14.9-34.3)	Ref	183/ 149	16.8 (14.5,18.7)	Ref
KRAS MT – EGFR-Ab	27/18	40.1 (27.4-NA)	0.42 (0.22,0.78) 0.006	214/ 184	12.6 (10.4,15.4)	1.36 (1.10,1.69) 0.005

3579 **Poster Session**

Phase 1b study of RGX-202-01, a first-in-class oral inhibitor of the SLC6A8/ CKB pathway, in combination with FOLFIRI and bevacizumab (BEV) in second-line advanced colorectal cancer (CRC). *First Author: Andrew Eugene Hendifar, Samuel Oschin Cancer Center, Cedars-Sinai Medical Center, Los Angeles, CA*

Background: A proprietary *in vivo* target discovery screen identified creatine kinase-B (CKB) as a cancer driver in KRAS mutant (KRAS-mut) CRC. CKB promotes tumor growth and survival under hypoxia. CKB generates the energetic metabolite phospho-creatine (PCr), which is imported into cells through the creatine transporter, SLC6A8. PCr generates intracellular ATP that enables tumoral survival. RGX-202-01 is a small molecule inhibitor of SLC6A8 that depletes intracellular PCr and ATP, resulting in apoptosis. In a completed Phase 1a study, RGX-202-01 monotherapy demonstrated objective anti-tumor activity in the relapsed/refractory KRAS-mut CRC setting without dose-limiting toxicity. The objectives of this ongoing Phase 1b study are to evaluate safety, PK/PD, and efficacy of RGX-202-01 in combination with standard-of-care (SOC) FOLFIRI + BEV in second-line CRC, a setting where SOC therapy results in an ORR and mPFS of approximately 15% and 6 months, respectively. **Methods:** Subjects with advanced CRC who had disease progression after receiving a first line oxaliplatin-containing regimen were eligible. The dose expansion phase of the study was restricted to CKB-expressing CRC tumors. As of 01-14-2022, 16 patients (pts) have been enrolled. 8 pts were enrolled in 2 dose escalation cohorts of RGX-202-01: 2400mg BID (4 pts) and 3000mg BID (4 pts) combined with FOLFIRI and BEV. 8 pts were enrolled in the dose expansion phase of the study and received RGX-202-01 3000mg BID combined with FOLFIRI and BEV **Results:** No DLTs were observed and the MTD was not reached in the dose escalation phase. Grade 3 TRAEs were observed in 25% of pts. Most common TRAEs were GI in nature. There were no Grade 4-5 TRAEs. PK analysis showed sustained RGX-202-01 drug exposures in both escalation cohorts above target levels (IC_{50}). Serum and urine creatine measurements indicated robust SLC6A8 target inhibition. 9 pts had KRAS-mut CRC, and all were evaluable for RECIST 1.1 response. 4 of these pts had cPR ,1 patient had uPR and 4 pts had SD as best response (ORR 56%, DCR 100%). 5 of these pts remain on therapy ranging from 11-54 weeks and a patient with a cPR at 16 weeks followed by surgery with curative intent remains with NED at 24 weeks after surgery. Seven pts had KRAS WT CRC, of which 3 were evaluable (2 pts are pending 1st scan assessment; 2 pts are off study and did not receive 1 full cycle of treatment). Of the 3 KRAS WT evaluable pts, all had SD as best response. 2 were on study for 38 and 24 weeks respectively and 1 is ongoing at 16 weeks. **Conclusions:** RGX-202-01 combined with FOLFIRI and BEV was well tolerated with no DLTs at the dose levels evaluated which induced potent inhibition of SLC6A8. Antitumor activity was noted in KRAS mutated colorectal cancer, consistent with preferential pre-clinical activity in RAS mutated tumors. Enrollment in the expansion phase continues. Clinical trial information: NCT03597581. Research Sponsor: Inspirna Inc.

3580 **Poster Session**

Predictive value of *MAOB* gene expression for targeted therapy in patients (pts) with metastatic colorectal cancer (mCRC) enrolled in CALGB (Alliance)/SWOG 80405. *First Author: Wu Zhang, Division of Medical Oncology, USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA*

Background: Monoamine oxidases (MAOs), including MAOA and MAOB, are mitochondrial enzymes responsible for catalyzing monoamine oxidation. Increased expression of MAOs were found in several cancer types and high MAOB was associated with worse disease stage and poorer survival in CRC. Positive and negative correlations of *MAOB* expression with mesenchymal type and epithelial type gene expressions, respectively, have been reported. Hence, we investigated whether *MAOB* expression is predictive for targeted therapies in mCRC. **Methods:** 430 mCRC pts treated with either bevacizumab (BEV, n = 224) or cetuximab (CET, n = 206) in combination with first-line chemotherapy within the CALGB/SWOG 80405 trial were included in the analysis. *MAOB* RNA was isolated from FFPE tumor samples and sequenced on the HiSeq 2500 (Illumina). Overall survival (OS) and progression-free survival (PFS) were compared between groups of pts categorized by tertiles of *MAOB* expression into high (H), medium (M) and low (L). Hazard ratios (HR) and 95% confidence intervals (CI) were computed from multivariable Cox proportional hazards model, adjusting for age, sex, location, number of metastases, *KRAS*, MSI status, and treatment with FOLFOX or FOLFIRI. Sensitivity analyses were conducted after stratifying by sex. Logrank *P*-values describe differences without adjustment for patient characteristics. **Results:** In CET-treated pts, *MAOB*-L showed significantly longer OS (median 39.2 vs 30.9 vs 15.9 months, logrank $P = 4.7E-05$, L vs H (as reference) adjusted HR 0.42, 95% CI [0.27, 0.65]) and PFS (median 13.2 vs 11.8 vs 7.6 months, logrank $P = 0.006$, L vs H adjusted HR 0.59 [0.40, 0.88]) compared to *MAOB*-M and *MAOB*-H, respectively. Similar results were observed when evaluating *MAOB* expression as a continuous variable. In BEV-treated pts, no significant differences were observed when comparing *MAOB* expression tertiles; however, pts with lower *MAOB* expression had significantly better OS, but not PFS, when evaluating *MAOB* as a continuous variable (Cox LRT $P = 0.015$, covariate adjusted). In CET-treated pts, the effect of *MAOB* expression was observed in male but not female pts (OS: median 40.3 vs 30.9 vs 16.1 months by *MAOB*-L, M, H, respectively, logrank $P = 6.8E-05$, L vs H adjusted HR 0.33 [0.19, 0.59]; PFS: median 13.8 vs 12.6 vs 7.9 months, logrank $P = 0.001$, L vs H adjusted HR 0.46 [0.28, 0.79]). A significant interaction was observed between *MAOB* expression and treatment for OS ($P = 0.010$) in males and females combined, but only in males ($P = 0.018$) when stratified by sex. **Conclusions:** Our results suggest that pts with *MAOB*-L tumors may have greater benefit from CET-based treatment and that targeting *MAOB* may be a promising strategy to improve patient outcomes. Further validation studies are warranted to develop a novel personalized approach based on *MAOB* expression in mCRC pts. Clinical trial information: NCT00265850. Research Sponsor: P30CA014089, U10CA180821, U10CA180882, U10CA180820 and UG1CA233277; U10CA180888; Pfizer, Genentech. https://acknowledgments.alliancefound.org.

3581 **Poster Session**

An immune-related gene expression profile to predict the efficacy of adding atezolizumab to first-line FOLFOXIRI plus bevacizumab in metastatic colorectal cancer: A translational analysis of the phase II randomized AtezoTRIBE study. *First Author: Alessandra Boccaccino, Department of Translational Research and New Technologies in Medicine and Surgery-Unit of Medical Oncology 2, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy*

Background: The phase II randomized AtezoTRIBE study demonstrated that the addition of atezolizumab (atezo) to first-line FOLFOXIRI plus bevacizumab (bev) prolongs PFS of mCRC patients, but benefit is limited among patients with proficient mismatch repair (pMMR) tumours. Among these patients, identifying a subgroup able to achieve benefit from immune-checkpoint inhibitors is a crucial challenge of translational research. To this end, we investigated the potential predictive role of an immunomodulatory gene expression signature (IO score), measuring the presence of infiltrating inflammatory cells and differentiated stromal microenvironment. **Methods:** AtezoTRIBE was a phase II comparative trial in which mCRC patients, unselected for MMR status, were randomized 1:2 to receive first-line FOLFOXIRI/bev (control arm) or FOLFOXIRI/bev/atezo (experimental arm). RNA was obtained from FFPE blocks of tumour specimens collected at baseline from 142 (65%) out of 218 enrolled patients. RT-qPCR was performed using DetermaIO™, to assess mRNA expression of a targeted panel of 27 genes. The established pan-cancer IO score and threshold were applied to dichotomize tumours as IO-positive (IO^+) or IO-negative (IO^-). **Results:** IO score was successfully determined in 122 (86%) cases, and 33 tumours were defined as IO^+ (27%). No differences in terms of baseline clinical and molecular features were observed between IO^+ and IO^- tumours. Patients with IO^+ and IO^- tumours showed similar PFS (median PFS: 14.4 vs 13.6; HR 0.84 [95%CI: 0.53-1.33], p = 0.468). An interaction between IO status and treatment effect was reported (p for interaction = 0.066), with higher PFS benefit in favour of the experimental arm among patients with IO^+ tumours (HR 0.39 [95% CI:0.15-1.02]) than among those with IO^- tumours (HR 0.83 [95% CI 0.50-1.35]). A similar trend was observed in the pMMR subgroup (n = 110) (IO^+ tumours: HR for PFS 0.47 [95% CI 0.18-1.25]; IO^- tumours: HR for PFS 0.93 [95% CI 0.56-1.55]) (p for interaction = 0.139). No differences in terms of ORR were reported between arms according to the IO status. **Conclusions:** The investigated immunomodulatory signature (IO score) may be helpful to predict benefit from the addition of atezolizumab to first-line FOLFOXIRI/bev in metastatic colorectal cancer, also in the cohort of pMMR tumours. Our results support the hypothesis that a deeper characterization of tumour immune microenvironment may help identifying mCRC patients more likely to benefit from ICI-based therapeutic strategies. These findings are worthy of further investigation in independent cohorts. Research Sponsor: None.

3582 **Poster Session**

A phase 1 dose-escalation study of GCC19 CART a novel coupled CAR therapy for subjects with metastatic colorectal cancer. *First Author: Jiuwei Cui, Cancer Center, First Hospital of Jilin University, Changchun, China*

Background: Chimeric antigen receptor (CAR) T-cell therapy has shown remarkable clinical efficacy in hematologic malignancies but limited success in solid tumors. GCC19CART, the first clinical candidate from the CoupledCAR solid tumor platform, is designed to overcome the limitations of conventional CAR T-cells in solid tumor malignancies by pairing solid tumor CAR T-cells with CD19 targeting CAR T-cells to amplify proliferation and activation of the solid tumor CAR T component. GCC19CART targets guanylate cyclase-C (GCC) which is expressed in the metastatic lesions of 70%-80% of subjects with colorectal cancers. A Phase 1 investigator-initiated clinical trial is underway in China for patients with relapsed or refractory metastatic colorectal cancer who have received at least 2 prior lines of therapy. Based on a data cutoff on December 13, 2021, 21 subjects have been enrolled in 2 dose escalation groups at 5 hospitals in China. **Methods:** Subjects are screened for GCC expression by immunohistochemistry. Eligible subjects undergo leukapheresis, a single dose of lymphodepleting chemotherapy (fludarabine 30mg/m2 and cyclophosphamide 300mg/m2) 3 days prior to infusion, and then administration of a single infusion of GCC19CART at one of two preassigned doses: $1x10^6$ or $2x10^6$ CAR T-cells/kg. Endpoints are safety and preliminary evidence of efficacy as determined by CT or PET/CT per RECIST 1.1 or PERCIST 1.0. All responses were confirmed by an independent third-party imaging contract research organization (CRO). **Results:** 13 subjects have been enrolled to dose level 1 ($1x10^6$ cells/kg) and 8 subjects have been enrolled to dose level 2 ($2x10^6$ cells/kg). The most common adverse events were cytokine release syndrome (CRS) in 21/21 subjects (Grade 1 19/21 (90.48%) or Grade 2 2/21 (9.52%)) and diarrhea in 21/21 subjects (Grade 1 6/21 (28.57%) Grade 2 5/21 (23.81%) Grade 3 9/21 (42.86%) or Grade 4 1/21 (4.76%)). Neurotoxicity was observed in 2/21 (9.52%) subjects at Grade 3 or 4 and resolved with corticosteroids. The combined overall response rate (ORR) for both dose levels was 28.6% (6/21). For dose level 1, the overall response rate (ORR) per RECIST 1.1 was 15.4% (2/13). Two subjects demonstrated a partial response (PR) while 3 additional subjects had partial metabolic response (PMR) on PET/CT with stable disease (SD) or progressive disease (PD) per RECIST 1.1. For dose level 2, The ORR per RECIST 1.1 was 50% (4/8). 4 subjects demonstrated a PR (3 at month 1, 1 at month 3 after being SD at month 1) and 2 additional subjects had PMR on PET/CT with SD per RECIST 1.1. **Conclusions:** GCC19CART demonstrated meaningful dose dependent clinical activity and an acceptable safety profile in relapsed or refractory metastatic colorectal cancer. This trial is ongoing and updated data will be presented. A United States based Phase 1 trial of GCC19CART is anticipated for mid-2022. Clinical trial information: ChiCTR2100053828. Research Sponsor: Innovative Cellular Therapeutics.

3583 **Poster Session**

FORECAST-1: Feasibility of organoid response assessment to define effective treatments for patients with colorectal cancer after failure of standard therapy. *First Author: Margaret Lee, Eastern Health, Western Health, Walter and Eliza Hall Institute of Medical Research, Melbourne, VIC, Australia*

Background: There are limited treatment options for patients with metastatic colorectal cancer (mCRC) who have progressed on standard therapies. A personalised approach to guide treatment selection would maximise efficacy whilst minimising unnecessary toxicity. Patient derived tumour organoids (PDTO) are self-organizing three-dimensional in vitro models cultured from a fresh tumour biopsy. Drug sensitivity testing on PDTO models have the potential to guide personalised treatment in this clinical setting. **Methods:** FORECAST-1 is a feasibility study, sponsored by the Australian Gastro-Intestinal Trials Group, of PDTO-based drug sensitivity testing for 30 patients with mCRC that have failed ≥two lines of therapy. Established PDTOs underwent drug sensitivity screening including regorafenib, TAS102, oxaliplatin, irinotecan, 5FU, gemcitabine, pemetrexed and temozolomide. Patients underwent treatment at clinician's discretion, with clinical response correlated with PDTO response. **Results:** Between September 2020 and December 2021, 30 patients were enrolled in the study with a median age of 59 years (range 36-71). All patients were ECOG 0-1 and eight patients had received prior TAS102 treatment. Fresh tumour biopsies were obtained from liver (N = 17), soft tissue/peritoneal metastases (N = 5), lung (N = 3), lymph node (N = 2), primary colon (N = 1), brain (N = 1) and bone (N = 1). 20/30 (67%) of patients had successful drug sensitivity screening performed at a median PDTO age of 62 days (range 42-128), nine PDTO cultures failed, and one is still undergoing culture. 15/17 (88%) of PDTO cultures obtained from a fresh liver biopsy were successfully cultured to drug sensitivity testing. 14/20 (70%) of PDTOs that underwent drug sensitivity testing identified therapies with intermediate to high likelihood of clinical response, including regorafenib (N = 7), TAS102 (N = 5), gemcitabine (N = 4), oxaliplatin (N = 3), irinotecan (N = 1), 5FU (N = 1) and temozolomide (N = 1). Subsequent anti-cancer treatment received by patients after study enrolment included TAS102 (N = 7), FOLFOX (N = 3), FOLFIRI+EGFR-inhibitor (N = 2), FOLFIRI (N = 2), regorafenib (N = 1), capecitabine (N = 1) and an immunotherapy based clinical trial (N = 2). As of February 2022, 11 patients remain on active anti-cancer therapy and 17 patients have died. **Conclusions:** Improving therapeutic selection in refractory mCRC patients remains an area of high clinical need. Two-thirds of patients achieved PDTO establishment to allow drug sensitivity testing in a timely manner. Of these further potentially efficacious treatments were able to be successfully identified. Methods to accelerate PDTO culture and drug testing are being pursued to increase the feasibility of a planned prospective study of PDTO sensitivity informing patient management. Clinical trial information: ACTRN12620001353987. Research Sponsor: Australiasian Gastro-Intestinal Trials Group (AGITG) Innovation Grant.

3584 **Poster Session**

Real-world experience on the efficacy and tolerability of biweekly trifluridine/tipiracil with or without bevacizumab in metastatic colorectal cancer. *First Author: Choon Seong Ang, Department of Haematology-Oncology, National Cancer Institute Singapore, Singapore, Singapore*

Background: Trifluridine/tipiracil (TAS-102) is currently approved as third-line treatment in metastatic colorectal cancer (mCRC). However, there is paucity of real-world data on the tolerability and efficacy with biweekly dosing as monotherapy or in combination with bevacizumab. In this study, we present our center's experience with biweekly TAS-102 with or without bevacizumab in mCRC patients (pts). **Methods:** We performed a single center retrospective observational study of pts receiving TAS-102 between 2018 and 2021. **Results:** A total of 83 pts were included (53 men, 30 women), with a median age of 64 years. Majority of pts were treated with TAS-102 in the 3rd-line (48.2%) and 4th-line (28.9%) setting. Almost all (94.0%) were of ECOG ≤ 1 at the initiation of treatment. The mean number of cycles administered was 3.8 and bevacizumab (5mg/kg on Day 1, every 2 weeks) was used in combination with TAS-102 in 18 pts (21.7%). Majority of pts (84.3%) were given TAS-102 using the biweekly regimen (35mg/m2 BD, on Day 1-5 and 15-19, q28 days) rather than standard regimen (35mg/m2 BD, on Day 1-5 and 8-12, q28 days) following a change in institutional practice. Fifteen pts (18.1%) had their initial dose reduced to 30mg/m2 BD at prescriber's discretion. Median PFS and OS were 2.37 and 10.15 months, respectively. In terms of tolerability, fatigue (any grade, 42.2%) and neutropenia (any grade, 44.6%) were the two most common adverse events reported. Grade 3 or higher neutropenia and febrile neutropenia were 16.9% and 3.6%, respectively. Dose reduction during treatment was required in 15 pts (18.1%), dose delay in 31 pts (37.3%) and six pts (7.2%) discontinued treatment due to toxicity. More than half (54.2%) had at least an additional line of therapy (regorafenib, clinical trials or re-challenge previous chemotherapy agents) following disease progression with TAS-102. **Conclusions:** We report the largest real-world experience with biweekly TAS-102. Our pts treated with TAS-102 had comparable median PFS to the RECOURSE cohort but with significantly better OS as more than half continued to receive treatment. Biweekly dosing of TAS-102 with or without bevacizumab is well tolerated with significantly lower rates of Grade 3 neutropenia compared to the published data in the literature. Research Sponsor: None.

3585 **Poster Session**

Clinical outcomes following termination of immunotherapy due to long-term benefit in MSI-H colorectal cancer. *First Author: Kristen Simmons, Baylor College of Medicine, Houston, TX*

Background: Immune checkpoint blockade therapy improves survival in patients (pts) with microsatellite instability-high (MSI-H) advanced colorectal cancer (CRC). Oncologists often discontinue immunotherapy after 2 years of disease control based on prior trial data. Recurrence outcomes following discontinuation of immunotherapy and clinicopathologic features associated with recurrence remain underreported given the recent advent of these agents for pts with MSI-H advanced CRC. **Methods:** Records from pts with MSI-H CRC from MD Anderson Cancer Center who received immunotherapy between 2015-2022 and stopped after clinical benefit were reviewed. Median survival was estimated according to the Kaplan-Meier method. Associations between the event of recurrence and coexisting mutations (*KRAS, NRAS, BRAF^{V600E}, PIK3CA, APC, TP53, POLE/POLD*), metastatic site (lung, liver, lymph nodes, or peritoneum), primary tumor sidedness (right vs. left colon), and prior immunotherapy (anti-PD-(L)1 alone or with anti-CTLA-4 antibodies) were measured by Fisher's exact tests. **Results:** Thirty-six pts with MSI-H CRC without progression on immunotherapy were reviewed. Of these 29 and 7 received anti-PDL1 antibody alone or in combination with anti-CTLA-4 antibody, respectively. Median exposure to prior immunotherapy was 24 months (range, 5-43). After a median follow-up of 19 months (95% CI, 14-26) after stopping immunotherapy, 30 of 36 pts (83%) remained without disease progression. For the 6 patients with progression after stopping, median time to relapse was 13 months (range, 5-31). Median disease-free survival (DFS) was not reached. The estimated 1-year, 2-year, and 3-year DFS probabilities were 90% (95% CI, 79-100), 79.1% (95% CI, 64-98), and 68% (95% CI, 47-98), respectively. Median overall survival from the time that immunotherapy was stopped was 54 months (95% CI, 47-NA). Only 1 pt died due to unrelated illness. There were no observed associations between disease recurrence and co-existing mutations, metastatic organ involvement, primary tumor sidedness, or immunotherapy used. **Conclusions:** Most pts with MSI-H advanced CRC who achieve initial clinical benefit and do not progress on immunotherapy do not recur after treatment is stopped. Our data suggest that favorable outcomes do occur following cessation of immunotherapy in this setting even with concomitant prognostically unfavorable clinical features (RAS, BRAFV600E mutations; liver, peritoneal metastases). Research Sponsor: None.

3586 **Poster Session**

Predictive value of *CDC37* gene expression for targeted therapy in metastatic colorectal cancer (mCRC). *First Author: Hiroyuki Arai, Division of Medical Oncology, USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA*

Background: HSP90 mediated chaperoning is a well-conserved biological mechanism for stabilization and activation of kinases. More than 60% of human kinases including VEGFR, CRAF, CSF1R, and FGFR are target of HSP90 (client kinases), whereas EGFR is non-client. CDC37 is a specific co-chaperone determining selectivity of client kinases recognized by HSP90. We hypothesized that gene expression levels of *CDC37* have predictive values for anti-angiogenic therapies in mCRC. **Methods:** The subjects of this study were mCRC patients treated with regorafenib (REGO, Japanese retrospective cohort) and those treated with bevacizumab (BEV) or cetuximab (CET) in combination with first-line chemotherapy (CALGB/SWOG 80405 trial cohort). *CDC37* expression levels were measured using RNA isolated from FFPE samples by nCounter gene expression profiling (Nanostring) and HiSeq 2500 (Illumina) in the Japanese and CALGB/SWOG 80405 cohorts, respectively. Overall survival (OS) and progression-free survival (PFS) were compared between patients with high *CDC37* expression (*CDC37*-H) and those with low expression (*CDC37*-L), grouped by median cutoff value in each cohort. **Results:** In total, 484 patients were included (50 treated with REGO, 227 treated with BEV, and 207 treated with CET). In REGO-treated patients, *CDC37*-H showed significantly better OS (median 11.3 vs 6.0 months, adjusted hazard ratio [HR] 0.24, 95% confidence interval [CI] 0.11-0.54, p <0.01) and PFS (median 3.5 vs 1.9 months, adjusted HR 0.51, 95% CI 0.28-0.94, p = 0.03) compared to *CDC37*-L. Similarly, in BEV-treated patients, *CDC37*-H showed significantly better PFS (median 13.5 vs 9.6 months, adjusted HR 0.59, 95% CI 0.43-0.79, p <0.01) and numerically better OS (median 34.1 vs 29.4 months, adjusted HR 0.81, 95% CI 0.60-1.11, p = 0.20) compared to *CDC37*-L. However, in CET-treated patients, *CDC37*-H and *CDC37*-L patients showed similar OS (median 33.7 vs 26.1 months, adjusted HR 1.00, 95% CI 0.73-1.38, p = 0.98) and PFS (median 11.3 vs 11.0 months, adjusted HR 1.08, 95% CI 0.81-1.45, p = 0.60). Significant interaction was observed between *CDC37* expression and treatment in terms of PFS in the CALGB/SWOG 80405 cohort (p = 0.01). **Conclusions:** Our results suggest patients with CDC37-dependent (*CDC37*-H) tumors may derive more benefit from REGO and BEV both of which target HSP90 client kinases or signaling pathways, but not from CET which target HSP90 non-client kinase. Further validation studies are warranted to develop a novel personalized approach for targeted therapies based on *CDC37* expression in mCRC patients. Support: U10CA180821, U10CA180888; Pfizer, Genentech; https://acknowledgments.alliancefound.org. ClinicalTrials.gov Identifier: NCT00265850. Research Sponsor: U.S. National Institutes of Health.

3587 **Poster Session**

Predictive and prognostic value of carcinoembryonic antigen (CEA) on maintenance therapy with 5-fluoruracil/leucovorin plus panitumumab or 5-fluoruracil/leucovorin alone in RAS wildtype metastatic colorectal cancer: Evaluation of the phase II PanaMa trial (AIO KRK 0212). *First Author: Annika Kurreck, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Hematology, Oncology, and Cancer Immunology (CVK), Berlin, Germany*

Background: Carcinoembryonic antigen (CEA) may reflect response to antitumor treatment in metastatic colorectal cancer (mCRC). The predictive value of CEA has not yet been proven for subsequent maintenance therapy. This analysis aims to evaluate the predictive and prognostic value of pre- and post-induction treatment CEA on maintenance with 5-fluoruracil/leucovorin (FU/FA) plus panitumumab (pmab) [arm A] or FU/FA alone [arm B] in RAS wildtype mCRC patients treated within the PanaMa trial. **Methods:** Patients with CEA measurements (pre- and post-induction therapy) were grouped as normal (both measurements ≤5 ug/l), stable (between +25% and -25%), decreasing (<-25%), and increasing (>+25%) CEA. Survival parameters (overall survival (OS), progression-free survival (PFS) from initiation of maintenance therapy) were expressed by the Kaplan-Meier method and compared by log-rank testing, and Cox regression. The objective response (OR) to maintenance therapy was analyzed by chi-square testing. **Results:** Out of 248 patients in the in the full analysis set, 245 patients were eligible for CEA analysis. Normal CEA occurred in 58 (23.7%), stable CEA in 16 (6.5%), decreasing CEA in 161 (65.7%), and increasing CEA in 10 (4.1%) patients. In the subgroup of decreasing CEA, there was a significant difference in the prediction of OR between both treatment arms with a better positive predictive value for the pmab-containing maintenance (44.0% vs. 27.5%, p=0.032). Increasing compared to decreasing CEA was associated with unfavourable survival outcome of maintenance irrespective of treatment arm (Table). **Conclusions:** CEA kinetics during induction therapy appears to have a predictive value for subsequent maintenance, notably pmab-based. Besides that, CEA levels had a significant impact on survival parameters of maintenance irrespective of the addition of pmab to FU/FA. This analysis is limited by the small number of patients in the subgroup of increasing CEA. Clinical trial information: NCT01991873. Research Sponsor: AIO Studien gGmbH, Pharmaceutical/Biotech Company.

Maintenance efficacy parameters according to CEA kinetics and treatment arm in the PanaMa trial.

	FU/FA+ pmab		FU/FA	
	Increasing CEA, N=6	Decreasing CEA, N=78	Increasing CEA, N=4	Decreasing CEA, N=83
Median PFS (months)	3.8*1	8.1*2	0.6*3	5.9*4
HR (95% CI), p (log-rank)	2.57 (1.02-6.49), p=0.045		64.27 (8.87-465.90), p<0.001	
Median OS (months)	3.6*1	24.8*2	4.1*3	23.5*4
HR (95% CI), p (log-rank)	5.62 (2.09-15.06), p<0.001		17.43 (4.38-69.37), p<0.001	
ORR (%)	1 (20.0%)*1	33 (44.0%)*2	0 (0.0%)*3	22 (27.5%)*4
p (chi-square)	p=0.293		p=0.386	

Legend: FU/FA, fluorouracil/folinic acid; pmab, panitumumab; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; ORR, objective response rate. *1 1 missing, *2 3 missing, *3 2 missing, *4 3 missing.

3588 **Poster Session**

HER3 expression in metastatic colorectal cancer: Defining the clinicomolecular profile of an emerging target. *First Author: Alisha Heather Bent, MD Anderson Hematology/Oncology Fellowship, Houston, TX*

Background: The success of tailored systemic therapies in treating distinct molecular subsets of patients (e.g., deficient mismatch repair, BRAF mutant, HER2 amplified) has spurred further exploration of novel targetable subsets within the heterogeneous landscape of metastatic colorectal cancer (mCRC). Human epidermal growth factor receptor 3 [HER3 (ErbB3)], a member of the HER (ErbB) receptor tyrosine kinase family, plays an important role in tumorigenesis and metastases and has emerged as a promising therapeutic target in a diverse array of cancers. For example, patritumab deruxtecan (U3-1402; HER3-DXd) is a HER3-directed antibody drug conjugate that has demonstrated clinically meaningful antitumor activity and acceptable safety profiles in metastatic breast cancer and EGFR-mutated non-small cell lung cancer. There is limited data, however, on the clinicopathological characterization of HER3 expression in mCRC. **Methods:** Tissue samples (surgical-metastatectomy) (N = 115) were obtained from a clinical cohort of patients (N = 99) with histologically proven mCRC and liver metastases who underwent liver resection with/without perioperative systemic chemotherapy. HER3 expression was analyzed on whole-mount preparations by immunohistochemistry (IHC). Staining was performed and visualized using the HER3 (D22C5) XP Rabbit-mAb (Cell Signaling Technology). Patients were categorized based on membranous intensity score as follows: Low with IHC 0 (absence of staining or staining in < 10% of tumor cells), 1+ (faint/barely perceptible staining in ≥10% of tumor cells) or 2+ (weak to moderate staining in ≥10% of tumor cells), or High with IHC 3+ (strong staining in ≥10% of tumor cells). Clinicomolecular and treatment data, including gender, tumor sidedness, mutational status (RAS or BRAF), and prior chemotherapy were collected by review of patient electronic medical records. Chi-squared (or Fisher's exact) test were used to determine associations between groups. Overall survival (OS) was calculated using Kaplan-Meier method and compared using log-rank tests. **Results:** Among 99 analyzed patients, 98 were evaluable for HER3 expression. Of these 25.5%, 26.5%, 40.8% and 7.2% showed HER3 IHC scores of 3+, 2+, 1+ and 0, respectively. No significant association was seen with HER3 expression and clinicopathological variables, mutational status, or prior treatment. Among patients with 2 samples analyzed from the same liver surgery, there was a moderate level of heterogeneity with concordance of 78.5% (kappa 0.43). Patients with high HER3 expression had poorer OS (5-year OS: 52%; median: 90.2 months) compared to low HER3 expression (5-year OS: 85%; median: not reached). **Conclusions**: In this large cohort of mCRC, HER3 expression was observed in 92.8% of patients and across diverse clinical and molecular features, supporting HER3 as a promising targetable biomarker in a large subset of mCRC. Research Sponsor: None.

3589 **Poster Session**

The prognostic significance of *TP53* mutations in patients with right-sided and left-sided colorectal cancer. *First Author: Moh'd M. Khushman, Department of Hematology-Oncology, University of Alabama at Birmingham/O'Neal Comprehensive Cancer Center, Birmingham, AL*

Background: In patients with colorectal cancers (CRCs), prior studies have reported that various *TP53* mutations have prognostic significance. The anatomic location of the primary CRC and the *TP53* mutation subtype influence patient survival. In this study, we explored the prognostic significance of *TP53* mutations *(mTP53)* classified as gain-of-function (GOF) or non-GOF in patients with right-sided (RCC) and left-sided CRCs (LCC). **Methods:** CRC specimens (6,248 RCCs and 14,215 LCCs) were tested at Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing (NGS) of DNA (592-gene panel or whole- exome sequencing). *R175H*, *R248W*, *R248Q*, *R249S*, *R273H*, *R273L*, and *R282W* were defined as GOF *mTP53* and all other *mTP53* were defined as non-GOF *mTP53*. MSI-H/dMMR status was determined by immunohistochemistry (IHC) of MMR proteins and/or NGS. Real-world median overall survival (mOS) was obtained from insurance claims data and calculated from tissue collection to last contact using Kaplan-Meier estimates. **Results:** GOF *mTP53* and non-GOF *mTP53* were identified in 15% and 39% respectively, in RCC and 17% and 46% respectively, in LCC. In RCC, the mOS for patients with wild-type *TP53* (*wtTP53*) vs. GOF *mTP53* was 34 months (m) vs. 23m ($p < 0.00001$), and the mOS for patients with *wtTP53* vs. non-GOF *mTP53* was 34m vs. 27m ($p < 0.001$). In LCC, the mOS for patients with *wtTP53* vs. GOF *mTP53* was 35m vs. 33m ($p = 0.056$), and the mOS for patients with *wtTP53* vs. non-GOF *mTP53* was 35m vs. 35m ($p = 0.32$). The mOS for patients with non-GOF *mTP53* vs. GOF *mTP53* in RCC and LCC was 28m vs. 24m ($p = 0.096$), and 35m vs. 34m ($p = 0.175$), respectively. The prognostic value of GOF *mTP53* and non-GOF *mTP53* was further explored in relation to MSI-H/dMMR, *RAS*, *BRAF*, and *PIK3CA* mutation status. The worse prognosis associated with *mTP53* in RCC was seen in all comparisons, except in GOF *mTP53*/MSI-H/dMMR, and non-GOF *mTP53*/*wtKRAS* subgroups. In patients with LCC, worse prognosis associated with GOF *mTP53* and non-GOF *mTP53* was only noticeable in *KRAS* and *PIK3CA* mutant subgroups. **Conclusions:** This is the largest study to explore *TP53* mutations and their prognostic significance in patients with RCC and LCC. The prevalence of GOF *mTP53* and non-GOF *mTP53* was higher in LCC compared to RCC. However, both GOF *mTP53* and non-GOF *mTP53* were associated with worse mOS for patients with RCC, but not LCC. Our study validates the sidedness-dependent prognostic significance of *TP53* mutations. It also shows that the worse prognosis of *mTP53* is independent of the approach of collectively classifying *TP53* mutations into GOF vs non-GOF. Given the sheer extent and diversity of *TP53* mutations, a more nuanced approach towards re-classification of GOF *mTP53* is warranted. Detailed information on p53 mutations will be crucial for the interpretation of future clinical trials and for the design of novel therapeutic strategies. Research Sponsor: None.

3590 **Poster Session**

Co-occurring alterations across molecular pathways in metastatic colorectal cancer (mCRC). *First Author: Alex John Liu, Mayo Clinic Arizona, Phoenix, AZ*

Background: Co-occurring alterations (COAs) in the *HER2* and MAPK pathway are rare in mCRC. *RAS, HER2* and *BRAF* alterations have been associated with resistance to EGFR inhibitor therapy (EGFR-mab). Typical co-occurring mutually exclusive gene mutations such as in *KRAS* and *BRAF* have been reported. This study aims to evaluate the prevalence of co-occurring alterations in the MAPK pathway or across MAPK/*HER2* and correlate to outcomes in patients with mCRC treated with EGFR-mab. **Methods:** This is a retrospective study of patients with mCRC within the Mayo Clinic database who have available blood-based NGS Guardant 360 data (September 2017-November 2021) and contained co-alterations in the MAPK pathway or across MAPK/*HER2*. MSI-high cases were excluded. Typical-RAS was defined as alterations in codons 12, 13, 59, 61, 117, and 146 of *KRAS*, *HRAS*, and *NRAS*. Atypical-RAS alterations were considered mutations at other codons of these genes. Patient characteristics, specific mutations, and outcome data were assessed. **Results:** 692 patients (pts) with mCRC were identified and 66 (9.5%) of those had COAs detected. 59/66 pts had clinical data available. Median age was 52 years, 55.9% were male, and 61.0% had left-sided tumors. The frequency of detected alterations was: *BRAF*-V600E (7.3%), *BRAF*-non-V600E (7%), *BRAF*-amplification (3.04%), *RAS*-typical (39.5%), *RAS*-atypical (2.1%), *HER2* amp (0.5%), *HER2*-mutation (1.2%) and PIK3CA (13%). COAs are described in the table. Twenty-three pts received EGFR-mab; COAs developed in 19 of them after progression on EGFR-mab. Four pts received EGFR-mab with documented COAs at baseline with none of them responding to treatment. **Conclusions:** COAs in MAPK and MAPK/*HER2* pathway are not uncommon in pts with mCRC emphasizing on the importance and feasibility of blood based NGS vs. selected gene testing. In pts with prior EGFR-mab treatment, COAs were detected after progression on treatment in the majority of pts, suggesting a mechanism of secondary treatment resistance. Further data including prospective validation is warranted. Research Sponsor: None.

Total pts 692	BRAF-V600E	BRAF-non-V600E	BRAF amp
RAS Typical	12 (1.7%)	26 (3.7%)	24 (3.5%)
RAS atypical	0	1 (0.1%)	1 (0.1%)
HER2 amp	0	2 (0.3%)	4 (0.6%)
HER2 mutation	1 (0.1%)	4 (0.6%)	2 (0.3%)

3591 **Poster Session**

Preliminary results of raltitrexed in Chinese patients with metastatic colorectal cancer: A prospective, multicenter, real-world study. *First Author: Jin Li, Department of Oncology, Shanghai East Hospital, Shanghai, China*

Background: Raltitrexed-based chemotherapy regimen is one of the common regimens for the treatment of metastatic colorectal cancer (mCRC). This prospective observational real-world study aimed to evaluate the safety and effectiveness of raltitrexed administered to Chinese patients with mCRC in real life setting. **Methods:** This is a prospective, multicenter, real-world study . Prospectively registered Patients received second-line treatment of raltitrexed plus irinotecan combined with or without target therapy until progression disease or unacceptable toxicity. The primary endpoint was progression-free survival (PFS), and the secondary endpoints were objective response rate (ORR), disease control rate (DCR), overall survival (OS), quality of life (QOL) and safety. Totally,1000 patients were required for primary point testing. **Results:** Between May 2018 and December 2021,a total of 1039 patients from 57 centers were screened for enrollment,among which 271 patients were treated with raltitrexed plus irinotecan, 753 patients accepted target therapy (bevacizumab or cetuximab) additionally, and 15 patients combined with other drugs. Overall mPFS was 6.8 months (95%CI: 6.5-7.1) ,ORR was 20.2%, and DCR was 85.7%; The ORR of combined with or without target therapy were 21.6% and 16.2% ($p = 0.038$) ,respectively, the DCR were 88.2% and 79.0% ($p < 0.001$). The mPFS of combined without or with target therapy were 5.2 months (95% CI: 4.7 to 5.7) and 7.3 months respectively (95% CI: 7.0-7.7) [HR = 0.67, 95% CI 0.56~0.80, $p < 0.001$], The mPFS of combined with bevacizumab or cetuximab were 7.4 months (95% CI: 7.0 -7.8) and 6.8 months (95% CI: 5.9-7.7) [HR = 1.15, 95% CI 0.88~1.51, $p = 0.3$]. mOS has not yet reached. Majority of treatment-related adverse events (TEAEs) were grade I or II. The most common grade III or IV TRAEs reported by 116 patients (11.2%) were aspartate aminotransferase increased (4.0%), alanine aminotransferase increased (3.7%), neutrocytopenia (2.7%), glutamyltransferase increased (2.5%), leukocytopenia (1.1%). **Conclusions:** The real-world study confirmd that raltitrexed was an effective and safe regimen for the second-line treatment in Chinese patients with mCRC, especially combined with target therapy additionally, which was aligned with previous trials. Clinical trial information: ChiCTR1800016185. Research Sponsor: None.

3592 **Poster Session**

***RAS* co-mutation and early onset disease represent an aggressive phenotype of atypical (non-V600) *BRAF* mutant metastatic colorectal cancer.** *First Author: Benny Johnson, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: While *BRAF*^{V600E} accounts for the majority of *BRAF* mutations in mCRC, non-V600 *BRAF* variants *(aBRAF)* have emerged in recent years as a distinct molecular subtype. There are no consensus recommendations regarding management. This study provides a comprehensive profile of a*BRAF*, their clonalities and co-mutations in mCRC using a large genomic database as well as a prospective treatment cohort of patients with a*BRAF* and mCRC managed at a single center. **Methods:** A systematic analysis was performed of patients with mCRC who underwent ctDNA testing (Guardant360 platform, Guardant Health) from September 2014 to May 2021. A variant was defined as clonal if the mutant allele frequency (MAF) was greater than 50% of the highest somatic MAF in the sample; otherwise it was defined as subclonal. Co-mutation analysis was conducted with *BRAF*, *KRAS*, *NRAS*, *NF1*, *ERBB2*, *PIK3CA* and *SMAD4*. Treatment history and overall survival (OS) for patients with a*BRAF* mCRC from MD Anderson Cancer Center were included. **Results:** 1,733 out of 14,742 mCRC patients had at least one *BRAF* variant, including 6.5% of patients with *BRAF*^{V600E} variants and 6.2% with a*BRAF* variants (1.1% with class II, 1.9% with class III, and 3.2% with unclassified variants). 431 unique BRAF variants were identified in a total of 1,905 BRAF variants. *BRAF* class II and III variants showed a higher rate of co-occurring *KRAS* mutations (25.6% and 21.5%) and co-occurring *NRAS* mutations (5.8% and 2.7%) compared with *BRAF*^{V600E} variants (2.4% for *KRAS* and 0.1% for *NRAS*); however, co-occurring *KRAS* G12C was only noted in one patient. In our MDACC cohort, 38 patients were included in the analysis. The median age was 55, 81% were Caucasian, and 74 % had left sided primary tumors (45% rectal, 24% sigmoid) with 37% being exposed to at least 2 lines of therapy. The most common mutations in clinical practice were class III, D594G (39%), followed by class II G469A (10%), & class III G466E (7%). The median follow-up time was 23.8 months (mo). While there were no survival differences between a*BRAF* classes II and III, there was a significant difference in OS in patients with *RAS* co-mutation (28.3 mo vs not reached [NR], p = 0.05) or liver involvement (28.8 mo vs NR, p = 0.02). Patients < 50 years of age had extremely poor survival with OS of 16.3 mo (vs. NR) and HR 7.51 (95% CI 1.82-31.0, p = 0.005). Treatment with anti-EGFR or use of metastasectomy was not associated with improved survival. **Conclusions:** a*BRAF* mutations have historically been considered a favorable prognostic marker in mCRC. Co-mutation with *RAS* is frequent for both classes and portends poor survival in our real-world cohort. Furthermore, early onset a*BRAF* mCRC is associated with more aggressive disease. These factors highlight the need for dedicated clinical trials for this unique subset of mCRC and may represent an opportunity to improve management in early onset colorectal cancer. Research Sponsor: U.S. National Institutes of Health.

3593 **Poster Session**

Codon-specific KRAS mutations predict overall survival benefit of trifluridine/tipiracil in metastatic colorectal cancer. *First Author: Joris van de Haar, Netherlands Cancer Institute (Netherlands), Amsterdam, Netherlands*

Background: Genomics-based precision medicine has greatly improved how patients with cancer are being treated with targeted agents, but clinical-grade genomic biomarkers for chemotherapies are currently lacking. The chemotherapeutic trifluridine/tipiracil (FTD/TPI) is approved for the treatment of late-stage metastatic colorectal cancer (mCRC). We aimed to find genomic biomarkers to improve patient selection for FTD/TPI treatment in mCRC. **Methods:** In a discovery cohort of FTD/TPI-treated mCRC patients (n = 37), genome-wide somatic variants were tested for association with treatment duration and overall survival (OS). *In vitro* drug testing on isogenic cell lines and patient-derived mCRC organoids, as well as a re-analysis of the double-blind, placebo-controlled, phase 3 RECOURSE trial (n = 800) were performed to support our findings. **Results:** In the discovery cohort, KRAS codon G12 (KRAS^{G12}) mutation status was the only significant genomic determinant of poor outcome of FTD/TPI treatment, which could be replicated *in vitro* by drug testing on isogenic cell lines and PDOs. In these models, KRAS^{G12} mutations were associated with increased resistance to FTD-induced (geno)toxicity *in vitro*. KRAS^{G12}-based resistance was absent for the closely related chemotherapeutic 5-FU. In the RECOURSE study, KRAS^{G12} mutations were predictive biomarkers for reduced OS benefit of FTD/TPI vs placebo (unadjusted interaction P= 0.0017, adjusted interaction P= 0.017). For patients with KRAS^{G12} mutations, OS was not significantly prolonged with FTD/TPI vs placebo (n = 279; HR, 0.97; 95% CI, 0.73–1.20; P= 0.85). An exploratory analysis showed that the KRAS^{G13} mutant subgroup demonstrated clearly prolonged OS with FTD/TPI vs placebo (n = 60; unadjusted HR, 0.29; 95% CI, 0.15–0.55; P< 0.001; adjusted HR, 0.20; 95% CI, 0.092–0.45; P< 0.001), which was significantly more pronounced as compared to the KRAS^{G12} mutant and KRAS^{WT} populations (adjusted interaction P< 0.001 and P= 0.036, respectively). **Conclusions:** Together, KRAS^{G12} mutations were associated with reduced OS benefit of FTD/TPI treatment, with potential implications for ~28% of patients with metastatic colorectal cancer now considered for treatment with FTD/TPI. Furthermore, our data show that genomics-based precision medicine may be possible for a subset of chemotherapies. Research Sponsor: Oncode Institute.

3594 **Poster Session**

Biweekly mXELIRI versus FOLFIRI in combination with bevacizumab as the first-line treatment for metastatic colorectal cancer (EXIST): A multicenter, randomized, open-label, phase 2 study. *First Author: Zhichao Jiang, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: Irinotecan and fluorouracil are the most effective drugs in the treatment of metastatic colorectal cancer (mCRC). But XELIRI (irinotecan plus capecitabine) has not been recommended in the 1st-L setting due to the toxicity in the Western countries. While, modified 3-weekly XELIRI has been proved to be effective and safe in the 2nd-L therapy in Asian mCRC patients. Therefore, this study aimed to assess the efficacy and safety of biweekly mXELIRI with reduced dose of irinotecan in the 1st-L treatment of mCRC. **Methods:** This was a randomized, open-label, non-inferiority study undertaken at 11 hospitals in China. Eligible patients were aged ≥18 years with unresectable metastatic histologically diagnosed colorectal adenocarcinoma; had an ECOG of 0 or 1 and at least one measurable disease according to the RECIST v 1.1 without any systemic chemotherapy for metastatic disease. Patients were randomly assigned (1:1) stratified by the location of primary tumor (left or right site) to receive 9 cycles of mXELIRI + bevacizumab (Bev) (irinotecan 150mg/m^2 D1, capecitabine 1000mg/m^2 bid D1-10, Bev 5mg/kg D1, Q2W) or FOLFIRI + Bev (irinotecan 180mg/m^2 D1, CF 400mg/m^2 D1, 5-Fu 400mg/m^2 bolus D1, 5-Fu 2400mg/m^2 civ 46h D1, Bev 5mg/kg D1, Q2W) followed by maintenance treatments with capecitabine + Bev or 5-FU + CF + Bev. The primary endpoint was 12-month progression-free survival (PFS) rate. The secondary endpoints included objective response rate (ORR), PFS, overall survival (OS) and safety. **Results:** From May, 2018 to Apr, 2021, 264 pts were randomized (mXELIRI + Bev 132; FOLFIRI + Bev 132). The median age was 61 (29-80) years old. 62.5% of the patients were men. With a median follow-up of 17.1 months, the 12-month PFS rates were 43.9% vs. 28.8% in the mXELIRI + Bev and FOLFIRI + Bev groups, respectively. The HR was 0.72 (95%CI 0.51 -1.02) which didn't cross the predefined non-inferiority margin of 1.18 (upper bound < 1.18). The median PFS were 10.5 months vs. 9.6 months (p = 0.056, HR 0.74, 95%CI 0.55-1.01). The median OS was still not mature. The ORR were 51.5% vs. 47.0% (p = 0.460), respectively. The incidence of treatment related adverse events (TRAEs) between these two groups were similar. The most common TRAEs were neutropenia (mXELIRI + Bev vs. FOLFIRI + Bev: 51.8% vs. 57.0%), leukopenia (43.9% vs. 55.3%), anemia (54.4% vs. 45.6%), nausea (31.6% vs. 40.4%), ALT/AST increased (22.8% vs. 23.7%), diarrhea (21.1% vs. 16.7%), fatigue (20.2% vs. 23.7%), vomiting (17.5% vs. 20.2%) and hyperbilirubinemia (14.9% vs. 17.5%). No treatment- related deaths were reported. **Conclusions:** Biweekly mXELIRI with reduced dose of irinotecan plus bevacizumab was noninferior to the standard dose of FOLFIRI + Bev in PFS, with similar safety profile in the patients with untreated mCRC. Clinical trial number: NCT04247984. Research Sponsor: No Clinical trial information: NCT04247984. Research Sponsor: None.

3595 **Poster Session**

Interim analysis of the phase II AVETUXIRI trial: Avelumab combined with cetuximab and irinotecan for treatment of refractory microsatellite stable (MSS) metastatic colorectal cancer (mCRC). *First Author: Nicolas Huyghe, Institut Roi Albert II, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium*

Background: Immune checkpoint inhibitors demonstrated poor efficacy in MSS mCRC. Cetuximab (anti-EGFR inhibitor) could initiate, independently from RAS mutation, an immunogenic tumor cell death and mediate antitumor immune response. In this trial, we aim to explore the clinical efficacy and safety of avelumab (anti-PDL1) combined with cetuximab and irinotecan for treatment refractory MSS mCRC and to understand its mechanisms of action through associated translational research. **Methods**: AVETUXIRI trial (NCT03608046) enrols MSS, chemorefractory (fluoropyrimidine, oxaliplatin, irinotecan and anti-EGFR treatment if RAS wt tumor) mCRC patients in 2 cohorts (A: RAS-wt, n = 10 – B: RAS-mut, n = 13). Primary endpoints are safety and tumor response rate ((i)RECIST1.1). Secondary endpoints include disease control rate (DCR), progression-free survival (PFS) and overall survival (OS). According to a Simon 2-stage design, 23 patients have been included in the first stage of the trial. Multiplex immunofluorescence and RNA sequencing were realized on metastasis biopsies performed before, during and after the treatment. Densities of CD3+ (T cells) and CD8+ (cytotoxic) were quantified and analyzed with to generate an immunoscore (IS). RNA-seq data was used to perform differential expression analysis (DESeq2), gene set enrichment analysis (GSEA), deconvolution analysis (Consensus^{TME}) and gene ontology analysis (GO). **Results**:: No unexpected safety signals were observed. 3/10 tumor responses were observed in cohort A, 0/13 in cohort B. DCR was 60.0% and 61.5% in cohort A and B, respectively. 6-months PFS and 12-months OS rates were respectively 40.0% and 50.0% (cohort A) and 38.5% and 46.2% (cohort B). Independently of RAS mutation, patients with a high IS (metastasis biopsy, baseline) had significantly higher tumor shrinkage (OR = 18.67 p = 0.019), median PFS (6.9 vs 3.4 months; HR = 0.16, p = 0.002) and median OS (13.7 vs 7.9 months, HR = 0.26, p = 0.009). Similarly, tumor shrinkage and survival outcome (PFS > 6 months, OS > 12 months) were associated with upregulation of an adaptive immune response signature (including Th1, chemokine, adhesion molecules, immune checkpoints and T-cell activation genes, p. adj = 0.009) and the GSEA hallmark of epithelial to mesenchymal transition (p. adj = 0.045). Few modifications of IS and gene expression profiles were observed on the different metastasis biopsies performed overtime in the included patients. **Conclusions:** AVETUXIRI met its preliminary primary efficacy endpoint for RAS-wt mCRC pts, justifying its current continuation. Encouraging survival data observed in RAS-mut cohort allow the opening of a new cohort (PFS as primary endpoint). IS and adaptive immune response signature evaluated on metastases biopsies were associated with treatment efficacy and survival. Clinical trial information: NCT03608046. Research Sponsor: Merck restricted grant (investigator initiated sponosorized trial), N.A.

3596 **Poster Session**

Homogeneity of pathological response (PR) and histopathological growth pattern (HGP) in resected colorectal liver metastases (CRLM) are associated with favorable survival outcome after surgery.

First Author: Pamela Baldin, Cliniques Universitaires Saint-Luc, Brussels, Belgium

Background: Surgical resection of CRLM aims to maximize patient survival. However, recurrence rates remain high post-surgery. We previously reported the prognostic relevance of tumor regression grading (TRG) and HGP of resected CRLM. Several studies reported the association of tumoral heterogeneity with anti-cancer drug resistance and prognosis. This study aims to explore tumoral heterogeneity for TRG and HGP in patients resected for CRLM and its prognostic implication. **Methods:** Tumor homogeneity for PR and HGP was evaluated in 2 independent cohorts. Cohort 1 included 57 patients (159 CRLMs) resected after chemotherapy/bevacizumab (prospective BEV-ONCO trial). Cohort 2 included 221 patients (582 CRLMs) operated after preoperative treatment or not. TRG (1 to 5 according complete to no response), HGP (desmoplastic, pushing, replacement or mixed) were evaluated for each CRLM. Max-TRG (higher TRG among all the CRLM) was used to define PR. Homogenous TRG (TRG-h) and HGP (HGP-h) was defined when all CRLMs had the same TRG or HGP pattern. HGP homogeneous desmoplastic (HGP-hd) was defined when all CRLM had a desmoplastic HGP. TRG-h, HGP-h and HGP-hd were combined into a homogeneity score (H-score: 0 to 3, 1 point given for each parameter and summed-up). Overall survival (OS for both cohorts), progression-free survival (PFS for cohort 1) and time to relapse (TTR for cohort 2) were estimated using the Kaplan–Meier method and compared by log-rank tests. Cox proportional hazard models were used for univariate and multivariate analyses. **Results:** Patient and disease characteristics were comparable in both cohorts excepted for preoperative treatment. In cohort 1, TRG-h and HGP-h were significantly associated with a longer PFS (HR = 0.21; 95CI:0.10-0.43, p < 0.001; HR = 0.27; 95CI = 0.14-0.54, p < 0.001) and better OS (HR = 0.23; 95CI = 0.07-0.70, p = 0.010; HR = 0.32; 95CI = 0.10-0.93, p = 0.037). Interestingly, the same significant results were observed in cohort 2 for TTR (TRG-h: HR = 0.60; 95CI = 0.43-0.85, p = 0.004; HGP-h: HR = 0.68; 95CI = 0.49-0.94, p = 0.017) and OS (TRG-h: HR = 0.51;95CI = 0.33-0.80, p = 0.003; HGP-h: HR = 0.63; 95CI = 0.41-0.97, p = 0.034). HGP-h reported a significant association with TRG-h, a Max-TRG < = 3, the absence of HGP replacement and mixed, a desmoplastic pattern, and the absence of sinusoidal obstruction syndrome in both cohorts. H-score was significantly associated with TTR (score 1-2: HR = 0.57; 95CI = 0.38-0.85, p = 0.004; score 3: HR = 0.4; 95CI = 0.24-0.64, p < 0.001) and OS (score 3: HR = 0.31; 95CI = 0.15-0.64, p < 0.001) in univariate analysis and with OS (HR = 0.74; 95CI = 0.59-0.94, p = 0.011) in multivariate analysis (cohort 2). **Conclusions:** TRG-h and HGP-h are strongly associated with patient's survival. H-score could be an easy morphological and prognostic score to assess. Validation studies are needed. Research Sponsor: None.

3597 **Poster Session**

Metastasis patterns and racial disparities in gastrointestinal cancers: A SEER database population study 2010–2018.

First Author: Abdul Rahman Al Armashi, St. Vincent Charity Medical Center, Cleveland, OH

Background: Metastatic disease at the time of diagnosis of gastrointestinal (GI) malignancies is a strong predictor of poor outcomes. Differences in metastatic patterns among Caucasians (C) and African-Americans (AA) needs further elucidation. In this study, we analyzed the patterns of metastasis in C and AA in colorectal cancer (CRC), pancreatic cancer (PC), gastric cancer (GC), and liver cancer (LC). **Methods:** We identified patients with CRC, PC, GC, and LC from the Surveillance, Epidemiology, and End Results Program (SEER) database from 2010-2018. We obtained metastasis data to lungs, liver, bone, and brain at the time of diagnosis. We calculated the relative risk (RR), confidence interval (CI), and standard error with the use of SPSS software, 28.0 (IBM). **Results:** The most common metastasis site was the liver being highest at 39% in AA with PC. Brain metastasis was the least common. Significant racial disparities were noted. In CRC, AA had a 35-37% increased risk of metastasis to the liver, lung, or bone. AA had a higher risk of liver metastasis in PC and GC, whereas C had a higher risk of lung metastasis. Table 1 summarizes the data findings. **Conclusions:** This study illustrates the disparities of metastasis from GI cancers among AA and C. While a delay in screening, earlier onset of CRC in AA and socioeconomic factors may explain the disparities witnessed in CRC. However, these factors will fail to explain the difference in metastasis pattern in PC and GC in that AA had a higher risk of liver metastasis, and C had a higher risk of lung metastasis. Moreover, In GC, the brain metastasis rate in C was double that of AA. Further studies of possible biological and other risk factors are needed. Research Sponsor: None.

Cancer	Total number of patients by race	AA compared to C. Metastasis site prevalence (%). RR, 95% CI, and *p*-value
Colorectal	AA: 30,365	Liver: AA 7,453 (24.5%) C 36.184 (19.7%) - RR 1.37 - CI [1.33 to 1.41] P < 0.001 Lung: AA 2,571 (8.5%) C 12,233 (6.6%) - RR 1.35 - CI [1.29 to 1.41] P < 0.001
	C: 184,141	Bone: AA 662 (2.2%) C 3,104 (1.7%) - RR 1.35 - CI [1.24 to 1.47] P < 0.001 Brain: AA 106 (0.4%) C 727 (0.4%) - RR 0.92 - CI [0.75 to 1.13] P = 0.41
Pancreas	AA: 13,577	Liver: AA 5,282 (38.9%) C 31.624 (35.7%) - RR 1.12 - CI [1.08 to 1.16] P < 0.001 Lung: AA 1,276 (9.4%) C 8,743 (9.9%) - RR 0.92 - CI [0.87 to 0.98] P < 0.001
	C: 88,674	Bone: AA 474 (3.5%) C 3,020 (3.4%) - RR 1.00 - CI [0.91 to 1.11] P = 0.98 Brain: AA 66 (0.5%) C 339 (0.4%) - RR 1.24 - CI [0.95 to 1.62] P = 0.10
Gastric	AA: 8,505	Liver: AA 1,431 (16.6%) C 6,503 (14.8%) - RR 1.14 - CI [1.07 to 1.21] P < 0.001 Lung: AA 365 (4.3%) C 2,155 (4.9%) - RR 0.86 - CI [0.77 to 0.96] P < 0.001
	C: 43,874	Bone: AA 274 (3.2%) C 1,971 (4.5%) - RR 0.70 - CI [0.62 to 0.80] P < 0.001 Brain: AA 31 (0.4%) C 313 (0.7%) - RR 0.51 - CI [0.35 to 0.73] P < 0.001
Liver	AA: 9,639	Lung: AA 668 (6.9%) C 2,658 (6.1%) RR 1.30 - CI [1.19 to 1.42] P < 0.001 Bone: AA 477 (5.0%) C 2,009 (4.0%) - RR 1.22 - CI [1.10 to 1.35] P < 0.001
	C: 50,225	Brian: AA 38 (0.4%) C 172 (0.3%) - RR 1.12 - CI [0.79 to 1.60] P = 0.52

3598 **Poster Session**

Phase I/II trial of encorafenib, cetuximab, and nivolumab in patients with microsatellite stable (MSS), *BRAF*^{V600E} metastatic colorectal cancer.

First Author: Van K. Morris, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Treatment with encorafenib (E) and cetuximab (C) offers response and survival benefit for patients (pts) with MSS, *BRAF*^{V600E} metastatic colorectal cancer (CRC). BRAF + EGFR inhibition induced a transient MSI-H phenotype in preclinical models of MSS, *BRAF*^{V600E} CRC and may prime these tumors for response to immunotherapy with anti-PD-1 antibodies like nivolumab (N). **Methods:** In this single-arm, single-institution, phase I/II clinical trial, pts with treatment-refractory MSS, *BRAF*^{V600E} metastatic CRC were eligible. No prior BRAF, MEK, or ERK inhibitors, anti-EGFR antibody, or immunotherapy was permitted. Pts received E (300 mg PO daily), C (500 mg/m^2 IV q14 days), and N (480 mg IV q28 days). The primary endpoints were best overall response (RECIST 1.1) and safety/tolerability (CTCAE v5). A Simon two-stage design (H_0: p≤ .22; H_a: p≥ .45, where p = percentage of pts with radiographic response) was employed using a one-sided α = .05 and β = .20. Median progression-free survival (PFS) and overall survival (OS) were estimated via Kaplan-Meier. To measure ex vivo treatment responses with an E-slice assay (EMPIRI), 300 μm fresh tissue slices from core biopsies were generated and cultured in serum-free media with E, C, and N. Longitudinal changes in viability were measured at days 4, 8, and 12 and compared to baseline viability in each tissue. Ex vivo "response" was defined if < 1X baseline tumor cell viability. **Results:** With a data cutoff of 2/8/2022, all pts are enrolled: 26 evaluable for toxicity and 23 for response. Median age is 60 years (range, 32-85), and 16 (62%) are female. Grade 3-4 treatment-related adverse events (AE) have occurred in 5/26 (19%) patients: colitis, maculopapular rash, leukocytosis, and myositis/myocarditis (all N = 1); asymptomatic elevated amylase/lipase (N = 2). Overall response rate is 48% (95% CI, 27-69), and disease control rate is 96% (95% CI, 78-100). Median PFS is 7.4 months (95% CI, 5.6-NA). For the 11 pts with responses, median duration of response is 7.7 months (95% CI, 4.5-NA). Median OS is 15.1 months (95% CI, 7.7-NA). E-slices showed concordance between pts with radiographic responses and reduction in cell viability, and between non-responders and increase in cell viability. Final results will be presented. **Conclusions:** E + C + N appears to be effective and well-tolerated for pts with MSS, *BRAF*^{V600E} metastatic CRC. Ex vivo analysis of pretreatment tissue predicted eventual clinical response in matched patients. A follow-up randomized phase II trial (SWOG 2107) to evaluate encorafenib/cetuximab with or without nivolumab in pts with MSS, *BRAF*^{V600E} metastatic CRC will activate in 2022. Clinical trial information: NCT04017650. Research Sponsor: Bristol Myers Squibb, Pfizer, Pharmaceutical/Biotech Company.

3599 **Poster Session**

First experience with ^{224}Radium-labelled microparticles (radspherin) after CRS-HIPEC for peritoneal metastasis in colorectal cancer (a phase 1 study).

First Author: Stein G Larsen, Section for Surgical Oncology, Norwegian Radium Hospital; Department of Gastroenterological Surgery, Oslo University Hospital, Oslo, Norway

Background: Peritoneal metastasis (PM) from colorectal cancer carries a dismal prognosis. Improved survival can be achieved by combining extensive cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC). However, median time to recurrence is short (11-12 months) and there is a need for novel therapies to prevent subsequent PM. Radspherin consists of the α-emitting radionuclide radium-224 (^{224}Ra), half-life 3.6 days, adsorbed to a suspension of biodegradable calcium carbonate microparticles, designed to give short-range radiation to the serosal peritoneal surface, aiming to kill remaining free cancer cells and small tumor cell clusters. **Methods:** A first-in-man phase 1 study (EudraCT 2018-002803-33) was conducted at two specialized CRS-HIPEC centers. Radspherin was injected in the abdominal cavity through a catheter 2 days after CRS-HIPEC. Dose escalation at increasing dose levels of 1-2-4-7-MBq, repeated injection and expansion cohorts evaluated the safety and tolerability of Radspherin, explored maximal tolerated dose and biodistribution by using single photon-emission computed tomography/computed tomography (SPECT/CT) imaging. Results from the planned safety interim analysis after completion of the dose-limiting toxicity (DLT) period are presented. **Results:** Twenty-three patients were enrolled, dose escalation cohort (14), repeated cohort (3) and expansion cohort (6). Nineteen patients were treated in Oslo/ 4 in Uppsala. Twelve patients had synchronous PM Stage IV and 11 metachronous PM (Stage II (6), Stage III (5). Disease-free interval 15 months (3-39); males (7), females (16); median age 64 years (28-78). Peritoneal cancer index was median 7 (3-19), operation time 395 minutes (194-515) and hospital stay 12 days (7-37). Accordion ≥3 grade events (6); including anastomotic leaks (2); abscess (1); drains (2) and missed lesion (1), all reported as serious adverse events (SAEs). The 7MBq dose was selected as recommended dose as no DLT was observed. A total of 185 treatment emergent adverse effects (TEAE) were recorded, most were of low grade and considered related to CRS and/or HIPEC. Few patients (7) had TEAEs considered related to a combined impact of Radspherin and CRS-HIPEC. The biodistribution of Radspherin showed a relatively even peritoneal distribution, and no patients had compartments of the abdominal cavity without radioactivity (cold spots), and low number had hot spots. Long-term safety, dosimetry and first efficacy results of Radspherin will be reported after 12 months follow up period. **Conclusions:** All dose levels of Radspherin were well tolerated with DLT not reached. No deaths occurred and no SAEs were considered related to Radspherin. The biodistribution of Radspherin showed good peritoneal distribution of the radiolabeled microparticles. Clinical trial information: 2018-002803-33. Research Sponsor: Oncoinvent A/S, N-0484 Oslo, Norway., Innovation Norway, Pb. 448, N-0104 Oslo, Norway.

3600 **Poster Session**

Effects of liver metastases on efficacy of immune checkpoint blockade in treatment refractory, metastatic colorectal cancer (CRC): CCTG CO.26. *First Author: Eric Xueyu Chen, Department of Medical Oncology and Haematology, Toronto, ON, Canada*

Background: Immune checkpoint blockade has limited activity in microsatellite-stable (MSS) or mis-match repair proficient (pMMR) CRC. Recent findings suggest that immunotherapy efficacy may be modulated by the presence of liver metastases. We conducted a retrospective analysis of the Canadian Cancer Trials Group (CCTG) CO.26 study to investigate the relationship between the presence of liver metastases and activity of immune checkpoint blockade. **Methods:** The CCTG CO.26 study was a randomized phase II study (NCT02870920). Pts with treatment refractory CRC were randomized to durvalumab, tremelimumab and best supportive care (BSC) or BSC alone in a 2:1 fashion. Treatment consisted of durvalumab (1500 mg) q 28 days and tremelimumab (75 mg) q 28 days for the first 4 cycles. The primary endpoint was overall survival (OS) and a two-sided p-value <0.10 was considered significant. **Results:** Between 08/20106-06/2017, 180 pts were enrolled and 179 treated as randomized. Pt baseline characteristics were balanced between groups. With a median follow-up of 15.2 months, the median OS was 6.6 months for durvalumab and tremelimumab and 4.1 months for BSC (p = 0.07; Hazard ratio (HR): 0.72, 90% confidence interval (CI): 0.54 – 0.97). Progression free survival (PFS) was 1.8 months and 1.9 months respectively (HR 1.01, 90% CI: 0.76 – 1.34). Disease control rate (DCR) was 22.6% for durvalumab and tremelimumab and 6.6% for BSC (p = 0.006). At study entry, liver metastases were absent in 29.4% pts. Pts without liver metastases had improved OS compared to those with liver metastases, irrespective of treatments. PFS was significantly longer in those without liver metastases on durvalumab and tremelimumab (HR: 0.55, 90% CI: 0.31 – 0.97, p = 0.08, interaction p = 0.02). DCR was 49% in patients without liver metastases with durvalumab and tremelimumab, compared to 10% in those with liver metastases (Odds Ratio: 0.12, 90% CI: 0.05 – 0.26). **Conclusions:** Pts without liver metastases had improved OS and PFS, and higher DCR. Absence of liver metastases may be an indicator for improved efficacy of immune checkpoint blockade and should be investigated in future studies. Research Sponsor: AstraZeneca.

	D + T	BSC	Hazard (Odds) Ratio
OS, months (90% confidence interval)			
Liver metastases: present	5.49 (3.98–6.44)	3.79 (3.25–5.22)	0.79 (0.58–1.08)
Absent	9.43 (7.39–12.3)	7.66 (3.02–11.2)	0.65 (0.37–1.16)
PFS, months (90% confidence interval)			
Liver metastases: present	1.82 (1.71–1.84)	1.84 (1.77–1.91)	1.36 (1.00–1.86)
Absent	2.04 (1.87–3.71)	1.87 (1.71–2.10)	0.55 (0.31–0.97)
Disease control rate % (90% confidence interval)			
Liver metastases: present	10 (4–16)	4 (0–9)	2.50 (0.66–9.52)
Absent	49 (36–62)	14 (0–30)	5.70 (1.46–22.3)

3601 **Poster Session**

Using cell-free circulating tumor DNA (cfDNA) to identify guideline-relevant biomarkers for therapy selection in 14,000 patients (pts) with metastatic colorectal cancer (mCRC). *First Author: Pashtoon Murtaza Kasi, Weill Cornell Medicine, New York City, NY*

Background: Two cfDNA assays are FDA-approved for use in advanced cancer pts across solid tumors. While several NCCN guidelines recommend cfDNA as a valid and useful method for molecular testing, the utility varies by cancer type. Despite the growing number of molecular alterations pertinent to first-line treatment in mCRC, current guidelines offer little guidance on the use of cfDNA in mCRC. Here we assess the ability of cfDNA to detect guideline-relevant actionable biomarkers informative for first-line therapy selection and beyond in patients with mCRC. **Methods:** We queried consecutive samples from advanced cancer pts with a diagnosis of CRC who underwent testing via a commercially available cfDNA assay (Guardant360) from September 2018 to January 2022. Validation and content of this assay has been previously described. To enrich for less heavily treated pts, we limited analysis to those whose first cfDNA test was done during the study period and only included the pt's first test. The maximum variant allele fraction (maxVAF) for each test was used as a proxy for tumor shed and was compared between cancers with a Mann-Whitney test. The frequency of suspected germline alterations was assessed only in pts who received testing via a panel version with expanded mismatch repair (MMR) gene coverage. Tissue frequencies for select biomarkers were obtained from the MSK-IMPACT Clinical Sequencing Cohort in cBioPortal. **Results:** In total, 14,345 pts with mCRC received their first cfDNA test during the study period, with 92% of pts (13,190) having >1 cfDNA alteration detected. Median age was 62 and 44% of pts were female. The frequencies of key biomarkers are listed in Table 1. The median maxVAF was 5.6%, compared to 2.5% and 1.8% for pts with advanced gastric and NSCLC, respectively (p = < 0.0001 for both). The average turnaround time (TAT) for tests was 7 calendar days. **Conclusions:** cfDNA results from pts with mCRC demonstrated detection of biomarkers essential to first-line treatment decisions at a frequency comparable to what has been reported via tissue genotyping. mCRC pts had significantly higher tumor shed compared to other cancer types with guidelines that recommend cfDNA as an option for molecular testing, suggesting a potential gap in coverage. Tissue availability in mCRC does not guarantee comprehensive testing is completed quickly (compared to the 7-day TAT seen for cfDNA here), making it an attractive alternative strategy for first-line therapy selection in mCRC. Research Sponsor: None.

Molecular Targets	N (%) of Pts (n = 13190)	Reported Frequency in Tissue
MSI-High	423 (3.2)	5-7.2%
***BRAF* V600E-mutant**	815 (6.2)	7.45%
***KRAS*-mutant**	5856 (44)	43%
***KRAS* G12C**	513 (3.9)	3.0%
***NRAS*-mutant**	804 (6.1)	4.4%
***ERBB2*(HER2)-amplified**	251 (1.9)	2.9%
Suspected germline variants	111 (2.7)	-
MMR genes versus non-MMR genes (e.g., *BRCA1/2*)	33 (30) versus 78 (70)	-
***NTRK1/2/3* fusions**	6 (0.05)	0.2%

3602 **Poster Session**

Effectiveness of nationwide insurance coverage for next-generation sequencing in advanced colorectal cancer: A real-world data study. *First Author: Sun-Kyeong Park, The Catholic University of Korea, Bucheon, South Korea*

Background: Next-generation sequencing (NGS) has been covered by Korean national health insurance since March 2017 for patients with advanced colorectal cancer (CRC). We explored the clinical and socioeconomic impact of NGS compared with that of a single gene test (SGT) alone. **Methods:** From the nationwide database, we identified patients who 1) are diagnosed with advanced CRC classified as a distant disease using Summary Stage between March 1, 2017, and December 31, 2018; 2) had NGS or SGT within 2 months after diagnosis of advanced CRC. Multivariate logistic regression with covariates including age, sex, Charlson comorbidity index, insurance type, year of diagnosis, and region and type of hospital with the initial diagnosis was conducted to identify factors affecting the performance of NGS. We conducted 1:3 propensity score matching to minimize the impact of confounding factors. The median overall survival and the adjusted hazard ratio (aHR) were estimated using the Kaplan-Meier method and the Cox proportional hazard model, respectively. We calculated the total medical cost, and per patient per year (PPPY) cost adjusted for the survival period. **Results:** Among 5,029 patients with advanced CRC, 655 patients were identified as NGS group and 1,995 as SGT group after matching. Old age, low household income, rural location, and non-tertiary hospital were all characteristics that reduced the likelihood of obtaining an NGS test. The NGS group showed significantly favorable survival compared to the SGT group (median survival 29.2 vs. 24.9 months, P = .031; adjusted hazard ratio [HR] 0.86, P = .034). The total medical cost was lower in the NGS group ($55,445) than the SGT group ($57,989), and the PPPY cost was also lower in the NGS group ($44,879 and $49,734, respectively). **Conclusions:** We found that some socioeconomic factors such as age, insurance type, region, and hospital type may hamper the implementation of NGS. Also, lowering the barrier of NGS tests by reimbursing NGS in a specific clinical setting may have survival and cost-benefit in patients with advanced CRC. Research Sponsor: Ministry of Health & Welfare (HI19C0481, HC19C0238).

3603 **Poster Session**

Phase 1b/ 2 study of a radio-enhancer, PEP503 (NBTXR3), in combination with concurrent chemo-radiation in locally advanced or unresectable rectal cancer. *First Author: Ching-Wen Huang, Division of Colorectal Surgery, Kaohsiung Medical University Chung-Ho Memorial Hospital, Kaohsiung, Taiwan*

Background: PEP503 (aka NBTXR3) is a novel radio-enhancer composed of functionalized hafnium oxide nanoparticles that increases the energy deposition of radiotherapy. A phase 3 study in soft tissue sarcoma patients has significantly increased pCR and R0 when PEP503 was added to preop radiotherapy. This phase 1b/2 study was conducted with the aim to identify a recommended phase 2 dose (RP2D), and evaluate the efficacy of PEP503 intratumoral injection in combination with concurrent chemoradiation (CCRT) in patients with locally advanced rectal cancer (LARC). **Methods**: Patients with stage T3-T4 LARC (or with unresectable disease) suitable for neoadjuvant CCRT were enrolled. An intratumoral single administration of PEP503 (multiple punctures) was done 24 to 72 hours prior to IMRT of 50 Gy in 25 fractions of 2 Gy per fraction over 5-6 weeks with concurrent capecitabine or 5-FU. Traditional 3 + 3 design with 4 levels, 5%, 10%, 15%, and 22%, of the baseline GTV as measured by MRI, of PEP503 were assessed in Phase Ib. PEP503 nanoparticles intratumoral dispersion was analyzed by CT-scan. Surgery was performed 8 to 12 weeks after the completion of CCRT for patients with resectable tumors. Body kinetics was evaluated in Phase Ib. (ClinicalTrials.gov, NCT02465593) **Results**: Thirty-two (32) patients (male/female: 20/12; median age 62 years, range 38 to 76) were enrolled (1 dropped out before starting CCRT). In Phase 1b, 20 patients were treated and dose was escalated to 22%. RP2D was then determined as 22% with 6 patients treated at this dose level without DLT. Twelve (12) patients were included in the Phase 2. One (1) (3.2%) and 19 (61.3%) of evaluable patients (n = 31) had CR and PR, respectively, as the best tumor response across dose levels. No patient progressed as all evaluable patients (n = 31) achieved disease control for a DCR of 100%. Furthermore, twenty-five patients underwent surgery, of which 24 (96%) had microscopically clear resection margins and 5 of them (20%) had pathological complete response (pCR). The G3 AEs were diarrhea, ileus, thrombocytopenia, urosepsis, procedural haemorrhage, wound complication, hypokalaemia, and myalgia (all in 3.1%). No G4 AE were observed. The results of CT scans for nanoparticles dispersion demonstrated PEP503 remained within the tumor without leakage to the surrounding healthy tissues, before and after CCRT. In most patients, hafnium was not detected or below the Lower Limit of Quantification (LLOQ) in the circulation 60 minutes after PEP503 injection and was not found in urine. **Conclusions**: A single intratumoral injection of PEP503 in locally advanced or unresectable rectal adenocarcinoma undergoing capecitabine or 5-FU based CCRT is feasible and safe. The preliminary observed efficacy results may warrant further examination in larger clinical studies. Clinical trial information: NCT02465593. Research Sponsor: PharmaEngine, Inc.

3604 **Poster Session**

Effect of more versus less frequent abdominopelvic computed tomography follow-up testing on overall survival in patients with stage II or III colon cancer. *First Author: Jeon Jeongseok, Yonsei University, College of Medicine, Seoul, South Korea*

Background: Patients with colon cancer undergo an abdominopelvic computed tomography (AP-CT) scan surveillance every 6-12 months for five years after surgery. However, evidence of survival benefit from more intensive AP-CT patients in stage II and III colon cancer is still elusive. **Methods:** A total of 2,137 patients with stage II-III colon cancer who received curative aim surgery were analyzed in the Yonsei Cancer Registry Database between Jan 1, 2005, to Dec 31, 2015. The surveillance start date was defined as 90 days after curative resection or one day after adjuvant chemotherapy. All patients had at least one AP-CT for two years after the surveillance period. The average interval of AP-CT per patient was calculated as the postoperative surveillance duration divided by the number of AP-CT examinations. Patients who underwent AP-CT with an average interval of 6 months and 12 months were assigned to the high-frequent and low-frequent surveillance groups. Association of AP-CT frequency and demographic factors with overall survival (OS) were evaluated. Univariate and multivariate analyses were conducted. **Results:** Among 2,137 patients who underwent curative aim surgery, the median intervals of AP-CT scan were 6.1 months in high-frequent surveillance and 10.8 months in the less-frequent surveillance group, respectively. The 5-year overall survival (OS) was not significantly different in both groups; however, OS was significantly longer in the high-frequent surveillance group of patients who harvested lymph nodes less than 12 in curative resection ($P = 0.015$) or measured postoperative serum carcinoembryonic antigen (CEA) level higher than 5 ng/ml ($P = 0.023$). Of note, high-frequent surveillance group detected liver metastasis earlier (6.7 months) than the low-frequent group, leading to more curative aim metastasectomy (28.0% vs 4.3%, $P = 0.020$), and significantly longer 5-year OS (62.2% vs 34.8%, $P = 0.017$). Multivariate analysis showed that harvesting lymph nodes less than 12 (HR = 4.37, P = 0.004) and postoperative CEA level higher than 5 ng/ml (HR = 7.39, P < 0.001) were prognostic factors for overall survival. **Conclusions:** The average interval of AP-CT in patients with stage II-III colon cancer is not associated with improved OS. However, a high-frequent AP-CT enabled early detection of liver metastases, leading to the improved OS in high-risk patients, including the number of harvested lymph nodes less than 12 or postoperative CEA level is higher than 5 ng/ml. The risk-stratified approach is warranted to guide postoperative colon cancer surveillance. Research Sponsor: None.

3605 **Poster Session**

Preoperative chemoradiotherapy with capecitabine with or without temozolomide in patients with locally advanced rectal cancer: A prospective, randomized phase 2 study stratified by MGMT (O^6-methylguanine DNA methyltransferase) status: KCSG-CO17-02. *First Author: Chung Ryul Oh, Department of Internal Medicine, Chung-Ang University Hospital, Chung-Ang University College of Medicine, Seoul, South Korea*

Background: We aimed to evaluate the clinical efficacy of adding temozolomide (TMZ) to preoperative capecitabine (CAP)-based chemoradiotherapy (CRT) in patients with locally advanced rectal cancer (LARC) and validate O^6-methylguanine DNA methyltransferase (MGMT) methylation status as a predictive marker for TMZ combined regimens. **Methods:** : LARC patients with clinical stage II (cT3-4N0) or III ($cT_{any}N+$) disease were enrolled. They were stratified into MGMT unmethylated (uMGMT) and MGMT methylated (mMGMT) groups by methylation-specific PCR before randomization, and then were randomly assigned (1:1) to one of four treatment arms: uMGMT/CAP (arm A), uMGMT/TMZ+CAP (arm B), mMGMT/CAP (arm C), and mMGMT/TMZ+CAP (arm D). The primary endpoint was the pathologic complete response (pCR) rate. **Results:** Between November 2017 and July 2020, 64 patients were randomized. Slow accrual caused early study termination. After excluding 4 ineligible patients, 60 were included in the full analysis set. The pCR rate was 15.0% (9/60), 0%, 14.3%, 18.8%, and 26.7% for arms A, B, C, and D, respectively ($p = 0.0498$ between arms A and D). The pCR rate was 9.7% in the CAP group (arms A+C), 20.7% in the TMZ+CAP group (arms B+D), 6.9% in the uMGMT group (arms A+B), and 22.6% in the mMGMT group (arms C+D). Grade 1–2 nausea or vomiting was significantly more frequent in the TMZ+CAP treatment groups (arms B+D) than in the CAP treatment groups (arms A+C, $p < 0.001$) with no difference in grade 3 adverse events (AEs). There were no grade 4 or 5 AEs. **Conclusions:** The addition of TMZ to CAP-based CRT tended to improve pCR rates, particularly in those with mMGMT LARC. MGMT status may warrant further investigation as a predictive biomarker for chemotherapeutic agents and radiotherapy. Clinical trial information: NCT03156036. Research Sponsor: This study was supported by a grant 2017-0274 from the Asan Institute for Life Sciences, Asan Medical Center, Korean Cancer Study Group, and a grant from the National R&D Program for Cancer Control, Ministry of Health and Welfare, Republic of Korea (17201.

3606 **Poster Session**

Using T stage to predict outcomes of adjuvant oxaliplatin (OX)-based chemotherapy (CT) in stage III colon cancer (CC): An ACCENT pooled analysis. *First Author: Romain Cohen, Sorbonne University, Department of Medical Oncology, Saint-Antoine Hospital, AP-HP, Paris, France*

Background: Standard adjuvant CT for stage III CC are FOLFOX and CAPOX. Recently, IDEA study separated stage III patients (pts) into low risk (T1 to 3, N1) and high risk (T4 or N2). We recently confirmed benefit of OX in both risk groups. However, we observed a difference in the two high-risk subgroups, with benefit in N2 but not in T4 (Margalit O et al; Clin Colorectal Cancer 2021). This prompted us to compare outcomes (OS/TTR) between treatment with OX vs. without OX within sub-stage III CC groups defined by T and N. **Methods:** We pooled 4941 stage III CC pts from the three studies evaluating 6 months of CT with fluoropyrimidine (FP) ± OX: MOSAIC, C-07 and XELOXA. Baseline characteristics were compared using χ^2 and *t*-test. OS was compared between OX and no OX in T and N subgroups. Kaplan-Meier analyses, adjusted and unadjusted Cox models stratified by study were used. Sub-groups classification was done according to OX benefit and verified by interaction test (Int) considered as significant with a $P<0.1$. We considered for recommendation of using OX-based adjuvant CT, 1) significant benefit in OS, 2) significant Int between substage and adjuvant therapy, and 3) the three individual trials showing similar results (benefit or non-benefit of OX). **Results:** In stage III population, T3 pts were 74.9%, T1-2 12.4%, T4 13.1%, while N stage was N1 64.7% and N2 35.3%. Population was well balanced according to treatment allocation in most subgroups. A significant benefit of OX was only observed in T3N1 and T3N2 (OS HR 0.76). Whatever N stage, there was no significant benefit of OX in the T1-2 and T4 subgroups. The effect of OX+FP vs FP alone in OS of the three studies differed between T3 and T1-2 subgroups (P = 0.047). Interaction was borderline between T3 and T4 subgroups (P = 0.10) but there was no interaction between T1-2 and T4 subgroups (P = 0.429). A benefit of OX in TTR remained in the T4 population. Discrepancy between advantage in time to relapse (TTR) and no advantage in OS was not explained by survival post relapse. **Conclusions:** Our analysis suggested that pts with T1-2N1-2 and T4N1-2 disease had no OS benefit of addition of OX to FP. The good survival achieved with FP alone in T1-2N1-2 pts (5-yr OS 89%) question the addition of OX. In the T4 population our results suggested that benefit of OX was limited and that further studies should assess this issue or at least stratify pts on T stage in the future adjuvant trials in CC. Research Sponsor: None.

The effect of OX use on OS according to T & N stage combinations.

Subgroup	N/Events HR (95% CI)	*P-value*
T1-2N1-2	613/116 1.09 (0.76-1.57)	0.644
T3N1-2	3674/1215 0.76 (0.68-0.85)	<0.001
T4N1-2	645/296 0.95 (0.76-1.19)	0.660
N1	3200/852 0.80 (0.70-0.92)	0.002
N1T1-2	500/91 1.06 (0.70-1.60)	0.779
N1T3	2310/617 0.72 (0.62-0.85)	<0.001
N1T4	383/141 1.01 (0.73-1.41)	0.934
N2	1740/778 0.85 (0.73-0.97)	0.02
N2T1-2	113/25 1.47 (0.66-3.31)	0.348
N2T3	1364/598 0.81 (0.69-0.95)	0.01
N2T4	262/155 0.90 (0.65-1.23)	0.499

3607 **Poster Session**

Testing of a machine learning (ML) model for ability to predict oxaliplatin and bevacizumab (bev) benefit in NRG Oncology/NSABP C-07 and C-08. *First Author: Xinghua Lu, University of Pittsburgh School of Medicine, Pittsburgh, PA*

Background: Through mining The Cancer Genome Atlas (TCGA) data and a large set of transcriptomes of CRC in GEO, we constructed 15 metagenes reflecting the transcriptomic impact of major driver genes of CRC. Independent of any clinical information, we used metagenes as features to further develop an ML model, then tested it using gene expression (GE) data from C-07 and C-08. **Methods:** We carried out a prospectively designed and double-blind study to evaluate the clinical utility of the ML model in the adjuvant setting. Samples were classified as Sig+ or Sig-. Association of signatures with recurrence free interval were tested using log-rank test, and significance was set at P<0.05. Cox regression models were used to estimate hazard ratios in univariate and multivariate models and for significance testing in multivariate models. Clinical variables included in multivariate models were nodal status, age, sex, and T stage. **Results:** We tested the ML model for its ability to predict oxaliplatin benefit in all C-07 pts with available GE data (n=846). Sig+ pts received significant benefit from oxaliplatin (HR=0.68, 95% CI=0.48-0.95, p=0.025) but Sig- did not (Sig- HR=1.05, 95% CI=0.72-1.53, p=0.79), however, the int p value showed only a trend for significance (int p=0.091). Sig+ remained significant for oxaliplatin benefit in multivariate analysis (HR=0.67, 95% CI=0.48-0.95, p=0.024). When we combined all C-07 pts (C-07 FULV-trtd n=298, FLOX n=304) with C-08 FOLFOX-treated pts (n=226) the Sig+ was significantly associated with oxaliplatin benefit (HR=0.65, 95% CI=0.48-0.89, p=0.0065) with a significant int p=0.03. We also tested the signature for association with bev benefit in C-08 (n=438), using a different cut off. Sig+ showed only a trend for an association with bev benefit (HR=0.63, 95% CI=0.35-1.12, p=0.11). To increase the power to detect bev benefit, we also tested the signature for association with bev benefit in all C-08 patients and C-07 pts treated with FLOX. The Sig+ group received significant benefit from bev (HR=0.58, 95% CI=0.36-0.94, p=0.025) but the Sig- group did not (HR=1.02, 95% CI=0.64-1.63, p=0.94), however, the int p was not significant (p=0.101). The model also showed an association with prognosis within the FULV treatment arm in C-07 (HR=1.51, 95% CI=1.07-2.14, p=0.018) and the FOLFOX+bev arm in C-08 (HR=0.55, 95% CI=0.30-1.01, p=0.049). **Conclusions:** Although our study is not optimally powered, our analyses indicate that the ML model was predictive for oxaliplatin benefit in stage II and III CC and may be useful for detecting bev benefit. Importantly, the Sig- population is candidate for omitting oxaliplatin (de-escalation) in adjuvant setting but will require further validation. Support: PA DOH, U10CA-180868, -180822, -196067, Genentech, Sanofi; NSABP. Clinical trial information: 00096278, 00004931. Research Sponsor: U.S. National Institutes of Health, Other Foundation, Other Government Agency, Pharmaceutical/Biotech Company.

3608 **Poster Session**

Computerized features of tumor diversity on pre-chemoradiation MRI are associated with pathologic complete response in rectal cancers: A multi-institutional study. *First Author: Sneha Singh, Case Western Reserve University, Cleveland, OH*

Background: Neoadjuvant chemoradiotherapy (nCRT) prior to total mesorectal excision (TME) reduces the risk of local recurrence and is a standard-of-care treatment for patients with locally advanced rectal cancer. Previous studies have indicated up to 30% of patients who undergo TME demonstrate a pathologic complete response (pCR) to nCRT [2], but current serum markers and clinical evaluation have limited utility in predicting benefit from nCRT. In this study, we evaluated if tumor diversity features on baseline pre-treatment MRI were predictive of pCR in rectal cancers. **Methods:** Pre-nCRT T2-weighted MRIs from 126 patients who later underwent nCRT and TME (without neoadjuvant chemotherapy) were retrospectively collected from 2 institutions. 69 patients (14 pCR, Institution 1) formed the training cohort D1, while 57 patients (10 pCR, Institution 2) formed the independent holdout validation cohort D2. Response groupings were based on AJCC tumor regression grade (TRG) evaluation where pCR corresponded to no residual tumor cells in excised histopathologic specimens after nCRT (i.e. TRG0) and non/partial response otherwise (TRG1-3). Computerized tumor diversity algorithms extracted measurements of fractal dimensions, surface topology, and persistent homology from annotated tumor regions on MRI to quantify visual patterns, spatial geometry, and prolonged structural similarity. Top tumor diversity features identified via Wilcoxon rank-sum testing were used to train a random forest (RF) machine learning classifier to predict the likelihood of pCR using D1 and then independently evaluated for predicting pCR in D2. **Results:** Machine learning analysis identified 5 tumor diversity measurements associated with pCR on pre-nCRT MRI. The associated RF classifier for pCR achieved an AUC of 0.98 (95% CI, 0.9808-0.9949) in D1 and an AUC of 0.9117 in hold-out validation on D2. This corresponded to predicting 100% of non/partial response prior to nCRT as well as 80% of pCR patients via tumor diversity features on pre-nCRT MRI. **Conclusions:** Computerized tumor diversity features on pre-nCRT MRI can predict pathologic complete response to nCRT in rectal cancers. These findings need to be validated in larger multi-institutional cohorts to establish independent predictive utility of MRI-based biomarkers, which could aid in the selection of patients who will see maximal response from neoadjuvant therapy and avoid unnecessary surgery. Research Sponsor: U.S. National Institutes of Health, Other Government Agency.

3609 **Poster Session**

PKUCH 04 trial: Total neoadjuvant chemoradiation combined with neoadjuvant PD-1 blockade for pMMR/MSS locally advanced middle to low rectal cancer. *First Author: Aiwen WU, Peking University Cancer Hospital and Institute, Beijing Cancer Hospital, Beijing, China*

Background: Total neoadjuvant therapy (TNT) with induction chemotherapy and chemoradiation is the standard of care for locally advanced rectal cancers. Incorporation of PD-1 blockade in the neoadjuvant setting is promising for mismatch repair deficient (dMMR) patients, yet the efficacy of TNT combined with PD-1 blockage for pMMR/MSS patients is little unknown. The purpose of this study is to evaluate the clinical benefit of neoadjuvant PD-1 blockade combined with TNT in pMMR/MSS locally advanced rectal cancer. **Methods:** We designed a prospective, single-arm, phase II study on locally advanced dMMR/MSS rectal cancer (PKUCH 04 trial). Patients will receiving neoadjuvant regimen (PD-1 inhibitor, camrelizumab, also called SHR01210, 200mg d1, oxaliplatin 130mg/m2 d1, capecitabine 1250mg/m2 bid1-14, for three cycles, then long course chemoradiation (IMRT, 1.8Gy/f*25f), then another two cycles of CapeOx (oxaliplatin 130mg/m2 d1, capecitabine 1250mg/m2 bid1-14, q3wks) if no disease progression occurs. The primary endpoint was pathologic complete response (pCR) rate, and the secondary outcome include adverse event and surgical complication. Tumor assessment was carried out after induction, chemoradiation, and before the decision of either surgery or watch and wait. **Results:** A total of 27 patients were screened and finally 25 patients were eligible for further analysis, with median age 58 years (range 31-70). The median distance from the anal verge was 5.3 cm (1.2-10). 76% were male, 76% had N2 disease, 56% positive MRF, 80% positive EMVI. All patients have completed the induction and chemoradiation phases. 21 patients underwent TME surgery, of which 7 had pathological complete response (33.3%). Four achieved clinical complete or near complete response and chose watch and wait. 7 had major pathological remission (over 90% remission). Another 7 had partial pathological remission. No progressive disease was found. 14 had LAR, 7 APR, and . The surgical complication rate was 14.3%, and the mortality rate was 0. The common adverse events included nausea (80%), lymphopenia (80%), paresthesia (76%), reactive cutaneous capillary endothelial proliferation (72%), neutropenia (68%). Grade 3 adverse events include lymphopenia (24%), diarrhea (8%), and thrombocytopenia (4%) and no grade 4 or 5 events were observed. Till January 2022, no recurrence or regrowth was found. **Conclusions:** Total neoadjuvant chemoradiation combined with neoadjuvant PD-1 blockade is safe and effective which can achieve good regression and sphincter preservation for pMMR/MSS rectal cancer. This suggests a potential new paradigm for treatment of pMMR/MSS locally advanced rectal cancer and necessitates further investigation. Clinical trial information: NCT04340401. Research Sponsor: Jiangsu Hengrui Medicine Co.

3610 **Poster Session**

Effect of adjuvant chemotherapy in patients with stage III colon cancer based on the Multi-Institutional Registry of Large Bowel Cancer in Japan. *First Author: Yasuhide Yamada, National Center for Global Health and Medicine, Tokyo, Japan*

Background: A fluoropyrimidine plus oxaliplatin is the standard of care for stage III colon cancer but a fluoropyrimidine alone is also recommended for stage III patients in Japanese and other practice guidelines. We assessed efficacy of adjuvant fluoropyrimidine with or without oxaliplatin across a population of stage III colon patients in the Multi-Institutional Registry of Large Bowel Cancer in Japan. **Methods:** 7,024 of stage III colorectal cancer patients in this registry were analyzed. Endpoints were relapse-free survival (RFS) and overall survival (OS). **Results:** All patients received adjuvant chemotherapy between 2008 and 2011.Patient characteristics except lymph node metastases were well balanced across groups. The RFS of fluoropyrimidine with or without oxaliplatin show comparable efficacy for stage III, even for stage IIIc patients, less than 70 years old, and T4 or N2b. Median follow-up was 74.9 months in oxaliplatin combined therapy and 74.7 months in fluoropyrimidine monotherapy. The additive efficacy of oxaliplatin was not shown for RFS and OS. **Conclusions:** Adjuvant fluoropyrimidine monotherapy and fluoropyrimidine plus oxaliplatin show comparable efficacy benefits for the treatment of stage III of Japanese colon cancer patients; supporting fluoropyrimidine alone as standard options for the adjuvant therapy of stage III in Japan. Research Sponsor: Funding for Nationwide Colorectal Cancer Registry by Japanese Society for Cancer of the Colon and Rectum.

	RFS		OS	
	Fluoropyrimidine	Fluoropyrimidine plus oxaliplatin	Fluoropyrimidine	Fluoropyrimidine plus oxaliplatin
Stage IIIa				
1-year	98 %	97 %	100 %	97 %
3-year	93	84	98	97
5-year	90	80	96	93
7-year	84	70	89	89
	HR, 1.96, 0.94 to 4.09; *P*= 0.075		HR, 0.94, 0.29 to 3.04; *P*= 0.917	
Stage IIIb				
1-year	90 %	86 %	99 %	98 %
3-year	74	67	93	88
5-year	70	62	86	81
7-year	67	58	80	74
	HR, 1.34, 1.08 to 1.64; *P*= 0.007		HR, 1.33, 1.02 to 1.74; *P*= 0.038	
Stage IIIc				
1-year	79 %	84 %	96 %	98 %
3-year	61	61	82	82
5-year	56	52	72	71
7-year	49	49	61	67
	HR, 1.00, 0.78 to 1.29; *P*= 0.999		HR, 0.93, 0.68 to 1.27; *P*= 0.637	

3611 **Poster Session**

Total neoadjuvant chemoradiation combined with neoadjuvant PD-1 blockade for patients with pMMR, high-risk, and locally advanced middle to low rectal cancer. *First Author: Aiwen Wu, Peking University Cancer Hospital and Institute, Beijing Cancer Hospital, Beijing, China*

Background: Total neoadjuvant therapy (TNT) with chemotherapy and chemoradiotherapy (CRT) is the standard treatment for locally advanced rectal cancer patients, especially for those with high risk factors. And the effects of immune checkpoint inhibitors (ICIs) on rectal cancer with defect mismatch repair (dMMR) have been demonstrated. However, the efficacy of TNT combined with PD-1 blockage for rectal cancer patients with proficient mismatch repair (pMMR) is unknown. The purpose of this study is to evaluate the clinical safety and efficacy of neoadjuvant PD-1 blockade combined with TNT in locally advanced rectal cancer with pMMR. **Methods:** We designed a prospective, single-arm, phase II study on stage II and III dMMR rectal cancer with high risk factors. Patients received neoadjuvant POC regimen (PD-1 inhibitor, camrelizumab, also called SHR01210, 200mg d1, Oxaliplatin 130mg/m2 d1 and Capecitabine 1250mg/m2 bid1-14, q3wks) for three cycles, then with long course chemoradiation (IMRT, 1.8Gy/f*25f). If there were no disease progression occurs, patients would be treated with another two cycles of CapeOx. The primary endpoint was pathological complete response rate (pCR rate), and the secondary outcome include adverse events and surgical complication. Biopsies and plasma pre-neoadjuvant therapy were collected and performed with whole-exome sequencing (WES), and ctDNA sequencing, respectively. **Results:** 27 patients were screened, of whom 25 patients were enrolled. All patients have completed the TNT. After neoadjuvant treatment, 21 patients underwent TME surgery. 7 (33.3%) patients were pCR, 3 (14.3%) achieved clinical complete or near complete response and 7 (33.3%) had a major pathological response. No progressive disease was found. WES and ctDNA sequencing analysis showed that tumor mutation burden (TMB) and level of ctDNA did not differ significantly between responders and non-responders. However, 3 responders with TMB high were found to be defective in other DNA damage repair pathways. **Conclusions:** Total neoadjuvant chemoradiation combined with neoadjuvant PD-1 blockade can achieve high pathological response rate, demonstrating its antitumor efficacy in pMMR locally advanced rectal cancer patients with high risk factors. Research Sponsor: None.

3612 **Poster Session**

Phase II, multicenter, open-label, non-randomized study of neoadjuvant chemotherapy NALIRINOX (5-FU/LV + oxaliplatin + nal-IRI) followed by chemoradiotherapy in patients with rectal cancer in a watch-and-wait program.

First Author: Cesar Gregorio Muñoz, HM-CIOCC, Madrid, Spain

Background: Despite optimal treatment sequence are still challenging, Neoadjuvant chemotherapy (NAC) followed by chemoradiotherapy (CRT) in patients with local rectal cancer (LRC), known as total neoadjuvant therapy (TNT), offers early treatment of micrometastases, with optimal exposure to systemic chemotherapy (CT) and rapid relief of local symptoms. In one hand, Nal-IRI has demonstrated efficacy and safety in the treatment of GI tumors. On the other hand, Watch and Wait (W&W) protocol is currently being imposed as an alternative to surgery in selected patients with LCR who achieve complete clinical response (cCR), offering the possibility of a rectum preservation strategy without the need to surgical intervention. Accordingly, TNT with NAC Nal-IRI, 5-FU, Oxaliplatin (NALIRINOX) could help to increase cCR rates in LRC treatment, allowing to enter W&W protocol. **Methods:** We performed a national, single arm, multicenter phase II study of patients with LRC treated with biweekly NAC NALIRINOX for 8 cycles followed by CRT. Main inclusion criteria were patients with confirmed histopathological diagnosis of LRC, good performance status and candidates for W&W protocol. Primary objective was the % of cCR rate obtained. Secondary objective was safety profile of NAC NALIRINOX combination. The first reassessment was carried out at 10 +/- 2 weeks after finish CRT, with digital rectal examination (DRE), pelvic MRI, CT body scan and rectoscopy. The results were evaluated and discussed by the multidisciplinary gastrointestinal Tumors Board (including Radiological Oncology, Medical Oncology, Surgery, Gastroenterology, Nuclear Medicine, Radiology and Pathology Departments) If patient achieved cCR, was included in W&W protocol with close follow-up with the same tests. **Results:** 30 subjects with LRC were recruited between March 2019 and July 2020 (22 men and 8 women); 26 (86.7%) subjects received 8 NAC NALIRINOX cycles. 1 subject received only 1 cycle, 2 subjects received 3 cycles and 1 received 7 cycles. A total of 25 (83.3%) subjects were evaluated for either W&W or surgery after CRT. 10 of them (45.5%) underwent surgery: 5 (50%) Low anterior resection (LAR) and 4 (40%) Abdominoperineal resection (APR). Therefore, 12 (54.5%) obtained cCR after first reassessment and underwent W&W protocol surveillance. Regarding safety endpoint, 6 (20%) subjects reported at least one grade 3 CTCAE toxicity related to any of the NALIRINOX medications. Diarrhea was the most frequent (13.3%), followed by asthenia (3.3%) and decreased appetite (3.3%). All of them had been resolved. **Conclusions:** TNT with NAC NALIRINOX is a safe and effective therapeutic approach to increase cCR rates and enable to select patients with LRC for W&W protocols Clinical trial information: NCT04009876. Research Sponsor: Fundación de investigación HM.

3613 **Poster Session**

Functional impact of somatic mutations in early-onset (EO) versus average onset (AO) microsatellite stable (MSS) stage III colorectal cancer (CRC).

First Author: Emily Harrold, Memorial Sloan Kettering Cancer Centre, Dublin, Ireland

Background: Analysis of the IDEA database demonstrates significantly worse disease-free survival in high-risk stage III EO CRC vs AO CRC, regardless of adjuvant therapy intensity or duration. Critically this analysis omits somatic mutational data and germline status. Enrichment of TP53 in EO metastatic CRC (mCRC) is well described and functionality of individual TP53 mutations has been proposed as a potential mechanism of chemotherapy resistance. The prognostic and functional impact of somatic mutations merits analysis in the EO high-risk Stage III cohort. **Methods:** The Memorial Sloan Kettering MSKCC IMPACT database was queried for MSS Stage III AO CRC (≥50 yrs) and EO CRC (< 50 yrs) patients(pts); clinico-pathological characteristics, systemic therapies received, and survival outcomes were reviewed. MSI, POLE mutated or hereditary syndrome associated tumors were excluded. We further classified TP53 mutations as GOF (gain of function) versus non GOF/ LOF (loss of function) (Pan M, JCO. 2022, Muller PA, Cancer cell. 2014). **Results:** 272 pts were included in the analysis (EO = 184, AO = 88). 50% of the EO and 62.5 % of the AO cohorts were male. Tumors were predominantly adenocarcinoma (EO 89% vs AO 91%), moderately differentiated (EO 78% vs AO 74%) and left sided (EO 77% vs AO 48.8%). 87% of the EO and 63.6 % of the AO cohort were TP53mut (p value 0.0003); TP53mut was enriched in the EO cohort regardless of sidedness but there was no significant difference in TP53 mutations between EO high vs low risk. Classifying by 7 putative GOF mutations (R175H, R248Q/W, R249S, R273H/L and R282W) 28.7% of the EO cohort harbored a GOF mutation vs 19.6% of the AO cohort. There was no statistically significant survival difference between pts with TP53mut tumors vs TP53 wild type (TP53wt) in the entire cohort (AO+EO) (p 0.041) or EO or AO cohorts (p 0.049). There was no significant difference in survival outcomes across all cohorts of TP53mut groups, both high and low risk, both GOF and non GOF, treated with 3 vs 6 months of chemotherapy (p 0.67). The EO TP53wt group was enriched relative to the EO TP53mut group for KRAS (60% vs 32%), BRAF (11% vs 4%), and PI3K driver alterations (PIK3CA, 20% vs 13%) and PTEN: (8% vs 3%) In the multivariate survival analysis of EO Stage III CRC BRAFmut status is highly statistically significant (p < 0.001). **Conclusions:** EO Stage III CRC is enriched for TP53 mutations regardless of sidedness and GOF mutations are identified in a higher proportion of EO CRC than AO CRC. We found no statistically significant difference in survival by TP53mut status across the entire MSS Stage III CRC cohort. There was no interaction between TP53mut status, duration of chemotherapy and overall survival. The functional impact of additional molecular features is being explored and the novel prognostic significance of BRAF demonstrated in this EO Stage III cohort requires further validation. Research Sponsor: None.

3614 **Poster Session**

Adiposity in resectable colorectal cancer.

First Author: Jessica Hopkins, Department of Surgery, University of Calgary, Calgary, AB, Canada

Background: Sarcopenia and myosteatosis affect survival in colorectal cancer (CRC). The role of adiposity is not yet fully elucidated. This study explores visceral and subcutaneous adipose tissue (VAT/SAT) distributions, and how they affect overall (OS), disease-free (DFS) and cancer specific survival (CSS). **Methods:** This retrospective cohort study, included resected stage I-III CRC in Alberta from January 2007 to December 2009. We excluded recurrent/metastatic disease or no CT scan. This study was approved by the Health Research Ethics Board at the University of Alberta. Body composition parameters were measured from CT scans. Sarcopenia and myosteatosis were defined by cohort-specific cut-off values. Total and visceral fat areas were indexed by height, and cohort-specific cut-offs defined total and visceral obesity (VO). SAT (SC:TFR) and VAT (V:TFR) to total adipose ratios were compared by gender, as described by Fleming. SAT and VAT fat radiodensity (Hounsfield units, HU) was measured and divided into quartiles. Differences between groups were compared with student's t-test and Fisher Exact test. Cox proportional hazard models were created, adjusting for important covariates, to assess adiposity effects on OS, DFS and CSS. **Results:** Our cohort included 968 patients with a median follow up of 63.5 months. The majority were stage II (38.6%) and III (51.0%). In total, 67.9% had total obesity and 51.0% had visceral obesity. In males, there was no difference in the incidence of myosteatosis or sarcopenia, regardless of V:TFR or SC:TFR. In women, those with a high V:TFR or SC:TFR had significantly higher incidence of myosteatosis, but not sarcopenia. Men and women with elevated V:TFR had significantly lower VAT and SAT HU (p<0.001, p=0.0113). Those with elevated SC:TFR had significantly higher VAT and SAT HU (p<0.001). VAT and SAT HU was lowest in those with myosteatosis alone (p<0.001; p=0.005). In survival analysis, VO and VAT HU quartiles predicted worse OS in uni-, but not multivariate analysis. SAT HU quartiles predicted worse survival in uni- and multivariate analysis, with the highest quartile of SAT HU predicting increased risk of death (HR 1.35, p=0.037). Adiposity was not predictive of CSS or DFS in uni- or multivariate analysis. **Conclusions:** This study demonstrated changes in VAT/SAT in relation to well described body composition parameters. SAT HU may have a more important role in OS than visceral adipose characteristics, despite known metabolic characteristics of VAT. True roles of adipose tissue in CRC outcomes remains unclear. VAT/SAT measurements using cross-sectional imaging allows for a detailed analysis and understanding of how adiposity may affect survival. Research Sponsor: Alberta Health Services.

Survival analysis.

	OS			
	Univariate		Multivariate	
	HR	p	HR	p
VO	0.695	0.018	0.895	0.539
VAT HU quartiles				
2	1.09	0.604		
3	1.30	0.092		
4	1.60	0.002	1.029	0.884
SAT HU quartiles				
2	1.36	0.061		
3	1.39	0.047		
4	2.21	<0.001	1.351	0.037
Sarcopenia	2.011	<0.001	1.378	0.008
Myosteatosis	2.025	<0.001	1.485	0.002

3615 **Poster Session**

Trend of sphincter-preserving surgeries for resectable low rectal cancer: A 20-year experience in China.

First Author: Qingqing Hu, Johnson & Johnson Epidemiology, Shanghai, China

Background: Over the last decades, patients with low rectal cancer have realized better functional, morbidity, and quality-of-life outcomes from improvements in surgical techniques in sphincter preservation. We aimed to quantify the trend in sphincter-preserving surgeries for low rectal cancer over 20 years in China. **Methods:** Between November 1999 and October 2021, a cohort of patients with pathologically confirmed primary malignant rectal tumor ≤5cm from the anal verge and who received selective surgery at Changhai Hospital, was identified. Demographic and clinical data were extracted from electronic medical records. Survival data were collected from outpatient medical records and follow-up phone interviews. A Joinpoint Regression Model was used to analyze trends in surgical procedures by average annual percentage change (AAPC). A Cox proportional hazards regression model adjusting for demographic and clinicopathological confounders was used to assess the overall survival for patients with sphincter-preserving surgery vs. abdominoperineal resection (APR). **Results:** Among 19,276 patients with colorectal cancer, 4,072 (21.1%) had a tumor in the low rectum during the study period; 3,025 (74.2%) underwent a sphincter-preserving surgery and 1,047 (25.7%) received APR. Sphincter-preserving surgery increased 3.6% per year (AAPC 3.6, p=.006). Anterior resection was the most performed procedure (86.3%) and maintained a steady trend (AAPC 0.13, p=.49), while intersphincteric resection (including conformal sphincter preservation operation) increased 49.4% annually (AAPC 49.4, p=.003). Laparoscopic techniques increased 15.1% per year (AAPC 15.1, p=.035). Sphincter-preserving surgery increased annually for tumors ≤2cm, 2-3cm and 3-4cm from the anal verge (AAPC 7.08, p=.001; 4.69, p=.001; 2.66, p=.001, respectively). A total of 2,854 patients had sufficient vital status data for inclusion in the survival analysis. The characteristics of those with and without a follow-up encounter were comparable. Patients with sphincter-preserving surgery had a lower risk of death compared to APR (adjusted HR 0.78, 95% CI, 0.65-0.93, p=.01). **Conclusions**: Utilization of sphincter-preserving surgeries increased significantly over the last 20 years. Patients with low rectal cancer who underwent sphincter preservation had better survival than similar patients who underwent APR. Research Sponsor: None.

Hazard ratios (HRs) for all-cause mortality among patients with low rectal cancer.

Characteristics		HR (95% CI)	P
Sphincter-preserving surgery (vs. APR)		0.78[a] (0.65-0.93)	0.01
Tumor location (vs. 4-≤5cm from the anal verge)	≤2cm	1.19 (0.95-1.48)	0.13
	2-≤3cm	0.92 (0.76-1.12)	0.40
	3-≤4cm	0.99 (0.83-1.20)	0.96
Pathological stage (vs. I)[b]	II	0.97 (0.80-1.18)	0.79
	III	2.01 (1.70-2.38)	<0.005

[a]Adjusted for age, sex, comorbidity, tumor location and stage. [b]Based on AJCC 8th edition staging system.

3616 **Poster Session**

Label-free and automated approach to rapidly classify microsatellite instability (MSI) in early colon cancer (CC) analyzing the AIO ColoPredictPlus 2.0 (CPP) registry trial. *First Author: Stephanie Schörner, Center for Protein Diagnostics (PRODI), Dept. of Biophysics, Ruhr-Universität Bochum, Bochum, Germany*

Background: MSI due to mismatch repair defects accounts for 15-20% of all CC, has high prognostic and predictive value and is broadly utilized in treatment decisions. Artificial intelligence (AI) integrated, label-free quantum cascade laser (QCL) based infrared (IR) imaging resolves spatial and molecular alterations such as MSI in unstained cancer tissue sections. We aimed to evaluate the method for microsatellite instability/stability (MSI/MSS) classification in samples from the prospective multicenter AIO CPP registry trial. **Methods:** Paraffin-embedded unstained cancer tissue slides from patients (pts.) participating in CPP were measured (avg. 30 min/slide) and analyzed. The cohort was split into training (train), test (test), and validation (vali) sets. Cancer regions were first preselected based on a self-developed convolutional neural network (CNN) CompSegNet (Schuhmacher, medrxiv 2021). A VGG-16 CNN then classified MSI/MSS in these regions. Endpoints were area under receiver operating characteristic (AUROC) and area under precision recall curve (AUPRC). **Results:** 547 pts. (train n=331, test n=69, vali n=147) were analyzed. The baseline characteristics for the sub-cohorts are illustrated in the table. Mutation (MT) status: RAS MT: train 30% / test 30% / vali 37%; BRAF MT: train 27% / test 23% / vali 14%. The preselection of cancer regions reached a validation AUROC of 1.0. The subsequent MSI/MSS classifier reached a validation AUROC of 0.9 and AUPRC of 0.74 (sensitivity 85%, specificity 84%). **Conclusions:** Our multicenter approach using AI integrated label-free IR imaging provides an automated, fast, and reliable classification for MSI/MSS with an AUROC of 0.9 (sensitivity 85%, specificity 84%) almost comparable to the present gold standard immunohistochemistry. The method described here requires less samples for training when compared to other AI approaches which could facilitate the development of prognostic/predictive classifiers in the setting of randomized controlled trials. This novel technique may support further understanding of the increasingly important MSI CC cohort and support treatment decisions e.g. in specific subgroups such as targetable fusions. We expect our approach to be a broadly applicable diagnostic tool in the future. Research Sponsor: Ministry of Culture and Science (MKW) of the State of North-Rhine Westphalia, Germany, Pharmaceutical/Biotech Company.

Baseline characteristics for cohorts.

		train (MSI)	train (MSS)	test (MSI)	test (MSS)	vali (MSI)	vali (MSS)
N		142	189	30	39	26	121
Age	mean	71	68	73	70	73	66
Sex	f/m in %	64/36	40/60	67/33	31/69	65/35	50/50
UICC	I (%)	9 (6)	1 (0)	2 (6)	0 (0)	1 (4)	0 (0)
	II (%)	64 (45)	37 (20)	14 (47)	8 (20)	16 (61)	13 (11)
	III (%)	69 (49)	151 (80)	14 (47)	31 (80)	9 (35)	108 (89)
Location	left (%)	30 (21)	98 (52)	6 (20)	21 (54)	3 (12)	53 (44)
	right (%)	112 (79)	90 (48)	24 (80)	18 (46)	23 (88)	64 (53)
	other (%)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	4 (3)

f: female; m: male.

3617 **Poster Session**

A phase II trial of TGFβ type I receptor inhibitor, galunisertib, plus neoadjuvant chemoradiation in patients with locally advanced rectal cancer. *First Author: Kristina Hoot Young, Earle A. Chile Research Institute, Providence Cancer Institute, Portland, OR*

Background: Transforming growth factor beta (TGFβ) is an immunosuppressive cytokine upregulated in colorectal cancer. Preclinical data demonstrated improved response to chemoradiation with TGFβ blockade in colorectal adenocarcinoma. Here we report the results of our single arm Phase II study combining the TGFβ type I receptor kinase inhibitor, galunisertib, with neoadjuvant chemoradiation in patients with locally advanced rectal adenocarcinoma. **Methods:** Eligible patients had T3+ or N+ rectal adenocarcinoma planned for surgical resection. Enrolled patients completed a 14-day course of galunisertib, followed by chemoradiation with continuous infusion 5-fluorouracil or capecitabine with radiation to 50.4-54Gy in 28-30 fractions. On day 30, patients underwent another 14-day course of galunisertib concurrent with ongoing chemoradiation. Five to nine weeks after completing neoadjuvant therapy, patients underwent response assessment. Those with complete response by physical exam, proctoscopy, and MRI, could opt for non-operative management and proceed to mFOLFOX6. Those with less than a complete response underwent surgical resection. The primary endpoint was complete response rate (CR), which was a composite of pathologic complete responses in those patients who proceeded to surgery, and clinical complete responses maintained at 1 year after completion of therapy for those who chose non-operative management. Using a Simon Two-Stage approach with 90% power and $\alpha = 0.05$, to detect a 20% improvement in complete response rate compared to historical control (15% vs 35%); we reject the null hypothesis if ≥10/38 patients have a CR. 38 patients were enrolled with 35 patients evaluable. **Results:** Median age was 51y, 68% of patients were male, 87% of patients were Stage III, 97% of patients were node-positive, and 97% were proficient in mismatch repair. 95% of patients completed study therapy. Toxicity attributed to galunisertib was Grade 1-2. 28 patients went to surgery, with a mean neoadjuvant rectal (NAR) score (NAR = 5pN-3(cT-pT)+12]^2/9.61) of 11.29, and pCR in 7 patients. 7 patients underwent non-operative management, with 5 achieving cCR at 1 year. Therefore, complete responses were observed in 12 patients. Peripheral immune monitoring revealed percent change in CD3+CD4-CXCR3+ T cells and activated $CD8_{EM}$ T cells correlated with response to therapy. 2y PFS and OS were 81.5% and 97%. **Conclusions:** The addition of TGFβ inhibition to neoadjuvant chemoradiation in locally advanced rectal cancer markedly improved response to therapy, was well tolerated, and warrants further investigation. Clinical trial information: NCT02688712. Research Sponsor: None.

3619 **Poster Session**

Clinical and radiological predictors of organ preservation in patients with rectal cancer treated with total neoadjuvant therapy. *First Author: Jonathan B Yuval, Colorectal Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Baseline rectal MRI is routinely used for tumor staging, selecting the initial treatment and prognostication of patients with rectal adenocarcinoma. However, associations of baseline clinical and MRI variables with organ preservation (OP) in a prospective randomized trial have not been reported. **Methods:** Patients with MRI staged clinical stage II or III rectal adenocarcinoma treated in a prospective phase II clinical trial were randomized to either induction chemotherapy (FOLFOX or CAPEOX) followed by chemoradiation or chemoradiation followed by consolidation chemotherapy (FOLFOX or CAPEOX) and recommended total mesorectal excision (TME) or watch-and-wait (WW) based on clinical response. The primary outcome was OP, defined as the time from randomization to the clinical decision of TME or last follow-up, whichever occurred first. Clinical variables included: age, sex, race, tumor grade, radiation dose and treatment arm. Radiological variables (evaluated by baseline MRI prior to randomization) included: distance from the anal verge, tumor length, clinical T stage, clinical N stage, relationship to the mesorectal fascia, presence of extramural vascular invasion (EMVI) and mucinous radiographic findings (>50%). Associations of OP with clinical and radiological variables were assessed utilizing the Cox regression model in univariate and multivariate settings. The final multivariate model was chosen using backward selection. Results were analyzed by intention to treat. **Results:** Case report forms (CRFs) from baseline MRI were available for 289 of 324 randomized patients (89%). Patients with CRFs differed from those without CRFs in race, distance of the tumor from the anal verge and clinical T stage. Median follow-up was 3.4 years. A total of 156 of 324 patients were recommended TME during the study period. The 3-year OP rate was 47%. Independent predictors of OP in the multivariate analysis can be seen in the table. **Conclusions:** Although the patients included in this analysis may not be fully representative of the entire cohort, our data shows that several radiological variables associated with unfavorable tumor biology – tumor involvement of the mesorectal fascia, presence of EMVI and involved mesorectal nodes – were negatively associated with organ preservation. This information will be useful in selecting rectal cancer patients for WW and should be used for patient stratification in future clinical trials. Clinical trial information: NCT02008656. Research Sponsor: U.S. National Institutes of Health.

Characteristic	HR[1]	95% CI[2]	p-value
Arm: *Consolidation vs. Induction*	0.76	0.54, 1.07	0.11
Tumor Length (cm)	1.10	0.99, 1.23	0.066
Mesorectal Fascia: *vs. Clear*			
Threatened	0.83	0.48, 1.42	0.5
Involved	1.55	1.05, 2.28	0.028
Not Applicable	1.15	0.58, 2.27	0.7
Clinical N Stage: *N+ vs. N0*	1.89	1.23, 2.90	0.004
EMVI Present: *vs. Absent/Indeterminate*			
Present	1.63	1.02, 2.59	0.041
Not Reported	0.93	0.63, 1.36	0.7

[1]HR = Hazard Ratio, [2]CI = Confidence Interval.

3620 **Poster Session**

Genetic ancestry differences in tumor mutation in early and average-onset colorectal cancer. *First Author: Brooke Rhead, Tempus Labs, Inc., Chicago, IL*

Background: The incidence and mortality of early onset colorectal cancer (EOCRC), defined as CRC diagnosed prior to age 50, are rising, in contrast to declining rates of average onset CRC (AOCRC). Epidemiologic trends for CRC appear to differ by race/ethnicity, which could be related in part to underlying differences in tumor mutation and gene expression. Previous research has used self-reported race/ethnicity categories, which has been shown to be missing or inaccurate, particularly in highly admixed groups such as Black and Hispanic patients. Hence, we examined tumor profiles of EOCRC and AOCRC using genetic ancestry. **Methods:** Genetic ancestry was inferred from de-identified data of 1,443 and 3,315 patients with EOCRC and AOCRC, respectively, who underwent tumor profiling with the Tempus xT NGS 648-gene panel and targeted RNAseq. Ancestry informative markers were used to estimate likelihoods for the five continental groups defined in the 1000 Genomes Project: Africa (AFR), Americas (AMR), East Asia (EAS), Europe (EUR), and South Asia (SAS). We assessed the association of genetic ancestry proportions (per 10% increase in each ancestry proportion) with presence of protein altering somatic mutations in key driver genes in CRC. We also assessed interactions between onset age (EOCRC vs. AOCRC) and genetic ancestry in somatic mutations. **Results:** Across all ages, African ancestry was associated with higher odds of mutations in APC and KRAS and lower odds of BRAF mutations (Table). East Asian ancestry was associated with higher odds of mutations in NTRK3 and TP53. For EOCRC, the association between KRAS and African ancestry remained significant (OR 1.07, p=0.04). Furthermore, there was an interaction (p=0.031) between onset age and race/ethnicity such that the association between African ancestry and APC mutation was significant in AOCRC (OR=1.09) but not EOCRC (OR=1.00). **Conclusions:** The use of genetic ancestry instead of categorical race/ethnicity provides a more quantitative and precise profile of shared genetic background that can underlie biological race differences in CRC cancer etiology and outcomes. Research Sponsor: Philanthropic funding (Dedman Family Scholar in Clinical Care).

Gene	Odds Ratio	p-value AFR	p-value AMR	p-value EAS	p-value SAS
APC	1.05 (AFR)	<0.001	1.00	1.00	1.00
BRAF	0.91 (AFR)	<0.001	0.51	1.00	1.00
KRAS	1.08 (AFR)	<0.001	1.00	1.00	1.00
NTRK3	1.11 (EAS)	1.00	1.00	0.036	1.00
TP53	1.06 (EAS)	1.00	1.00	0.036	1.00

3621 **Poster Session**

The impact of African ancestry on colorectal cancer disparity. *First Author: Yoo Jin Joung, Morehouse School of Medicine, Atlanta, GA*

Background: Colorectal cancer is the second leading cause of cancer deaths in the world to affect both men and women. Racial disparities have been known to affect the disease diagnosis and progression, and proliferative genomic studies have been undertaken to elucidate their relationship. In this study, we investigate the tumor mutation profile in colorectal adenocarcinoma (COAD) based on genetic ancestry using The Cancer Genetic Ancestry Atlas (TCGAA). **Methods:** 59 AA (African American) individuals in TCGAA COAD dataset were identified. To account for and eliminate the biases introduced by self-identification of races, we utilized TCGAA genomic analysis to accurately estimate the ancestral genomic composition of each individual. For each individual, percentages of European (EA), West African (WA), East Asian (EAA), and Native American (NA) ancestry were identified based on Local Ancestry in adMixed Populations (LAMP). Individuals were screened for dominant WA ancestry (≥50% based on LAMP) and assigned to three groups, ≥90%, 80-89%, and 50-79%. Differences in gene mutation frequency and overall survival were compared among the three subgroups of individuals with WA ancestry. **Results:** Based on genomic ancestry analysis, 58 individuals with dominant WA ancestry (Range 53%-100%) were identified. We classified them into three groups based on percentage of WA ancestry: ≥90% (n = 17), 80-89% (n = 26), and 50-79% (n = 15). *APC* was the most frequently mutated gene in all groups except ≥90% WA ancestry, which had the most mutation frequency in *TP53*. ≥90% WA ancestry showed the highest rate of mutation of 81.3% in *TP53* compared to 70.8% (80-90% WA ancestry) and 40.0% (50-79% WA ancestry). Interestingly, ≥90% WA ancestry had the highest average rate of mutation (33%) for 7 tumor suppressor genes (*AMER1, APC, ARID1, FBXW7, TCF7L2, TGFBR2,* and *TP53*), compared to 29% and 22% in 80-89% WA ancestry and 50-79% WA ancestry, respectively. In addition, ≥90% WA ancestry had a lower rate (19%) of mutation in 6 oncogenes (*BRAF, NRAS, KRAS, PIK3CA, SMAD4,* and *SOX9*) compared to 24% in both 80-89% and 50-79% WA ancestry. Although not statistically significant, a higher percentage of WA ancestry in an individual was correlated with a downward trend in the overall survival rate (median survival 56.3 months in ≥90% WA ancestry vs 61.8 months in 80-89% WA ancestry). **Conclusions:** In this study, we analyzed different gene mutations correlated with African ancestry and their potential relationship to the etiology, progression, and prognosis of COAD. The mutation profile of these genes will allow us to investigate altered pathways associated with African ancestry and draw insight into colon cancer pathogenesis in various ancestry groups. Further studies are warranted to elucidate the role of genetic ancestry in tumorigenesis and disease progression and to identify potential therapeutic targets specific to groups disproportionately affected by cancer. Research Sponsor: None.

3622 **Poster Session**

Radical versus local surgical excision for early rectal cancer: A systematic review and meta-analysis. *First Author: Sarah El-Nakeep, Ain Shams University, Department of General Internal Medicine MD, Cairo, Egypt*

Background: Colorectal cancer is the third common cancer worldwide. Radical excision (RE) as total mesorectal excision for rectal cancer carries a higher risk of mortality and morbidity, while local excision (LE) could decrease these postoperative risks. However, the long-term oncologic outcomes of LE are still debatable. We aim to study the effect of LE versus RE in T1 and T2 rectal cancer. **Methods:** We conducted a systematic review and meta-analysis. We searched PubMed and CENTRAL databases, using an optimized search-strategy from inception until 15 June 2021, without restriction on publication date or status. We included only cohort and randomized controlled trials (RCTs). Two authors independently screened the title, abstracts, and full-text manuscripts for inclusion and data extraction. All included trials contained at least one of the primary outcomes. We used RevMan 5.4 tool for data analysis. We calculated both hazards ratio (HR) and risk ratio (RR) for the 5-years survival analyses, with their 95% confidence intervals (CI). We assessed both clinical and statistical heterogeneity of the studies; I^2 >75% was considered highly heterogeneous. We used random effect model (REM). We used standardized mean difference (SMD) for hospitalization days. We conducted a subgroup analysis of patients with T1-only without adjuvant chemo/radiotherapy (CRT). **Results:** We retrieved from the search a total of 1243 reports. A total of 18 studies were included for final meta-analysis (4 RCTs and 14 retrospective cohorts). Nine studies were multi-central while ten were unicentral studies. We did not find any difference in risk ratio (RR) between overall survival (OVS) and disease-free survival (DFS). But there were higher HRs in OVS and DFS with LE as compared to RE. A higher recurrence rate was also seen with LE. Six studies showed absent 30-days postoperative mortality in both groups so we used peto-odds ratio. Postoperative mortality and morbidity were lower with LE rather than RE. **Conclusions:** LE for early stage rectal cancer has a higher risk of decreased 5-year OVS and DFS than RE, with higher local recurrence rate. However, LE is associated with lower early postoperative mortality, morbidity, and hospitalization days, as compared to RE. Patient selection is key to balance these risks for the optimal outcome. Research Sponsor: None.

LE vs. RE meta-analysis results.

Outcome or Subgroup	Number of Studies	Number of Participants	Statistical methods	Estimate effect, 95% CI
1- OVS in 5-years	14	23717	HR	1.41 [1.14, 1.74]
2- OVS in 5-years %	15	27037	RR	0.95 [0.91, 0.99]
3- DFS in 5-years	10	2568	HR	1.95 [1.36, 2.78]
4- DFS in 5-years %	10	3541	RR	0.93 [0.87, 1.01]
5- Local recurrence rate %	13	6952	RR	2.85 [1.86, 4.36]
6- Mortality in 30-days	10	8800	Peto Odds Ratio	0.36 [0.22, 0.59]
7- Total post-operative morbidity	7	671	RR	0.38 [0.18, 0.80]
8- Hospital stay post-operative	5	3336	SMD	-2.23 [-3.64, -0.83]
9- OVS T1 only- without CRT	6	14275	HR	1.46 [1.08, 1.99]

3623 **Poster Session**

Circulating tumor DNA (ctDNA) as a minimal residual disease (MRD) assessment and recurrence risk in patients undergoing curative intent resection with or without adjuvant chemotherapy in colorectal cancer: A systematic review and meta-analysis. *First Author: Anusha Chidharla, University of Illinois at Peoria, Peoria, IL*

Background: Minimal residual disease (MRD) assessment may effectively detect cure in patients with colorectal cancer (CRC). Emerging data have suggested that circulating tumor DNA (ctDNA) can be a reliable biomarker for MRD in patients. Recent studies have shown the ability to detect MRD using ctDNA assay to assess recurrence risk and patient selection for adjuvant chemotherapy. We performed a systematic review and metanalysis of post operative ctDNA in Stage I-IV (oligometastatic) CRC patients after curative intent resection with or without adjuvant chemotherapy. **Methods:** We searched PubMed/Medline, EMBASE, Web of Science, Cochrane Library, and Google from inception to February 3, 2022 using keywords related to colorectal cancer, ctDNA, and MRD. The search also includes paper and conference presentations. The search resulted in 427 studies after removing the duplicates. Data were extracted to perform a meta-analysis using RevMan 5.4. software. Subsequent subgroup analysis was performed for stages I-III and oligometastatic stage IV CRC patients. **Results:** After the initial abstract screening, 48 studies were identified. The final review led to the inclusion of 27 studies representing 3459 patients with evaluable ctDNA, with 623 having +ve post-surgery ctDNA levels. Seven studies had analyses of patients specifically with oligometastatic disease, the rest 20 studies subdivided within stages I-III. The pooled HR for RFS in post-surgical ctDNA +ve vs -ve patients in all stages was 7.16 (95% CI 6.12-8.36) p <0.00001. Subgroup analysis revealed pooled HR = 8.27 (95% CI 6.16-11.09) and 6.07 (95% CI 4.54-8.13) for stage I-III and IV CRC, respectively. Only 11 studies did analysis for post adjuvant chemotherapy patients based on ctDNA status. The pooled HR for RFS in post-adjuvant chemotherapy ctDNA +ve versus -ve patients in all stages was 12.40 (95% CI 9.24-16.64) p <0.00001. Subgroup analysis revealed pooled HR = 13.95 (95% CI 9.08-21.43) and 11.39 (95% CI 5.99-21.66) for stage I-III and IV CRC, respectively. **Conclusions:** This is the largest and most current meta-analysis done on ctDNA levels as MRD assessment in CRC. Our analysis emphasizes that post operative ctDNA is a strong prognostic marker of RFS. Based on our results ctDNA can be a significant and independent predictor of RFS. Several ctDNA-based randomized adjuvant trials are ongoing internationally to confirm the clinical utility of ctDNA in colorectal cancer. Research Sponsor: None.

RFS by ctDNA status.

	HR (95%CI)	P value
RFS by Post-surgery ctDNA status		
All Stages	7.16 (6.12-8.36)	<0.00001
Stage I-III	8.27 (6.16-11.09)	<0.00001
Stage IV	6.07 (4.54-8.13)	<0.00001
RFS by Post-adjuvant ctDNA status		
All stages	12.40 (9.24-16.64)	<0.00001
Stage I-III	13.95 (9.08-21.43)	<0.00001
Stage IV	11.39 (5.99-21.66)	<0.00001

3624 **Poster Session**

Total cost of care differences in National Comprehensive Cancer Center (NCCN) concordant and non-concordant patients with colon cancer. *First Author: Ujwal Sapkota, CVS Health, Lincoln, RI*

Background: National Comprehensive Cancer Network (NCCN) colon cancer treatment guidelines have been developed to standardize and improve quality of care. While studies have shown that concordance to these guidelines improves survival, little information exists regarding the impact of concordance and total cost of care (TCOC). This study aimed to evaluate the economic impact of NCCN concordance in patients with colon cancer versus those receiving non-concordant therapies. **Methods:** This is a retrospective study of patients throughout the United States with colon cancer at a large national Medicaid, Medicare, and commercial insurer from January 1, 2019 - December 31, 2020. NCCN regimen concordance was identified from pharmacy and medical claims and defined as concordant if the entire prescribed treatment regimen matched an NCCN regimen (Level 1 and 2a); patients not receiving an NCCN recommended regimen were deemed to be non-concordant. TCOC and its cost components were contrasted on a matched population of concordant and non-concordant patients with a ratio of 2:1. To eliminate possible selection bias and differences in baseline characteristics that could affect cost, propensity scores were developed using logistic regression and used to match patients on age, comorbidity, socioeconomic status (SES) index and treatment type (chemotherapy and radiation). **Results:** A total of 937 patients with colon cancer were included (Medicare n = 588; commercial fully insured n = 149; commercial self-insured n = 200). Beginning with and including the first treatment and for up to 180 days after, the TCOC in the concordant group was significantly less among Medicare patients; a reduction of 33% (a difference of $2,986, p < 0.001) in TCOC per member per month (PMPM) was observed. This cost difference was driven primarily by medical chemotherapy spend as concordant patients spent 26% less (a difference of $1,160, p < 0.001). Concordant patients spent 29% less PMPM than non-concordant patients (a difference of $35, p < 0.001) on Evaluation and Management compared to non-concordant patients. There were no significant differences in Inpatient, Emergency Room and Radiation Oncology costs among all patients (p > 0.05). No significant differences were seen in TCOC among commercial fully insured (a difference of $69, p = 0.99) and commercial self-insured (a difference of $5,413, p = 0.07) patients, likely due to smaller sample sizes. **Conclusions:** In this study, Medicare patients who received NCCN concordant colon cancer regimens spent significantly less in TCOC than patients receiving non-concordant regimens. These savings highlight the importance of evidence-based guidelines in treatment determinations to optimize the value of cancer care. More extensive studies are needed to assess if these findings translate to commercially insured patients and the long-term economic impact of concordance. Research Sponsor: None.

3625 **Poster Session**

The differential response to immune checkpoint inhibitors in colorectal and endometrial cancer patients according to different mismatch repair alterations. *First Author: Moh'd M. Khushman, Department of Hematology-Oncology, University of Alabama at Birmingham/O'Neal Comprehensive Cancer Center, Birmingham, AL*

Background: In colorectal cancer (CRC) and endometrial cancer (EC) patients (pts), preliminary data suggest a differential response to immune checkpoint inhibitors (ICIs) according to different MMR alterations. The drivers of this difference remain unknown and no reliable predictive biomarker has been found. We explored the genomic alterations, tumor mutation burden (TMB), immune-related gene expressions and signatures, tumor microenvironment (TME), neoantigen load and median overall survival (mOS) inCRC and EC pts treated with ICIs with different MMR alterations. **Methods:** 13,701 CRC and 3,315 EC specimens were tested at Caris Life Sciences (Phoenix, AZ) with Next Gen Sequencing (NGS) of DNA (592-gene or whole exome) and RNA (whole transcriptome). MMR/MSI status was determined by IHC of MMR protein and/or NGS. Immune cell abundance was quantified using quanTIseq. Gene expression profiles were analyzed for T cell-inflamed signature (TIS) and IFN-gamma scores. Immune epitope prediction was performed using the NetMHCpan v4.0 method in the Immune Epitope Database. Real-world mOS was obtained from insurance claims data and calculated from tissue collection or ICIs start to last contact. Statistical significance was determined using chi-square/Fisher-Exact and adjusted for multiple comparisons (adjusted $p < 0.05$). **Results:** In CRC, 84 (0.6%) pts had intact expression of MLH1 and PMS2 and co-loss of MSH2 and MSH6 (MutS) and 648 (4.7%) had co-loss of MLH1 and PMS2 and intact MSH2 and MSH6 (MutL). 117 (0.9%) had other MMR IHC loss. APC, KRAS, ERBB2, ERBB3 and MSH2 mutations rates were higher in MutS while BRAF mutation rate was higher in MutL. B cell, NK cell content and neoantigen load (high affinity epitopes: $p < 0.05$, intermediate: $p < 0.01$, low: $p < 0.001$) were higher in MutS. The mOS in MutS (N = 149) vs. MutL (N = 980) was 56 months (m) vs. 36 m ($p = 0.003$). In ICI-treated pts, the mOS in MutS (N = 28) vs. MutL (N = 149) was not reached (NR) vs. 32 m ($p = 0.005$). BRAF mutation didn't impact survival in MutL. In EC, 48 (1.4%) pts had MutS and 915 (27.6%) had MutL. 81 (2.4%) had other MMR IHC loss. IHC-PD-L1, TMB, neoantigen load (high affinity epitopes: $p < 0.01$, intermediate: $p < 0.0001$, low: $p < 0.0001$), TIS, IFN-gamma scores, immune related gene expressions, TME (Macrophage M1, CD8+) were higher in MutS. The mOS in MutS (N = 94) vs. MutL (N = 1804) was NR vs. 47 m ($p < 0.001$). In ICI-treated pts, the mOS in MutS (N = 11) vs. MutL (N = 273) was NR vs. NR ($p = 0.559$). **Conclusions:** This is the largest study to explore differential response to ICIs in CRC and EC pts with different MMR alterations. In pts with CRC and EC, the mOS was longer in MutS compared to MutL. In ICI-treated pts, the mOS was longer in MutS compared to MutL in CRC but not in EC. Among the explored biomarkers, neoantigen load was higher in MutS compared to MutL in both CRC and EC and maybe the driving factor for differential response to ICIs. Research Sponsor: None.

3626 **Poster Session**

Impact of the COVID-19 pandemic on colorectal cancer (CRC) care: Data from 22 German cancer centers (CC) and the Institute of Pathology, Ruhr-University Bochum - the AIO (Working Group for Internal Oncology of the German Cancer Society) CancerCOVID Consortium - AIO-YMO/KRK 520/ass. *First Author: Celine Lugnier, Department of Hematology, Oncology and Palliative Care, St. Josef-Hospital, Ruhr-University Bochum, Bochum, Germany*

Background: CRC still is one of the leading causes of cancer related death though prognosis has improved through guideline based management. The COVID-19 pandemic lead to re-allocation of resources subordinating all sections of care for CRC patients. We present data on changes of CRC care during the pandemic from 22 German AIO CC and our high volume Institute of Pathology (pathology). **Methods:** Data was collected retrospectively comparing the months (mo) of the first wave (fw) (4-6/2020) and second wave (sw) (11-12/2020) of the pandemic with corresponding periods (cp) in 2019 focusing on the number of precancerous (ICD-O/0+2) and malignant (ICD-O/3+6) colorectal lesions (CRL) diagnosed by our pathology, the number/stage of primary diagnoses (PD) and the number of surgeries (surg) at AIO CC. There, quality criteria of CRC care were also assessed (number of PD discussed within a multidisciplinary tumor board (tb), received social service (soc)/ psychological (psy) counseling or recruited into a clinical trial). Statistical analysis was performed using students t-test for paired data. **Results:** Numbers of CRL detected upon histology (row 1-3), number of cases, surg and quality criteria from AIO CC (row 4-9) are displayed in the table. We saw a dip in diagnosed CRL and number of surg ($p=0.007$) only during fw, whereas PD dipped significantly in both waves. A significant reduction in diagnosis of stage III CRC was detected for 2019 vs. 2020 ($p=0.001$), not for other stages. Quality criteria showed a significant reduction in clinical trial inclusion, a small dip in soc/psy counseling and persistently high tb presentation. **Conclusions:** We detected a significant decrease of premalignant lesions and primary cancers during the first year of the pandemic which may impact cancer mortality in the future. Certified German CC provided CRC care with significant reduction in clinical trial inclusion only, suggesting high stability of established certified cancer care infrastructure. Research Sponsor: Bundesministerium fuer Bildung und Forschung.

Detailed data from pathology (1-3) and AIO CC (4-9).

	2019 total	2020 total	fw/cp 2019	fw 2020	*fw p=*	sw/cp 2019	sw 2020	w *p=*	*2019/20 p=*
Total (pathology)	30794	29901	2531	2122		2462	2390		
ICD-O/0+2	27848	27046	2294	1927		2250	2161		
ICD-O/3+6	2848	2750	233	191		206	224		
PD (AIO CC)	2322	1995	8.5	6.8	0.004	8.4	5.7	0.005	<0.001
surg	1604	1505	7.4	5.5	0.007	7	5.6	0.23	0.003
trial	313	160	2.9	1.9	0.06	2.6	2	0.3	<0.001
%/PD	42.93	27.77	41.28	27.59		37.90	29.96		
tb	872	792.76	6.6	4.9	0.06	6.5	5.6	0.26	0.18
%/PD	94.44	67	92.02	94.25		97.16	92.48		
psy	417	354	3.1	2.3	0.1	3.3	2.9	0.4	0.04
%/PD	47.48	42.83	45.97	44.46		47.31	37.35		
soc	611	521	4.9	3.7	0.08	5.2	3.6	0.03	0.012
%/PD	63.31	63.31	64.93	63.93		78.08	53.97		

Numbers in column fw/ sw, 2019/ 2020 represent the mean numbers of cases per mo (1-3) or per mo and site (4-9).

3627 **Poster Session**

Validation of a multi-modal blood-based test for the detection of colorectal cancer with sub single molecule sensitivity. *First Author: Kevin D'Auria, Guardant Health, Redwood City, CA*

Background: Blood-based colorectal cancer (CRC) screening tests can improve adherence to screening guidelines. Yet, current commercially available options have poor sensitivity and specificity inhibiting incorporation into routine clinical care. Here we report the validation of a blood-based test for the detection of colorectal cancer and advanced neoplasia. **Methods:** This blood-based test aims to detect colorectal neoplasia by identifying tumor-associated biomarkers including genomic or epigenomic (methylation and fragmentomics) signatures in cell-free DNA (cfDNA). cfDNA is partitioned based on methylation level, enriched for informative genomic regions, and sequenced. This novel workflow enables high-fidelity analysis of multimodal information in majority of extracted cfDNA molecules. Results are integrated into a binary "detected" versus "not-detected" result using a proprietary bioinformatic pipeline (Guardant Health, USA). The assay was trained on samples obtained from >6,000 unique individuals (2,685 cancer-free and 1,698 with advanced colorectal neoplasia (ACN) for training, 1,072 cancer-free and 551 with ACN for threshold setting). The thresholds were frozen prior to validation targeting a specificity of > 91.5%. Each aspect of the validation study followed Nex-StoCT CLIA working group and CLSI guidelines. **Results:** Limit of detection (LoD) was established across six dilutions. Even for low cfDNA mass inputs of less than 4ng, the 95% LoD was determined to be less than 1 tumor-derived genomic equivalent (0.5), indicating over at least 10-fold increase in assay sensitivity compared to best-in-class assays for somatic mutation detection. Precision studies in 60 positive and negative replicates from clinical samples yielded >90% average positive and negative percent agreement both within and between batches. Endogenous interference studies yielded > 90% positive and negative percent agreement between reference control and common endogenous substances, including albumin, bilirubin, hemoglobin, triglycerides, and genomic DNA, in clinical positive and negative samples and minimally manipulated samples. The clinical validation of the test was conducted in > 300 cases (biobanked pre-operative cohort for CRC cases and screening cohort for advanced adenoma and negative cases). **Conclusions:** Here we present the validation of a multi-modal blood-based test for the detection of colorectal cancer. This test is currently being evaluated in a registrational study (ECLIPSE: NCT04136002). Research Sponsor: Guardant Health.

3628 **Poster Session**

Disproportionate morbidity and mortality in African American and Asian patients from colorectal cancer: A nationwide analysis. *First Author: Jorge Franco, Universidad Latina, San José, Costa Rica*

Background: Published literature points towards the disproportionate prevalence of colorectal cancer (CRC) in ethnic groups. Racial minorities are also prone to higher mortality due to inequalities in access to healthcare. Therefore, we examined the disparities in hospital-related outcomes among racial groups from CRC. **Methods:** We investigated the National Inpatient Sample 2019 employing International Classification of Diseases-10 (ICD-10) codes to include adult patients with CRC. We compared various outcomes stratified by racial groups with White as the reference group. Analyses were performed using STATA (v 14.2), considering 2 sided *P*< 0.05 as statistically significant. Proportions were compared using Fisher exact test and continuous variables using Student's t-test. Confounding variables were adjusted using multivariate logistic and linear regression analyses and included: gender, Charlson Comorbidity Index, median household income for patients' zip codes, hospital location/region/bedside, and insurance status. **Results:** Out of 732,492 included patients, 72.77% White, 13.66% African American (AA), 9.91% Hispanics, and 3.65% Asians were in the cohort. AA and Asians had higher mortality odds than White, while Hispanics had mortality similar to White. AA had a lower mean length of stay by 0.74 days than White. All racial groups incurred higher mean total charges compared to White. AA and Hispanics had lower odds of undergoing colectomy. Overall, all racial groups had high morbidity compared to White. Among subgroups, the odds of morbidity markers (sepsis, lower GI bleed, and acute renal failure) were higher in AA and Asians than Hispanics. Post-op adhesions and DVT/PE were not significantly different among racial groups. **Conclusions:** AA and Asians disproportionately suffer from higher mortality from colorectal cancer than Hispanics and White. Lower colectomy rates (a definitive CRC treatment) in AA and higher in-hospital complication burden in Asians are possible explanations; however, further research needs to establish if race-specific genomics are also responsible for disparities. Research Sponsor: None.

Outcomes	Whites (n= 533069)	African Americans (n= 100060) aOR (*P*-value)	Hispanics (n= 72599) aOR (*P*-value)	Asians (n= 26764) aOR (*P*-value)
Mortality	Reference	1.27 (<0.01)	0.99 (0.98)	1.18 (0.02)
Colectomy	Reference	0.78 (<0.01)	0.87 (<0.01)	1.01 (0.85)
Sepsis	Reference	1.25 (<0.01)	1.12 (<0.01)	1.16 (<0.01)
Acute Respiratory Failure	Reference	0.92 (0.04)	0.85 (<0.01)	0.94 (0.33)
Lower GI Bleed	Reference	1.14 (<0.01)	1.07 (<0.01)	1.18 (<0.01)
Acute Renal Failure	Reference	1.48 (<0.01)	1.07 (0.01)	1.03 (0.53)
Post-op DVT/PE	Reference	1.09 (0.59)	0.82 (0.36)	0.09 (0.02)
Post-op Adhesions	Reference	1.02 (0.51)	0.97 (0.46)	0.89 (0.11)
Length of Stay, Days	Reference	0.74 (0.01)	0.04 (0.58)	0.03 (0.76)
Total Charges, USD	Reference	5021 (<0.01)	12304 (<0.01)	6839 (<0.01)

3629 **Poster Session**

Outcomes of appendiceal cancer treated at a state peritonectomy service.

First Author: Madeleine Cornelia Strach, Department of Medical Oncology, Chris O'Brien Lifehouse, Sydney, Australia

Background: Appendiceal cancers (AC) are rare with varied prognosis. Nomenclature refined by the WHO 2019 classification is: appendiceal mucinous neoplasms (AMNs), adenocarcinomas (AA) including mucinous (MAC), not otherwise specified (ANOS), signet ring (SRC) and goblet cell (GCA), and neuroendocrine tumours (NET). Cytoreductive surgery and heated intraperitoneal chemotherapy (CRS+HIPEC) is the definitive treatment. The role of chemotherapy remains unclear with conflicting outcomes and there is need to delineate the optimal regimen in different disease settings. The aim of this study was to evaluate AC treatment and clinical outcomes by the WHO 2019 classification and analyse the impact of perioperative chemotherapy. **Methods:** We reviewed prospective data from the database at an Australian state peritonectomy service, Apr 2017-Dec 2021. Variables included demographics, tumour characteristics, treatment details and survival outcomes. Analysis was by the Kaplan-Meier method using the log-rank test for statistical comparison (SPSSv27). **Results:** 115 patients (of 207 referred) with confirmed AC proceeded to CRS. Histopathology comprised 49 AMNs (43%), 62 (63%) AA, 3 SRCs and 1 NET. The mean age was 56y (21-78), 53% female. 94% had CRS+HIPEC (Mitomycin 85%). 70% had cytoreductive score 0. The median peritoneal cancer index was 23 (0-39). 20 (17%) had localised (M0) disease, 10 acellular mucin (M1a) and 85 (74%) metastases (M1b/c). 71% were lymph node negative (N0). 40% had chemotherapy (oxaliplatin/5-fluorouracil 57%). 8 of 15 who had molecular testing had a KRAS mutation. Median follow-up was 26m (1.9-167). The table shows univariate survival analysis. **Conclusions:** This is the first study evaluating outcomes of perioperative chemotherapy for AC in a cohort of patients since the WHO 2019 classification. MAC have worse survival compared to ANOS, but similar to GCAs. Peritoneal acellular mucin has a similarly improved prognosis to patients with no peritoneal disease compared to those with cellular disease. Chemotherapy demonstrated worse survival compared to no chemotherapy, also seen in the literature and likely influenced by selection of more aggressive disease. There is a need to develop biomarkers and better treatments to improve the survival of these patients. Further multivariate analysis for prognostic and predictive factors is planned. Research Sponsor: None.

Appendiceal cancer survival outcomes.

	N	4y OS (%)	P	4y DFS (%)	P
All, median (95% CI), m	115	97 (36.8-157.2)		45 (22.7-67.4)	
Stage					
M0/1a	30	100	0.01*	100	<0.001*
M1b/c	85	55		37	
Nodal status					
N0/X	82	77	<0.001*	60	<0.001*
N1	23	53		39	
N2	10	17		24	
Subtype					
AMN	49	87	0.005*	69	0.007*
MAC	33	42		28	
ANOS	12	68		28	
GCA	17	40		54	
SRC	3	33		33	
NET	1				
Cytoreduction score					
0	81	76	<0.001	66	<0.001*
1-3	33	30		18	
Missing	1				
Peritoneal cancer index					
<10	32	90	0.023*	82	0.008*
≥10	82	52		37	
Missing	1				
Chemotherapy					
Perioperative	44	46	0.009*	32	0.004*
Palliative	2	0		0	
No	69	90		75	
KRAS mutant					
Yes	8	48	0.48	14	0.016*
No	6	53		63	
Unknown	101	65		51	

TPS3630 **Poster Session**

CoRInTH: A phase Ib/II trial of checkpoint inhibitor, pembrolizumab (PD-1 antibody [Ab]) plus standard intensity modulated chemoradiotherapy (IMCRT) in HPV-induced stage III squamous cell carcinoma (SCC) of the anus.

First Author: Marcia Hall, Mount Vernon Cancer Centre, Northwood, United Kingdom

Background: SCC of anus (SCCA) are considered rare tumours, but the incidence is increasing. Only 65% patients with later stage T3/T4 +/-N1 SCCA remain disease free at 3 years (Gunderson 2013, James 2013). The cytotoxicity of IMCRT enhances tumour antigen presentation and promotes cytokine release as well as enhancing the MHC (Demaria 2004, Reits 2006). Immune therapy, against PD-1, have been approved for patients with SCC arising from other primary sites eg. head and neck, lung cancer. The addition of such checkpoint inhibitors might also result in improved PFS and OS for higher risk SCCA patients. **Methods:** A multicentre, single arm, open-label, non-randomised study to evaluate the safety and tolerability of different schedules of exposure to pembrolizumab (P) with standard IMCRT in 50 patients with locally advanced T3/4 anal cancer. The first cohort of 6 patients commenced standard IMCRT and received P 200mg every 21d beginning at Week 5 day 1 of the IMCRT schedule. If this is considered safe and tolerable with not more than 3/6 SAEs within first 6 weeks after completion IMCRT, a second cohort of 6 patients will be recruited where P is introduced on Week 1 Day 1 with standard IMCRT. Pembrolizumab monotherapy will be continued for a total of 6 months. Primary endpoint is safety and tolerability by assessing AEs and protocol adherence. Secondary endpoints include feasibility, clinical response assessment by RECIST (MRI) for ORR at 3, 6 and 12 months, imaging response assessments by TRG MRI using changes in Apparent Diffusion Coefficient (ADC) on diffusion weighted sequences and patient reported outcomes, using EORTC quality of life questionnaires. Patients are being asked to contribute to translational endpoints with the donation of tissue and blood samples. Eligible patients will have Stage IIIA/B (T3/4, any N, M0) SCCA, performance status 0 or 1 and be suitable for IMCRT. Patents with anal tumours of non-epithelial origin, metastatic disease or a diagnosis of immunodeficiency are excluded. Single phase IMRT with a simultaneous integrated boost to achieve 53.2Gy in 28 fractions over 5.5 weeks to PTV_A, according to the UK consensus is mandated. Concomitant chemotherapy can either be cisplatin 60mg/m2/ or mitomycin 12mg/m2 with either 5FU 1000mg/m2 or capecitabine 825mg/m2 at investigator discretion. The first cohort has completed recruitment with Safety Review Committee / IDMC review planned for April 2022. Patients will then be sought to start P on Week 1 Day 1 with IMCRT. Further safety review will be undertaken following the first 6 patients entered into the second cohort but recruitment will continue in an expansion phase to a maximum of 44 patients. Clinical trial information: NCT04046133. Research Sponsor: Merck Shard & Dohme (UK) Limited.

TPS3631 **Poster Session**

Five- or 10-year colonoscopy for 1-2 non-advanced adenomatous polyps (FORTE) NRG-CC005 study: A randomized phase III non-inferiority trial comparing colorectal cancer incidence in participants with 1-2 non-advanced adenomas randomized to a 5- and 10-year surveillance colonoscopy exam schedule versus a 10-year surveillance colonoscopy exam schedule.

First Author: Robert E Schoen, University of Pittsburgh Medical Center, Pittsburgh, PA

Background: Adenomatous polyps are the acknowledged precursors of colorectal cancer (CRC). Identification and removal of adenomas is the mechanism by which screening is effective in reducing CRC incidence and mortality. Patients with 1-2 non-advanced adenomas (< 1 cm with neither villous components nor high grade dysplasia) are recommended to return at a timing ranging from 5-10 yrs. However, evidence for the benefit, optimal timing, and recommended frequency of surveillance colonoscopy is not available. A randomized, clinical trial to demonstrate the difference in results between 5- or 10-yr surveillance for participants with non-advanced adenoma can guide clinical practice. **Methods:** NRG-CC005/FORTE is a prospective, randomized, non-blinded, Phase III, non-inferiority clinical trial comparing CRC incidence in participants randomized to recommendation for a 5- and 10-yr vs. a 10-yr only surveillance colonoscopy exam schedule. Other pre-defined exploratory endpoints include incidence of advanced adenomas, CRC mortality, and incidence of stage III-IV CRCs. Stratification factors include age, gender, and time from qualifying colonoscopy to randomization. Participants ≥50 and < 70 yrs of age at the time of randomization with a first-time diagnosis of 1-2 non-advanced tubular adenomas from the qualifying colonoscopy within 4 yrs prior to randomization will be eligible. Participants with a clinical diagnosis of a significant genetic risk for CRC or with a family history of CRC diagnosed at ≤60 yrs in a first degree relative or in two first degree relatives diagnosed at any age are ineligible. Other ineligibility criteria include prior history of CRC or colorectal adenomas, a hyperplastic polyp measuring ≥1 cm or traditional serrated adenomas, or life expectancy < 10 yrs due to comorbid conditions. Collection of blood, stool, and tissue samples is planned. Statistics: The primary endpoint for the trial is CRC incidence. The trial is focused on CRCs diagnosed between year 5 and year 10. By incorporating a window of +/- 1 yr to allow for somewhat earlier and later procedures, as typically occurs in clinical medicine, the primary endpoint will include incident cancers identified in years 4 through 11. A crude 4- to 11-yr incidence rate of 0.387% is assumed for the 5- and 10-yr schedule arm. The study is powered at 90% to detect a non-inferiority margin difference of 0.387% at alpha 5% in CRC incidence rate between two schedules. 9,500 participants are to be enrolled. Support: U10CA180868, -180822, UG1CA189867, U24CA196067 Clinical trial information: NCT05080673. Research Sponsor: U.S. National Institutes of Health.

TPS3632 **Poster Session**

NSAB C-14: CORRECT-MRD II—Second colorectal cancer clinical validation study to predict recurrence using a circulating tumor DNA assay to detect minimal residual disease.

First Author: Mohamed E. Salem, Levine Cancer Institute, Atrium Health, Charlotte, NC

Background: Patients (pts) with stage II and III colon cancer (CC) have unique post-operative decisions regarding adjuvant chemotherapy (ACT). There is a subset of stage II pts with defined clinicopathologic features associated with poor prognosis who may benefit from ACT, although more discriminating and objective predictors of benefit are needed. In addition, there may be a subset of Stage III CC pts who could tolerate a de-escalation of ACT or who may require intensification of ACT to improve clinical outcome. Detectable ctDNA after resection of early-stage solid tumors has been associated with very high risk of recurrence, suggesting ctDNA is evidence of minimal residual disease (MRD). Several studies are ongoing to investigate the role of ctDNA in the optimal management of pts with CC using different assay technologies. **Methods:** This is a prospective, observational, multicenter study in the United States and Canada of 750 pts who have undergone complete surgical resection for stage II or III CC, have FFPE tissue available from the primary resection sufficient for a novel bespoke MRD assay, and are willing to provide serial whole blood specimens for ctDNA analysis. Subjects are asked to provide study specimens at baseline, pre-recurrence follow-up, and clinical recurrence (if applicable) study visits. ctDNA will be analyzed with an NGS-based MRD assay that identifies somatic genetic alterations from DNA derived from the pt's tumor tissue, subtracts germline variants, and detects a subset of these tumor-specific (bespoke) ctDNA in the pt's blood. The primary objective is to validate the association of post-definitive therapy and pre-recurrence follow-up ctDNA positivity with recurrence-free interval (RFI). Further objectives are to assess the: sensitivity and specificity of ctDNA positivity for subsequent clinical recurrence; contribution of post-surgery baseline, post-adjuvant therapy, and pre-recurrence follow-up ctDNA results on RFI; time from positive ctDNA to clinical recurrence in subjects who had a positive ctDNA result; and compare the Oncotype Colon Recurrence Score estimate of 3 yr recurrence risk with the observed 3 yr recurrence rate. The primary analysis will use a Cox proportional hazards regression applied to the RFI with ctDNA result (positive or negative) measured at post-surgical baseline (or end of ACT if ACT was used) and serially after that as a single, time-dependent covariate. Protocol: 16-002/NSABP C-14. Support: NSABP Foundation. Clinical trial information: 05210283. Research Sponsor: Exact Sciences, Other Foundation.

TPS3633 **Poster Session**

A biomarker enrichment trial of anti-EGFR agents in right primary tumor location (rPTL), *RAS* wild-type (*RAS*-wt) advanced colorectal cancer (aCRC): ARIEL (ISRCTN11061442). *First Author: Christopher Williams, Leeds Cancer Centre, Leeds, United Kingdom*

Background: Meta-analysis of 6 RCTs indicates that anti-EGFR agents are ineffective in rPTL *RAS*-wt aCRC (Arnold D, et al. *Ann Oncol.* 2017;28:1713-1729). However, data from the phase III PICCOLO and COIN trials suggest high tumor expression of the EGFR ligands, EREG and AREG, confers sensitivity to anti-EGFR agents in a subset of this population (Adams RA, et al. *J Clin Oncol.* 2012;30(30_suppl):32-32; Seligmann JF, et al. *Ann Oncol.* 2020;31:1021-1029). More data is needed before ligand assessment can be integrated into routine care: to date, *EREG/AREG* mRNA has only been assessed retrospectively, and feasibility of timely delivery of results must be demonstrated. The ARIEL trial aims to determine whether first-line chemotherapy plus cetuximab or panitumumab is more effective than chemotherapy alone in achieving early tumor shrinkage (ETS) after 8 weeks of treatment in patients (pts) with *EREG/AREG*-high rPTL *RAS*-wt aCRC. **Methods:** ARIEL is a multicentre, phase IV, open label, biomarker enrichment RCT. Pts with previously untreated rPTL *RAS*-wt (or *RAS*-unknown) aCRC are eligible for registration and *EREG/AREG* assessment using archival FFPE tumor tissue. Those confirmed as *RAS*-wt *EREG/AREG*-high (expression above 30th centile based on PICCOLO)[3] are eligible for randomization to chemotherapy alone (fluoropyrimidine backbone plus irinotecan or oxaliplatin) *vs* chemotherapy (FOLFOX or FOLFIRI) plus anti-EGFR therapy (panitumumab or cetuximab) (options at physician's discretion). Pts with *EREG/AREG*-low tumors are not eligible for randomization but may consent to translational research and follow-up. The primary endpoint is ETS at 8 weeks (≥30%, yes *vs* no). Secondary endpoints are depth of response at 16 weeks, overall survival, overall treatment utility, pt-reported quality of life, cost per QALY, pt acceptability of trial procedures, and safety. Pre-trial work-up included cross-validation of the *EREG/AREG* RT-qPCR assay at trial laboratories in Leeds and Birmingham, UK demonstrating reproducibility of biomarker results. Recruitment to an internal pilot phase is currently ongoing to demonstrate feasibility of timely delivery of biomarker results to sites (lower limit of 90% CI of mean result delivery time for first 20 pts must include 3 weeks). Mean monthly recruitment rate will be assessed at 18 months to determine likelihood of completion of the trial within the 3 year recruitment period. ARIEL is funded by the UK National Institute for Health Research (NIHR) and opened the first of 40 sites in February 2022. 440 pts will be registered for biomarker assessment in order to randomize 162 pts. All pts will be followed-up to 1 year post-randomisation, with a final assessment in all pts when the last pt has completed a year of follow-up (median 3.5 years). ARIEL is participating in the NIHR Associate PI scheme. Clinical trial information: 11061442. Research Sponsor: National Institute for Health Research, United Kingdom.

TPS3634 **Poster Session**

SEAMARK: Randomized phase 2 study of pembrolizumab + encorafenib + cetuximab versus pembrolizumab alone for first-line treatment of *BRAF* V600E-mutant and microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC). *First Author: Scott Kopetz, MD Anderson Cancer Center, Houston, TX*

Background: Among patients with MSI-H/dMMR CRC, *BRAF* mutations occur in approximately 30%. MSI-H/dMMR and *BRAF* mutations are both associated with poor prognosis; in patients who have both biomarkers, poor prognosis is thought to be driven by the *BRAF* mutation. Pembrolizumab is indicated for the treatment of patients with MSI-H/dMMR unresectable or metastatic CRC (mCRC). The BRAF inhibitor encorafenib, in combination with cetuximab, is indicated for previously treated patients with *BRAF* V600E-mutant mCRC. Currently, there are no first-line treatment options indicated specifically for patients with both MSI-H/dMMR and *BRAF* V600E-mutant mCRC. To assess the safety and efficacy of combining pembrolizumab with encorafenib + cetuximab, the SEAMARK study (NCT05217446) will evaluate this combination vs pembrolizumab alone in patients with previously untreated *BRAF* V600E-mutant MSI-H/dMMR mCRC. **Methods:** SEAMARK is an open-label, multicenter, randomized, phase 2 study. Approximately 104 patients (randomized 1:1; stratified by Eastern Cooperative Oncology Group Performance Status [ECOG PS] 0 vs 1) will receive either pembrolizumab + encorafenib + cetuximab or pembrolizumab. Enrolled patients must be aged ≥16 or ≥18 years (per country-specific regulations) and have previously untreated *BRAF* V600E-mutant MSI-H/dMMR mCRC; measurable disease (Response Evaluation Criteria in Solid Tumors v1.1); ECOG PS 0 or 1; and adequate bone marrow, hepatic, and renal function. Patients who received prior treatment with BRAF/EGFR inhibitors or immune checkpoint inhibitors, or who have brain metastases (unless radiologically stable) or *RAS* mutation (or unknown *RAS* status), will be excluded. The primary endpoint is investigator-assessed progression-free survival. Secondary endpoints include safety and tolerability, overall survival, objective response rate, duration of response, and quality of life. Enrollment will begin in April 2022. Clinical trial information: NCT05217446. Research Sponsor: Pfizer.

TPS3635 **Poster Session**

Phase 2/3, randomized, open-label study of an individualized neoantigen vaccine (self-amplifying mRNA and adenoviral vectors) plus immune checkpoint blockade as maintenance for patients with newly diagnosed metastatic colorectal cancer (GRANITE). *First Author: J. Randolph Hecht, David Geffen School of Medicine at UCLA, Santa Monica, Los Angeles, CA*

Background: Treatment options for most patients with metastatic colorectal cancer (mCRC) are largely limited to cytotoxic chemotherapy, with little advancement in the last decade. Encouragingly, a small subset of patients deficient in mismatch repair (dMMR/MSI-hi) benefit from checkpoint inhibitors (CPI) whereas those proficient in mismatch repair (pMMR/MSS) do not. The absence of clinical benefit in patients with pMMR/MSS mCRC may relate to a lack of neoantigen-specific T cells and immune infiltration. An individualized neoantigen vaccine that induces CD8 T cells capable of tumor lysis has the potential to expand the number of patients with mCRC who may benefit from immunotherapy. Data from a Phase 1/2 study evaluating neoantigen vaccines in combination with CPIs in patients with previously treated mCRC demonstrated a 44% molecular response (MR) rate (≥50% decrease in ctDNA relative to baseline) in 4/9 patients; this correlated with improvement in OS relative to those without a MR. To further investigate neoantigen vaccines in earlier lines of treatment, a Phase 2/3 study in the1L maintenance setting in mCRC was initiated. **Methods:** GO-010 is a Phase 2/3, randomized, open-label, multi-center study evaluating the efficacy and safety of 2 neoantigen-containing vectors (GRT-C901-adenoviral vector plus GRT-R902-self-amplifying mRNA vector) as prime/boost in combination with CPIs as an add-on to fluoropyrimidine/bevacizumab (bev) following 1L therapy with FOLFOX/bev in patients with mCRC. During Phase 2, up to 90 patients will be randomized 1:1 to the vaccine or control arm with a primary objective of assessing efficacy by MR. During Phase 3, up to 226 patients will be randomized with a primary objective of assessing PFS per iRECIST in a blinded, independent manner. There are two stages to the study. In the vaccine production stage, while patients receive FOLFOX/bev 1L therapy, neoantigen prediction is performed using a tumor biopsy and Gritstone's EDGE™ neoantigen prediction model. For patients in the vaccine arm the top 20 predicted neoantigens are included in the vaccine vectors. After completing oxaliplatin, patients will enter the study treatment stage. Patients in the control arm will continue with maintenance therapy whereas patients in the vaccine arm will add the vaccine regimen to maintenance therapy. The vaccine regimen consists of GRT-C901/GRT-R902 as well as SC ipilimumab (30 mg) and IV atezolizumab (1680 mg). Over the first year of treatment, 6 vaccinations will occur. Ipilimumab will be administered SC with the first doses of GRT-C901 and GRT-R902. Atezolizumab will be administered every 4 weeks for up to 2 years. Study assessments include imaging, ctDNA, safety, immunogenicity and exploratory biomarker analysis. Clinical trial information: NCT05141721. Research Sponsor: Gritstone bio.

TPS3636 **Poster Session**

Phase III study to compare bevacizumab or cetuximab plus FOLFIRI in patients with advanced colorectal cancer RAS/BRAF wild type (wt) on tumor tissue and RAS mutated (mut) in liquid biopsy: LIBImAb Study. *First Author: Angela Damato, Medical Oncology Unit, Azienda USL-IRCCS Reggio Emilia, Reggio Emilia, Italy*

Background: KRAS, NRAS, and BRAF mutations are well-established negative predictive biomarkers of response to anti-EGFR monoclonal antibodies (MoAbs) in metastatic colorectal cancer (mCRC) patients (pts). In clinical practice, RAS/BRAF wild-type (wt) patients receive first-line therapy regimens containing anti-EGFR agents. However, tumor heterogeneity might drive primary and acquired resistance to anti-EGFR MoAbs. In fact, circulating tumor DNA (ctDNA) testing reveals RAS/BRAF mutations in approximately 10% of pts who resulted in wt at tumor tissue. In addition, 30% to 50% RAS wt pts develop, during the treatment with anti-EGFR MoAbs, RAS mut can be detected in the ctDNA several weeks before clinical progression. As today, it is not known whether revealing RAS mut in liquid biopsy (LB) earlier than the appearance of a clinical/radiological disease progression, could impact pts' outcomes. Similarly, there are no data suggesting the best therapeutic approach in patients with RAS/BRAF wt tissue and mutated ctDNA. **Methods:** This is a phase III, randomized, open-label, comparative, multicenter study to assess the superiority of Bevacizumab (BEV) compared to Cetuximab (CET) plus FOLFIRI in treatment naïve mCRC RAS/BRAF wt on tumor tissue (TT) and mutated in plasma samples. RAS/BRAF wt pts on TT will undergo the first LB, and RAS mut pts will be randomized 1:1 to receive FOLFIRI/CET (control arm) or FOLFIRI/BEV (experimental arm). Instead, RAS wt pts at first LB will be treated with FOLFIRI/CET up to 8 cycles. Pts who have not progressed after 8 cycles of treatment will undergo a second LB. If RAS mut was detected, pts will be randomized 1:1 to continue FOLFIRI/CET or switch to FOLFIRI/BEV. If not, pts will continue FOLFIRI/CET outside the clinical trial. Pts will be treated until disease progression, unacceptable toxicity, or withdrawal of consent. Among 26 pts screened at the first LB, actually 1 KRAS mut and 1 BRAF mut pts were detected. The primary endpoint is the PFS Plasma samples will be analyzed for KRAS, NRAS, and BRAF mutations by Idylla ctKRAS and Idylla ctNRAS-BRAF-EGFGR. All samples will be also analyzed by NGS, in order to better evaluate the correlation of tumor heterogeneity with pts' outcomes. Clinical trial information: EudraCT Number: 2020-005078-82, NCT04776655. Research Sponsor: Agenzia Italiana del Farmaco/Italian Drug Agency (AIFA) Independent Research Fund 2018.

TPS3637 **Poster Session**

A multi-arm, phase 2, open-label study to assess the efficacy of RXC004 as monotherapy and in combination with nivolumab in patients with ring finger protein 43 (RNF43) or R-spondin (RSPO) aberrated, metastatic, microsatellite stable colorectal cancer following standard treatments. *First Author: Scott Kopetz, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The Wnt pathway is a critical driver of cancer. RXC004 is a potent, selective, orally active inhibitor of the key Wnt pathway regulator, Porcupine. Inhibition of Porcupine blocks the release of all Wnt ligands from cells, preventing both tumour growth and tumour immune evasion. Wnt pathway alterations, including loss-of-function (LoF) RNF43 mutations and RSPO gene fusions, increase expression of the Wnt receptor Frizzled (Fzd) on the tumour cell surface, driving Wnt-ligand signalling. These alterations are present in ~8% (Gao, 2013; Cerami, 2012; Shesagiri, 2012; Shinmura, 2014; Kleeman, 2019) of colorectal cancers (CRC). LoF RNF43 mutations are associated with poor prognosis in MSS CRC (Yaeger, 2018*)*. Preclinical genetically selected CRC models showed disease stabilisation, differentiation towards a normal colonic phenotype with increased mucin secretion, and reduced metabolic activity on FDG-PET. In a Phase 1 study in patients with advanced solid tumours (NCT03447470), RXC004 was safe and tolerated at doses up to 2mg QD, the recommended phase 2 dose (RP2D), and showed a differentiated efficacy signal in Wnt-ligand dependent tumours (Cook, 2021*)*. **Methods:** The PORCUPINE (NCT04907539) trial is a 2-arm Phase 2 trial of RXC004 monotherapy (Arm A) and RXC004 in combination with nivolumab (Arm B). 20 evaluable patients will be enrolled into each Arm. The study initially opened with Arm A; Arm B will be opened once the RP2D for RXC004 in combination with nivolumab is established in a separate phase 1 study. Once Arm B is opened, patients in Arm A may be treated with RXC004 + nivolumab if they have progressive disease on the first RECIST assessment scan. To be eligible for this study, patients must have metastatic microsatellite stable (MSS) CRC that has progressed following standard therapies. Tumours must have a LoF RNF43 mutation, or an RSPO2/3 fusion. As Wnt inhibition can affect bone metabolism, patients undergo a screening DEXA scan and receive prophylactic denosumab throughout the treatment period. The primary endpoint for Arm A is the disease control rate (DCR= CR+PR+SD at 16 wks), and for Arm B is objective response rate (ORR). Secondary endpoints are Safety and PK. Exploratory endpoints include FDG-PET changes and on-treatment changes in protein and gene expression in tumour biopsies. For Arm A, a target value (TV) of 60% DCR is considered a clinically significant improvement over standard of care against a lower reference value (LRV) of 40% DCR (Grothey, 2013; Mayer, 2015*)*. For Arm B, a TV of 30% ORR is considered clinically significant against a LRV of 10% ORR (Eng, 201*9)*. RXC004 is also being investigated in a second Phase 2 trial, PORCUPINE 2 (NCT04907851), in Biliary Tract Cancers and RNF-43 mutated Pancreatic Cancers. Clinical trial information: NCT04907539. Research Sponsor: Redx Pharma.

TPS3638 **Poster Session**

STOPTRAFFIC-1: A phase I/II trial of SX-682 in combination with nivolumab for refractory *RAS*-mutated microsatellite stable (MSS) metastatic colorectal cancer (mCRC). *First Author: Benny Johnson, Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Refractory RAS mutated MSS mCRC represents a critical unmet need with minimal response to immune checkpoint blockade (ICB). Preclinical CRC models reveal that *KRAS* mutations activate the CXCR2 axis promoting an immunosuppressive tumor microenvironment (TME). This occurs via KRAS repression of interferon regulatory factor 2 (IRF2) resulting in upregulation of CXCL3 chemokines, which bind CXCR2 and recruit myeloid-derived suppressor cells (MDSC; Liao et al, Cancer Cell 2019; Grover et al, Cancer Discovery, 2022). SX-682 is a novel oral small-molecule inhibitor of the CXCR1/2 chemokine receptors involved in MDSC-recruitment to the TME. This proof-of-concept study investigates whether de novo immunotherapy resistance in MSS *RAS* mutated mCRC can be overcome by treatment with a small molecule CXCR1/2 antagonist in combination with anti-PD-1 therapy. **Methods:** STOPTRAFFIC-1 (NCT04599140, enrolling) is a phase I/II, open-label, dose-escalation/dose expansion study of SX-682 in combination with nivolumab to evaluate safety and clinical activity for patients (pts) with refractory *RAS* (*KRAS* and *NRAS*) mutated MSS mCRC. Key eligibility criteria: patients (pts) with MSS mCRC with measurable disease, progression or intolerance to at least 2 prior lines of standard therapy, and ECOG 0 or 1. Pts will receive SX-682 (5 dose levels: 25 mg, 50 mg, 100mg, 200mg, or 400 mg by mouth twice daily) administered in an 8-week cycle with intravenous nivolumab (480 mg) on days 1 and 29 of each cycle. Adverse events are assessed according to CTCAE v5.0. Response assessments (per RECIST) occur every 8 weeks. In dose escalation, pts enter a 3-week monotherapy safety run-in of SX-682 followed by 3-week combination with nivolumab for a six-week dose-limiting toxicity (DLT) period. Cohorts 1-4 have been completed without DLT. Enrollment to cohort 5 began in January 2022. Following determination of maximum tolerated dose (MTD), dose expansion design is a Simon's optimal two-stage design. Efficacy will be assessed in the first 15 pts with a requirement of at least 2 responses in order to enroll 14 additional pts (N=29) in the second stage. Pre- and on-treatment tissue biopsies will be collected in the expansion phase. The primary objectives are to determine the safety profile of SX-682 alone and in combination with nivolumab, including the MTD, recommended phase 2 dose, and the DLT. The secondary objectives include overall response rate, progression-free survival, overall survival, and pharmacokinetic profiles of SX-682. Translational analyses include correlations of clinical outcomes with genomic and immune biomarkers from paired tissue and plasma samples. Clinical trial information: NCT04599140. Research Sponsor: Bristol Myers Squibb; Syntrix.

TPS3639 **Poster Session**

Phase 2 study of pembrolizumab-based combination therapy in patients with microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) stage IV colorectal cancer (CRC). *First Author: Thierry Andre, Hôpital Saint-Antoine, Paris, France*

Background: Robust clinical activity has been observed with anti–PD-1 pembrolizumab (pembro) in patients (pts) with dMMR/MSI-H metastatic CRC tumors. However, given the response rate of 45% with first-line pembro demonstrated in KEYNOTE-177, there is room for improvement. Adding a second checkpoint inhibitor targeting a different pathway such as CTLA-4, LAG-3, TIGIT, or ILT4 may improve the efficacy of PD-1 inhibition. This ongoing, open-label, multicenter, multiarm, randomized, phase 2 trial (NCT04895722) will evaluate efficacy and safety of coformulated pembro and anti–CTLA-4 quavonlimab compared with pembro monotherapy in chemotherapy-refractory stage IV dMMR/MSI-H CRC in cohort A; the study will also evaluate the efficacy and safety of 4 pembro-based combinations (coformulation of pembro with either quavonlimab, anti–LAG-3 favezelimab, or anti-TIGIT vibostolimab; anti-ILT4 MK-4830 given sequentially with pembro) compared with pembro monotherapy in previously untreated stage IV dMMR/MSI-H CRC in cohort B. **Methods:** Pts aged ≥18 y with histologically confirmed stage IV dMMR/MSI-H CRC who have measurable disease per RECIST v1.1 by investigator and confirmed by blinded independent central review (BICR), will be enrolled. Pts in cohort A must have experienced PD after fluoropyrimidine, irinotecan, and oxaliplatin, with or without anti-VEGF antibody, and anti-EGFR antibody for pts with left-sided tumors that are *RAS* WT. Pts in cohort B will not have been previously treated for metastatic disease. Additional eligibility criteria include ECOG PS 0 or 1, adequate organ function, and availability of archival or newly obtained tissue sample. Pts with autoimmune disease, active CNS metastases, and those who received systemic therapy within 4 wks or radiotherapy within 2 wks before intervention will be excluded. Pts in cohort A will be randomly assigned 1:1 to receive either coformulated quavonlimab 25 mg/pembro 400 mg IV Q6W or pembro 400 mg IV Q6W. Pts in cohort B will be randomly assigned 1:1:1:1:1 to receive coformulated quavonlimab 25 mg/pembro 400 mg IV Q6W, favezelimab 800 mg/pembro 200 mg IV Q3W, vibostolimab 200 mg/pembro 200 mg IV Q3W, MK-4830 800 mg + pembro 200 mg IV Q3W (given sequentially), or pembro 400 mg IV Q6W. Pts will be stratified by *RAS* mutation (mutant vs WT). Treatment will continue for ≤2 y or until unacceptable toxicity, disease progression, confirmed CR (after ≥6 mo of study treatment and pts have received ≥6 wk of treatment after initial CR), or withdrawal from study. Disease assessment by CT or MRI will be performed Q9W. For both cohorts, primary end point is ORR by BICR per RECIST v1.1; secondary end points are ORR assessed by investigator, DOR and PFS assessed by BICR and by investigator per RECIST v1.1, OS, and safety and tolerability graded per NCI CTCAE v5.0. Enrollment in this trial is ongoing. Clinical trial information: NCT04895722. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

TPS3640 **Poster Session**

Myopenia and mechanisms of toxicity in older adults with colorectal cancer (CRC): The M&M study (WF-1806). *First Author: Grant Richard Williams, Institute for Cancer Outcomes and Survivorship, University of Alabama at Birmingham, Birmingham, AL*

Background: CRC is the 2nd most common cause of cancer death in the US, and nearly 60% of CRC cases occur among older adults. There is a critical unmet need to understand the underlying cause(s) of observed variability in chemotherapy toxicity (chemotoxicity) outcomes to minimize adverse outcomes and appropriately personalize therapy for older adults. Low muscle mass, known as myopenia, is prevalent in older adults with CRC (~60%) and is associated with chemotoxicity and decreased overall survival (OS). However, little is known about trajectories of myopenia and underlying mechanisms of increased toxicities and decreased survival in myopenic patients. We address these gaps in a prospective cohort study, with the central goal of examining the role of myopenia in chemotoxicity in older adults with metastatic CRC undergoing 5-Fluouracil (5FU) based chemotherapy, and to explore the mediating influence of germline genetic variants and pharmacokinetics (PKs) in the association between myopenia and chemotherapy toxicity. **Methods:** This prospective cohort study is accruing through the Wake Forest NCI Community Oncology Research Program Research Base (WF NCORP) and funded by the NCI grants 2UG1CA189824 and K08CA234225. The study examines the impact of myopenia on chemotoxicity and OS in older adults with newly diagnosed metastatic CRC planning to receive systemic 5FU-based chemotherapy (either as monotherapy or in combination with oxaliplatin and/or irinotecan +/- biologics) (NCT03998202). All patients undergo the Cancer & Aging Resilience Evaluation and Life-Space Evaluation at baseline, 3 and 6 months. Standard of care Computed Tomography (CT) images will be obtained to assess muscle measures (skeletal muscle area/density) at the L3 cross-section. The primary outcome is grades 3 to 5 chemotoxicity measured up to 6 months after initiation of chemotherapy using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. We will assess the association of baseline myopenia and trajectories of myopenia with severe chemotherapy toxicities. Secondary outcome measures include OS at 1 year and chemotoxicities using the Patient Reported Outcomes (PRO) version of the CTCAE. The study also explores the mediating/moderating influence of genetic variation and altered PKs (n = 60) in the association between myopenia and chemotherapy toxicity. To date, the study has accrued 73 of the 300 targeted patients from 110 NCORP practices. Clinical trial information: NCT03998202. Research Sponsor: U.S. National Institutes of Health.

TPS3641 **Poster Session**

A phase 2 multicenter, open-label, randomized, controlled trial in patients with stage II/III colorectal cancer who are ctDNA positive following resection to compare efficacy of autogene cevumeran versus watchful waiting. *First Author: Scott Kopetz, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Colorectal cancer (CRC) is one of the most commonly occurring cancers with high recurrence and mortality rate. Circulating tumor DNA (ctDNA) can be used as a marker of minimal residual disease after completion of surgical resection of stage II/III CRC, where detectable ctDNA levels (positive) post-AdCTx are associated with an increased risk of disease recurrence and novel therapies are needed. Autogene cevumeran is an investigational individualized neoantigen-specific immunotherapy that is designed to harness an immune response against patient-specific, tumor neoantigens. This clinical trial is in progress in patients with Stage II (high risk) / Stage III colorectal cancer who are ctDNA positive following resection. **Methods**: Autogene cevumeran is being evaluated in an open-label, Phase 2, randomized, controlled trial in patients with Stage II / III CRC patients who are ctDNA positive following resection. Patients are randomized to adjuvant therapy followed by autogene cevumeran compared to adjuvant therapy followed by watchful waiting. The primary endpoint is disease-free survival (DFS). The trial has a Biomarker Cohort of 15 patients who will receive autogene cevumeran irrespective of the ctDNA status to pursue exploratory objectives. The main study of the phase 2 trial consists of a randomized (1:1) design comparing the experimental arm (autogene cevumeran) with the observational arm (watchful waiting) in ctDNA positive CRC patients. A third Exploratory Cohort explores the efficacy and safety of autogene cevumeran in ctDNA positive CRC patients with early recurrence/relapse during or after completion of AdCTx. Patients enrolled onto the experimental group, the biomarker and exploratory cohorts will receive autogene cevumeran 6x q1w, followed by 2x q2w, followed by 7 "booster" doses q6w, to receive a total of 15 doses (dosed at 25μg). AEs are assessed according to CTCAE v5. DFS will be determined by an independent central radiology assessment. Key eligibility criteria include 1) Patients must have stage II/III rectal cancer or stage II (high risk)/III colon cancer that has been surgically resected (R0 confirmed by pathology report); 2) patients must be ctDNA positive following resection; and 3) at least 5 tumor neoantigens must be identified in the provided tumor sample for autogene cevumeran manufacturing (RNA lipoplex, RNA-LPX). ClinicalTrials.gov identifier: NCT04486378. Research Sponsor: Pharmaceutical/Biotech Company.

TPS3642 **Poster Session**

NSABP FC-12: A single-arm, phase II study to evaluate treatment with gevokizumab in patients with stage II/III colon cancer who remain ctDNA+ after curative surgery and adjuvant chemotherapy. *First Author: Thomas J. George, The University of Florida Health Cancer Center, Gainesville, FL*

Background: Detection of circulating tumor DNA (ctDNA) in patients (pts) following surgery is indicative of presence of minimal/molecular residual disease (MRD) and confers a near-certain risk of disease recurrence. Therapeutic strategies to treat MRD following standard curative therapies are needed because the risk of recurrence is high and therapeutic intervention may provide clinical benefit to patients. Gevokizumab is a recombinant humanized monoclonal antibody targeting interleukin-1β (IL-1β), which is involved in all phases of the malignant process (tumorigenesis, invasion, metastasis, angiogenesis, progression, and the modulation of anti-tumor immunity). Gevokizumab has been validated in pre-clinical colon cancer (CC) models and safety established in the advanced-stage clinical setting. In this trial in progress, we aim to test the efficacy of gevokizumab in pts with early-stage CC with MRD (ctDNA-positivity) following definitive treatment. **Methods:** NSABP FC-12 is a single-arm, multi-centered phase II study that will include pts with stage II/III CC who test MRD+ within 6 wks following completion of curative surgery and ≥3 mos of adjuvant chemotherapy. MRD will be assessed using a personalized and tumor-informed ctDNA assay (Signatera bespoke assay). Gevokizumab will be given at a flat dose of 120 mg IV every 28 days for 13 cycles. The primary endpoint is relapse-free survival (RFS) following initiation of study therapy through one year of follow-up. Secondary endpoints are rate of ctDNA clearance at 8 wks from start of study therapy, as well as safety, toxicity, pharmacokinetics, and immunogenicity of gevokizumab. Exploratory and correlative endpoints will include outcomes associated with ctDNA clearance kinetics, tumor mutations, tumor mutational burden, circulating methylated DNA, tumor immune microenvironment profile, peripheral blood immune profile, and stool microbiome analyses. The enrollment period will be ~12 mos. Pts will be followed for 18 mos following enrollment with ctDNA analysis at prespecified timepoints until imaging is positive for recurrence of disease or death. CT scans will be at 6-mo intervals. RFS will be determined in pts who clear ctDNA at 8 wks compared to those who do not. A single-stage design to test the null hypothesis that the 12-mo RFS is P≥0.20 versus the alternative (HA) that P≥0.35 has a sample size of 31 (alpha=0.151; power 0.811). If ≥9 of 31 pts (29%) are alive and recurrence-free at 12 mos, then gevokizumab will be considered promising for further study. Enrollment continues towards the primary endpoint. Clinical trial information: 05178576. Research Sponsor: Novartis, Natera, Other Foundation.

TPS3643 **Poster Session**

Colon adjuvant chemotherapy based on evaluation of residual disease (CIRCULATE-US): NRG-GI008. *First Author: Arvind Dasari, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Currently, there are no biomarkers validated prospectively in randomized studies for resected colon cancer (CC) to determine need for adjuvant chemotherapy (AC). However, circulating tumor DNA (ctDNA) represents a highly specific and sensitive approach (especially with serial monitoring) for identifying minimal/molecular residual disease (MRD) post-surgery in CC patients (pts), and may outperform traditional clinical and pathological features in prognosticating risk for recurrence. CC pts who do not have detectable ctDNA (ctDNA-) are at a much lower risk of recurrence and may be spared the toxicities associated with AC. Furthermore, for CC pts with detectable ctDNA (ctDNA+) who are at a very high risk of recurrence, the optimal AC regimen has not been established. We hypothesize that for pts whose CC has been resected, ctDNA status may be used to risk stratify for making decisions about AC. **Methods:** In this prospective phase II/III trial, up to 1,912 pts with resected stage III A, B (all pts) and stage II, IIIC (ctDNA+ only) CC will be enrolled. Based on the post-operative ctDNA status using personalized and tumor informed assay (SignateraTM, bespoke assay) , those who are ctDNA- (Cohort A) will be randomized to immediate AC with fluoropyrimidine (FP) + oxaliplatin (Ox) for 3-6 mos per established guidelines *vs.* serial ctDNA monitoring. Patients who are ctDNA+ post-operatively or with serial monitoring (Cohort B) will be randomized to FP+Ox *vs.* more intensive AC with addition of irinotecan (I) for 6 mos. The primary endpoints for Cohort A are time to ctDNA+ status (phase II) and disease-free survival (DFS) in phase III in the immediate *vs.* delayed AC arms. The primary endpoint for Cohort B is DFS in the FP+Ox *vs* FP+Ox+I arms for both phase II and phase III portions of the trial. Secondary endpoints include prevalence of detectable ctDNA post-operatively, time-to-event outcomes (overall survival and time to recurrence) by ctDNA status, and the assessment of compliance to adjuvant therapy. Biospecimens including archival tumor tissue, post-operative and serial matched/normal blood samples will be collected for exploratory correlative research. Active enrollment across the NCTN started in early 2022. Support: U10-CA-180868, -180822; UG1CA-189867; Clinical trial information: NCT05174169. Research Sponsor: Natera, U.S. National Institutes of Health.

TPS3644 **Poster Session**

EA2201: An ECOG-ACRIN phase II study of neoadjuvant nivolumab plus ipilimumab and short course radiation in MSI-H/dMMR rectal tumors. *First Author: Kristen Keon Ciombor, Vanderbilt University Medical Center, Nashville, TN*

Background: Trimodality therapy including chemoradiation, chemotherapy and surgical resection is standard for patients with T3-4 and/or node-positive (N+) rectal adenocarcinomas. Pathologic complete response (pCR) rates after neoadjuvant chemoradiation approach 15% in all-comers and 27% in patients with microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) rectal cancer. Additionally, preclinical data suggest that hypofractionated radiation (large dose per fraction) may enhance immunogenicity. Given high response rates to immunotherapy in MSI-H/dMMR early stage and metastatic colorectal cancer (CRC), we hypothesized that neoadjuvant nivolumab plus ipilimumab and short course radiation in locally advanced MSI-H/dMMR rectal cancer (LARC) would result in increased pCR rates. **Methods:** EA2201 (NCT04751370) is an NCTN phase II clinical trial for patients with treatment-naïve locally advanced (T3-4Nx or TxN+) rectal adenocarcinoma that is dMMR or MSI-H. Patients receive nivolumab (480 mg) and ipilimumab (1 mg/kg) every 28 days for 2 cycles, followed by short course radiation (5 Gy x 5 fractions; total 25 Gy) and an additional 2 cycles of nivolumab and ipilimumab prior to disease reassessment and TME. The primary endpoint is pCR at TME. Secondary endpoints include 5-year disease-free survival, overall survival, treatment-related toxicities, and sphincter preservation rate for low-lying tumors. This study has a single-arm, two-stage design; a pCR rate of 50% or more will be taken as evidence of promising activity in this patient population. We plan to enroll 31 patients, with accrual currently ongoing. Clinical trial information: NCT04751370. Research Sponsor: U.S. National Institutes of Health.

TPS3645 **Poster Session**

NEOPRISM-CRC: Neoadjuvant pembrolizumab stratified to tumor mutation burden for high-risk stage 2 or stage 3 deficient-MMR/MSI-high colorectal cancer. *First Author: Kai-Keen Shiu, University College Hospital, NHS Foundation Trust, London, United Kingdom*

Background: The prognostic advantage of early stage deficient-MMR/MSI-High CRC is lost after relapse, so there is a pressing clinical need to maximize the chance of cure in the early stages where prevalence of dMMR is higher comprising approximately 12% of Stage 3 and 20% of Stage 2 CRC. The efficacy of adjuvant checkpoint inhibition in this patient group has yet to be demonstrated in the context of micrometastatic disease without a supporting immune-competent microenvironment. Longitudinal studies especially in the neoadjuvant setting would optimally interrogate post-immunotherapy changes both in time and space. The NEOPRISM-CRC (NEOadjuvant PembRolizumab In Stratified Medicine – ColoReCtal) study is a Phase II Trial to determine whether neoadjuvant Pembrolizumab stratified to tumour mutation burden (TMB) is efficacious and safe. It will also be a platform to explore the relationships between possible predictive novel biomarkers and response to Pembrolizumab in blood, tumour tissue and microbiome. **Methods:** The study population consists of subjects with newly diagnosed operable dMMR/MSI-H CRC. Patients must be fit and eligible for planned curative surgery based on a) radiological node positive T1-4 CRC or b) high risk T3 defined as EITHER ≥ 5mm of extramural depth of invasion or unequivocal EMVI on imaging (regardless of depth), or T4 disease. They will receive one of two pre-operative regimens depending upon their TMB based on the FoundationOne®CDx test (FM1CDx). All patients will have one 21 day cycle of Pembrolizumab 200 mg IV. Prior to cycle 2 and with the result of the FM1CDx test, patients will continue their treatment as follows: A) TMB-high (defined as ≥20 mutations per Mb) or TMB-medium (defined as 6-19 mutations per Mb), or MSI-H on PCR if FM1CDx test is not evaluable: A further 2 cycles of Pembrolizumab 200 mg IV every 21 days. B) TMB-low (defined as ≤5 mutations per Mb), or if FM1CDx and PCR tests are not evaluable: No further Pembrolizumab given. Surgery to remove the CRC will be performed 4-6 weeks after the last dose of Pembrolizumab in both arms. Following resection patients may receive adjuvant chemotherapy in accordance with local institutional guidelines. The primary end point is pathological complete response rate (pCR). Secondary endpoints include 3 year RFS, OS, safety and health-related quality of life. Up to 32 patients will be registered over a 18-24 month period assuming that the pCR with 3 cycles of Pembrolizumab will be ≥ 33% for patients with high or medium TMB based on the FM1CDx profile, and intend to rule out a percentage ≤10%. To reach 80% power with 5% statistical significance, 19 patients are required in the high/medium TMB arm. The trial will be considered a success if at least 5/19 patients have a pCR after 3 cycles of Pembrolizumab. Enrolment will commence in March 2022. Clinical trial information: NCT05197322. Research Sponsor: Merck Sharpe and Dohme, To be confirmed. Other sources of funding will be obtained for any additional translational exploratory work using research funds at UCL/UCLH and scientific collaborators.

TPS3646 **Poster Session**

SPAR: A randomized placebo-controlled phase 2 trial of simvastatin in addition to standard chemotherapy and radiation in preoperative treatment for rectal cancer: An AGITG clinical trial. *First Author: Michael B. Jameson, Waikato Clinical Campus, Hamilton, New Zealand*

Background: In retrospective studies statin use during preoperative chemo-radiation (pCRT) for rectal cancer is associated with improved overall survival, pathological tumor response and treatment toxicity. In vivo preclinical studies show that statins radiosensitize cancer cells, with improved tumor control and reduced radiation-induced gastrointestinal (GI) and skin toxicities. A prospective randomized trial is justified to confirm these clinically important benefits. Tumor regression following pCRT has strong prognostic significance, as assessed radiologically (MRI-based tumor regression grading [mrTRG]) prior to, or pathologically (pathTRG) following, surgery. Using mrTRG after each treatment phase in total neoadjuvant therapy (TNT) programs could assess incremental tumor regression and optimize patient management including surgery. **Methods:** Design: This double-blind phase 2 trial is recruiting 222 patients planned to receive long-course fluoropyrimidine-based pCRT for rectal adenocarcinoma at 17 sites in New Zealand and Australia. Patients are randomized to simvastatin 40mg or placebo daily for 90 days, starting 1 week prior to pCRT, with minimization for major prognostic variables. Pelvic MRI at baseline and 6-8 weeks after pCRT will assess mrTRG. A protocol amendment allows TNT using consolidation chemotherapy after pCRT; MRI timing is unchanged. Primary objective: comparison of rates of grades 1-2 mrTRG following pCRT with simvastatin or placebo, considering mrTRG in 4 ordered categories (1, 2, 3, 4-5). Secondary objectives: comparison of rates of grades 1-2 pathTRG in resected tumors; incidence of > grade 2 acute GI and non-GI adverse events (AE); incidence of late GI AE; compliance with intended pCRT and trial medication; proportion of patients undergoing surgical resection post-pCRT; 3-year local recurrence rate, disease-free and cancer-specific survival; and pathological scores for radiation colitis. Tertiary and correlative objectives: association between mrTRG and pathTRG grouping; inter-observer scoring agreement on mrTRG and pathTRG; comparison of the association between tumor CD3+ and/or CD8+ T-cell infiltrates in diagnostic biopsies and pathTRG; intensity and distribution of subsets of infiltrating T-cells in irradiated resected normal and malignant tissue; and the effect of simvastatin on markers of systemic inflammation (modified Glasgow prognostic score and the neutrophil-lymphocyte ratio). Eligibility criteria exclude statin use within 6 weeks prior to trial entry, patients intolerant of statins, and planned use of oxaliplatin or biological agents during pCRT. Trial recruitment commenced April 2018 and 95 of 222 patients have been recruited as at 21 January 2022. Clinical trial information: ACTRN12617001087347. Research Sponsor: Health Research Council of New Zealand, Other Foundation.

TPS3647 **Poster Session**

Colorectal cancer metastatic dMMR immuno-therapy (COMMIT) study: A randomized phase III study of atezolizumab (atezo) monotherapy versus mFOLFOX6/bevacizumab/atezo in the first-line treatment of patients (pts) with deficient DNA mismatch repair (dMMR) or microsatellite instability high (MSI-H) metastatic colorectal cancer (mCRC)—NRG-GI004/SWOG-S1610. *First Author: Caio Max Sao Pedro Rocha Lima, Wake Forest University Baptist Medical Center, Winston-Salem, NC*

Background: Despite the superiority in progression-free survival (PFS) of inhibition of programmed cell death-1 (PD-1) pathway in dMMR/MSI-H as compared to chemotherapy with either anti-vascular endothelial growth factor receptor (VEGFr) or anti-epithelial growth factor receptor (EGFr) antibodies in mCRC, more pts had progressive disease as the best response in the anti-PD1 monotherapy arm (29.4% *v* 12.3%) with mean PFS of 13.7 mos, with ~45% of pts in the IO arm progressed at 12 mos (*N Engl J Med* 2020; 383:2207). We hypothesize that the dMMR/MSI-H mCRC pts may be more effectively treated with the combination of PD-1 pathway blockade and mFOLFOX6/bevacizumab (bev) rather than with anti-PD-1 therapy (atezo) alone. Preclinical work demonstrated synergistic effects between anti-PD-1/anti-VEGF and between oxaliplatin/anti-PD-1 in murine CRC models and phase II data, which showed activity of anti-PD-1/anti-VEGF in chemotherapy refractory colon cancer. A recent randomized trial subgroup analyses of 8 pts with dMMR metastatic colon cancer treated with FOLFOXIRI+bev+atezo, with the first patient having progression ~16 mos (*ESMO 2021, Abstt LBA20*). Additionally, in other solid tumor malignancies, anti-PD1 plus anti-VEGFr (i.e., HCC and RCC) as well as anti-PD1 plus chemotherapy (i.e., gastric and esophageal cancers) combinations are standard first-line treatments. **Methods:** The redesigned COMMIT study was reactivated on 1/29/2021 as a two-arm prospective phase III open-label trial randomizing (1:1) mCRC dMMR/MSI-H to atezo monotherapy *v* mFOLFOX6/bev+atezo combination. Assuming our control arm, atezo monotherapy (48% PFS at 24 mos as assessed by site investigator), we have 80% power to detect a hazard ratio of 0.6 (equivalent to 64.4% PFS at 24 mos) with alpha 0.025 one-sided. Stratification factors include BRAFV600E status, metastatic site, and prior adjuvant CRC therapy. Secondary endpoints include OS, objective response rate, safety profile, disease control rate, and duration of response. Health-related quality of life is an exploratory objective. Archived tumor tissue and blood samples will be collected for correlative studies. Key inclusion criteria are: mCRC without prior chemotherapy for advanced disease; dMMR tumor determined by local CLIA-certified IHC assay (MLH1/MSH2/MSH6/PMS2) or MSI-H by local CLIA-certified PCR or NGS panel; and measurable disease per RECIST. Enrollment actively continues to the target accrual of 211 patients randomized between the two immunotherapy arms. Support: U10CA180868, -180822, -180888, UG1CA189867, U24CA196067. Clinical trial information: NCT02997228. Research Sponsor: Genentech, Inc, U.S. National Institutes of Health.

4001 **Oral Abstract Session**

The first report of K-Umbrella Gastric Cancer Study: An open label, multicenter, randomized, biomarker-integrated trial for second-line treatment of advanced gastric cancer (AGC). *First Author: Sun Young Rha, Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea*

Background: To explore proper agents for AGC patients as 2nd-line treatment based on optimal biomarker, we conducted K-Umbrella GC study with standard of care (SOC) controlled umbrella trial design. **Methods:** HER2-negative AGC patients from 6 Korean cancer centers were centrally screened for druggable targets by IHC and *in situ* hybridization. Patients were randomized to the biomarker *vs.* control group with SOC as 4:1 ratio. In the biomarker group, patients were treated with specific targeted agents in combination with weekly paclitaxel; 1) EGFR 2+/3+ patients for pan-ERBB inhibitor (afatinib; EGFR cohort), 2) PTEN loss/null (H-score <100) patients for PIK3Cβ inhibitor (GSK2636771; PTEN cohort), and 3) PD-L1+, dMMR/MSI-high, or EBV-related cases for anti-PD-1 inhibitor (nivolumab; NIVO cohort). Control group and NONE cohort in biomarker group without predefined biomarkers were treated with SOC (weekly Paclitaxel±Ramucirumab). Primary endpoint was PFS between control and biomarker groups. Secondary endpoints included efficacy and safety of each cohort. **Results:** Between Feb 2016 and Feb 2021, total 722 patients were centrally screened. 329 patients were enrolled and randomized to control group (n=63) or biomarker group (n=266; EGFR cohort n=67; PTEN cohort n=42; NIVO cohort n=54; NONE cohort n=103). With a median follow-up of 35 months (95%CI 26.1-55.3), median PFS and OS were 3.8 (95%CI 3.2-4.3) and 8.9 (95%CI 7.8-10.1) months for biomarker group and 4.1 (95%CI 3.0-4.8) and 8.7 months (95%CI 7.2-10.2) for control group. In control group, PTEN loss/null was poor prognostic marker; patients with PTEN loss/null (n=12) showed worse survival compared to PTEN intact patients (n=51) (mPFS, 2.8 vs 4.3 months, *P*=0.03; mOS, 8.7 vs 9.1 months), where other biomarkers showed similar prognosis. Afatinib for EGFR cohort or GSK2636771 for PTEN cohort did not show significant survival benefit compared to control group (Table). Among patients with immune-related biomarkers, addition of nivolumab showed durable survival benefit (mOS 12.0 vs 7.6 months, *P*=0.08) compared to SOC. **Conclusions:** Considering the characteristics of umbrella design with multiple biomarkers having different biological roles, biomarker group did not show the improved survival over control arm with these 3 drugs. For optimal biomarker-driven targeted agent applications, NGS-based biomarker driven K-Umbrella GC-2 study is ongoing. Clinical trial information: NCT02951091. Research Sponsor: National R&D Program for Cancer Control, Ministry of Health and Welfare, Republic of Korea (1520190), and the National R&D Program for Cancer Control, Ministry of Health and Welfare, Republic of Korea (HA16C0018).

Group	Cohort	Regimen	N	mPFS (95%CI)	mOS (95%CI)
Control	Control	Paclitaxel±Ramucirumab	63	4.1 (3.0–4.8)	8.7 (7.1–10.2)
Biomarker		Total	266	3.8 (3.2-4.3)	8.9 (7.8–10.1)
	EGFR	Paclitaxel+Afatini	67	4.0 (3.3–4.6)	7.6 (5.8–10.1)
	PTEN	Paclitaxel+GSK263677	42	2.9 (1.9–4.1)	7.4 (5.2–9.2)
	NIVO	Paclitaxel+Nivolumab	54	4.0 (2.7–5.6)	12.0 (7.1–18.7)
	NONE	Paclitaxel±Ramucirumab	103	3.8 (2.9–5.3)	9.1 (7.6–11.3)

4003 **Oral Abstract Session**

Surgical and pathological outcome, and pathological regression, in patients receiving perioperative atezolizumab in combination with FLOT chemotherapy versus FLOT alone for resectable esophagogastric adenocarcinoma: Interim results from DANTE, a randomized, multicenter, phase IIb trial of the FLOT-AIO German Gastric Cancer Group and Swiss SAKK. *First Author: Salah-Eddin Al-Batran, Institut für Klinische Krebsforschung IKF am Krankenhaus Nordwest, Frankfurt Am Main, Germany and Krankenhaus Nordwest, University Cancer Center Frankfurt, Frankfurt Am Main, Germany*

Background: DANTE evaluates atezolizumab in the perioperative treatment of resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma in combination with FLOT. Here, we report interim results. **Methods:** DANTE is a multicenter, investigator-initiated, phase IIb trial. Patients (pts) with resectable adenocarcinoma of the stomach and GEJ (≥cT2 and/or N+) were randomized to receive 4+4 cycles of periop. FLOT chemotherapy (arm B) or the same regime with additional atezolizumab at 840 mg, q2w, followed by atezolizumab monotherapy for 8 cycles at 1200 mg, q3w (arm A). The primary endpoint is progression-free survival. The secondary endpoints surgical outcome (pTNM, R0 resection rate and periop. morbidity/mortality), path. regression and safety are reported here. TNM stage was evaluated by local pathologists and path. regression (Becker-Classification) by local and central pathologists. PD-L1 and MSI status were centrally evaluated. **Results:** In total, 295 pts were randomized (A, 146; B, 149) with baseline characteristics as follows: median age 61y, male 74%, intestinal type 42%, GEJ 61%, cT3/4 77%, N+ 78%. Twenty-five pts (8.5%) were MSI; 50% had PD-L1 CPS ≥1, 23% PD-L1 CPS ≥5 and 15% PD-L1 CPS ≥10. Pre-op FLOT cycles were completed in 93% of pts and post-op cycles in 43% of pts, with no difference between arms. Surgical morbidity (A, 45%; B, 43%) and mortality (overall 2.5%) were comparable between arms, as were R0-resection rates (arm A, 92% vs. arm B, 91%). Downsizing favored arm A vs B (pT0, 23% vs 15%; pN0, 68% vs 54%). Increases in path. regression rates were seen, particularly with higher PD-L1 expression (Table). **Conclusions:** The analysis shows beneficial effects of atezolizumab combined with FLOT vs FLOT alone on path. stage and path. regression that seem to be more pronounced with higher PD-L1 expression. Sponsor: Institut für Klinische Krebsforschung IKF am Krankenhaus Nordwest. EudraCT: 2017-001979-23. Clinical trial information: NCT03421288. Research Sponsor: Roche.

Path. regression by PD-L1 expression and MSI status for arms A vs B.

Path. reg. for arms A vs B	Local assessment		Central assessment*	
	TRG1a	TRG1a/b	TRG1a	TRG1a/b
All pts (n=295)	24% vs 15%	48% vs 39%	25% vs 24%	49% vs 44%
PD-L1 CPS ≥1 (n=146)	26% vs 16%	53% vs 49%	27% vs 25%	54% vs 50%
PD-L1 CPS ≥5 (n=67)	30% vs 24%	58% vs 47%	36% vs 27%	55% vs 50%
PD-L1 CPS ≥10 (n=45)	38% vs 14%	71% vs 38%	46% vs 24%	71% vs 52%
MSI high (n=25)	50% vs 27%	70% vs 47%	50% vs 27%	70% vs 47%

*Central assessment was done by one pathologist based on a representative tumor sample.

4004 **Oral Abstract Session**

A randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors: Final analysis of efficacy and evaluation of MGMT as a predictive biomarker (ECOG-ACRIN E2211). *First Author: Pamela L. Kunz, Yale Cancer Center, Yale School of Medicine, New Haven, CT*

Background: Patients with advanced pancreatic neuroendocrine tumors (NETs) have few treatment options that yield objective tumor response. Retrospective and small, prospective studies suggest that the combination of capecitabine and temozolomide is associated with high response rates (RR) and relative long progression-free survival (PFS). This trial was conducted to establish a role for the combination of capecitabine and temozolomide. **Methods:** E2211 was a multicenter, randomized, phase II trial comparing temozolomide (200 mg/m2 PO QD days 1-5) vs. capecitabine/temozolomide (capecitabine 750 mg/m2 PO BID days 1-14; temozolomide 200 mg/m2 PO QD days 10-14) in patients with advanced pancreatic NETs. Eligibility criteria included: metastatic or unresectable, low or intermediate grade pancreatic NETs, progression within preceding 12 months, and no prior temozolomide, DTIC, capecitabine or 5-fluorouracil. The primary endpoint was PFS; secondary endpoints were Overall Survival (OS), RR, safety, and MGMT as evaluated by immunohistochemistry (IHC) and promoter methylation. Allowing for 5% ineligibility, 145 randomized patients were required to obtain 138 eligible patients to detect a difference in median PFS of 9 versus 14 months (hazard ratio of 0.64) using a two-sided log-rank test at the overall 0.20 significance level with 81% power. **Results:** 144 patients were enrolled between 4/2013 to 3/2016 to temozolomide (n = 72) or capecitabine/temozolomide (n = 72); the efficacy analysis population included 133 eligible patients. At the scheduled interim analysis in January 2018, median PFS was 14.4 months for temozolomide vs. 22.7 months for capecitabine/temozolomide (HR = 0.58), which was sufficient to reject the null hypothesis for this final primary endpoint (stratified log rank p = 0.022. In the final analysis (5/2021), median OS was 53.8 months for temozolomide and 58.7 months for capecitabine/temozolomide (HR = 0.82, p = 0.42) and RR was 34% for temozolomide and 40% for capecitabine/temozolomide (p = 0.59). Capecitabine/temozolomide was associated with higher rates of grade 3-4 AEs (45% vs. 22%, p = 0.005). MGMT deficiency, defined as either low IHC or positive promoter methylation, was associated with greater odds of response (OR [95% CI] = 6.38 [2.19, 18.60] and 9.79 [1.09, 87.71], respectively). **Conclusions:** E2211 is the first prospective randomized trial of capecitabine/temozolomide and shows the longest PFS and highest RR reported for patients with pancreatic NETs in a prospective randomized study. MGMT deficiency was associated with greater odds of objective response. Clinical trial information: NCT01824875. Research Sponsor: U.S. National Institutes of Health.

4005 **Oral Abstract Session**

NET-02: A multicenter, randomized, phase II trial of liposomal irinotecan (nal-IRI) and 5-fluorouracil (5-FU)/folinic acid or docetaxel as second-line therapy in patients (pts) with progressive poorly differentiated extrapulmonary neuroendocrine carcinoma (PD-EP-NEC). *First Author: Mairead Geraldine McNamara, University of Manchester, Manchester, United Kingdom*

Background: The prognosis for pts with PD-EP-NEC is poor. A recognised first-line (1L) treatment for advanced disease is etoposide/platinum-based chemotherapy; there is no standard second-line (2L) treatment (area of unmet need). **Methods:** This was a multi-centre, randomised (1:1), phase II trial of IV nal-IRI (70mg/m^2 free base)/5-FU (2400 mg/m^2)/folinic acid, Q14 days (ARM A), or IV docetaxel (75mg/m^2), Q21 days (ARM B), as 2L therapy in a planned 102 pts with progressive PD-EP-NEC, aimed at selecting a treatment for continuation to a phase III trial. Pts with histologically-confirmed PD-EP-NEC (Ki-67>20%; Grade 3, WHO 2019), who had prior 1L platinum-based chemotherapy and radiological disease progression or discontinuation of 1L therapy due to intolerance, with an ECOG performance status ≤2 were eligible. Randomisation was stratified by Ki-67, ECOG PS, presence of liver metastases, and response to previous platinum-based therapy. Primary endpoint was 6 month (mo) progression-free survival (PFS) rate; 80% power to demonstrate the one-sided 95% confidence interval (CI) of the 6 mo PFS rate excluded 15%, if the true rate was at least 30%, where 30% was the required level of efficacy; a rate of <15% would give grounds for rejection. Intention was to show that the regimens were sufficiently active, but not to assess superiority of one regimen over the other. Secondary endpoints included objective response rate (ORR), PFS, overall survival (OS), and toxicity. Based on futility analysis, the DSMB recommended closure of recruitment in Dec 21. **Results:** Of 58 patients in 15 UK centres (Nov 18-Dec 21), 29 in ARM A, 29 in ARM B, 57% were male, median age (range): 63.5 years (22-85), 90% ECOG PS 0/1, 10% PS 2, 90% Ki-67≥55%, 33%/38%/29% small/large cell/unknown morphology, primary site: 69% gastrointestinal, 12% unknown, 9% genitourinary, 5% head & neck, 3% gynae, 2% breast, 60% had liver mets, 91%/7%/2% were resistant/sensitive/intolerant to 1L platinum-based treatment. At a median follow up of 6.6 mo, the primary end-point of 6-mo PFS rate was met in ARM A; ORR, median PFS and OS are also presented (Table). Adverse events ≥ grade 3 occurred in 51.7% and 55.2% in ARM A and B and there were 1 and 6 discontinuations due to toxicity in ARM A and B, respectively. Data cleaning is on-going. **Conclusions:** nal-IRI/5-FU, but not docetaxel, met the primary endpoint (exceeding the threshold for efficacy), with manageable toxicity, and warrants evaluation in a phase III trial. Clinical trial information: 03837977. Research Sponsor: Servier.

	ARM A (N=29) nal-IRI/5-FU	ARM B (N=29) Docetaxel
6 mo PFS rate (%)	32.1 (lower 95% CI 17.9)*	14.8 (lower 95% CI 5.2)**
ORR (%)	10.3 (95% CI 2.2-27.4)	10.3 (95% CI 2.2-27.4)
Median PFS (mo)	3 (95% CI 2-6)	2 (95% CI 2-2)
Median OS (mo)	9 (95% CI 3-15)	5 (95% CI 3-11)

*N=28, **N=27 (6 mo PFS rate awaited for 3 pts).

4006 **Oral Abstract Session**

Trastuzumab deruxtecan (T-DXd; DS-8201) in patients (pts) with HER2-expressing unresectable or recurrent biliary tract cancer (BTC): An investigator-initiated multicenter phase 2 study (HERB trial).

First Author: Akihiro Ohba, National Cancer Center Hospital, Tokyo, Japan

Background: BTCs have an aggressive tumor biology with limited treatment options. With a HER2-positivity rate of 5–20% in BTCs, case series and small clinical trials have shown signs of activity for HER2 blockade in these pts. T-DXd is an antibody-drug conjugate composed of a humanized monoclonal anti-HER2 antibody, a cleavable linker, and a topoisomerase I inhibitor. The HERB trial is an investigator-initiated, multicenter, single-arm phase 2 trial of T-DXd in pts with HER2-expressing BTCs. **Methods:** Centrally confirmed HER2-expressing (HER2-positive: IHC3+ or IHC2+/ISH+, and HER2-low-expressing [HER2-low]: IHC/ISH status of 0/+, 1+/-, 1+/+, or 2+/-) pts with BTCs who were refractory or intolerant to gemcitabine containing regimen received 5.4 mg/kg of T-DXd every 3 weeks. The primary endpoint was the confirmed objective response rate (ORR) in HER2-positive pts by independent central review. The sample size of 22 had 80% power with one-sided alpha error of 5%; threshold ORR, 15%; and expected ORR, 40%. The ORR, disease control rate (DCR), progression-free survival (PFS), overall survival (OS) in HER2-positive/-low pts, and incidence of treatment-emergent adverse events (TEAEs) were assessed as secondary endpoints. **Results:** A total of 32 pts, 24 with HER2-positive and 8 with HER2-low BTCs, received T-DXd. Twenty-two pts with HER2-positive, excluding 2 ineligible pts, were identified for primary efficacy analysis. Among the 22 pts, IHC3+ and IHC2+/ISH+ were 45.5% and 54.5%, primary sites: gallbladder/extrahepatic/intrahepatic/Vater were 11/6/3/2, median number of prior regimens was 2 (range, 1–4). The confirmed ORR in HER2-positive pts was 36.4% (8/22; 2 CR and 6 PR; 90% CI, 19.6–56.1), indicating statistically significant improvement in ORR (P = 0.01). The DCR, median (m) PFS, mOS were 81.8% (95% CI, 59.7–94.8), 4.4 months (mo) (95% CI, 2.8–8.3), 7.1 mo (95% CI, 4.7–14.6), respectively. In addition, encouraging efficacy were seen even in HER2-low pts; ORR, DCR, mPFS, and mOS were 12.5% (1/8; 1 PR; 95% CI, 0.3–52.7), 75.0% (95% CI, 34.9–96.8), 4.2 mo (95% CI, 1.3–6.2), and 8.9 mo (95% CI, 3.0–12.8), respectively. In the safety analysis set (n = 32), TEAEs of > = grade (G) 3 occurred in 81.3% (26/32); the common TEAEs were anemia (53.1%), neutropenia (31.3%), and leukopenia (31.3%). TEAEs leading to drug discontinuation occurred in 8 pts (25.0%). Eight pts (25.0%) had interstitial lung disease (ILD; G1/G2/G3/G5 were 3/1/2/2) not adjudicated by an independent committee. **Conclusions:** T-DXd showed promising activity in pts with HER2-expressing BTCs. Although the safety profile was generally consistent with other T-DXd studies, ILD, an important identified risk of T-DXd, requires more careful monitoring and intervention. These results support further exploration of T-DXd in this patient population. Clinical trial information: JMA-IIA00423. Research Sponsor: Japan Agency for Medical Research and Development, Pharmaceutical/Biotech Company.

4007 **Oral Abstract Session**

Adapted physical activity in patients (Pts) with advanced pancreatic cancer (APACaP): Results from a prospective national randomized GERCOR trial.

First Author: Cindy Neuzillet, Department of Medical Oncology, Institut Curie-Site Saint Cloud, Versailles Saint-Quentin University, Paris Saclay University, Saint Cloud, France

Background: The benefit of adapted physical activity (APA) on health-related quality of life (HRQoL) in Pts with advanced pancreatic ductal adenocarcinoma (aPDAC) treated by chemotherapy (CTx) has never been prospectively assessed. **Methods:** Pts with aPDAC and ECOG performance status (PS) 0–2 were randomized 1:1 to receive usual care (UC) including first-line CTx at the investigator's choice (standard arm), or UC plus a home-based 16-week APA program (APA arm). The APA program consisted of personalized aerobic and resistance exercises, with a weekly remote supervision by an APA professional trainer, and unsupervised sessions with a family member or friend (APA partner). The primary objective was the effect on HRQoL at week 16 (W16) measured by 3 dimensions of the EORTC QLQ-C30, global health status (GHS), physical functioning (PF), and fatigue (FA), with a one-sided type I error of 0.016 for each dimension. The primary HRQoL analysis was performed in Pts with available baseline and W16 scores for the 3 targeted dimensions (mITT1). Secondary analyses of HRQoL changes by the mixed model for repeated measures (MMRM) and time until definitive deterioration (TUDD) methods included Pts with baseline and ≥1 follow-up score (mITT2). Differences > 5 points in scores were considered clinically significant. **Results:** A total of 313 Pts (median age: 64 years; men: 55%, ECOG PS 0-1: 93%; metastatic: 77%; FOLFIRINOX: 78%, gemcitabine-based: 13%) were included from 11/2014 to 10/2020 (standard arm: n = 157, APA arm: n = 156). In the mITT1 population (n = 172), mean differences in HRQoL at W16 adjusted from baseline were -0.98 (SD 23.87; p = 0.39), -2.08 (SD 21.34; p = 0.26), and 4.16 (SD 29.18; p = 0.18) for GHS, PF, and FA, respectively. In the mITT2 population (n = 259), APA was associated with significant improvements in 5 (GHS, PF, cognitive functioning [CF], social functioning [SF], appetite loss) and 8 (GHS, CF, emotional functioning [EF], SF, insomnia, constipation, pain, financial difficulties) dimensions of HRQoL by MMRM and TUDD, respectively (Table). Secondary endpoints, including overall survival, progression-free survival, and chemotherapy toxicity will be presented. **Conclusions:** APA in combination with usual care improved several dimensions of HRQoL in Pts with aPDAC receiving first-line CTx. Clinical trial information: NCT02184663. Research Sponsor: GERCOR, A.R.CA.D Foundation.

Scores	MMRM mean difference with 95%CI*	TUDD Hazard Ratio with 95%CI**
GHS	-5.80 (-9.92,-1.68)	0.69 (0.52,0.92)
PF	-5.60 (-9.65,-1.54)	0.82 (0.62,1.08)
EF	-3.85 (-7.88, 0.17)	0.75 (0.56,1.00)
CF	-5.42 (-9.46,-1.39)	0.73 (0.55,0.96)
SF	-8.58 (-14.23,-2.93)	0.68 (0.51,0.90)
Pain	-5.57 (-11.20,0.05)	0.75 (0.56,1.00)
Insomnia	-3.95 (-10.12,2.22)	0.73 (0.55,0.98)
Appetite loss	-10.76 (-17.15,-4.37)	0.76 (0.57,1.02)
Constipation	-3.30 (-8.84,2.24)	0.72 (0.54,0.96)
Financial difficulties	1.27 (-3.31,5.84)	0.73 (0.54,0.99)

In favor of APA arm - *a negative change ** HR < 1

4008 **Oral Abstract Session**

Randomized phase III trial of induction chemotherapy followed by chemoradiotherapy or chemotherapy alone for nonresectable locally advanced pancreatic cancer: First results of the CONKO-007 trial.

First Author: Rainer Fietkau, Department of Radiation Oncology, Universitatsklinikum Erlangen, Friedrich-Alexander-Universitat Erlangen-Nürnberg, Erlangen, Germany

Background: Chemotherapy (CT) is the standard of care in nonresectable locally advanced pancreatic cancer. The CONKO-007 trial studied the role of sequential CT and chemoradiotherapy (CRT). **Methods:** In this randomized multicenter phase III trial resectability was judged by an independent surgical board. Patients (pts) received induction chemotherapy (IC) for 3 months (3 cycles gemcitabine (Gem, 1000 mg/m^2 d1, 8, 15, q4w) or FOLFIRINOX (6 cycles, q2w)). After IC pts without progression were randomized to either continuing CT for another 3 months or receiving CRT (cumulative dose of 50.4Gy, single dose 1.8Gy + Gem 300 mg/m^2 weekly, followed by 1 cycle of Gem 1000 mg/m^2 at d1, 8, 15). The primary endpoint of the study was overall survival (OS) since the begin of IC. Determination of sample size calculated 590 pts to be randomized. Due to the exclusion of pts with progressive disease after IC a total of 830 pts should be enrolled. Due to delayed patient accrual the primary endpoint was changed to R0 resection rate resulting in an estimated sample size of 525 pts. **Results:** Between 04/2013 and 02/2021 a total of 525 pts were enrolled in 47 sites. 402 pts received IC with FOLFIRINOX and 93 pts with Gem. After IC 190 pts were excluded due to progression or toxicity, 335 were randomized, their median FU was 16 months. Hematological toxicities were significantly increased in the CRT arm, non-hematological toxicities were comparable. R0 CRM- resection rate and pCR rate was significantly higher in the CRT arm. R1-resections occurred significantly more often in the CT arm. Median progression-free survival (PFS) (HR 0.919, 95% CI 0.702-1.203, p=0.540) and OS (HR 0.964, 95% CI 0.760-1.225, p=0.766) did not differ significantly in both arms, whereas the PFS rate tended to be higher in the CRT arm after 2 years. OS rates for CRM- R0 surgery with 87.5. ± 0.05% (1y) and 67.2 ± 0.05% (2y) were significantly higher (p<0.01) than for CRM+ R0 surgery with 66.7 ± 0.15% (1y) and 41.2 ± 0.1% (2y) as well as for patients without or incomplete surgery with 68.5 ± 0.03% (1y) and 26.4 ± 0.03% (2y). **Conclusions:** The addition of radiotherapy after IC improves the R0 CRM - resection and pCR rate without significant change in R0 resection rate (primary endpoint). Pts with R0 CRM - resections had a better prognosis compared to patients with either R0 CRM+ or incomplete or without surgery. However, this effect on resectability did not translate into a statistically significant PFS or OS benefit in the whole cohort. Clinical trial information: NCT01827553. Research Sponsor: Deutsche Krebshilfe.

	CT	CRT	p
Total (n)	167	168	
Surgery (n)	60 (35.9%)	61 (36.3 %)	1.000
R0	30 (18.0%)	42 (25.0%)	0.1433
R0 CRM – (n)	15 (9.0%)	33 (19.6%)	0.0015
R0 CRM + (n)	15 (9.0%)	9 (5.4%)	0.1777
R1 (n)	16 (9.6%)	5 (3.0%)	0.0085
pCR (n)	0	10 (6.0%)	0.0013
1-yr PFS rates	59.0 ± 0.04%	56.3 ± 0.04%	
2-yr PFS rates	17.5 ± 0.04%	24.1 ± 0.04%	
1-yr OS rates	71.3 ± 0.04%	71.1 ± 0.04%	
2-yr OS rates	32.5 ± 0.04%	34.8 ± 0.04%	

4009 **Clinical Science Symposium**

Updated results of the FOENIX-CCA2 trial: Efficacy and safety of futibatinib in intrahepatic cholangiocarcinoma (iCCA) harboring *FGFR2* fusions/rearrangements.

First Author: Lipika Goyal, Mass General Cancer Center, Harvard Medical School, Boston, MA

Background: Survival outcomes are historically poor in patients (pts) with advanced/metastatic iCCA, with median overall survival (mOS) times of approximately 1 year with first-line gemcitabine plus cisplatin and approximately 6 months with second-line chemotherapy. Futibatinib, a highly selective, irreversible FGFR1–4 inhibitor, demonstrated efficacy with durable responses in pts with iCCA harboring *FGFR2* fusion/rearrangements in the pivotal FOENIX-CCA2 phase 2 study (NCT02052778). At the primary analysis of this trial (data cutoff: October 1, 2020), an objective response rate (ORR) of 41.7% was observed, with a median duration of response (mDOR) of 9.7 mo. Here, we report updated efficacy (including mature OS data) and safety data from the final analysis with an additional 8 mo of follow-up. **Methods:** FOENIX-CCA2 was a single-arm phase 2 study that enrolled pts with advanced/metastatic iCCA with *FGFR2* fusion/rearrangement and progressive disease (PD) after ≥1 prior treatment (tx; including gemcitabine plus platinum-based chemotherapy). Pts received futibatinib 20 mg once daily until PD/intolerability. The primary endpoint was ORR per RECIST v1.1 by independent central review. Secondary endpoints were DOR, disease control rate (DCR), progression-free survival (PFS), OS, safety, and patient-reported outcomes. **Results:** At the time of the final data cutoff (May 29, 2021), median follow-up was 25.0 mo, and 96/103 pts (93%) had discontinued tx. The median number of tx cycles was 13.0 for a median tx duration of 9.1 mo. The confirmed ORR was 41.7% (43/103) and thereby the same as of the primary analysis, as was the DCR (at 82.5%). The ORR was consistent across pt subgroups. The mDOR was 9.5 mo, and 74% of responses lasted ≥6 mo. mPFS was 8.9 mo, with a 12-mo PFS rate of 35.4%. Mature mOS was 20.0 mo, with a 12-mo OS rate of 73.1%. No new safety signals were identified. Common tx-related adverse events (TRAEs) included hyperphosphatemia (85%), alopecia (33%), dry mouth (30%), diarrhea (28%), dry skin (27%), and fatigue (25%). TRAEs resulted in tx discontinuation in 4 pts (4%). No tx-related deaths occurred. Quality of life was maintained from baseline to tx cycle 13. **Conclusions:** Findings from the final analysis of FOENIX-CCA2 confirm the results of the primary analysis and reinforce the durable efficacy and continued tolerability of futibatinib in previously treated pts with advanced/metastatic iCCA harboring *FGFR2* fusion/rearrangements. Mature OS data were consistent with data from the primary analysis and far exceed historical data in this patient population. Clinical trial information: NCT02052778. Research Sponsor: Taiho Oncology, Inc., and Taiho Pharmaceutical Co. Ltd.

4010 **Clinical Science Symposium**

Distinct biosignatures associate with survival after chemoimmunotherapy in a randomized, three-arm phase II study in patients with metastatic pancreatic cancer. *First Author: Lacey J. Padrón, Parker Institute for Cancer Immunotherapy, San Francisco, CA*

Background: Preclinical and small clinical studies of chemoimmunotherapy for metastatic pancreatic ductal adenocarcinoma (mPDAC) point to a yet unrealized potential of clinically significant immune activation. In our phase II study of the CD40 agonist antibody sotigalimab (sotiga) and/or nivolumab (nivo) with gemcitabine and nab-paclitaxel (chemo), we observed promising improvements in overall survival (OS) in 105 patients with newly diagnosed mPDAC (NCT03214250); the primary endpoint of 1-year OS rate was 57.7% (p = 0.006) in the nivo/chemo arm, 48.1% (p = 0.062) in the sotiga/chemo arm and 41.3% (p = 0.233) in the nivo/sotiga/chemo arm (O'Hara, ASCO 2021) as compared to a historical control of 35%. Here, we report results of multi-omic translational analyses designed to identify signatures predictive of OS benefit. **Methods:** Longitudinal blood and tumor tissue samples were collected for immune and tumor biomarker analysis. Tumor samples underwent RNA sequencing and multiplex immunofluorescence (mIF). Peripheral blood was analyzed by mass cytometry time of flight (CyTOF), high parameter flow cytometry, and proteomics. Machine learning (ML) algorithms were applied to the data to identify biosignatures related to OS in each arm. **Results:** Comprehensive multi-omic, multi-parameter immune and tumor biomarker analyses identified distinct pretreatment immune signatures predictive of longer OS specific to nivo/chemo or sotiga/chemo (Table, representative examples). Because patients in each arm received chemotherapy, these and other arm-unique biomarkers suggest a relationship to the immunotherapy rather than chemotherapy in this randomized study. There was evidence of immune exhaustion in the sotiga/nivo/chemo arm that may explain the lack of survival benefit. **Conclusions:** From in-depth translational and ML analyses of randomized phase II trial of first-line chemoimmunotherapy in mPDAC patients, we identified novel biomarkers that associated with OS distinctly in each arm. Clinical trials in first-line mPDAC exploiting these previously unappreciated biomarkers and aiming to enrich patients for response, are warranted to further advance chemoimmunotherapy in this disease. Clinical trial information: NCT03214250. Research Sponsor: Parker Institute for Cancer Immunotherapy, Cancer Research Institute, Pharmaceutical/Biotech Company.

Selected pretreatment immune features associated with overall survival benefit.

Immune Feature	Sample	Nivo/Chemo (p-value, by log rank)	Sotiga/Chemo (p-value, by log rank)
Lower expression of TNF-α signaling via NFκB hallmark gene signature	Tumor	0.001	Not significant (ns)
Lower expression of the E2F targets hallmark gene signature	Tumor	ns	0.021
Higher frequencies of Tfh cells	Blood	< 0.0001	ns
Higher frequencies of PD-1+ CD39+ CD4 Central Memory T cells	Blood	0.037	ns
Higher frequencies of Tbet+ Eomes+ CD4 T cells	Blood	ns	0.013
Higher frequencies of PD-1+ Tbet+ CD4 T cells	Blood	ns	0.004

LBA4011 **Clinical Science Symposium**

Nimotuzumab combined with gemcitabine versus gemcitabine in K-RAS wild-type locally advanced or metastatic pancreatic cancer: A prospective, randomized-controlled, double-blinded, multicenter, and phase III clinical trial. *First Author: Shukui Qin, Department of Medical Oncology, Cancer Center of Jinling Hospital, Nanjing, China*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

4012 **Poster Discussion Session**

A randomised phase II clinical trial of low-dose cyclophosphamide and transarterial chemoembolization (TACE) with or without vaccination with dendritic cells (DC) pulsed with HepG2 lysate ex vivo in patients with hepatocellular carcinoma (HCC): The ImmunoTACE trial. *First Author: Yuk Ting Ma, University of Birmingham, Birmingham, United Kingdom*

Background: A previous study by our group using autologous monocyte-derived DC pulsed ex vivo with HepG2 cell lysate showed some clinical benefit with evidence of antigen-specific T-cell responses in patients with advanced HCC. The current trial reports the activity of this vaccine in combination with TACE in patients with HCC. All patients also received low-dose cyclophosphamide to deplete regulatory T cells and thereby enhance vaccination. **Methods:** Patients with intermediate stage HCC (performance status 0-2, Child Pugh A/B7) were randomised 1:1 to TACE plus low-dose cyclophosphamide (Group 1) or TACE plus low-dose cyclophosphamide plus dendritic cell vaccination (Group 2). Cyclophosphamide was administered on Day 1 and 29 followed by TACE on Day 31 (+/- DC infusion), with further cyclophosphamide on Days 60, 90 and 120 (+/- additional DC infusions on Days 62, 92 and 122). The primary endpoint was progression free survival (PFS) by RECIST v1.1. Secondary endpoints included radiological response by RECIST v1.1, PFS and radiological response according to modified (m) RECIST, overall survival (OS), immune response and toxicity. Target recruitment was 48 evaluable patients (24 patients in each arm) to detect a 20% increase in PFS rate at 1 year (30% vs 50%) with a relaxed one-sided statistical significance level of 20% and 80% power using a logrank test. **Results:** Between March 2016 and October 2019, 55 patients from 3 UK centres were randomised of whom 48 were evaluable (24 each arm). Median PFS by RECIST criteria was significantly longer in Group 2 compared to Group 1 (18.6 vs 10.4 months: hazard ratio (HR) 0.43, 80% CI -∞-0.59; one-sided p = 0.02). Median PFS using mRECIST criteria showed a similar magnitude of benefit (18.6 vs 10.8 months: HR 0.48, 95% CI 0.22-1.02). Median OS was 25.7 months in Group 2 vs 21.5 months in Group 1 (HR 0.61, 95% CI 0.27-1.38). Group 2 showed a higher overall response rate (complete and partial response) by RECIST (54% vs 29%) and mRECIST (75% vs 54%) and a higher disease control rate (complete and partial response and stable disease) by RECIST (92% vs 67%) and mRECIST (88% vs 67%). Treatment with DC infusions was well tolerated; the most common adverse events were chills (30%), fatigue (22%) and nausea (22%), all of which were low grade. Immune response analyses are currently ongoing. **Conclusions:** The addition of tumour lysate pulsed DC infusions to treatment with TACE plus low-dose cyclophosphamide significantly increased PFS in patients with HCC. To the best of our knowledge, this is the first randomised study to demonstrate efficacy using DC in HCC. Further investigation of the role of DC infusions in the treatment of HCC are warranted but will need to take into account the current evolving immunotherapy landscape. Clinical trial information: 11889464. Research Sponsor: National Institute for Health Research (UK): The Efficacy and Mechanism Evaluation (EME) Programme.

4013 **Poster Discussion Session**

Postoperative adjuvant hepatic arterial infusion chemotherapy (HAIC) with FOLFOX to improve outcomes of patients with hepatocellular carcinoma with microvascular invasion: A prospective multicenter, phase 3, randomized, controlled clinical trial. *First Author: Shaohua Li, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: To report the efficacy and safety of postoperative adjuvant hepatic arterial infusion chemotherapy (HAIC) with FOLFOX (5- fluorouracil, leucovorin, and oxaliplatin) in hepatocellular carcinoma (HCC) patients with microvascular invasion (MVI). **Methods:** In this randomized, open label, multicenter, phase 3 trial, histologically confirmed HCC patients with MVI were randomized (1:1) to receive either 1 to 2 cycles of adjuvant HAIC-FOLFOX (treatment group) or routine follow-up without any adjuvant treatment (control group). The primary endpoint was disease free survival (DFS), Secondary endpoints included overall survival (OS), recurrence rate and safety. Survival rates were calculated by the Kaplan-Meier plots. Adverse events (AE) were graded according to NCI-CTCAE version 5.0. **Results:** Between June, 2016 and August, 2021, a total of 315 patients in 5 centers were enrolled in to the study and eligible patients were randomly assigned to the treatment group (n = 157) or control group (n = 158) and were included in the intention-to-treat (ITT) population. Among these 14 patients from treatment group and 15 patients from control group were excluded from the per-protocol (PP) population. 148 patients in treatment group underwent at least 1 cycle of HAIC were included in safety analyses. The median DFS of treatment group and control group were 27.0 months (95% CI, 17.0-37.0) and 11.3 months (95% CI, 7.9-14.7), respectively in ITT population, while which was 20.4 months (95% CI, 9.5-31.3) and 9.7 months (95% CI, 6.9-12.4), respectively in PP population. The DFS were significantly better in the treatment group than in the control group in both ITT population and PP population (p = 0.001 and < 0.001, respectively). The DFS rates at 1, 2, and 3-years were 64.3%, 50.4%, and 44.3% in treatment group and 47.3%, 33.3%, and 24.2% in control group, respectively in ITT population, while which were 64.0%, 48.2%, and 42.2% in treatment group and 43.3%, 27.1%, and 18.4% in control group, respectively in PP population. The OS rates at 1, 2, and 3-year for the treatment group were 94.7%, 87.6%, and 80.5%, and were 91.9%, 85.9%, and 77.0% for the control group, respectively in ITT population, while which were 94.9%, 86.7%, and 80.9% in treatment group and 91.8%, 84.9%, and 75.3% in control group, respectively in PP population. Furthermore, in ITT population, there were 63 (40.1%) patients in the treatment group and 88 (55.7%) patients in the control group had recurrence. Majority of the AEs observed were grade 0-1 (n = 124 (83.8%)) and no treatment related death was observed during the study period. **Conclusions:** Postoperative adjuvant HAIC with FOLFOX significantly improved the survival benefits with acceptable toxicities in HCC patients with MVI. Clinical trial information: NCT03192618. Research Sponsor: None.

4015 **Poster Discussion Session**

Preoperative chemoradiation (CRT) with carboplatin (CBP)/paclitaxel (PCL) (CP) or with 5-fluorouracil (FU)/oxaliplatin (OX) (Fx) for esophageal or junctional cancer: A randomized phase 2 trial. *First Author: Antoine Adenis, Department of Medical Oncology, Montpellier Cancer Institute (ICM), Montpellier, France*

Background: Preoperative CRT with a FU/platinum regimen has been used for years for esophageal or junctional cancer before the CP regimen became a standard of care following the results of the CROSS study (van Hagen 2012). We aimed at evaluating the complete resection (R0) rate and severe postoperative morbidity rate associated with these 2 neoadjuvant regimens, each being combined with the radiation (RT) regime used in the CROSS trial. **Methods:** PRODTECT is a multicenter, randomized, non-comparative, phase 2 trial (NCT02359968) in patients (pts) with resectable esophageal or Siewert type I-II junctional cancer, stage II (T1-2N1 or T3N0) or stage III (T3N1 or T4anyN) tumors (UICC-7 classification), and ECOG PS ≤2. Following randomization (balanced by ECOG PS 0 vs 1-2, stage II vs III, squamous-cell (SCC) vs adenocarcinoma (ADK), center), pts received CP (AUC2 CBP plus PCL 50mg/m^2 / week x 5 weeks), or Fx (FU 400 mg/m^2 bolus Day 1, then FU 1600 mg/m^2 continuous infusion over 2 days, plus OX 85 mg/m^2, and Folinic acid 200 mg/m^2, 2-h infusion, Day 1; 3 cycles every 2 weeks). RT technique was similar in both arms: 3D-conformal as published in the CROSS trial or IMRT (n = 35); total dose of 41.4Gy, 5 fractions of 1.8Gy / week, starting at Day 1 of chemotherapy. Surgery was performed 4 to 8 weeks after completion of CRT through a transthoracic or mini-invasive approach with a two field extended lymphadenectomy. Co-primary endpoints were R0 (failure: R1 or disease progression under CRT), and severe postoperative morbidity rate ≤30 days after surgery (Clavien-Dindo grade ≥ III). Based on a Bryant and Day 2-stage design (p0 = 75% and p1 = 90% for resection; p0 = 45% and p1 = 25% for morbidity; α = 10% and β = 15%), 48 evaluable pts were required by arm. **Results:** 100/104 pts recruited from 02/2015 to 08/2020, started the study treatment: 50 CP & 50 Fx. Overall, median age = 64 (range, 33-79); 82/100 males; 62 ADK and 38 SCC; 66 esophageal and 34 junctional site; 31 stage II; 68 stage III, 1 Nx. R0 resection was obtained in 46/50 CP pts (92.0%, 95% CI: 80.8-97.8%), and in 42/48 Fx pts (87.5%, 74.8-95.3%); 2 non evaluable pts because of event unrelated to disease progression. Severe postoperative adverse events (AEs) occurred in 34/91 pts who underwent surgery: 21/48 CP (43.8%, 29.5-58.8%) and 13/43 Fx (30.2%, 17.2-46.1%). Severe AEs were respiratory disorders (CP 26%; Fx 26%), esophageal fistula (CP 18%; Fx 6%), infection (CP 5%; Fx 3%), haemorrhage (CP 5%; Fx 0%) and gastric tube necrosis (CP 6%; Fx 3%). 5 pts died from AEs (3 CP, 2 Fx). A TRG1-2 was observed in 29/48 (60.4%, 95% CI: 44.3-74.2%) CP pts, and in 19/43 (44.2%, 29.1-60.1%) Fx pts. **Conclusions:** When combined to preoperative radiation therapy at 41.4Gy, both regimens (CP and Fx) provided short-term benefit on R0 resection; however, CP is associated with a severe postoperative morbidity rate higher than expected. Clinical trial information: NCT02359968. Research Sponsor: PHRC 2014.

4016 **Poster Discussion Session**

Nimotuzumab plus concurrent chemo-radiotherapy versus chemo-radiotherapy in unresectable locally advanced esophageal squamous cell carcinoma (ESCC): Interim analysis from a prospective, randomized-controlled, double-blinded, multicenter, and phase III clinical trial (NXCEL1311 Study). *First Author: Xue Meng, Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Jinan, China*

Background: 70% of esophageal carcinoma are unresectable at diagnosis. Despite active clinical research on the treatment of esophageal squamous cell carcinoma (ESCC), the long-term survival rate of advanced patients is still very low, with a 5-year survival rate of 30%-40%. A prospective, randomized-controlled, double-blinded, multicenter, and phase III study (NXCEL1311) was designed to investigate the efficacy and safety of nimotuzumab (anti-EGFR humanized monoclonal antibody;abbreviate,Nimo) plus concurrent chemo-radiotherapy compared with placebo plus chemo-radiotherapy in unresectable locally advanced ESCC. **Methods:** Unresectable locally advanced ESCC patients were randomized (1:1) to receive Nimo (400 mg, qw) or placebo in combination with concurrent chemo-radiotherapy (paclitaxel+ cisplatin+3DCRT/IMRT) for seven weeks. Patients were followed for five years.The primary endpoints were OS, and the secondary endpoints included ORR, DCR, PFS. **Results:** 200 patients were assigned to the Nimo group (n = 99) or placebo group (n = 101). An interim analysis was conducted for short term efficacy, i.e secondary endpoints (ORR, DCR) and safety, after completing the 6 months follow-up. The OS events are not enough for analysis. The two groups were comparable on baseline characteristics. Eighty patients in the Nimo group and eighty-two patients in the placebo group were evaluable. The ORR of the Nimo group (75/80, 93.8%) was significantly higher than the placebo group (59/82, 72.0%;Chi-square test, p < 0.001). Twenty-six patients in the Nimo group reached the complete response (CR), and ten placebo group patients were CR. The CR rate in the Nimo group was significantly higher than placebo group (32.5% vs.12.2%, p = 0.002). The DCR of the Nimo group and placebo group were 98.8% (79/80) and 91.5% (75/82), respectively (p = 0.064). Single factor logistic aggression analysis showed that age, sex, target lesion number, and BMI did not affect ORR, CR, and DCR (p > 0.05). Multiple factor correction analysis showed the difference of CR, ORR and DCR between two groups is 20% (95%CI 6.0%~40.2%), 30% (95%CI 10.6%~52.1%) and 10% (95%CI -5.2%~31.1%). The incidence of grade 3-5 drug-related AEs was 11.1%vs.10.9% (p > 0.05). Common drug-related AEs in patients with Nimo plus chemo-radiotherapy treatment were leucopenia, neutrophilic granulocytopenia, thrombocytopenia, hemoglobin, bone marrow inhibition, nutritional anemia, and radioactive inflammation. **Conclusions:** This interim analysis showed that nimotuzumab in combination with chemo-radiotherapy is safe and can increase the CRR and ORR of the treated patients. The OS needs to be followed and finally analyzed. Clinical trial information: 02409186. Research Sponsor: None.

4017 **Poster Discussion Session**

Safety, tolerability, and preliminary efficacy results in patients with advanced gastric/gastroesophageal junction adenocarcinoma from a phase Ib/II study of CLDN18.2 CAR T-cell therapy (CT041). *First Author: Changsong Qi, Department of Gastrointestinal Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital & Institute, Beijing, China*

Background: Claudin18.2 (CLDN18.2) has emerged as a promising therapeutic target, which is normally confined to gastric mucosa tight junctions but is often expressed in gastric/gastroesophageal junction (G/GEJ) cancer. CT041, an CLDN18.2-redirected CAR T-cell therapy, showed promising anti-tumor activity in preclinical studies (Hua J. J Natl Cancer Inst. 2019). Recently reported results of a phase I study (Qi C. Ann. Oncol 2021) showed that CT041 was well tolerated and had encouraging efficacy in previously treated patients with CLDN18.2-positive advanced G/GEJ cancer. Here we report the preliminary safety and efficacy data on patients with G/GEJ cancer in an ongoing phase Ib/II study (CT041-ST-01, NCT04581473). **Methods:** This open-label, 2-part, multicenter, phase Ib/II study was conducted to assess the safety, tolerability and efficacy of CT041 in patients with previously treated, CLDN18.2-positive advanced G/GEJ cancer. The study consisted of a dose escalation/dose-expansion phase (phase Ib) and a safety/efficacy confirmatory phase (phase II). In the dose escalation/de-escalation phase, CT041 dose levels of 2.5×10^8 and 3.75×10^8 were investigated using 3 + 3 design. The primary objective of the phase Ib part was to determine the safety, tolerability and recommended phase 2 dose (RP2D) of CT041. Data are reported as of December 22, 2021. **Results:** From November 2020 to May 2021,14 eligible patients with G/GEJ cancer were enrolled in phase Ib. The median (range) age was 44.5 (23-71); 85.7% had received 2 prior lines of treatment and 14.3% had at least 3 lines; 57.1% had ≥ 3 metastatic organs, with 92.9% had peritoneal dissemination; 64.3% had signet ring cell carcinoma. Among them, 3 received 3.75×10^8 and 11 received 2.5×10^8 dose level with up to 3 doses, respectively. Most commonly reported AEs of grade 3 or higher were hematologic toxicity related with lymphodepletion. There were no dose-limiting toxicities, treatment-related death, neurologic toxicity (ICANS) or gastrointestinal toxicities observed. Most CRS were grade 1 or 2, and only one patient experienced grade 4 CRS and fully recovered. As of the data cut-off, 8 of 14 (57.1%) patients achieved partial response (PR); 2 of 14 (14.3%) patients showed stable disease (SD). With a median follow-up time of 8.9 months (95%CI 5.91, NE), the median progression-free survival (PFS) was 5.6 months (95%CI 1.9, 7.4), and median overall survival (OS) was 10.8 months (95%CI 5.1, NE) with 7 patients still alive at last follow-up. **Conclusions:** These preliminary results suggest that CT041 had manageable safety/tolerability profile and promising efficacy in patients with previously treated advanced G/GEJ cancer. This study is ongoing with further investigation of CT041 in phase II underway. Clinical trial information: NCT04581473. Research Sponsor: CARsgen Therapeutics Ltd., Co.

4018 **Poster Discussion Session**

Comprehensive genomic and transcriptomic characterization of small bowel adenocarcinoma. *First Author: Karan Pandya, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ*

Background: Small bowel adenocarcinoma (SBA) is a rare cancer with rising incidence and worse overall survival (OS) compared to other intestinal cancers. Clinical management of SBA is primarily extrapolated from colorectal cancer (CRC). Comprehensive genomic and transcriptomic profiling of SBA will facilitate development of disease-specific therapeutic strategies. We investigated molecular alterations and association with clinical outcomes in a large cohort of SBA pts. **Methods:** Tumors were analyzed using 592 gene next-generation sequencing of DNA (592 genes or WES), RNA (WTS) and IHC (Caris). Immune infiltration was calculated by QuantiSeq. OS was calculated from treatment start/tissue collection to last contact from insurance claims. **Results:** We analyzed 823 SBA tumors: 448 primary/312 metastases, 586 duodenal (DA)/95 jejunal (JA)/38 ileal (IA). Median age of JA pts was lower (57yo) than DA (67yo) and IA (68yo). Upon subsite comparison, HER2 overexpression (2.5%) and amplification (3.6%) was only seen in DA, while HER2 mutations (mts) were most common in JA (10%) and absent in IA. IA had the lowest rate of KRAS (30%) and APC (11%) mts and highest rate of DDR mts (37%). JAs were enriched in RSPO3 fusion (19%) and BRAF mts (21%). Among BRAF mts in SBA, class 3 comprised 53%, class 2 37% and class 1 10%. MSI/dMMR was seen in 8% SBA and TMB-H in 11% with no difference among subsites. Compared to 14000 CRC tumors, SBA had significantly higher immune infiltrates regardless of MSI status (p<0.001), with highest fold change in myeloid dendritic cells (15.5), Tregs (9.4), neutrophils (3.6) and M2 Macrophages (3.5). When investigating clinical outcome of SBA pts (n=751), favorable prognostic markers included TMB^{3}8 mts/Mb (HR: 0.65, 95%CI: 0.50-0.85), mts in APC (HR: 0.76, 95% CI: 0.62-0.93), MSH6 (HR: 0.45, 95% CI: 0.20-0.99), HNF1A (HR: 0.268, 95% CI: 0.11-0.65), PRKDC (HR: 0.45, 95% CI: 0.20-1.01) and ERBB3 (HR: 0.46, 95% CI: 0.26-0.82), while TP53 (HR: 1.32, 95% CI: 1.10-1.59) and CDKN2A (HR: 1.7, 95% CI: 1.25-2.3) mts and positive PD-L1 (HR: 1.44, 95% CI: 1.09-1.90) predicted worse OS. Among SBA pts treated with chemotherapy (n=258), DA had worse OS than IA/JA (HR: 1.44, 95% CI: 1.05-1.98), which had worse OS than left-sided [LS] (HR: 1.86, 95% CI: 1.39-2.46) and right-sided [RS] CRC pts (HR: 1.35, 95% CI: 1.01-1.79). DA pts had significantly worse OS compared to LS (HR=2.97, 95% CI: 1.73-5.08) and RS (HR=1.88, 95% CI: 1.08-3.24) CRC pts. **Conclusions:** This study represents the largest SBA cohort with comprehensive genomic and transcriptomic profiling. We identified subsite-specific enrichment in targetable alterations, including HER2 overexpression/amplification in DA, BRAF/HER2 mts and RSPO3 fusions in JA, and DDR mts in IA. SBAs harbor higher immune infiltrates than CRC, suggesting active immune modulation. DA is characterized by poor overall outcomes and decreased therapeutic benefit from chemotherapy compared to LS- and RS- CRCs. Research Sponsor: None.

4019 **Poster Discussion Session**

Adjuvant gemcitabine plus cisplatin (GemCis) versus capecitabine (CAP) in patients (pts) with resected lymph node (LN)-positive extrahepatic cholangiocarcinoma (CCA): A multicenter, open-label, randomized, phase 2 study (STAMP). *First Author: Changhoon Yoo, Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea*

Background: Adjuvant CAP is the standard of care for resected CCA according to the BILCAP trial. However, the prognosis of patients with resected CCA is still poor. As GemCis is the standard first-line therapy for unresectable/metastatic BTC, we investigated the role of adjuvant GemCis in resected BTC. Because BTC is heterogeneous disease according to the primary tumor site, this study included only pts with resected LN+ extrahepatic CCA. **Methods:** STAMP is a multicenter, open-label, randomized phase 2 study. Pts with ≥ 19 years, ECOG PS 0/1, adenocarcinoma of perihilar or distal bile duct, at least one regional LN metastasis (N1 or greater), complete macroscopic (R0 or R1) resection within 12 weeks before randomization were eligible. Distant metastasis or R2 disease, previous chemotherapy or radiotherapy, or a serum CA 19-9 level ≥ 100 U/mL were ineligible. Pts were randomized 1:1 to GemCis (Gem 1,000 mg/m2 IV, and Cis 25 mg/m2 IV on day 1 and 8, every 3 weeks) or CAP (1,250 mg/m2 orally twice daily on days 1-14, every 3 weeks) for 8 cycles. Tumor response was performed every 12 weeks for the first 2 years, followed by every 24 weeks for the next 3 years. Primary endpoint was disease-free survival (DFS). Secondary endpoints were overall survival (OS) and safety. This study was designed to improved 2-year DFS rates from 22% (CAP) to 40% (GemCis). Considering follow-up loss rates of 10% with a 1-sided type I error of 0.1 and a type II error of 0.2, a total of 100 patients (50 in each arm) were required. **Results:** Between JUL 2017 and NOV 2020, a total of 101 pts (50 for GemCis group and 51 for CAP group) were included in the ITT population. Perihilar and distal bile duct were primary tumor sites in 45 pts (44.6%) and 56 pts (55.4%), respectively and 32 pts (31.7%) had R1 resection. Pts characteristics were well balanced between two arms. With median follow-up duration of 28.7 mo (IQR 17.2-39.4), the 2-year DFS rates were 38.5% (1-sided 90% CI, 29.5-47.4%) in GemCis group and 25.1% (17.4-33.5%) in CAP group. The median DFS were 14.3 mo (10.7-16.5 mo) in GemCis group and 11.1 mo (8.4-12.7 mo) in CAP group (HR=0.96 [0.71-1.30], p=0.86). The median OS were 35.7 mo (29.5 mo-not estimated [NE]) in GemCis group and 35.7 mo (30.9 mo-NE) in CAP group (HR=1.08 [0.72-1.64], p=0.81). Grade 3-4 adverse events (AEs) occurred in 42 pts (84.0%) and 8 (16.0%) in GemCis and CAP groups, respectively. The most common AE of grade 3-4 was neutropenia (n = 36, 72.0%) in GemCis group and hand-foot skin reaction (n = 4, 8.0%) in CAP group. **Conclusions:** In this study including prognostically homogeneous pts population, GemCis was feasible as adjuvant therapy, but failed to improve survival outcomes compared to CAP. CAP should remain standard adjuvant therapy for resected BTC. Clinical trial information: NCT03079427. Research Sponsor: CKD pharmaceuticals and Ildong pharmaceuticals.

4020 **Poster Discussion Session**

Randomized phase II study of platinum and etoposide (EP) versus temozolomide and capecitabine (CAPTEM) in patients (pts) with advanced G3 non-small cell gastroenteropancreatic neuroendocrine neoplasms (GEPNENs): ECOG-ACRIN EA2142. *First Author: Jennifer Rachel Eads, University of Pennsylvania, Abramson Cancer Center, Philadelphia, PA*

Background: High grade (G3) GEPNENs are a rare and heterogeneous disease entity for which there is little prospective treatment data. EP chemotherapy is the treatment standard but this may not be appropriate for all G3 GEPNEN pts. CAPTEM has demonstrated activity in G3 GEPNENs and may be a promising alternative. EA2142 aimed to determine if CAPTEM was superior to EP in pts with G3 GEPNENs. **Methods:** This was a multicenter, randomized (1:1) phase II trial for pts with a locally advanced and unresectable or metastatic well differentiated G3 neuroendocrine tumor (NET) or a poorly differentiated, non-small cell G3 neuroendocrine carcinoma (NEC) of suspected gastrointestinal origin and an ECOG PS of 0-2. Pathology must have demonstrated a Ki-67 of 20-100% or at least 10 mitoses/10 high powered field. Pts were randomized to receive capecitabine 750 mg/m2 orally every 12 hours on days 1-14 and temozolomide 200 mg/m2 orally once daily on days 10-14 of a 28-day treatment cycle (Arm A) or etoposide 100 mg/m2 daily on days 1-3 with either cisplatin 25 mg/m2 daily on days 1-3 or carboplatin AUC 5 on day 1 of a 21-day treatment cycle (Arm B). Restaging scans were performed every 8 weeks and toxicity monitored per CTCAEv4. Final statistical plan was to accrue 80 pts to detect a 67% improvement in progression free survival (PFS) (primary endpoint) with CAPTEM as compared to EP, 80% power and one-sided significance level of 0.10. A planned interim analysis for efficacy and futility was conducted. **Results:** A total of 67 pts were enrolled (Arm A, n=32; Arm B, n=35). Male 58%, African American 4%, Asian 3%. Mean age 61. Among 63 eligible pts, primary tumor site pancreatic 56%, non-pancreatic 43%. Poorly differentiated 57%, well differentiated 33%, unknown 10%. Mean Ki-67 48% (Arm A), 60% (Arm B). The study was closed prior to full accrual due to futility at 57.7% information time. In the interim analysis, among 62 eligible pts, PFS, overall survival and response rate with CAPTEM were 2.43 months (mos) (95% CI 2.04, 7.72), 12.6 mos, 9% respectively vs 5.36 mos (95% CI 2.14, 7.23), 13.6 mos and 10% with EP. Toxicity was evaluable in 57 pts with Grade (G) 3/4 events occurring in 29% of pts on Arm A, 66% of pts on Arm B. G3/4 events occurring in more than 5% of pts on Arm A—febrile neutropenia (n=2); abdominal pain (n=2); diarrhea (n=2); nausea (n=2); neutropenia (n=2); dehydration (n=2) and on Arm B—anemia (n=8); febrile neutropenia (n=2); fatigue (n=2); lymphopenia (n=2); neutropenia (n=12); thrombocytopenia (n=4); leukopenia (n=6). There was one G5 event on Arm A due to sepsis. **Conclusions:** CAPTEM does not appear to be superior to EP chemotherapy as front-line treatment for pts with G3 NENs but does demonstrate a more favorable toxicity profile. Studies assessing G3 NET independently of G3 NEC are needed. Clinical trial information: NCT02595424. Research Sponsor: U.S. National Institutes of Health.

4021 **Poster Discussion Session**

A randomized phase Ib/II study of niraparib (nira) plus nivolumab (nivo) or ipilimumab (ipi) in patients (pts) with platinum-sensitive advanced pancreatic cancer (aPDAC). *First Author: Kim Anna Reiss, University of Pennsylvania Abramson Cancer Center, Philadelphia, PA*

Background: Establishing alternatives to perpetual chemotherapy for pts with aPDAC has been proposed to address inevitable chemotherapy resistance and cumulative toxicity. Poly (ADP ribose) polymerase (PARP) inhibitors have shown clinical efficacy in this setting, and preclinical data suggest that the addition of immune checkpoint blockade (ICB) may offer synergistic tumor control. We performed a randomized, phase Ib/II study of nira plus anti-PD-1 (nivo) or nira plus anti-CTLA-4 (ipi) maintenance for pts with aPDAC who had not progressed after >4 mo of platinum-based therapy. **Methods:** After discontinuation of chemotherapy, pts were randomized 1:1 to nira 200mg PO daily plus either nivo 240mg IV q2 weeks (later amended to 480mg IV q4 weeks) or ipi 3mg/kg IV q3 weeks for four doses. Nira could be escalated to 300mg PO daily if tolerated. Pts were treated until progression or unacceptable toxicity. The primary endpoint was progression free survival at six months (PFS6) in each arm. Secondary endpoints included safety, OS, ORR, and outcomes by DNA damage repair (DDR) deficiencies. Pts were evaluable for safety if they had received > 1 dose of study treatment and for efficacy if they had also received > 1 follow-up imaging study. Based on historical data, the null hypothesis of PFS6 = 44% vs a 2-sided alternative hypothesis of PFS ≠ 44% was tested. 42 pts per arm provided 81% power for testing at a 5% significance level to detect inferior PFS6 < 27% or superior PFS6 > 61%. **Results:** As of Oct 2021, 91 pts were enrolled, of whom 84 were evaluable for efficacy (44 nira/nivo; 40 nira/ipi). The median potential follow-up was 23 mos. Most common treatment-related AEs were nira/nivo: thrombocytopenia (28%), arthralgia (25%), nausea (23%), and fatigue (23%) and nira/ipi: thrombocytopenia (45%), anemia (43%), fatigue (43%), nausea, (41%), AST increase (36%), rash (34%) and ALT increase (29%). 88% of AEs were grade 1-2. Efficacy results were: nira/nivo: PFS6 20.6% (95% CI 8.3-32.9, p = 0.0002), mPFS 1.9 mo and nira/ipi: PFS6 59.6% (95% CI 44.3-74.9, p = 0.045), mPFS 8.1 mo. Fifteen pts (8 nira/nivo; 7 nira/ipi) had pathogenic variants in *BRCA* or *PALB2*. Excluding these: mPFS on nira/nivo was 1.9 mo (95% CI 1.8-1.9) and mPFS on nira/ipi was 7.6 mo (95% CI 4.0 – 11.1). **Conclusions:** In a randomized phase 1B/II study, nira/ipi as maintenance therapy met the primary endpoint of superior PFS6 while nira/nivo yielded inferior PFS6 for pts with aPDAC who had not progressed on first-line platinum-based chemotherapy. The benefit of nira/ipi maintenance persisted in pts without known DDR variants. Clinical trial information: NCT03404960. Research Sponsor: Glaxo-Smith-Kline and Bristol-Myer-Squibb.

Arm	PFS6	mPFS	ORR	mOS	mPFS (non-DDR pts)
nira/nivo n = 44	20.6% 95% CI 8.3-32.9% p = 0.0002 vs 44%	1.9 mo 95% CI 1.4-2.3	7.1%	14.0 mo 95% CI 7.4-20.6	1.9 mo 95% CI 1.8-1.9
nira/ipi n = 40	59.6% 95% CI 44.3-74.9% p = 0.045 vs 44%	8.1 mo 95% CI 5.5-10.6	15.4%	17.3 mo 95% CI 12.8-21.9	7.6 mo 95% CI 4.0-11.1

4022 **Oral Abstract Session**

Sequential *nab*-paclitaxel/gemcitabine followed by modified FOLFOX for first-line metastatic pancreatic cancer: The SEQUENCE trial. *First Author: Alfredo Carrato, IRYCIS, CIBERONC, Alcalá University, Hospital Universitario Ramón y Cajal, Madrid, Spain*

Background: Sequential treatment with nab-paclitaxel, gemcitabine followed by oxaliplatin, leucovorin and 5-fluorouracil (*nab*-P/Gem-mFOLFOX) have shown a good safety profile and clinical activity in metastatic pancreatic ductal adenocarcinoma (mPDAC) in a previously published phase I SEQUENCE trial. **Methods:** We have compared nab-P/Gem-mFOLFOX to the standard *nab*-P/Gem in first-line treatment, in an open-label multi-institutional prospective randomised phase II trial in patients with untreated mPDAC from 14 Spanish hospitals. Patients were allocated 1:1 to *nab*-paclitaxel (125 mg/m^2) plus gemcitabine (1000 mg/m^2) on days 1, 8 and 15, followed by modified FOLFOX-6 (oxaliplatin [85 mg/m^2], L-leucovorin [200 mg/m^2] or racemic leucovorin [400 mg/m^2], 5-fluorouracil bolus [400 mg/m^2], and 5-fluorouracil 48-hour continuous infusion [2400 mg/m^2]) on day 29 of a 6-week cycle or *nab*-paclitaxel (125 mg/m^2) plus gemcitabine (1000 mg/m^2) on days 1, 8 and 15 of a 4-week cycle. The primary endpoint was the 12-month overall survival rate (OS) in randomised patients. EudraCT number 2014-005350-19; ClinicalTrial.gov identifier NCT02504333. **Results:** Between July 27, 2017, and April 16, 2019, 182 patients were screened and 157 randomised: 78 to *nab*-P/Gem-mFOLFOX and 79 to *nab*-P/Gem. Patients receiving *nab*-P/Gem-mFOLFOX showed a significantly higher 12-month, and 24-month OS (95% CI): 55.3% (44.2-66.5%) versus 35.4% (24.9-46.0%) (p = 0.016), and 22.4% (13.0-31.8%) versus 7.6% (1.8-13.4%) (p = 0.012), respectively. The median OS (95% CI) reached 13.2 (10.1-16.2) months with nab-P/Gem-mFOLFOX and 9.7 (7.5-12.0) months with nab-P/Gem (HR = 0.676, 95% CI 0.483-0.947, p = 0.023). 39.7% patients in the nab-P/Gem-mFOLFOX group and 54.4% in nab-P/Gem group received subsequent anticancer treatments. Safety was comparable except for grade ≥3 neutropenia (46.1% versus 24.1%, p = 0.004) and grade ≥3 thrombocytopenia (23.7% versus 7.6%, p = 0.007) that were higher in the *nab*-P/Gem-mFOLFOX regimen. Two (2.6%) patients died due to adverse events in the *nab*-P/Gem-mFOLFOX arm. **Conclusions:** *Nab*-P/Gem-mFOLFOX showed significantly higher clinical activity than the standard *nab*-P/Gem treatment, with a manageable safety profile. This regimen represents a feasible and efficient new option for first-line treatment of mPDAC. Clinical trial information: NCT02504333. Research Sponsor: Celgene (a Bristol Myers Squibb Company).

4023 **Poster Discussion Session**

Phase 3, multicenter, randomized study of CPI-613 with modified FOLFIRINOX (mFFX) versus FOLFIRINOX (FFX) as first-line therapy for patients with metastatic adenocarcinoma of the pancreas (AVENGER500). *First Author: Philip Agop Philip, Karmanos Cancer Center, Wayne State University, and SWOG, Farmington Hills, MI*

Background: Metastatic pancreatic cancer (mPC) remains a deadly disease with very limited treatment options. FFX is a standard first-line therapy for mPC with a median overall survival (mOS) of 11.1 months. CPI-613 is a stable intermediate of a lipoate analog that inhibits pyruvate dehydrogenase and α-ketoglutarate dehydrogenase enzymes of the tricarboxylic cycle preferentially within the mitochondria of cancer cells. In a phase I study, CPI-613+mFFX was safe and exhibited promising signal of efficacy. **Methods:** A global, randomized phase 3 trial was conducted across 73 sites to investigate the efficacy and safety of CPI-613 in combination with mFFX compared to standard dose FFX in treatment-naïve patients with mPC. Treatment was administered in 2-weekly cycles until progression or intolerable toxicity. In the experimental arm, CPI-613 at 500 mg/m^2 was given intravenously on days 1 and 3. The doses of irinotecan, oxaliplatin, and 5-fluorouracil in the experimental arm were 65 mg/m^2, 140 mg/m^2, and 2,400 mg/^{2}, respectively. Primary endpoint was OS. Secondary endpoints were progression-free survival (PFS), overall response rate (ORR), duration of response, pharmacokinetics, patient reported outcomes and safety. **Results:** 528 patients were randomly assigned (266 in test and 262 in control arm). There were 362 deaths, with a mOS of 11.1 months for CPI-613+mFFX vs. 11.7 months for FFX [hazard ratio (HR), 0.95; 95% CI, 0.77 to 1.18; P = 0.655]; mPFS was 7.8 months vs. 8.0 months respectively [HR, 0.99; 95% CI, 0.76 to 1.29; P = 0.94]; ORR was 39% in the test arm vs. 34% in the control arm [ORR ratio, 1.23 (95% CI, 0.86 to 1.75)]. Grade $\geq$ 3 treatment-emergent adverse events with $\geq$ 10% frequency in CPI-613 plus mFFX vs. FFX arm were diarrhea (11.2% vs. 19.6%), hypokalemia (13.1% vs. 14.9%), anemia (13.9% vs. 13.6%), neutropenia (11.2% vs. 14.0%), thrombocytopenia (11.6% vs. 13.6%) and fatigue (10.8% vs. 11.5%). **Conclusions:** The addition of CPI-613 to mFFX failed to show significant improvements of ORR, PFS or OS. The mFFX in the test arm that had the lowest prospectively tested doses of FFX was without compromise on PFS or OS and may be considered as a reference for future FFX administration. Clinical trial information: NCT03504423. Research Sponsor: Rafael.

4024 **Poster Session**

Molecular characterization of long-term and short-term survivors of advanced pancreatic ductal adenocarcinoma. *First Author: Jesús Fuentes Antrás, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, Canada*

Background: Median overall survival (mOS) for advanced pancreatic ductal adenocarcinoma (PDAC) is $\leq$1 year. However, there are patients (pts) who live for >2 years on chemotherapy and those who rapidly progress prior to a first scan, underscoring biological heterogeneity in PDAC subgroups. Understanding these differences is important in clinical trial design and provides prognostic information for pts. **Methods:** Clinical and molecular data (WGS and RNAseq) from pts with a diagnosis of locally advanced or metastatic PDAC enrolled in the COMPASS (NCT02750657) and POG/PanGen (NCT02155621, NCT02869802) studies were available for analysis as part of the TFRI's EPPIC program and Marathon of Hope Cancer Centres Network, a multi-institutional collaborative network aiming to implement precision medicine in Canada. Clinical data were collected prospectively from both cohorts. Pts had an ECOG PS 0-1 and chemotherapy regimen was based on clinician's preference. Profiling was performed on fresh biopsies and homologous recombination deficiency was identified with the HRDetect assay. We compared pts with very short OS (STS; $\leq$3 months, mo) vs long OS (LTS; $\geq$24 mo). **Results:** 341 pts were included in the analysis of which 47 were STS (mOS 1.6 mo) and 42 LTS (mOS 29.7 mo). There was no difference in median age, BMI or sex (p>0.1) between cohorts. STS were more likely to have an ECOG PS 1 vs 0 (p=0.03), higher tumor burden (RECIST) (p<0.001) and higher CA19.9 (p=0.04) at diagnosis. In STS, 71% had non evaluable responses as a result of clinical decline or death before first scan, and 28% PD as best response; in LTS, ORR to chemotherapy was 69%. Sixty-four % and 33% of LTS and 32% and 36% of STS had received mFFX and GA, respectively. There was no difference in the prevalence of *KRAS* mutations (90% vs 98%, ns) or specific mutant alleles, however amplification of mutant *KRAS* was more common in STS (35% vs 65%, p=0.01). The prevalence of inactivating driver mutations in *TP53*, *CDKN2A*, and *SMAD4* (90% vs 98%, ns), and in genes involved in chromatin modification (*ARID1A*, *SMARCA4*, *PBRM1*, *KDM6A*) (17% vs 30%, ns) was similar in both groups. However, STS had a higher prevalence of mutations resulting in activation of the PI3K/AKT/mTOR pathway (*PIK3CA*, *PTEN* loss, *STK11*) (10% vs 26%, p=0.049). Genotypes consistent with HRD were present (17% vs 11%); however, in LTS 6/7 were a result of germline pathogenic variants, compared with only 1/5 in STS. Median structural variant loads, ploidy, TMB and substitution base signatures were similar in both cohorts. More basal-like PDAC were present in STS vs LTS (3% vs 30%, p=0.006). **Conclusions:** Pts who survive $\leq$3 mo with advanced PDAC are characterized by a higher tumor burden and molecular profiles consistent with enhanced RAS signaling, a deregulation of the PI3K/AKT/mTOR pathway, and a basal-like transcriptomic subtype. HRD genotypes are heterogeneous with germline carriers accounting for some of the LTS. Research Sponsor: Ontario Institute of Cancer Research; Pancreatic Cancer Canada; Terry Fox Foundation.

4025 **Poster Session**

The association of B7-H6 expression to the immune microenvironment in gastric cancer. *First Author: Jian Chen, The Affiliated Yantai Yuhuangding Hospital of Qingdao University, Yantai, China*

Background: B7-H6, also known as NCR3LG1, is a promising molecule in B7 family and a ligand of natural killer (NK) -cell-activating receptor NKp30. B7-H6 can bind NKp30 and induce NK activation and cytokine secretion to exert anti-tumor effects. Studies have reported that the B7-H6 expression is significantly correlated with post-operative prognosis and distant metastasis status in patients with cancer. In patients with gastric cancer, B7-H6 high expression is significantly associated with longer OS. However, the effects of B7-H6 on immunotherapy and immune microenvironment are unknown. Herein, we used the data from TCGA database of gastric cancer to analyze the influence of B7-H6 expression on immune microenvironment. **Methods:** The gene expression profile and clinical data in gastric cancer were extracted from TCGA database (http://cancergenome.nih.gov). According to the previous reported article, 15 was chosen as the cutoff value for the expression of B7-H6, and the expression of B7-H6 is divided into two groups, high group (B7-H6 expression $>$ 15) and low group (B7-H6 expression$\leq$15). Kaplan-Meier analysis was used to verify the influence of B7-H6 expression on OS prognosis. "Cell Type Identification by Estimating Relative Subsets of RNA Transcripts" (CIBERSORT) algorithm was used to analyze the proportion of immune-related cells in the two groups. "Estimation of STromal and Immune cells in Malignant Tumours using Expression data" (ESTIMATE) algorithm was used to analyze stromal and immune scores in the two groups. The differences of immune-related signatures between the two groups were calculated according to previous reports. **Results:** Kaplan-Meier survival analysis showed that high group was significantly associated with longer overall survival (p value = 0.016), which was consistent with previous reports. The result of CIBERSORT algorithm showed that the proportion of activation immune correlation CD8(+) T cells and NK active cells was significantly higher in low group than in high group ($p < 0.05$). Meanwhile, the proportion of immune suppressive correlation CD4 resting memory T cell was significantly lower in low group than in high group ($p < 0.05$). The result of ESTIMATE algorithm showed that the stromal score, immune score, and ESTIMATE score in low group were significantly higher than in high group ($p < 0.01$). The immune-related signatures, including immune signature, expanded immune signature, TLS signature, myeloid cell chemotaxis, tertiary lymphoid structure, were significantly higher in low group than in high group ($p < 0.05$). **Conclusions:** The low B7-H6 expression was correlated with better immune microenvironment. The effect of B7-H6 expression on immunotherapy needs to be further explored. Research Sponsor: None.

4026 **Poster Session**

Choice of PD-L1 immunohistochemistry assay influences clinical eligibility for gastric cancer immunotherapy. *First Author: Ryan Yong Kiat Tay, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore*

Background: Immune checkpoint inhibitors (ICI) are now standard-of-care treatment for patients with metastatic gastric cancer (GC). To guide patient selection for ICI therapy, programmed death ligand-1 (PD-L1) biomarker expression is routinely assessed via immunohistochemistry (IHC). Regulatory approval for ICIs is granted based on PD-L1 expression status, scored using metrics such as the combined positive score (CPS). However, with an increasing number of approved ICIs, each paired with a different PD-L1 antibody IHC assay used in their respective landmark trials, there is an unmet clinical and logistical need for harmonization. We thus investigated the interchangeability between the Dako 22C3, Dako 28-8 and Ventana SP-142 assays in GC PD-L1 IHC. **Methods:** In this cross-sectional study, samples were obtained via biopsy or resection of gastric cancer at the National University Hospital, Singapore. We scored 362 GC samples for PD-L1 CPS, tumor proportion score (TPS) and immune cells (IC) using a multiplex immunohistochemistry/immunofluorescence technique. 344 samples were developed into a tissue microarray (TMA), while 18 samples were used as whole slides for orthogonal validation. The samples selected for whole slide analysis were obtained from GC patients treated with ICI therapy. **Results:** The percentage of PD-L1 positive samples at clinically relevant CPS $\geq$1, $\geq$5 and $\geq$10 cut-offs (Table) for the 28-8 assay were approximately two-fold higher than that of the 22C3 (CPS$\geq$1: 70.3% vs 49.4%, p<0.001; CPS$\geq$5: 29.1% vs 13.4%, p<0.001; CPS$\geq$10: 13.7% vs 7.0%, p=0.004). The mean CPS score on 28-8 assay was nearly double that of the 22C3 (6.39 $\pm$14.5 vs 3.46$\pm$8.98, p<0.001). At the clinically important CPS$\geq$5 cut-off, there was only moderate concordance between the 22C3 and 28-8 assays. **Conclusions:** Our findings suggest that scoring PD-L1 CPS with the 28-8 assay may result in higher proportion of PD-L1 positivity and higher PD-L1 scores compared to assessment with the 22C3 and other assays. Clinically, this could lead to a larger number of patients eligible and approved for ICI therapy. If assays are viewed and used interchangeability, a substantial number of patients may be inaccurately denied or granted treatment with ICIs based on the assay chosen. As such, until stronger evidence of inter-assay concordance is found, we urge caution in treating the assays as equivalent. Research Sponsor: National Medical Research Council.

The percentage of PD-L1 positive samples at clinically relevant CPS $\geq$1, $\geq$5 and $\geq$10 cut-offs.

Assay	CPS $\geq$1	CPS $\geq$5	CPS $\geq$10
22C3	49.4%	13.4%	7.0%
28-8	70.3%	29.1%	13.7%
SP-142	49.4%	19.8%	9.6%

4027 **Poster Session**

Combination of oligo-fractionated irradiation with nivolumab can induce immune modulation and replacement of T cell clones in patients with gastric cancer (phase I/II clinical study). *First Author: Koji Kono, Fukushima Medical University, Fukushima, Japan*

Background: Although basic, translational and clinical research suggest a possibility of synergistic effect of radiation-induced immunogenic cell death with immune checkpoint inhibitors, the effectiveness of the combination therapy is not fully established. Therefore, we conducted a single-arm, phase 1/2 trial (ClinicalTrials.gov, NCT03453164) in gastric cancer (GC) patients treated with a combination of nivolumab and oligo-fractionated irradiation (22.5 Gy/5 fractions/5 days). **Methods:** Eligible patients (n = 40) had un-resectable advanced or recurrent GC which progressed after primary and secondary chemotherapy with more than one lesion assessable in diagnostic imaging (one lesion must be ≥2cm). PBMCs from enrolled patients underwent high-dimensional flow cytometry-based, multiplexed MHC multimer analysis using a total of 46 tumor-associated antigens (TAA) and 10 virus epitopes and next-generation sequencing-based repertoire analysis of TCR β-chain. **Results:** The disease control rate (DCR) for the non-irradiated target as abscopal effect as the primary endpoint was 22.5%, and the DCR for the irradiated lesion was 40.0%. The median survival time was 230 days (157-330 days, 95%CI) and probability of 1-year survival rate was 28.6%. Although most TAA-specific T cells could be tracked longitudinally pre- and post-treatment, some several novel TAA-specific CD8 T cells were detected de novo after irradiation, indicating that potential irradiation-driven antigen spreading. Moreover, irradiation was associated with phenotypical changes of TAA-specific CD8 T cells towards higher expressions of KLRG1, HLA-DR, TIGIT and CD160 and lower expression of CD27 and CD127. Furthermore, the T cell clonality evaluated by the inverted Pielou's evenness indicated that longer survival patients had more diverse TCR beta repertoire during treatment in comparison to shorter survivors. Also, we confirmed several new sequence-reads after radiation and nivolumab treatment in the top 30 most frequent clonotypes. **Conclusions:** Taken together, our results suggest that irradiation may induce, through immunogenic cell death, an immune-modulating effect with potential antigen spreading and a more diverse TCR repertoire, ultimately resulting in better survival during combination therapy of radiation with nivolumab. Clinical trial information: NCT03453164. Research Sponsor: Ono Pharmaceutical company.

4028 **Poster Session**

VOYAGER (KSCC1902): A single-arm, multicenter, phase II study of early induction of nivolumab during second-line treatment with taxane ± ramucirumab for advanced gastric or gastro-esophageal junction cancer. *First Author: Hiroo Katsuya, Division of Hematology, Respiratory Medicine and Oncology, Department of Internal Medicine, Faculty of Medicine, Saga University, Saga, Japan*

Background: Although nivolumab prolonged overall survival in 3rd or later line treatment for advanced gastric cancer in the ATTRACTION-2 study, only a small number of patients respond or achieve stable disease. Previous reports have shown that low tumor burden at the start of treatment was potentially associated with efficacy to immunotherapy in some types of tumors, but it has not been studied in advanced gastric cancer. We conducted a clinical trial to evaluate the early induction of nivolumab. **Methods:** Eligible patients were unresectable advanced or recurrent gastric or gastro-esophageal junction cancer, histologically confirmed to be adenocarcinoma regardless of PD-L1 expression. Patients who were refractory to or intolerant of fluoropyrimidines had a complete or partial response after at least three cycles of taxane ± ramucirumab, and were confirmed to be either of the following conditions; disease progression by imaging tests, an increase of tumor markers, exacerbation of symptoms, and intolerant of pretreatment. Patients received 240mg/body nivolumab every 2 weeks. The primary endpoint was the rate of progression-free survival (PFS) at 6 months (M), and the secondary endpoints included safety, overall survival (OS), response rate (RR), time to treatment failure (TTF), and duration of response (DOR). Based on assuming a threshold PFS at 6M of 16% and an expected PFS of 30% with the early induction of nivolumab, 39 patients were required for a power of 0.8 with a one-sided α of 0.1. **Results:** Between September 2019 and February 2021, 42 patients were enrolled in this study. The characteristics of patients were male/female: 28/14, median age: 71 years (range: 39-87), and performance status 0/1/2: 21/19/2. The PFS at 6M was 35.7% (80% confidence interval 26.4-45.1%), which means this trial met the primary endpoint. The median PFS and OS were 4.0M (95%CI:2.3–5.7) and 10.9M (95%CI:9.9–16.0), respectively. Of 34 patients with baseline target legions, RR was 17.5% (all confirmed partial response) and the rate of stable disease was 41.2%. TTF, and DOR were 3.6M (95%CI:2.2–5.1), and 14.3M (95%CI:3.9–14.3), respectively. No new safety signals were observed. **Conclusions:** This study demonstrated an improvement of PFS at 6M in patients with advanced gastric cancer and might justify the strategy of early induction of nivolumab. Clinical trial information: jRCTs071190025. Research Sponsor: Ono Pharmaceutical.

4029 **Poster Session**

Durvalumab (D) and PET-directed chemoradiation (CRT) after induction FOLFOX for esophageal adenocarcinoma: Final results. *First Author: Darren Cowzer, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Induction FOLFOX followed by PET-directed CRT prior to surgery demonstrated positive results in the CALGB 80803 study. We investigated the safety and efficacy of adding D, an anti-PD-L1 antibody, to PET-directed CRT. **Methods:** Patients (pts) with locally advanced esophageal/GEJ adenocarcinoma were enrolled. Pts received 2 cycles of mFOLFOX6 prior to repeat PET/CT. PET responders (≥35% reduction in SUV (PETr)) received 5-FU/capecitabine and oxaliplatin with RT to 50.4Gy, while induction PET non-responders (PETnr) received carboplatin/paclitaxel with RT. All Pts received D 1,500 mg q4W ×2 starting 2 weeks prior to CRT. Esophagectomy was planned 6-8 weeks after CRT. Pts with R0 resections received adjuvant D 1,500mg q4W ×6. The primary endpoint was the pathologic complete response (pCR) rate. **Results:** 36 pts were enrolled. Clinical ≥T3 disease was seen in 32 pts (88.9%, cT4 = 3) and ≥N1 in 23 (63.9%) pts. PD-L1 CPS was ≥1 in 25 (71.4%) of 35 tested with 14 (40%) ≥5. Microsatellite instability (MSI) was identified in 3 (8.3%) pts. 25 (70%) pts were PETr. Preop treatment was well tolerated with no new safety signals. Three pts had disease progression prior to surgery. pCR was identified in 8 (22.2%) pts and 22 (64.7%) had major pathologic response (MPR; ypTanyN0 + ≥90% response). Those with MSI tumors had ≥90% treatment response (1 pCR, 1: ypT1aN0 99% response, 1: ypT2N0, 90% response). 17 (73.9%) of 23 cN+ pts had ypN0 disease. MPR was associated with PD-L1 ≥1 (p = 0.03) and with a higher tumor mutational burden (TMB; p = 0.016) on MSK-IMPACT testing. Adjuvant D was commenced in 27 pts, with a median number of 6 cycles. Early discontinuation was due to risks of visits due to COVID19 (4, 15%), progressive disease (3, 11%), late surgical complications (2, 7%) and immune toxicity (1, 4%). With a median follow-up of 30 months, OS rates were 92% [95%CI: 83%-100%] and 85 % [95%CI: 74%-98%] at 12 and 24 months post induction. 12 and 24-month PFS rates were 81% [95%CI: 69%-95%] and 71% [95%CI: 58%-88%] respectively. In the 33 operated pts, 12 and 24-month disease free survival was 82% [95%CI: 70%-96%] and 78% [95%CI: 65%-94%], respectively. In addition to SUV on PET, total lesion glycolysis (TLG) was correlated with pathologic response. In cases with borderline change in SUV, TLG could predict response to treatment. One PETnr with 30.8% reduction in SUV had 88.1% reduction in TLG and pCR. Conversely, a PETr (-36.3%) who had an increase in TLG (39.3%) had only 40% treatment response on pathology. **Conclusions:** The addition of D to induction FOLFOX and PET-directed CRT prior to surgery is safe and appears effective with a high rate of pathologic response, as well as encouraging survival data. PD-L1 CPS≥1 and higher TMB may be associated with MPR. TLG is a novel PET variable that should be studied prospectively. Additional correlatives and comparison to a cohort treated with standard PET-directed CRT will be presented. Clinical trial information: NCT02962063. Research Sponsor: Astra Zeneca, Other Foundation.

4030 **Poster Session**

Tandem CAR-T cells targeting CLDN18.2 and NKG2DL for treatment of gastric cancer. *First Author: Hui Xu, Nanjing Kaedi Biotherapeutics Co. Ltd., Nanjing, China*

Background: Gastric cancer (GC) is one of most common malignant tumor which is fifth for melanoma incidence and second for mortality rates worldwide. Novel therapeutic strategies are urgently needed. Recently people are exploring the potential of chimeric antigen receptor T (CAR-T) cell therapy in GC, yet the clinical outcome is limited. Reportedly, the bispecific CAR-T cell with tandem scFvs exhibited superior response rates or synergistic response compared with CAR-T cell with single scFv. It's reported that Claudin18.2 (CLDN18.2) is the most potential target of gastric cancer. Here, we construct a novel bispecific CAR-T cells (KD-496), which simultaneously recognize NKG2D ligands and CLDN18.2, to show superior antitumor efficacy and safety *in vitro* and *in vivo*. **Methods:** Gastric cancer cell lines as well as GC patient tissue samples were evaluated for NKG2DL and CLDN18.2 expression. The KD-496 CAR-T cells showed antigen-specific stimulation by cytokine secretion and tumor cell cytotoxicity assay. The patient tumor tissue fragments (8 mm^3) were implanted subcutaneously into B-NDG mice to establish PDX models. When the tumor volume reached 50-100mm^3, the mice received a single treatment of 5 million KD-496 CAR-T cells intravenously. The effect of KD-496 CAR-T *in vivo* was detected by measuring tumor volume twice a week. **Results:** CLDN18.2 and NKG2DL were detected on NUGC4, AGS-18.2 and MKN-28-18.2 cells and most of screened BM patient samples. The bispecific CAR-T cell KD-496 was generated with CD8 hinge region and transmembrane region, 4-1BB costimulatory region and CD3 zeta region. The KD-496 expression was > 50% on the surface of T cells confirmed by flow cytometry. Co-incubation of KD-496 CAR-T cells with NUGC4 and MKN-28-18.2 cell specifically upregulates IFN-γ cytokines and strongly lysis tumor cells even at low E:T ratio (50-60% at 4:1). Strikingly, KD-496 CAR more efficiently eliminated xenograft tumors in vivo and did not exhibit significant treatment-related toxicity in the treated mice. No obvious pathological changes were found in the tested organs. **Conclusions:** Our work construct a tandem CAR molecule targeting two tumor-associated antigens, NKG2DL and CLDN18.2, and found that Tan-CAR-T cells (KD-496) distinctly recognize the antigens and exhibited superior antitumor effect. KD-496 CAR-T cells potently respond to GC and more efficient tumor elimination than single CAR such as KD-025 and KD-182 CAR-T cells in PDX model with no obvious safety issue. The results support future clinical trial of KD-496 CAR in patients with GC, where the need for effective treatment is great. Research Sponsor: Nanjing Kaedi Biotherapeutics Co. Ltd.

4031 **Poster Session**

Perioperative chemotherapy with docetaxel plus oxaliplatin and S-1 (DOS) versus oxaliplatin plus S-1 (SOX) for locally advanced gastric or gastro-esophageal junction adenocarcinoma (MATCH): An open-label, randomized, phase 2 study. *First Author: Wen Zhang, Department of Medical Oncology, National Cancer Center/ National Clinical Research Center for Cancer/ Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: The optimal perioperative chemotherapy of locally advanced gastric or gastro-esophageal junction (G/GEJ) cancer has not been established in Asia, though FLOT was considered as standard therapy in Europe. Therefore, we aimed to assess efficacy and safety of DOS versus SOX as perioperative treatment in patients with locally advanced G/GEJ cancer in this study. **Methods:** This was a single center, open-label, randomized, phase 2 study. Eligible pts were aged ≥18 years with histologically diagnosed HER2 negative cT3-4 Nany M0 G/GEJ (Siewert II/III type) adenocarcinoma. Pts were randomized (1:1) to receive either 4 preoperative and 4 postoperative cycles of DOS (docetaxel 60mg/m2 D1, oxaliplatin 100mg/m2 D1, S-1 40-60mg bid D1-14 depending on body surface area (BSA), Q3W) or SOX (oxaliplatin 130mg/m2 D1, S-1 40-60mg bid D1-14 depending on BSA, Q3W). Pts underwent D2 gastrectomy after preoperative treatment. The primary endpoint was major pathological response (MPR) analyzed in the modified intention to treat (mITT) population according to Becker TRG criteria. Secondary endpoints included the 3-year progression free survival (PFS), the 3-year overall survival (OS), pathological complete response, R0 resection rate and safety. **Results:** From Aug, 2015, to Dec, 2019, 154 pts were enrolled, 7 pts withdrew consent, 147 pts were included as mITT population (DOS 71; SOX 76). 80.3% and 67.1% of the pts in the DOS and SOX groups accepted surgery respectively. More pts achieved MPR (25.4% vs. 11.8%, p = 0.035) and R0 resection (78.9% vs. 61.8%, p = 0.024) in the DOS group than the SOX group. With a median follow-up of 42.4 months, the 3-year PFS and the 3-year OS were 52.3% vs. 35% (p = 0.065, HR 0.667, 95%CI 0.432-1.029) and 57.5% vs. 49.2% (p = 0.114, HR 0.685, 95%CI 0.429-1.095) in the DOS and SOX groups, respectively. Pts who acquired MPR had a significant longer survival than non-MPR pts. The 3-year PFS were 89.4% vs. 38.6% (p < 0.001, HR 0.076, 95%CI 0.018-0.314). The 3-year OS were 100% vs. 50.1% (p = 0.008, HR 0.024, 95%CI 0.002-0.371). 56.1% and 60.8% of the pts completed at least 6 cycles of the perioperative chemotherapy in the DOS and SOX groups, respectively (p = 0.625). The most common grade ≥3 TRAEs included neutropenia (8.5% vs.10.5%), leucopenia (1.4% vs. 5.3%), thrombocytopenia (1.4% vs 15.8%, p = 0.002), anemia (1.4% vs. 3.9%) and diarrhea (1.4% vs. 2.6%). The incidence of grade 1-2 thrombocytopenia was also significant lower in the DOS group (15.5% vs. 31.6%, p = 0.022). No treatment-related deaths occurred. **Conclusions:** Perioperative DOS improved MPR significantly and tended to have better PFS compared with SOX in locally advanced G/GEJ cancer, might be regarded as a prefered option of perioperative chemotherapy. Clinical trial information: NCT02725424. Research Sponsor: None.

4032 **Poster Session**

Zanidatamab (zani), a HER2-targeted bispecific antibody, in combination with chemotherapy (chemo) and tislelizumab (TIS) as first-line (1L) therapy for patients (pts) with advanced HER2-positive gastric/gastroesophageal junction adenocarcinoma (G/GEJC): Preliminary results from a phase 1b/2 study. *First Author: Keun-Wook Lee, Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, South Korea*

Background: Zani, also known as ZW25, is a novel HER2-targeted bispecific antibody that targets two distinct extracellular domains of HER2. Zani has shown preliminary antitumor activity and tolerability in pts with HER2+ gastroesophageal adenocarcinoma as monotherapy/with chemo in Phase 1/2 studies (NCT02892123, NCT03929666). TIS, an anti-PD-1 antibody, has demonstrated antitumor activity in pts with advanced solid tumors. Combining anti-HER2 therapy with anti-PD-1 therapy and chemo increased tumor response in G/GEJC in a Phase 3 clinical trial. **Methods:** Cohort 2 of this ongoing open-label, Phase 1b/2 study was in pts with untreated locally advanced/metastatic HER2+ G/GEJC (NCT04276493). Cohort A received zani 30 mg/kg IV, Cohort B received zani 1800 mg IV (weight < 70 kg) or 2400 mg IV (weight ≥ 70 kg), both with TIS 200 mg IV and capecitabine/oxaliplatin (CAPOX) Q3W. Primary endpoints were safety and investigator (INV)-assessed objective response rate (ORR) per RECIST v1.1. Secondary endpoints included INV-assessed duration of response (DoR), disease control rate (DCR) and progression-free survival (PFS). **Results:** As of Nov 26, 2021, 33 pts with a median age of 64.0 years (range: 29.0–80.0) were assigned to Cohort A (n=19) or B (n=14). Median study follow-up was 7.7 months (range: 2.1–19.0) and the median number of treatment cycles was 10 (range: 1–28), 20 (60.6%) pts remained on treatment. All pts were efficacy evaluable ([EE], n=33), confirmed ORR was 72.7% (95% CI: 54.5, 86.7). Median PFS was 10.9 months (95% CI: 6.9, NE). Efficacy data are summarized in the Table. All pts experienced ≥ 1 treatment emergent adverse event (TEAE), and 24 (72.7%) pts experienced ≥ Grade 3 TEAEs. All pts experienced treatment related TEAEs (trTEAEs), 20 (60.6%) pts experienced ≥ Grade 3 trTEAEs and trTEAEs leading to death occurred in two (6.1%) pts. Immune-mediated AEs (imAEs) occurred in nine (27.3%) pts, of which seven (21.2%) pts experienced ≥ Grade 3 imAEs. **Conclusions:** Zani, TIS and CAPOX combination demonstrated a manageable safety profile and antitumor activity as 1L therapy for pts with HER2+ G/GEJC. Clinical trial information: NCT04276493. Research Sponsor: This study was sponsored by BeiGene, Ltd. Medical writing support for the development of this abstract, under the direction of the authors, was provided by Victoria Dagwell, MSc, of Ashfield MedComms, an Ashfield Health company, and was funded by BeiGene,.

Summary of efficacy results (EE analysis set).

	Cohort A (n=19)	Cohort B (n=14)	Total (n=33)
Confirmed best overall response, n (%)			
Complete response	1 (5.3)	0 (0)	1 (3.0)
Partial response	13 (68.4)	10 (71.4)	23 (69.7)
Stable disease*	5 (26.3)	4 (28.6)	9 (27.3)
Progressive disease	0 (0)	0 (0)	0 (0)
Confirmed ORR, n (%)	14 (73.7)	10 (71.4)	24 (72.7)
95% CI	48.8, 90.9	41.9, 91.6	54.5, 86.7
Confirmed DCR, n (%)	19 (100.0)	14 (100.0)	33 (100.0)
95% CI	82.4, 100.0	76.8, 100.0	89.4, 100.0
Confirmed DoR, range	2.4–15.3	2.8–7.2	2.4–15.3

*One pt's partial response is to be confirmed.
Data cut off: Nov 26, 2021.

4033 **Poster Session**

Effect of neutrophil extracellular traps on tumor lymph nodes. *First Author: Xin Su, RI-MUHC, Montreal, QC, Canada*

Background: In most human cancers, regional lymph nodes (LNs) are the first sites of metastasis. In addition to being an important part of the tumor staging system, with the advent of novel therapies, lymph node metastasis has become a crucial clinical intervention point before distant metastasis, the leading cause of cancer-associated deaths. To initiate metastasis, the conditions of LNs need to be optimized for tumor cell deposition and growth. This process is believed to be mediated by the activation of immune cells including polymorphonuclear neutrophils (PMNs). However, the cellular mechanism is not well defined. Our early observations suggest that PMNs and neutrophil extracellular traps (NETs), DNA comprising structures that are extruded in response to inflammatory cues, are associated with adverse oncologic outcomes. Thus, one potential mechanism of increased LN metastasis is that tEVs recruit PMNs and propend NETs formation. **Methods:** Human tissue micro-arrays (TMAs) of gastroesophageal (GEA) cancer patients were stained with PMN and NETs markers and quantified by HALO software. C57BL/6 or *pad4-/-* mice were injected with B16F10 or H59 cells alone or treated with neutrophil elastase inhibitor (NEi) or PMN depletion antibody. LN sections were stained with NETs markers and quantified by ImageJ (NIH). **Results:** In the study of 175 GEA cancer patients, lymphatic NET deposition was observed in both tumor infiltrated lymph nodes and tumor negative lymph nodes. We also demonstrated high LN NETs deposition was associated with reduced survival, even in the absence of overt metastasis (p=0.03). Next, we sought to investigate the dynamic and the consequence of LN NETs deposition using animal models. We found that LN Neutrophil Recruitment and NET deposition happens in a pre-metastatic manner. Moreover, LN metastasis was abrogated through different kinds of NETs inhibition (neutrophil depletion, *pad4* knockout and NEi treatment, n=10, p<0.001), demonstrating the consequences of LN NETs deposition and its potential as a treatment target. Finally, we showed that the LN PMN recruitment and NETs formation was mediated by increased production of IL-8 by Lymphatic Endothelial Cells (LEC). **Conclusions:** Together, we demonstrated that NETs can contribute to LN metastasis, and can serve as a potential therapeutic targets. By further investigating the detailed mechanism, this project will lead to major advances in the management of cancer patients. Research Sponsor: Thoracic Surgery Foundation.

4034 **Poster Session**

Phase I/II trial of perioperative avelumab in combination with chemoradiation (CRT) in the treatment of stage II/III resectable esophageal and gastroesophageal junction (E/GEJ) cancer. *First Author: Nataliya Volodymyrivna Uboha, UW Carbone Cancer Center, Madison, WI*

Background: Neoadjuvant CRT followed by surgery is the standard of care for patients (pts) with stage II/III E/GEJ cancer, yet recurrence rates remain high. Immunotherapy has demonstrated activity in advanced E/GEJ cancer and was recently approved for adjuvant treatment of early stage disease. This trial evaluated the safety and efficacy of avelumab with perioperative CRT in resectable E/GEJ cancer. **Methods:** This is a two part phase I/II trial. Phase I was a safety run-in of 6 pts. Phase II planned to enroll an additional 18 pts in an expansion cohort. Pts with E/GEJ adenocarcinoma or squamous cell cancer received CRT (41.4 Gy in 23 fractions) with weekly carboplatin and paclitaxel. Three doses of avelumab (10 mg/kg IV, q14 days) were administered starting on day 29 of treatment, to coincide with the last chemotherapy dose. Surgery was performed 8-10 weeks after CRT completion. Pts received 6 doses of avelumab after resection (10 mg/kg IV, q14 days). The primary endpoint of the Phase 1 was safety and tolerability. The primary endpoint of the Phase II was pathologic complete response (pathCR) rate, assessing patients from the safety run in and expansion cohorts. **Results:** Between 6/2018 and 10/2021, 22 pts (20 males, median age 64) enrolled in the study. Enrollment was stopped after 16 patients in the expansion cohort due to accrual delays and changes in standard treatment. 19/22 patients (86%) had adenocarcinoma; 15/22 (68%) had lymph node positive disease at diagnosis. 19 pts underwent successful resection while on study. 3 pts went off study before resection due to grade 3 avelumab-related infusion reaction (1), patient preference (1), and non-adherence (1). There were no unexpected surgical complications. 4 pts (21%) had R1 resection with 3/4 having positive radial margin and 1/4 positive proximal margin. At resection, 5 pts (26%) had pathCR (3/16 adenocarcinomas, 2/3 squamous cell), 4 ypT1N0 disease, and 14/19 were ypN0. 42% had tumor regression score of 0 or 1. The combination of CRT and avelumab had an acceptable toxicity profile. No grade ≥3 immune-related AEs were observed. Immune-related hypothyroiditis was seen in 2 patients (grade 2). Three patients had grade 2 infusion-related reaction, but were able to continue with treatment. 21/22 pts had reversible grade ≥3 lymphopenia; 13/22 grade ≥ 3 wbc decrease; 6/22 grade 3 neutropenia. As of data cutoff on 2/1/2022, 1 patient remains on study treatment, 15 in follow up, 5 expired, 1 off study. Additional efficacy data is being collected. Correlative studies are ongoing. **Conclusions:** Perioperative CRT with avelumab is well tolerated with no unexpected toxicities. Neoadjuvant chemoradiation with immunotherapy is a promising approach for patients with E/GEJ tumors. Additional safety, efficacy and correlative analysis from this study will be presented at the meeting. Clinical trial information: NCT03490292. Research Sponsor: This research was financially supported by EMD Serono (CrossRef Funder ID: 10.13039/100004755), as part of an alliance between the healthcare business of Merck KGaA, Darmstadt, Germany and Pfizer, UW Carbone Cancer Center Support Grant P30 CA014520.

4035 **Poster Session**

Nivolumab (NIVO) plus chemotherapy (chemo) or ipilimumab (IPI) versus chemo as first-line (1L) treatment for advanced esophageal squamous cell carcinoma (ESCC): Expanded efficacy and safety analyses from CheckMate 648. *First Author: Ian Chau, Royal Marsden Hospital, London & Surrey, United Kingdom*

Background: NIVO + chemo and NIVO + IPI demonstrated significant overall survival (OS) benefit vs chemo in previously untreated patients (pts) with advanced ESCC in the phase 3 CheckMate 648 study. We report expanded results from the primary analysis with 13-month (mo) minimum follow-up. **Methods:** Pts with previously untreated, unresectable advanced, recurrent, or metastatic ESCC were randomized to NIVO (240 mg Q2W) + chemo (fluorouracil + cisplatin Q4W), NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W), or chemo. Primary endpoints were OS and progression-free survival (PFS) per blinded independent central review (BICR) in pts with tumor cell programmed death ligand 1 (PD-L1) ≥ 1%. Secondary endpoints planned for hierarchical testing included OS, PFS, and objective response rate (ORR) per BICR in all randomized pts. Duration of response (DOR) per BICR and PFS2 per investigator (time from randomization to progression after subsequent systemic therapy, initiation of second subsequent systemic therapy, or death) were exploratory endpoints. **Results:** Among all pts randomized to NIVO + chemo (n = 321), NIVO + IPI (n = 325), or chemo (n = 324), PFS2 favored NIVO + chemo (HR 0.64, 95% CI 0.54–0.77) and NIVO + IPI (HR 0.74, 95% CI 0.62–0.88) vs chemo. ORR (95% CI) was 47% (42–53), 28% (23–33), and 27% (22–32), respectively. More responders with NIVO + chemo or NIVO + IPI vs chemo had prolonged DOR (≥12 mo; 39%, 48%, and 23%, respectively). Efficacy data by tumor cell PD-L1 and PD-L1 combined positive score will be presented. Grade 3/4 treatment-related adverse events with potential immunologic etiology (select TRAEs) occurred in ≤ 6% of pts with NIVO + chemo and NIVO + IPI, and non-endocrine select TRAEs resolved in 57%–95% of pts across organ categories (Table). **Conclusions:** NIVO + chemo and NIVO + IPI demonstrated favorable PFS2 and a higher proportion of pts with prolonged DOR vs chemo, as well as acceptable safety profiles. These results provide further support for each regimen as a new potential 1L standard of care in advanced ESCC. Clinical trial information: NCT03143153. Research Sponsor: Bristol Myers Squibb.

	NIVO + chemo (n = 310)			NIVO + IPI (n = 322)		
Select TRAEs	Any grade, n (%)	Median time to onset (range), wk	Median time to resolution (range), wk	Any grade, n (%)	Median time to onset (range), wk	Median time to resolution (range), wk
Endocrine	36 (12)	13.0 (5.0–100)	NR (4.1–125.6+)	88 (27)	8.2 (1.9–72.9)	NR (0.4+ to 154.0+)
Gastrointestinal	64 (21)	5.1 (0.3–53.1)	1.5 (0.1–65.9+)	38 (12)	9.1 (0.6–50.3)	2.9 (0.3–79.1+)
Hepatic	32 (10)	7.9 (0.3–84.1)	2.4 (0.4–24.0+)	42 (13)	5.0 (1.0–50.1)	5.1 (1.1–30.9+)
Pulmonary	18 (6)	31.2 (5.0–85.1)	12.1 (1.0–39.9+)	26 (8)	11.9 (1.9–72.3)	12.1 (0.1+ to 119.3+)
Renal	74 (24)	10.1 (0.7–60.7)	17.1 (0.4–128.1+)	8 (2)	7.1 (1.1–47.1)	9.6 (0.7–142.3+)
Skin	54 (17)	5.9 (0.1–61.1)	7.1 (0.1–157.0+)	110 (34)	3.9 (0.1–54.3)	11.4 (0.3–146.6+)

+ indicates a censored value. NR, not reached; wk, weeks.

4036 **Poster Session**

The PRODIGE 59-DURIGAST trial: A randomized phase II study evaluating FOLFIRI plus durvalumab and FOLFIRI plus durvalumab plus tremelimumab in second-line treatment of patients with advanced gastric or gastro-esophageal junction adenocarcinoma. *First Author: David Tougeron, Gastroenterology Department, Poitiers University Hospital, Poitiers, France*

Background: Efficacy of 2nd line chemotherapy in advanced gastric/gastro-oesphageal junction (GEJ) adenocarcinoma remains limited. No study up until now has evaluated the efficacy of immune checkpoint inhibitors combined with chemotherapy as 2nd line treatment of advanced gastric/GEJ adenocarcinoma. **Methods:** DURIGAST PRODIGE 59 is a randomized, multicenter, phase II study designed to assess the efficacy and safety of the combination of FOLFIRI plus durvalumab (anti-PD-L1 until progression) (FD) versus FOLFIRI plus durvalumab and tremelimumab (anti-CTLA-4 for 4 cycles) (FDT). Key eligibility criteria included advanced gastric/GEJ adenocarcinoma, platinum-based first-line chemotherapy and ECOG performance status (PS) 0 or 1. Patients were randomized in a 1:1 ratio to FD versus FDT. The primary endpoint is progression-free survival (PFS) at 4 months, which was expected to be 70% (H_0:50%). With an α risk of 5%, a power of 85% and 5% of non-evaluable patients, 47 evaluable patients are needed by arm. Secondary endpoints included safety, overall survival (OS) and quality of life. **Results:** Between August 2020 and June 2021, 96 patients were randomized, 48 in each arm. The median age was 59.7 years, 30.4% were women and 66.3% ECOG PS 1. All in all, 22.8% had HER2+ tumors and 4.3% dMMR/MSI tumors. The 4-month PFS were 44.7% [90%CI: 32.3–57.7] and 57.8% [90%CI: 44.5–70.3] in the FD and FDT arms, respectively. Primary endpoint was not met. Median PFS were 3.8 and 5.9 months, disease control rates 68.9% and 73.8% and median OS not reached and 10.1 months in FD and FDT arms, respectively. Eight patients in FDT arm had tremelimumab re-introduction at progression. Twenty-one patients, 8 in FD arm and 13 in FDT arm, are still being treated with a median duration of treatment of 7.8 and 10.9 months. All in all, 50.0% and 47.8% of patients experienced at least one grade 3-4 adverse events related to the treatment (neutropenia: 13.0 vs 21.7%, anemia: 10.9 vs 6.5%, diarrhea: 2.2 vs 8.7% and vomiting: 6.5 vs 10.9%), in FD and FDT arms, respectively. In both arms there was no clinically significant deterioration of quality of life superior to 10 points according to EORTC QLQ-C30 global health status. **Conclusions:** The DURIGAST PRODIGE 59 trial demonstrates an acceptable safety profile of immune checkpoint inhibitors plus FOLFIRI in 2nd line treatment for advanced gastric/GEJ adenocarcinoma. FDT combination demonstrates a clinically relevant efficacy never before achieved with a median PFS of 6 months and should be evaluated in a phase III trial. Updated results including PFS according to centralized review and PD-L1 status will be presented during ASCO meeting. Clinical trial information: NCT03959293. Research Sponsor: Federation francaise de cancerologie digestive (FFCD) and Astra Zeneca.

4037 **Poster Session**

SOURCE beyond first-line: A survival prediction model for patients with metastatic esophagogastric adenocarcinoma after failure of first-line palliative systemic therapy. *First Author: Steven C. Kuijper, Amsterdam University Medical Centers, Amsterdam, Netherlands*

Background: Prediction models for survival may aid shared decision making between physicians and patients. Prior models have been developed that predict survival for patients with potentially curable esophagogastric cancer and patients with metastatic esophageal cancer who start first-line therapy (the SOURCE models). The aim of this study was to develop and internally validate a registry-based clinical prediction model, called SOURCE beyond first-line, for survival of patients with metastatic esophagogastric cancer after failure of first-line palliative systemic therapy. **Methods:** Patients with unresectable or metastatic (synchronous or metachronous) esophageal or gastric cancer who received first-line systemic therapy (N = 1067) between 2015-2017 were selected from the Netherlands Cancer Registry. Follow-up data were retrieved in 2019. Patient, tumor and treatment characteristics at primary diagnosis and at progression of disease, were used to develop the prediction model. A Cox proportional hazards regression prediction model was developed through forward and backward selection using Akaike's Information Criterion. The model was internally validated through 10-fold cross-validations to assess performance on unseen data. Model discrimination (C-index) and calibration (slope and intercept) were used to evaluate performance of the complete and cross-validated models. **Results:** The final model consisted of 10 patient, tumor and treatment characteristics. The C-index was 0.75 (0.74-0.77), the calibration slope 0.99 (0.98-0.99) and the calibration intercept 0.02 (0.01-0.02). Internal cross-validation of the model showed that the model performed adequately on unseen data: C-index 0.79 (0.76-0.80), calibration slope 1.02 (1.00-1.04) and calibration intercept -0.01 (-0.01-0.02). **Conclusions:** The SOURCE beyond first-line model predicted survival with fair discriminatory ability and good calibration, and is a valuable addition to the existing SOURCE prediction models. In the future this model will be integrated in an online decision support tool that can be used in clinical practice to aid personalized treatment. Research Sponsor: KWF Dutch Cancer Society.

4038 **Poster Session**

Phase II trial of perioperative chemotherapy of esophageal cancer: PIECE trial. *First Author: Motoo Nomura, Department of Clinical Oncology, Kyoto University Hospital, Kyoto, Japan*

Background: Neoadjuvant chemotherapy followed by surgery (NAC-S) is the standard therapy for locally advanced esophageal squamous cell cancer (ESCC) in Japan. The aim of this phase II trial was to assess the efficacy and safety of the addition of adjuvant S-1 after R0 resection in patients treated with NAC-S. **Methods:** Key eligibility criteria were as follows: ESCC of clinical stage IB-III (without T4 disease); aged 20 to 75 years; ECOG performance status 0 or 1; and performed neoadjuvant chemotherapy (5-FU + cisplatin). All patients registered before surgery. Patients received adjuvant therapy with 4 cycles of S-1 (80 mg/m^2/day) that is administered orally for 4 weeks of a 6-weeks cycle. The primary endpoint was three-year relapse free survival (RFS). **Results:** A total of 52 patients were enrolled between January 2016 and January 2019. Two patients (one with small cell carcinoma and the other with synchronous malignancy) were excluded from analysis. Five patients were diagnosed as R1 or R2. Seven patients did not receive adjuvant S-1 due to adverse events of surgery in 5 patients, refusal to adjuvant S-1 in a patient, and forgot to start in a patient. Thirty-eight patients received adjuvant S-1, with 32 patients completing 4 cycles. The median relative dose intensity of adjuvant S-1 was 85.8%. Median follow-up time among survivors after surgery was 4.5 years (range 0.2-5.6). Three-year RFS in intention to treat population was 72.3% (90% confidence interval [CI] 59.9-81.5), suggesting that the primary endpoint was met, and 3-year overall survival was 85.0% (90% CI 73.9-91.6). Grade 3 or higher adverse event with an incidence 10% of greater were neutropenia (13.2%), anorexia (13.2%), and diarrhea (10.5%). There was no treatment-related death. **Conclusions:** Adjuvant S-1 showed promising efficacy with manageable safety profile for patients with resectable ESCC after NAC-S, and warrants further evaluation in larger studies. Clinical trial information: UMIN000020204. Research Sponsor: Taiho Pharmaceutical Co.,Ltd.

4039 **Poster Session**

The adjudication rates between readers in Blinded Independent Central Review (BICR) of advanced esophageal cancer trials with or without immune checkpoint initiators as first-line therapy. *First Author: Yan Liu, Median Technologies, Valbonne, France*

Background: It is challenging to use RECIST 1.1 for the response assessment in esophageal cancer, because it excludes certain examines such as the use of barium meal and endoscopy. In some esophageal trials, the study protocols also recommend not selecting the primary tumor as a target lesion, because esophageal lesion could be infiltrative in a cavity organ and difficult to measure reliable especially after treatment. Moreover, it can even be more difficult for independent central readers, as they are often blinded to patient clinical symptoms and outcomes. The aim of this study is to analyze a pool of advanced esophageal cancer trials which used RECIST 1.1, and to document the proportion of reader discrepancies, reader performance through monitoring procedures, and to provide suggestions for the reduction of read inconsistency. This study provides benchmarks of reader adjudication rate in novel esophageal cancer therapeutic trials with or without immune checkpoint inhibitors, which will help to trigger corrective actions, such as reader initial training and follow up re-training. **Methods:** We analyzed 4 esophageal cancer BICR trials that included 1,875 patients (8,501 time-points) involving 14 radiologists. We analyzed the adjudication rate of each trial as well as testing inter-trial differences. The analysis of adjudication allowed to compute trial and reader adjudication rate, readers endorsement rate, root causes of adjudications. **Results:** Trials had an average adjudication rate of 45.28% [42.60%-47.99%], while readers endorsement rates ranged [23.1%-81.6%]. The differences of target lesion selection (34.4%) and lesion measurement (40.3%) are the two main reasons that led to discordance per adjudicators' assessment. The difference of new lesion determination and identification of non-target lesion progression contributed 17.8% and 7.5% of the discordance reasons, respectively. **Conclusions:** We provided benchmark performances for monitoring reader performance in trials with double reads. The discordances of baseline lesion selection and lesion measurement in follow up visits are the main reasons triggering adjudications in esophageal cancer central reading. Appropriate reader training and monitoring are solutions which can not only mitigate a large portion of the commonly encountered reading errors and help to reach more consensus on lesion selection and measurement between readers. Research Sponsor: None.

4040 **Poster Session**

A phase II study evaluating KN026 monotherapy in patients (pts) with previously treated, advanced HER2-expressing gastric or gastroesophageal junction cancers (GC/GEJC). *First Author: Jianming Xu, Department of Gastrointestinal Oncology, The Fifth Medical Center of the PLA General Hospital, Beijing, China*

Background: Outcomes of second or later-line treatment for pts with advanced GC/GEJC remain inferior. KN026 is a novel HER2-targeted bispecific antibody composed of VH regions of trastuzumab and pertuzumab, targeting the HER2 juxtamembrane domain (IV) and the dimerization domain (II) simultaneously. KN026 has shown promising antitumor efficacy in preclinical and phase I studies. Here we present the results of KN026 monotherapy in previously treated, advanced HER2-expressing GC/GEJC. **Methods:** In this multi-center, single-arm, open-label, 2-cohort phase II study, adult pts with previously treated, advanced GC/GEJC were assigned into a HER2 high-level cohort (Cohort 1: IHC3+ or IHC 2+ ISH+) or a HER2 low-level cohort (Cohort 2: IHC 1+/2+ ISH- or IHC 0/1+ISH+). KN026 was given intravenously in 10 mg/kg QW, 20 mg/kg Q2W, or 30 mg/kg Q3W. Primary endpoints were objective response rate (ORR) and duration of response (DoR) assessed by investigators per RECIST 1.1. Secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety outcomes. This trial is registered at ClinicalTrials.gov (NCT03925974). **Results:** At data cut-off (Oct. 29, 2021), 45 pts were enrolled and treated with KN026; 39 were eligible for response evaluation (25 pts in Cohort 1 and 14 pts in Cohort 2). In Cohort 1, ORR was 56% (95%CI 35%-76%) with 14 PR; the median DoR was 9.7 months (mo) (95%CI 4.2-not evaluable (NE)). At a median follow-up of 14.7 mo (95%CI 9.4-16.5), the median PFS was 8.3 mo (95%CI 4.2-11.4), and median OS was 16.3 mo (95% CI 11.0-NE). In Cohort 2, ORR was 14% (95%CI 2%-43%), with median DoR being 6.2 mo (95%CI 3.2-NE). At a median follow-up of 27.5 mo (95%CI 4.1-NE), the median PFS was 1.4 mo (95%CI 1.4-4.1), and median OS was 9.6 mo (95% CI 3.5-14.9). The table shows efficacy in Cohort 1 pts who have progressed on the prior trastuzumab treatment. KN026-related adverse events (TRAEs) were observed in 37 (82%) pts; the most common TRAEs (any grade) were increased aspartate aminotransferase (12, 27%), increased alanine aminotransferase (9, 20%), rash (7,16%), anemia (7,16%), and infusion-related reaction (7,16%). Four pts reported 5 grade 3 TRAEs, including infusion-related reaction, renal hydrocele, ureteral stenosis, increased blood pressure, and abnormal hepatic function (1 each). No grade 4 or 5 TRAEs occurred. **Conclusions:** KN026 monotherapy yielded promising efficacy with mild to moderate toxicities in pts with previously treated, advanced GC/GEJC. Further investigation is warranted. Clinical trial information: NCT03925974. Research Sponsor: Alphamab Oncology Ltd.

The efficacy in Cohort 1 pts who have progressed on the prior trastuzumab treatment (n = 14).

Best overall response, n (%)	
PR	7 (50%)
SD	4 (29%)
PD	3 (21%)
ORR, n (%; 95% CI)	7 (50%; 23%-77%)
DoR, mo, median (95% CI)	7.0 (2.8-NE)
Time to response, mo, median (IQR)	1.4 (1.4-1.5)
PFS, mo, median (95% CI)	5.5 (1.5-11.0)
OS, mo, median (95% CI)	14.9 (11.0-NE)

4041 **Poster Session**

Perioperative chemotherapy with LP002, an anti-PD-L1 antibody, in patients with resectable gastric and gastroesophageal junction cancer: A prospective, open-label, phase Ib trial. *First Author: Jialin Tang, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: Immune checkpoint inhibitors were effective, either alone or in combination with chemotherapy, in pts with metastatic gastric or gastroesophageal junction (GEJ) cancers, but their role for resectable disease remained unknown. We report the safety and pathological response of gastric/GEJ cancer pts receiving LP002, an anti-PD-L1 antibody, plus chemotherapy as perioperative treatment in a phase Ib trial. **Methods:** We enrolled pts with previously untreated, PD-L1 positive, resectable (cT2-4a, any N, M0) gastric/GEJ cancer. Eligible pts received three preoperative and six postoperative 2-week cycles of intravenous LP002 900mg on day 1, intravenous cisplatin 50 mg/m^2 on day 1, and 2000 mg/m^2 5-fluorouracil as 48-h infusion starting on day 1. The standard surgery was scheduled 4-6 weeks after completion of 3 cycles of preoperative treatment. The primary endpoint was safety. Secondary endpoints included proportion of pts with R0 resection and pathological complete response (pCR), disease-free survival, and overall survival. With pre- and post-treatment samples, we also characterized genomic changes in tumor tissue with next generation sequencing (NGS), and alterations in the tumor immune microenvironment (TIME) using multiplex immunofluorescence staining. **Results:** From September 2020 to July 2021, 30 pts were enrolled into this study. The median age was 64.5 years (range, 50-74). Most primary tumors were in the GEJ (N=28, 93.3%). 29 pts (96.7%) had adenocarcinoma, and 1 had small cell neuroendocrine tumor. The median follow-up duration was 7.9 months (range: 5.1-10.6) as of data cut-off (November 1, 2021). All pts completed the planned preoperative treatment, and 27 pts (90.0%) proceeded to surgery. Reasons for surgery not being performed were metastatic disease in 1 patient, and patient request in 2 cases. 24 pts had R0 resection, while 3 underwent R1 resection. 1 patient achieved pCR (TRG 1 per the Mandard's tumor regression grading system) and 5 pts (18.5%) reached TRG 2-3. Treatment-related adverse events (TRAEs) were observed in 27 pts during perioperative treatment. Most of the TRAEs were of grade 1 to 2. The most common grade 3 toxicities were nausea (23.3%), neutrophil count decreased (16.7%) and anorexia (6.7%). 11 pts had immune-related adverse events, mostly grade 1 hyperthyroidism (45.5%). There were no grade 4-5 TRAEs. NGS analysis revealed that the mutation frequencies of the 733 genes in the sequencing panel decreased after preoperative treatment in pts with TRG 2-3. The analysis of TIME is undergoing. **Conclusions:** LP002 plus cisplatin and 5-fluorouracil was safe in pts with resectable gastric or GEJ cancer, and could be a new perioperative treatment option for PD-L1 positive disease. Pts are followed-up for survival outcomes. Clinical trial information: NCT04755543. Research Sponsor: Taizhou HoudeAoke Biomedical Co., Ltd.

4042 **Poster Session**

Perioperative ramucirumab in combination with FLOT versus FLOT alone for resectable esophagogastric adenocarcinoma (RAMSES/FLOT7) with high rate of signet cell component: Final results of the multicenter, randomized phase II/III trial of the German AIO and Italian GOIM. *First Author: Thorsten Oliver Goetze, Krankenhaus Nordwest, University Cancer Center Frankfurt and Institut für Klinische Krebsforschung IKF am Krankenhaus Nordwest, Frankfurt Am Main, Germany*

Background: Periop. FLOT has become SOC for resectable, esophagogastric adenocarcinoma. However, patient's outcome is still poor. This trial evaluates the addition of the VEGF-R2 inhibitor ramucirumab (RAM) to FLOT for resectable patients (pts). **Methods:** This is a prospective, international, randomized, investigator-initiated phase II/III trial. Pts with resectable, Her2-negative, adenocarcinoma of the stomach and GEJ type II and III (≥ cT2 or cN+) were enrolled. Pts were randomized to 4 pre-and post-operative cycles of FLOT (docetaxel 50 mg/m^2; oxaliplatin 85 mg/m^2; leucovorin 200 mg/m^2; 5-FU 2600 mg/m^2, q2w) alone (Arm A) or the same regimen with RAM 8mg/kg q2w, followed by 16 cycles RAM (Arm B, FLOT-RAM). Important endpoints of phase II (exploratory) were major pathological (complete and nearly complete) response, centrally assessed acc. to Becker criteria, R0-resection rate, overall survival (OS), disease-free survival (DFS) and safety. GEJ type I tumors and pts requiring trans-thoracic esophagectomy were excluded for safety reasons during the conduct of the study. **Results:** In total, 152 pts were analyzed within the intention to treat population. Baseline characteristics were similar between arms (male, 70%; median age, 60y; cT3/T4, 82%; cN+, 77%; GEJ, 45%). The rate of cancers with signet-ring cell component was at 45%. The FLOT-RAM arm included more unfavorable pts with T4 (8% vs. 5%), impaired ECOG PS of 1 (32% vs. 20%), and concomitant disease (86% vs. 76%). 92% of pts with FLOT as well as with FLOT-RAM completed the 4 pre- cycles. R0-resection could be achieved in 82% of pts with FLOT and 96% of pts with FLOT-RAM ($p = 0.0093$). The rate of major path response was similar in both arms and was 29% for FLOT and 26% for FLOT-RAM. Median DFS was slightly improved in pts with FLOT-RAM (32 months vs. 21 months), while median OS was similar in both treatment arms (FLOT 45 months, FLOT-RAM 46 months). Surgical morbidity was observed in 32% of pts with FLOT and 41% of pts with FLOT-RAM. Mortality at 60 days after surgery was 4.1% with FLOT and 2.8% with FLOT-RAM. There were bit more G≥3 adverse events with FLOT-RAM (76% vs. 92%). **Conclusions:** In this phase II trial, the addition of ramucirumab to perioperative FLOT significantly improved R0-resection rates and slightly prolonged DFS without an impact on path response or overall survival. FLOT-RAM is feasible and safe, when type I tumors are excluded. Clinical trial information: NCT02661971. Research Sponsor: Lilly.

4043 **Poster Session**

FOLFOX versus FOLFOX plus nivolumab and ipilimumab administered in parallel or sequentially versus FLOT plus nivolumab administered in parallel in patients with previously untreated advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction: A randomized phase 2 trial of the AIO. *First Author: Sylvie Lorenzen, Third Department of Internal Medicine (Hematology/Medical Oncology), Klinikum Rechts der Isar, Technische Universitat München, München, Germany*

Background: FOLFOX plus nivolumab (nivo) has become standard of care for first-line therapy of patients (pts) with esophagogastric adenocarcinomas. The aim of Moonlight trial is to generate signals for whether (a) dual checkpoint inhibition or (b) a triplet chemotherapy is beneficial in the context of nivolumab therapy in this setting. **Methods:** The AIO-STO-0417 trial (Moonlight) is a four-arm investigator-initiated trial. Pts were randomized to FOLFOX alone (Arm B) or FOLFOX plus nivo 240 mg; q2w and ipilimumab (ipi) 1 mg/kg; q6w administered in parallel (Arm A/A1) or sequentially (Arm A2) or pts were treated in a non-randomized fashion with FLOT plus nivo 240 mg; q2w (Arm C). PD-L1 expression was centrally assessed. Primary endpoint is progression-free survival (PFS). **Results:** The study completed enrollment with 260 pts. Arms A1/A2 and C started later and will be analyzed in Mar 2022 and presented at the meeting. The abstract, therefore, focuses on Arms A (n = 60) vs B (n = 60). Baseline characteristics were: median age 62.5y, GEJ, 55%, intestinal type, 36%. Forty-one percent had PD-L1 CPS≥1 (available in 79% of pts). Pts received a median of 10 and 9 cycles Arms A and B. Adverse events of grade 3/4 were seen in 86% for Arm A and 60% for Arm B, respectively, and serious adverse events (SAE) in 78% in Arm A and 50% in Arm B. Median follow-up was 9.7 mo. No difference in PFS (5.7 and 6.6 mo), OS (10 vs. 12 mo) or objective response rate (45% and 48%) was seen in Arms A and B, respectively. The results were similar in the PD-L1+ group. **Conclusions:** FOLFOX plus dual checkpoint inhibition administered in parallel is associated with an increase in toxicity but not activity. This portion of the moonlight trial does not generate a signal for further trials on FOLFOX plus nivo and ipi for adenocarcinoma of stomach and GEJ. Clinical trial information: NCT03647969. Research Sponsor: Bristol-Myers Squibb.

4044 **Poster Session**

Circulating tumor DNA (ctDNA) in predicting residual disease after neoadjuvant chemoradiotherapy (nCRT) for esophageal squamous cell carcinoma (ESCC). *First Author: Zhichao Liu, Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China*

Background: For ESCC patients who receive nCRT, high pathological complete response (pCR) rates could be achieved. An active surveillance strategy has been proposed for patients with clinically complete response (cCR) after nCRT. However, clinical assessment may misclassify non-pCR as cCR. This study aimed to investigate the value of ctDNA in predicting tumor response and residual disease after nCRT in ESCC patients. **Methods:** This was a side study of the prospective, diagnostic pre-SINO trial (NCT03937362). After completion of nCRT, all patients underwent one or two clinical response evaluations (CREs) before planned surgery. The first (CRE-1) was 4–6 weeks after completion of nCRT. A second examination (CRE-2) was 10–12 weeks after nCRT for patients without histological evidence of residual tumor at CRE1. Serial ctDNAs were analyzed by ultra-deep unique molecular identifiers -based next-generation sequencing using 168 cancer-related genes at three time points: at baseline (B0), CRE1, CRE2. pCR was defined as ypT0N0M0. cCR was defined as no evidence of residual tumor during CRE1 & CRE2 in endoscopic biopsies and endoscopic ultrasonography with fine-needle aspiration cytology. We correlated quantitative ctDNA levels and ctDNA presence with pCR and major locoregional residual disease (MLRD) (> 10% residual carcinoma or any residual nodal disease). **Results:** At the time of this initial analysis, 62 consecutive ESCC patients received perprotocol treatments had sufficient sample to test ctDNA. The pCR rate was 32.3% (20/62). ctDNA was detectable in 73.77% at B0, 27.12% at CRE1 and 17.24% at CRE2. Maximum allelic fraction (maxAF) with a > 2-fold decrease post-nCRT (B0-CRE1) was seen in 67% patients with pCR, and 65.2% patients without MLRD. At B0, the high frequency mutated genes detected were TP53 (74%), PIK3CA (13%), CCND1 (11%), FGF19 (11%), FGF3 (11%), and FGF4 (11%). Baseline TP53 mutation status was significantly associated with pathological evaluations. A combining model, which incorporated both CRE1&2 positivity (cCR) and TP53 missense mutation at B0, was developed and demonstrated lower false-negative rate (FNR) in predicting non-pCR (4.9%, 2/41) and MLRD (2.8%, 1/36) compared with clinical assessment only (14.3%, 6/42) and (13.5%, 5/37), respectively. Of note, the FNR of combining clinical assessment and dynamic ctDNA change (continuous drop in maxAF ≥80% [B0-CRE1-CRE2]) was 7.3% (3/41) for non-pCR and MLRD (5.6%, 2/36). **Conclusions:** ctDNA testing combining with clinical assessment further optimized the tumor response and residual disease evaluations after nCRT for ESCC. ctDNA provides complementary information of response to nCRT and might become useful in an active surveillance strategy for the management of ESCC. Tumor-informed ctDNA analysis designed to track patient-specific somatic variants is ongoing. Clinical trial information: NCT03937362. Research Sponsor: National Key Research and Development Program of China (2021YFC2501005).

4045 **Poster Session**

Phase II study of ceralasertib (AZD6738) in combination with durvalumab in patients with advanced gastric cancer. *First Author: Minsuk Kwon, Department of Hematology-Oncology, Ajou University, Suwon, South Korea*

Background: Alterations in DNA damage response (DDR) and repair are associated with genomic instability and increased somatic tumor mutational burden, and modulating DNA repair using specific inhibitors is a promising strategy to boost the efficacy of cancer immunotherapy. Ceralasertib is an oral inhibitor of the serine/threonine protein kinase Ataxia Telangiectasia and Rad3 Related (ATR), which is crucial to the cell's response to replication stress. **Methods**: This phase 2 trial was designed to evaluate the efficacy and safety of ceralasertib in combination with durvalumab in patients with advanced gastric cancer (AGC). The study drug regimen was ceralasertib 240 mg BD days 15 to 28 in a 28-day cycle in combination with durvalumab at 1500 mg day 1 every 4 weeks. The primary end point was overall response rate (ORR) by RECIST (v1.1). Exploratory biomarker analysis was performed using fresh tumor biopsies in all enrolled patients. **Results**: 31 patients (median no. of prior lines, 2; range, 2-5) were enrolled between Jul 2019 and Mar 2020. All enrolled patients had confirmed microsatellite stable tumors, 5 patients were EBV positive, and 24 patients were PD-L1 positive (CPS≥1). Two patients had received prior anti-PD-1 treatment. At the time of data cut-off (Dec 2020), 30 patients were evaluable for response: 7 partial responses (one patient with prior anti-PD-1 treatment), 11 stable disease, and 12 disease progression were observed. The ORR was 22.6%, DCR 58.1 %, median PFS 3.0 months (95% confidence interval (CI), 2.1-3.9), median duration of response 5.7 months (95% CI, 4.9-6.5), and median OS was 6.7 months (95% CI, 3.8-9.6). A subgroup of patients (n = 11) who with loss of ATM expression and/or high proportion of mutational signature attributable to homologous repair deficiency (sig. HRD) demonstrated significantly longer PFS than those (n = 12) who had intact ATM and low sig. HRD (5.60 vs 1.65 months, hazard ratio 0.13, 95% CI 0.045-0.39, long-rank P < 0.001). The most common adverse events of any grade were fatigue (n = 22, 71.0%), nausea (n = 20, 64.5%) and anorexia (n = 19, 61.3%), and the most common adverse events of grade 3 or more were anemia and thrombocytopenia (n = 11, 35.5% each). **Conclusions:** Ceralasertib in combination with durvalumab demonstrated promising anti-tumor activity with durable responses in refractory AGC. Clinical trial information: NCT03780608. Research Sponsor: Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (HR20C0025), Pharmaceutical/Biotech Company.

4046 **Poster Session**

Characterization of *NY-ESO-1* gene expression in gastric cancer (GC). *First Author: Annika Lenz, Keck School of Medicine at USC, Los Angeles, CA*

Background: Tumor specific antigens, such as NY-ESO-1, are emerging as key tumor immune modulating factors with great potential to be used as therapeutic targets to enhance immunotherapy efficacy and expand treatment options for GC. We sought to compare GC tumors expressing high vs low levels of *NY-ESO-1* in terms of immune cell abundance in the tumor microenvironment (TME) as well as distinct molecular features and immune biomarkers. **Methods:** 1967 tumor samples tested with NextGen Sequencing on DNA (592 genes or WES) and RNA (WTS) by Caris Life Sciences (Phoenix, AZ) were retrospectively reviewed. The top quartile of transcripts per million was considered high while the bottom quartile was considered low *NY-ISO-1* expression. Tumor mutational burden (TMB) was calculated based on somatic nonsynonymous mutations. Mismatch repair deficiency/microsatellite instability (dMMR/MSI) status was evaluated by a combination of IHC, fragment analysis and NGS of known MSI loci. Gene fusions were detected based on WTS. X^2, Fisher-exact, and Mann Whitney tests were used for comparison and significance adjusted for multiple testing by Benjamini-Hochberg correction ($q < 0.05$). Cell infiltration in the TME was estimated by quanTIseq. Gene expression profiles were analyzed for a transcriptional signature predictive of response to immunotherapy (T cell-inflamed signature: TIS). **Results:** The analysis was focused on primary tumors (N = 1323) in this initial study. Expression of *NY-ESO-1* was lower in primary/local than metastases (Fold Change FC met vs primary: 1.60, $q < 0.05$). *NY-ESO-1* expression did not appear to be strongly associated with distinct gene mutation profiles in GC. There were no significant differences between low and high expression of *NY-ESO-1* with regards to well established immuno-oncology markers (dMMR/MSI, TMB, PD-L1). However, high *NY-ESO-1* expression was positively associated with immune related gene expression including *CD274*, *CD80*, *CD86*, *CTLA4*, *HAVCR2*, *IDO1*, *IFNG*, *LAG3*, *PDCD1*, and *PDCD1LG2* (FC low vs high: 0.56 to 0.79, $q < 0.0001$). High *NY-ESO-1* expression was also positively associated with cell abundance in the TME including NK cells (FC = 0.87, $q < 0.0001$), monocytes (FC = 0.29, $q < 0.05$), myeloid dendritic cells (FC = 0.66, $q < 0.0001$), CD4+ non-reg T cells (FC = 0.54, $q < 0.0001$), and CD8+ T cells (FC = 0.73, $q < 0.05$). Similarly, tumors with high *NY-ESO-1* expression were associated with higher TIS scores ($q < 0.0001$). **Conclusions:** In our large cohort of GC, tumors expressing high *NY-ESO-1* displayed a distinct landscape of immune cells in the TME and were associated with high expression of immune related genes, as well as high TIS score, which has been reported to predict benefit from anti-PD-1 treatment. The results of our analysis support an association between a more immunologically active tumor microenvironment and *NY-ESO-1* gene expression which may have relevant implications on immunotherapy treatment for GC. Research Sponsor: Partly supported by NCI P30CA014089, Dhont Family Foundation, Ming Hsieh research fund, Daniel Butler Research Fund, Victoria and Philip Wilson Research Fund.

4047 **Poster Session**

A phase II study of perioperative mFOLFOX plus pembrolizumab combination in patients with potentially resectable adenocarcinoma of the esophageal, gastroesophageal junction (GEJ) and stomach. *First Author: Weijing Sun, University of Kansas Medical Center, Kansas City, KS*

Background: Surgical rection is the only potentially curative intervention for locally advanced adenocarcinoma of esophagus, GEJ and stomach. Results from various studies have demonstrated the benefits of perioperative treatment including neoadjuvant and adjuvant chemotherapy or chemoradiation, however, there is lack of universally accepted standard. Recent data demonstrated the benefit of immune checkpoint inhibitor in adjuvant setting in patients who had pre-operative chemoradiation. This single arm phase 2 trial is aimed to evaluate efficacy and safety of pembrolizumab, an immune checkpoint inhibitor, in combination with mFOLFOX in patients with potentially resectable adenocarcinoma of distal esophagus, GEJ and stomach. The primary objective is pathological response rate (ypRR with tumor regression score, TRS ≤ 2). **Methods:** Newly diagnosed locally advanced (T1N1-3M0 or T2-3NanyM0), potentially resectable adenocarcinoma of distal esophagus, GEJ and stomach by PET, EUS, CT C/A/P and staging laparoscopy were treated with pre-operative mFOLFOX6 (oxaliplatin 85mg/m^2, Leucovorin 400mg/m^2, 5-FU bolus 400mg/m^2, and 5-FU 2400mg/m^2 infusion every 2 weeks) for 4 cycles and pembrolizumab (200 mg IV q3week) for 3 cycles. Patients with no evidence of metastatic disease by PET and CT C/A/P who are eligible for resection underwent surgery. Post-operative treatment consisted of 4 cycles of mFOLFOX and 13 cycles of pembrolizumab 4-8 weeks postoperatively. **Results:** Up to 2/10/2021, all 37 patients eligible for the study finished preoperative treatment. 27 had curative intended operations, and all had R0 resection. 5 of 27 (19%) achieved ypCR and 6/27 (22 %) with regression score of 0 in the primary cancer. All except 2 patients (25/27, 93%) had shown pathologic response to the treatment with TRS ≤ 2. 21 patients completed all planned treatment with an average follow-up of 27 months. 2 patients had recurrence/metastatic disease (at 9 and 10 months from the enrollment) with 1 died at 23 months, and the other is still alive at 20 month. The rest patients (19/21) are all free of disease. G3/4 toxicities were reported in 21 of all 37 treated patients. There were no unexpected toxicities. **Conclusions:** The combination of mFOLFOX and pembrolizumab as peri-operative (pre- and post-operative) therapy in patients with locally advanced adenocarcinoma of distal esophagus, GEJ and stomach is safe. The preliminary benefit data are very encouraging with ypRR of 93%, ypCR of 19 %, and the long-time survival. The data support the combination of chemotherapy and Immune checkpoint inhibitor at perioperative setting. In addition, the data supports the staging laparoscopy for peritoneal disease assessment as the standard in resctacbility evaluation. Clinical trial information: NCT03488667. Research Sponsor: Merck.

4048 **Poster Session**

Claudin 18 (*CLDN18*) gene expression and related molecular profile in gastric cancer (GC). *First Author: Annika Lenz, Keck School of Medicine at USC, Los Angeles, CA*

Background: Claudins are transmembrane proteins which maintain the tight junction between cells. The stomach specific isoform, CLDN18 isoform 2 (CLDN18.2), is emerging as a promising treatment target because of high expression in GC cells, including targeting via adoptive T-cell strategies. We characterized the molecular features associated with *CLDN18* isoform 1 and 2 (*CLDN18.1/18.2*) gene expression in GC. **Methods:** Tumor profiling was performed from 1967 samples by NextGen Sequencing on DNA (592 genes or WES) and RNA (WTS) at Caris Life Sciences (Phoenix, AZ). EBER (Epstein Barr Virus) was tested by CISH. Top quartile transcripts per million for *CLDN18.1/18.2* were considered high while bottom quartile low expression. X2, Fisher-exact, and Mann Whitney tests were used and significance adjusted for multiple testing by Benjamini-Hochberg ($q < .05$). Cell infiltration in the tumor microenvironment (TME) was estimated by quanTIseq. Gene expression profiles were analyzed for a transcriptional signature predictive of response to immunotherapy (T cell-inflamed signature, TIS). **Results:** *CLDN18.2* expression was detected in 97% of the samples and *CLDN18.1* in 63%. Primary tumors had significantly higher expression levels of both *CLDN18.1/18.2* (Fold Change *18.1*: 0.50; *18.2*: 0.65), compared to metastatic tumors ($p < .05$), thus we focused on the comparison of *CLDN18* high and low in primary tumors. *CLDN18.2* high expression group had higher *CLDN18*:*ARHGAP26* fusion positive rate (low vs high: 0.91% vs 5.5%, $q < .0001$), and a trending association with *CDH1* mutation (11.7% vs 20.7%, $p < .01$, $q > .05$) and EBER (2.15% vs 6.31%, $p < .05$, $q > .05$). There were more prevalent *ARHGAP26* fusions in the *CLDN18.1/18.2* high group (18.1: 9.5% vs 3.86%, $p = .001$; 18.2: 10.1% vs 0.9%, $q < .0001$), with the most common fusion between *CLDN18* exon 5 and *ARHGAP26* exon 12. *CLDN18.2* high expression demonstrated an inverse trending correlation with PD-L1 (24.9% vs 18.3%, $p < .05$; $q > .05$) and TMB-H (19.6% vs 12.2%, $p < .05$; $q > .05$). Similarly, *CLDN18.1/18.2* displayed an inverse relationship with M1 Macrophages, NK cells, CD4+ T cells, myeloid dendritic cells in the TME ($q < .05$); with higher *CLDN18* expression associated with fewer immune cells and a colder TME, especially in isoform 2. The TIS score was significantly higher in the *CLDN18.2* high expression group ($q < .05$), but lower in *CLDN18.1* high expression group ($q < .0001$), respectively. **Conclusions:** This is one of the most comprehensive dedicated analyses on *CLDN18* related to tumor molecular features, TME and immunotherapy response in GC. Tumors expressing high *CLDN18*, especially 18.2, displayed distinct genomic and transcriptomic alterations in immune biomarkers and immune cell infiltration in the TME. Anti-CLDN18.2 monoclonal antibodies are being tested in GC and CLDN18 is a target for ADC and CAR-T therapies. Our data suggest that expression may play a role in guiding patient selection and treatment combinations. Research Sponsor: Partly supported by NCI P30CA014089, Dhont Family Foundation, Ming Hsieh research fund, Daniel Butler Research Fund, Victoria and Philip Wilson Research Fund.

4049 **Poster Session**

A 107-gene Nanostring assay effectively characterizes complex multiomic gastric cancer molecular classification in a translational patient-derived organoid model. *First Author: Daniel Skubleny, University of Alberta, Edmonton, AB, Canada*

Background: Multi-omics profiling of gastric cancer (GC) has produced numerous molecular classification systems. However, widespread clinical implementation and testing of molecular subtypes are currently limited. Here, we develop, validate and implement a custom Nanostring assay capable of allocating GC molecular subtypes to clinical specimens in a translational patient-derived organoid model. **Methods:** Using publicly available whole-transcriptome data, machine learning models were developed to predict GC molecular subtypes from 376 Cancer Genome Atlas (TCGA) and 1797 Tumour Microenvironment Score (TME) patients. Models were generated using feature selection with 10-fold nested cross-validation. GC biopsies from 10 local patients were preserved in paraffin (tumour) and established as an organoid culture (organoid). Gene expression was measured using Nanostring. The allocation of molecular subtypes was internally and externally validated using gold-standard reference features in public databases comprising 2202 GC patients and 10 tumour-organoid pairs, respectively. We evaluated the concordance of tumour-organoid molecular subtypes and explored the correlation between subtype scores and *in-vitro* chemotherapy response. **Results:** Classification models for TCGA (57 genes) and TME (50 genes) predicted subtypes with an accuracy ± standard deviation of 89.46% ± 0.04 and 89.33% ± 0.02, respectively. Subtype assignment of microsatellite instability (MSI) in reference to capillary electrophoresis was found to have 99.3% [95% CI 97.4-99.9, n = 277] internal and 100% [95% CI 83.2-100, n = 20] external accuracy. In reference to Epstein-Barr Virus (EBV) *in-situ* hybridization, EBV type internal and external accuracy was 98.7% [95% CI 97.4-99.5, n = 552] and 100% [95% CI 83.2-100, n = 20], respectively. TCGA Genomically Stable (GS) scores followed a previously characterized enrichment of diffuse-type histology compared to intestinal-type in internal and external cohorts (Dunn's Test, $p < 0.0001$ and $p < 0.05$, n = 1471 and n = 15, respectively). Statistically similar subtype scores (Paired Wilcoxon, $p > 0.05$) were found for tumour-organoid pairs. Discordance occurred in three tumour-organoid pairs. *In-vitro* Drug Sensitivity Score was not statistically efficacious in any molecular subtype, but Pearson correlation identified increasing efficacy with increasing EBV and MSI scores. **Conclusions:** Patient-derived organoids generally recapitulate the molecular subtype of parent tumours; however, in specific cases, subtype discordance occurs. Although additional external validation is required, our 107 gene assay effectively captures multi-omics classification systems in GC and allows future inquiry into the prognostic and therapeutic implications of these molecular subtypes. Research Sponsor: Edmonton Civic Employees, Other Government Agency.

4050 **Poster Session**

Clinical efficacy of laparoscopic sentinel node navigation surgery for early gastric cancer: Five-year results of SENORITA trial. *First Author: Hoon Hur, Ajou University School of Medicine, Suwon, South Korea*

Background: A phase III multicenter randomized controlled clinical trial (SEntinel Node ORIented Tailored Approach [SENORITA] trial) has been performed to confirm the oncologic safety of laparoscopic sentinel node navigation surgery (LSNNS) for early gastric cancer (EGC). The results did not show the non-inferiority of LSNNS relative to laparoscopic standard gastrectomy (LSG) in terms of 3-year disease-free survival (DFS), the primary endpoint of the SENORITA trial even though the improved quality of life (QOL) in the LSNNS group. However, the long-term oncologic outcomes of LSNNS have not been compared with conventional surgery. This study was planned to investigate the comparison of LSG and LSNNS for EGC in terms of 5 years survival. **Methods:** We collected 5-year follow-up data of 527 patients recruited in the SENORITA trial. The overall survival (OS), disease-free survival (DFS), and recurrence pattern were evaluated in full analysis sets of both LSG (n = 269) and LSNNS (n = 258). **Results:** The mean follow-up period was 58.5 and 57.7 months in LSNNS and LSG groups. There was no statistically significant difference in 5-year OS (p = 0.7403) and DFS (p = 0.0561) between LSG and LSNNS. In terms of DFS, additional five events in the LSG group and 7 in LSNNS occurred after a 3-year follow-up until 5-years. Primary site recurrence in 1 LSNNS, and metachronous gastric cancer occurred in one LSG and two in LSNNS were diagnosed from 3 to 5-year follow-up period. Other organ cancer developed in two *vs.* three and other deaths occurred in two *vs.* one in each group, respectively, from 3 to 5-year follow-up. Overall survival events were 6 in LSG and 7 in LSNNS, and disease-specific death events were two patients in both groups until five years. **Conclusions:** Although the SENORITA trial did not show non-inferiority of LSNNS in the primary endpoint, 3-year DFS relative to LSG, the 5-year DFS and OS did not reveal the statistical difference between the two groups. Considering the benefit of LSNNS regarding the postoperative QOL, LSNNS could be recommended as an alternative treatment option of LSG for EGC. Clinical trial information: NCT01804998. Research Sponsor: National Cancer Center, Korea.

4051 **Poster Session**

Ramucirumab, avelumab, and paclitaxel (RAP) as second-line treatment in gastro-esophageal adenocarcinoma, a phase II trial of the Arbeitsgemeinschaft Internistische Onkologie (AIO). *First Author: Peter C. Thuss-Patience, Charité–University Medicine Berlin, Department of Haematology, Oncology and Cancer Immunology, Campus Virchow-Klinikum, Berlin, Germany*

Background: Combination of ramucirumab and paclitaxel is a standard second line therapy in gastro-esophageal adenocarcinoma (GEAC) (RAINBOW trial, Wilke et al., 2014). We integrated the PD-L1 inhibitor avelumab into this regimen aiming for synergistic efficacy. **Methods:** In a multicenter phase II trial (NCT03966118) pts with metastatic GEAC, after progression on platinum / fluoropyrimidine based palliative 1st-line, ECOG 0 or 1, were treated with ramucirumab 8 mg/kg (d1,15) + avelumab 10 mg/kg (d1,15) + paclitaxel 80 mg/m^2 (d1,8,15), q4w. Sample size calculation was based on a Simon 2-stage design with overall survival rate at 6 months as the primary endpoint (H0≤50%, H1≥65%). **Results:** 60 pts were enrolled, 59 were evaluable (ITT), median age 64.0 yrs (range 18-81), male 80%, female 20%, primary gastric 52%, GEJ 48%, histology intestinal 59.6%, diffuse 24.6%, mixed 15.8%. Previous treatment with platin/fluoropyrimidine 100%, previous taxanes 66%. At central pathology MSI-H 7%, PD-L1 CPS < 5: 54%; ≥5: 41%, NA 5%. Response by investigator (%) CR 3.4, PR 27.1, SD 49.2, PD 20.3; DCR 79.7%, independent radiology review will be presented. DOR: 8.2 mo (95%CI 6.7-9.7), PFS 5.4 mo (95%CI 4.2-6.6); 6-mo OS rate 71.2%; 12-mo OS rate 45.8%; med OS (ITT) 10.6 mo (95%CI 8.2-13.1), med OS CPS < 5: 9.4 mo (95%CI 7.2-11.2), CPS ≥5: 14.0 mo (95%CI 12.8-15.3), translational data (ct-DNA) will be analysed. Treatment was generally well tolerated and no unexpected toxicities occurred: Grade 3/4 AE above 5%: anemia 5%, leucopenia 12%, neutropenia 22%, diarrhea 5%, pain 10%, peripheral neuropathy 10%, hypertension 5%, non-neutropenic infection 5% including 1 CTC grade 5 due to an esophagotracheal fistula. **Conclusions:** The med OS of 10.6 mo (in a population of 66% pretreated with taxanes) compares very favourably to 8.6 mo in the Western population RAINBOW trial (Shitara et al., 2016) and 7.6 mo in the RAMIRIS trial (Lorenzen et al., 2022). PD-L1 CPS≥ 5 seems to predict for an even better efficacy (med OS 14.0 mo). Second-line RAP is a very efficacious and well tolerated combination. Clinical trial information: NCT03966118. Research Sponsor: This research was financially supported by Merck Serono GmbH, Darmstadt, Germany, an affiliate of Merck KGaA, Darmstadt, Germany, as part of an alliance between the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009.

4052 **Poster Session**

A randomized, controlled, multi-center, open-label study of adjuvant nab-paclitaxel plus S-1 (AS) versus capecitabine plus oxaliplatin (CapeOX) for stage III gastric cancer after D2 resection. *First Author: Yu Pengfei, Zhejiang Cancer Hospital (University of Chinese Academy of Sciences Cancer Hospital), Hangzhou, China*

Background: There was no prospective randomized study compared taxanes plus fluoropyrimidine versus platinum plus fluoropyrimidine in adjuvant chemotherapy for advanced gastric cancer. Nab-paclitaxel is nanoparticle albumin-bound formulation, showed a potentially efficacy in gastric cancer. We designed this trial to compare the effective and safety of AS and CapeOX regimen for gastric adenocarcinoma adjuvant therapy. **Methods:** Patients with stage III gastric or gastroesophageal junction adenocarcinoma who had D2 surgery and achieved R0 resection were randomized 1:1 to AS group and CapeOX. Randomization was stratified by differentiation type (differentiated vs. undifferentiated) and AJCC/UICC pathological stage (IIIA vs. IIIB, IIIC). AS group: Nab-paclitaxel 100 mg/m^2 on d1 and d8; S-1 80-120mg/d, p.o., bid on d1-d14; repeated every 21 days for 8 cycles. CapeOX group: oxaliplatin 130 mg/m^2 on d1; capecitabine 1000 mg/m^2, p.o., bid on d1-d14; repeated every 21 days for 8 cycles. The primary endpoint is 3-year disease-free survival (3-year-DFS) rate, the secondary endpoints included overall survival (OS), and safety. **Results:** Between March, 2020 to Jan, 2022, 146 subjects were enrolled to receive either AS regimen (n = 71) or CapeOX regimen (n = 75). The baseline characteristics between two arms were generally balanced. The 1-year DFS rate was 95.50% and 72.84% in AS and CapeOX group, respectively. At the cutoff date, 3 patients (the recurrence sites were peritoneum [n = 1], locoregional [n = 1] and distant [n = 1]) in AS group had relapsed, compared with 10 patients (peritoneum [n = 2], locoregional [n = 4] and distant [n = 4]) in CapeOX group. 4 subjects in CapeOX group died compared with 0 in AS group. A total of 42 patients (AS, n = 21 [29.58%]; CapeOX, n = 21 [28.00%]) needed dose reduction main due to hematological toxicity. The median relative dose intensity of Nab-paclitaxel, S-1, oxaliplatin and capecitabine was 82.55%, 91.30%%, 83.16%% and 78.95%, respectively. Treatments were delayed in 82 of 297 (27.61%, 24 due to hematological and 15 due to non-hematological toxicity) cycles at AS group and in 100 of 319 (31.35%, 18 due to hematological and 13 due to non-hematological toxicity) cycles at CapeOX group. There were 34 (47.89%) patients in AS group and 30 (40.00%) patients in CapeOX group occurred treatment-related adverse events (TRAEs), though most of them were grade I-II. Main grade III-IV AEs were neutropenia (28.16% in AS group vs 8.00% in CapeOX group), leucopenia (15.49% vs 1.33%), thrombocytopenia (0% vs 8.00%) and anemia (5.63% vs 1.33%). **Conclusions:** Adjuvant AS regimen showed a trend towards better DFS compared with CapeOX regimen, and is a potentially regimen for stage III gastric cancer after curative D2 gastrectomy, with tolerable toxicity. Long-term survival benefit requires more data. Clinical trial information: NCT04135781. Research Sponsor: CSPC Pharmaceutical Group Co., Ltd.

4053 **Poster Session**

Tumor microenvironment (TME) dynamics following capecitabine/oxaliplatin (CapeOx) plus pembrolizumab in patients with advanced gastric cancer. *First Author: Minae An, Samsung Medical Center, Seoul, South Korea*

Background: Immune checkpoint inhibition (ICI) has made significant breakthroughs in several tumor types including gastric cancer (GC) in recent years. However, single-agent pembrolizumab demonstrated remarkable and durable response in MSI and EBV GC because they are immune-enriched types. Recently, we reported on-treatment remodeling of the TME during chemotherapy in MSS AGC (*Cancer Discov.* 2021). We defined altered features including decreased tumor-associated macrophages (TAM), M1- macrophages repolarization and recruitment of NK cells, effector T cells. **Methods:** This phase 2, open-label, single-arm study was designed to assess the safety and efficacy of the CapeOx-pembrolizumab combination in advanced gastric cancer patients with HER2-negative. 38 patients were enrolled onto our CapeOx plus Pembrolizumab trial (NCT #04249739). All patients had MSS status with EBV-negative. Endoscopic biopsies were collected at baseline, after 1 cycle of chemotherapy alone and after 4 to 5 cycles of CapeOx + pembrolizumab to understand the impact of treatment to tumor TME. We performed coupling whole exome sequencing and whole transcriptome sequencing. Molecular features were extracted by exonic analysis. TME subtype was estimated by gene expression analysis. **Results:** Between 2020 and 2021, 38 patients were enrolled. There were 2 CR, 25 PR, 11 SD as best response.First, we found a number of somatic mutations (median 157.5, range 7-25,719) in pre-and on-treatment samples. Despite the creation and destruction of somatic mutation, we observed that ancestor mutations including *TP53*, *MUC6* and *APC* previously reported in TCGA GC cohort, were preserved. At baseline (before chemotherapy), patients were classified to 5 immune-enriched (IE) subtye, 21 immune-depleted (D) subtype, ETC. Second, we observed a dynamic change following one cycle of CapeOx before the addition of pembrolizumab to chemotherapy. Nine (23.68%) out of thirty eight patients with immune-depleted or fibrotic pre-treatment TME became immune-favorable during treatment. Interestingly, seventeen (58.62%) out of twenty nine patients with immune-unfavorable pre-treatment TME became immune-favorable following CapeOx plus Pembrolizumab chemotherapy. **Conclusions:** This is the first study to demonstrate TME change during CapeOx plus pembrolizumab at molecular levels and will have clinically meaningful performance in patients with metastatic GC. Clinical trial information: NCT#04249739. Research Sponsor: None.

4054 **Poster Session**

Circulating tumor DNA and recurrence risk in stage II-III gastric cancer. *First Author: Shu-Qiang Yuan, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Circulating tumor DNA (ctDNA) is a promising biomarker for detecting molecular residual disease (MRD) and relapse after definitive treatment in multiple solid cancers. However, the significance of ctDNA is rarely clarified in locoregional gastric cancer (GC). Here, we conducted a prospective and observational study to evaluate the utility of ctDNA in predicting the recurrence risk of GC. **Methods:** From October 2016 to June 2019, 100 patients with stage II/III resectable GC were recruited in this study (NCT02887612). Primary tumors and plasma samples were collected perioperatively and after adjuvant chemotherapy (ACT). Somatic variants were captured via a targeted sequencing panel of 425 cancer-related genes. The plasma of patients was defined as ctDNA positive only if one or more variants detected in the plasma presented in at least 2% of the primary tumors. All the patients received curative-intent standard-of-care therapy. **Results:** Preoperative ctDNA was detectable in 38 (38.0%) patients but showed limited value for predicting recurrence. After surgery (median days, 4), the plasma of 25 (25.0%) patients were still ctDNA positive and they had higher recurrence risk than the non-positive patients (hazard ratio [HR], 2.74 (95% CI: 1.37–5.48); P = 0.003). Forty-one patients had evaluable plasma after ACT and 10 (24.4%) of them who were ctDNA positive had remarkably higher recurrence and death risk compared with ctDNA-negative patients (recurrence-free survival [RFS] HR = 14.99 (95% CI: 3.08–72.96); P < 0.001; overall survival HR, 11.88 (95% CI: 2.38–59.24); P < 0.001). In particular, post-ACT ctDNA achieved better predictive performance (sensitivity, 77.8%; specificity, 90.6%) than both postoperative ctDNA and post-treatment tumor biomarkers (i.e., CEA, CA199, and CA72-4). In all multivariate analyses, ctDNA positivity was an independent factor of RFS. Patients with ERBB4 mutation in their primary tumors had poorer RFS compared to those were ERBB4 wildtype (HR = 3.46 (95% CI: 1.32–9.03); P = 0.007). A comprehensive model incorporating ctDNA status for recurrence risk prediction showed a higher concordance index (0.78; 95%CI, 0.71–0.84) than the model without ctDNA status (0.71; 95%CI, 0.64–0.79; P = 0.009). **Conclusions:** Postoperative and post-ACT ctDNA was associated with MRD and high risk of relapse in patients with stage II/III GC and can be utilized to guide GC management in post-surgical settings. Research Sponsor: the Science and Technology Program of Guangdong (2019B020227002), the CAMS Innovation Fund for Medical Sciences (CIFMS) (2019-I2M-5-036), the International Cooperation and Exchanges National Natural Science Foundation of China (82061160373), Other Foundation.

4055 **Poster Session**

Prognostic role of tumor stroma ratio, tumor-infiltrating lymphocytes, and tumor budding in patients with intestinal-type gastric cancer after radical resection.

First Author: Dan Sha, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, China

Background: Tumor microenvironmental (TME) features including tumor stroma ratio (TSR), tumor infiltrating lymphocytes (TILs) and tumor budding (TB), may be associated with tumor metastatic potential. We sought to identify the association of these features with prognosis of patients with resectable intestinal-type gastric cancer. **Methods:** Radical resection of gastric carcinoma (> 15 LNs removed) was performed in 493 patients (stage I, n=225; stage II, n=119; stage III, n=149) at two university hospitals between 2010 and 2016. Cutpoints were as follows: TSR (50%), TILs (median), and TB (Bd0-Bd3). TME features and their association with clinicopathological characteristics, time-to-recurrence (TTR) and overall survival (OS) were analyzed by univariate and multivariate Cox methods.. **Results:** Among 493 patients, high TSR, low TILs and high TB (Bd1-Bd3) were significantly associated with higher histological grade, larger tumor size, and increased T and N stages. Each of these features was significantly associated with poorer TTR and OS at 5 years. In Cox multivariable analysis, N stage and TSR were the only variables that were significantly associated with TTR and OS (Table). The relative contribution (%) of TSR to TTR ranked second (17.5%) behind N stage (49.2%) and ahead of TILs (7.2%) and TB (0.1%). **Conclusions:** Among TME features, TSR was the most robust and was significantly and independently associated with TTR and OS. The relative contribution of TSR to TTR was second only to nodal status. Research Sponsor: the Natural Science Foundation of Shandong Province of China (grant no. ZR2021MH140), the Science and Technology Innovation Development Program of Jinan, Shandong Province, China (grant no. 202019085).

Cox multivariable analysis of TTR and OS.

Features	TTR HR (95%CI)	TTR *P* value	OS HR (95%CI)	OS *P* value
Gender (female vs male)	1.37 (0.89-2.10)	0.16	-	-
Age (>60 years vs ≤60 years)	-	-	1.78 (1.22-2.61)	0.00
Histological grade (moderate vs well)	1.20 (0.71-2.03)	0.49	1.38 (0.82-2.32)	0.23
Tumor size (>3cm vs ≤3cm)	1.36 (0.83-2.25)	0.23	1.61 (0.98-2.63)	0.06
T stage (T3-T4 vs T1-T2)	1.58 (0.94-2.65)	0.08	1.02 (0.64-1.63)	0.93
N stage (N1-N3 vs N0)	2.36 (1.48-3.74)	0.00	3.59 (2.26-5.71)	0.00
TSR (high vs low)	1.59 (1.05-2.42)	0.03	1.60 (1.08-2.39)	0.02
TILs (low vs high)	1.35 (0.88-2.07)	0.17	1.26 (0.85-1.86)	0.26
TB (Bd1-Bd3 vs Bd0)	0.97 (0.65-1.46)	0.89	1.17 (0.80-1.72)	0.42

4056 **Poster Session**

A biological network approach for mining target genes in EBV-positive gastric cancer.

First Author: Williams Fernandes Barra, Universidade Federal do Para - Nucleo de Pesquisas em Oncologia, Belem, Brazil

Background: Epstein–Barr virus (EBV) discriminates a molecular group of gastric cancer (GC) that seems to have peculiar treatment responses and prognosis. Nevertheless, the gene expression pattern of such tumors needs additional investigations due to the heterogeneity of the tumor microbiome and the small number of studied samples. Biological networks analysis of gene expression patterns, in this complex scenario, might lead to the discovery of putative "hubs" genes, supposed to have important roles in cancer occurrence and consequences. This study aimed to explore the biological value of hub genes in EBV-positive gastric cancer patients. **Methods:** Fresh tumor samples collected during gastrectomies from individuals with gastric adenocarcinoma (n = 41, 59.0±11.0 years) were included. Gene expression of tumor samples was evaluated in the Illumina sequencing platform. A weighted correlation network analysis (WGCNA) was used to find highly correlated gene patterns. The gene's correlation to EBV status was also explored, including eight EBV positive and 33 EBV negative cases. Gene Ontology (GO) term enrichment was performed to predict the involved biological functions. The expression level of the hubs gene was measured by differential expression analysis. **Results:** A gene cluster including 636 genes able to discriminate EBV status (ρ = 0.65, p-value = 6e-05) was identified. GO analysis (padj <0.05) showed that this cluster of genes is related to T cell activation, regulation of immune effector process, and response to the biotic stimulus. In this cluster, 54 genes were differentially expressed (log2FoldChange (FC) >1 and padj< 0.05). The top hub genes were LAPTM5, PTPN22, C1QA, CD84, CD53, ADAMDEC1, DPYD, TYROBP, RARRES3, IFI16, CYBB, CMKLR1, PHF21A, GPNMB, and C1QC, according to cluster significance and gene expression level. In positive EBV-GC, all hub genes were overexpressed (FC 1.24 - 2.49) (Table). The average area under the ROC curve (AUC) for hub genes was 0.9 (0.84-0.99). Overexpression of LAPTM5 (p-value = 0.013) and DPYD (p-value =0.0065) and low expression of ADAMDEC1 (p-value = 0.05) were strongly related to poor survival outcome. **Conclusions:** EBV-positive status was correlated with overexpression of hub genes. Genes found in this investigation have high sensitivity and specificity to discriminate EBV status in GC. Some of them seem to be related to patients' survival, opening an avenue for future scientific explorations in this field. The biological network's approach may be a promising tool for mining target genes for potential clinical applications. Research Sponsor: Ministerio Publico do Trabalho 8a Regiao.

Top 9 hub genes of biological network ordered by log2FC.

Gene	log2FC	padj	AUC
C1QA	2.49	0.000	0.98
GPNMB	2.36	0.000	0.93
ADAMDEC1	2.36	0.001	0.84
C1QC	2.24	0.000	0.99
RARRES3	2.03	0.010	0.86
CMKLR1	1.95	0.000	0.97
PTPN22	1.75	0.000	0.86
LAPTM5	1.68	0.002	0.91
DPYD	1.6	0.006	0.86

4057 **Poster Session**

Comparison of four clinical prognostic scores in patients with advanced gastric and esophageal cancer.

First Author: Lucy Xiaolu Ma, Princess Margaret Cancer Center, University Health Network, Toronto, ON, Canada

Background: While several clinical scoring systems exist to aid prognostication and patient (pt) selection for clinical trials in oncology, none are standardly used. We compared the ability of four prognostic scores to predict overall survival (OS) in pts with advanced gastric and esophageal (GE) cancer. **Methods:** Pts with advanced (unresectable or metastatic) GE cancer receiving first-line palliative-intent systemic therapy at the Princess Margaret Cancer Centre from 2007 to 2020 were included. High prognostic risk pts were identified using four scoring systems: Royal Marsden Hospital (RMH), MD Anderson Cancer Centre (MDACC), Gustave Roussy Immune Score (GRIm-S) and MD Anderson Immune Checkpoint Inhibitor (MDA-ICI) score. OS was estimated using the Kaplan-Meier method and compared between risk groups (high vs. not-high) for each scoring system using the log-rank test. Cox proportional hazards models were used to analyze the association between each prognostic score and OS, adjusting for baseline clinical factors. Harrell's c-index was used to evaluate predictive discrimination of the models. Time-dependent AUCs were used to measure predictive ability for early death (within 90 days). **Results:** In total, 451 pts with advanced GE cancer were included. The median age was 59 years, 68% were male, 51% had ECOG status 0-1, 63% presented with de novo metastatic disease. The proportion of pts categorized as high risk was: RMH 25% (N=113), MDACC 13% (N=95), GRIm-S 24% (N=109), MDA-ICI 26% (N=117). In all scoring systems, high risk pts had significantly shorter OS (median OS 7.9 versus 12.2 months for RMH high vs. low risk, p<0.001; 6.8 vs. 11.9 months p<0.001 for MDACC; 5.3 vs. 13 months p<0.001 for GRIm-S; 8.2 vs. 12.2 months p<0.001 for MDA-ICI). On multivariable analysis, each prognostic score was significantly associated with OS (Table). The GRIm-S had the highest predictive discrimination (c-index 0.645 [0.612-0.678]) and highest predictive ability for early death (AUC 0.754 [0.675-0.832]). **Conclusions:** All four prognostic scoring systems compared had reasonable accuracy in predicting OS for patients with advanced GE cancer. The higher accuracy for predicting early death may render the GRIm-S as preferable. These tools can aid oncologists in discussions about prognosis, therapeutic decision-making and patient selection for clinical trials. Research Sponsor: None.

Multivariable analyses of association between high risk designation and OS for each prognostic score.[1]

Score	Hazard ratio (95% CI)	p-value
RMH	1.48 (1.08-2.02)	0.013
MDACC	1.64 (1.19-2.25)	0.0022
GRIm-Score	2.61 (2.01-3.38)	<0.001
MDA-ICI	1.53 (1.17-1.99)	0.0019

[1]Each multivariable model adjusted for baseline characteristics: age, sex, histology, ECOG, and number of metastatic sites.

4058 **Poster Session**

The 27-gene IO score is associated with molecular features and response to immune checkpoint inhibitors (ICI) in patients with gastric cancer.

First Author: Matthew Gordon Varga, 2 International Plaza Drive, Nashville, TN

Background: Gastric cancer (GC) is the 3rd leading cause of cancer-related death worldwide. Unfortunately, most gastric cancer patients are asymptomatic until the cancer has progressed to an advanced stage. ICIs have improved patient outcomes in a variety of cancers, including GC. A variety of biomarkers have been used to identify patients most likely to benefit from ICI therapies such as high PD-L1 expression, MSI-high, Epstein Barr virus (EBV) positive, or TMB . Despite these potential biomarkers, most patients with advanced GC do not respond to ICI treatment Thus, there remains an unmet clinical need for a biomarker that can better predict response to ICI therapies. Herein, we demonstrate that the 27 gene IO score, a tumor immune microenvironment (TIME) classifier is associated with the existing molecular markers of gastric cancer and with objective response to ICI therapy in a clinical cohort. **Methods:** RNA-seq expression data was obtained from 3 independent cohorts including TCGA (STAD), ACRG (GSE84437, GSE84426), and clinical cohort with ICI response data (PRJEB25780, PRJEB40416). The 27 gene IO algorithm was applied to all available patient data to derive IO scores. Fisher's exact test was used to examine the associations between IO score and clinical features and molecular subtypes in each cohort. R (version 4.1.2) was used to calculate ORs with 95%CIs, and ordinal logistic regression modeling. **Results:** From the TCGA cohort, the IO score was associated with the molecular features of EBV, MSI, TMB, and PD-L1 (n = 135, p < 0.05 for all). Similarly, in the ACRG cohorts, the IO score was significantly associated with EBV, MSI, and PD-L1 (n = 294, p < 0.001 for all). To determine whether the IO score was associated with response to ICIs, we examined a cohort of Korean patients with advanced stage GC curated by Kim *et. al.* In this cohort of 59 patients, the IO score was associated with ICI response (Fisher's exact test, p < 0.05). When response was grouped by responders vs. non-responders (CR/PR vs SD/PD), the odds ratio for the association between IO score and response was 5.3 (95% CI: 1.3 to 23.92, p = 0.01). The linearity of continuous value of the IO score was indicative of a direct relationship between IO score and improved objective response (ordinal logistic regression, t = 2.59, p < 0.01). **Conclusions:** PD-L1 and TMB have shown marked levels of both spatial and temporal heterogeneity in GCs, thus there exists a need for a more comprehensive biomarker that can fully assess the TIME. The 27 gene IO score is associated with many existing biomarkers in GC and has now been shown to also be associated with response to ICIs. As such, further studies are warranted to demonstrate that the 27 gene IO score may be a more comprehensive biomarker for assessing the TIME and provide complementary data to tumor-specific biomarkers, which together could aid in clinical decision making for ICI treatment of GCs. Research Sponsor: Oncocyte.

4059 **Poster Session**

Neoadjuvant atezolizumab plus docetaxel/oxaliplatin/capecitabine in non-metastatic gastric and gastroesophageal junction adenocarcinoma: The PANDA trial. *First Author: Yara L. Verschoor, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: Immune checkpoint blockade improves clinical outcomes for patients with gastric and gastro-esophageal junction (GEJ) cancers, but its efficacy and impact on the tumor microenvironment in non-metastatic, resectable disease remains largely unknown. Peri-operative FLOT, the current standard-of-care, leads to pathologic complete responses (pCR) and major pathologic responses (MPR) in 16% and 37% of patients, respectively. An important open question is whether PDL-1 blockade monotherapy can prime the tumor microenvironment in a favorable manner, prior to combination with chemotherapy. **Methods:** We report results from the phase 2 PANDA trial (NCT03448835) of neoadjuvant atezolizumab (anti-PDL-1) plus docetaxel, oxaliplatin, and capecitabine (DOC) in patients with resectable gastric or GEJ adenocarcinoma. Patients received a single cycle of atezolizumab monotherapy, followed by 4 cycles of atezolizumab+DOC. Tumor tissue was collected at baseline, after atezolizumab monotherapy, the first atezolizumab+DOC, and at resection. The primary endpoints were safety and feasibility in 20 patients, and secondary endpoints included MPR (<10% viable tumor rest) and disease-free survival. **Results:** Twenty patients, of which 18 with mismatch repair (MMR) proficient and two with MMR-deficient tumors, were evaluable for safety and efficacy analyses. MPR was observed in 14/20 patients (70%; 95% CI 46–88%), including 9 pCR (45%; 95% CI 23-68%). Among patients with intestinal type adenocarcinoma, 12/15 (80%; 95% CI 52-96%) had an MPR, with 9/15 (60%; 95% CI 32-84%) pCR. Treatment was well tolerated, with two patients (10%) experiencing a grade 3 immune adverse event. At a median follow-up of 29 months (IQR 16-34), 15 patients (75%) were alive and disease-free. None of the patients with an MPR recurred. All patients underwent resections without treatment-related delays and no unexpected surgical complications were documented. Translational analyses, including baseline PDL-1 CPS score and whole exome sequencing (WES), plus CD8 T-cell infiltration and RNA sequencing at 4 timepoints will be presented at the meeting. **Conclusions:** Our data show that the addition of atezolizumab to neoadjuvant chemotherapy leads to promising pathologic responses in gastric/GEJ adenocarcinoma, which appears to be higher than in historical controls, with no recurrences in responders. These data should be validated in a large randomized controlled trial. Clinical trial information: NCT03448835. Research Sponsor: Roche-Genentech.

4060 **Poster Session**

REGOMUNE: A phase II study of regorafenib plus avelumab in solid tumors—Results of the oesophageal or gastric carcinoma (OGC) cohort. *First Author: Sophie Cousin, Early Phase Clinical Trials Unit and Thoracic Unit, Institut Bergonié, Bordeaux, France*

Background: Combination VEGF and PD-1/PD-L1 axis blockade has shown benefit in various tumors and is emerging as a promising combination strategy. **Methods:** This is a single-arm open-label multicentric phase II trial assessing the efficacy and safety of regorafenib (R) (160 mg QD 3weeks/4) + avelumab (A) (10 mg/kg every 2 weeks) combination in advanced or metastatic oesophageal or gastric carcinoma (OGC) patients (pts). The primary endpoint was the confirmed objective response rate, based on central review according to RECIST 1.1. Secondary endpoints included: 1-year progression free survival (PFS), 1-year overall survival (OS), and safety using NCI-CTCAE v5.0. Correlative studies were planned from pts tumor samples obtained at baseline. **Results:** Between Dec. 2018 and Mar. 2021, 49 pts were enrolled in 6 centers: 33 adenocarcinoma (ADK), 16 squamous cell carcinoma (SCC). Median age was 63.9 (range 33 – 80). Median follow-up was 14.5 months. Median number of previous treatment lines was: 2 (range 1 – 6). 29 (59.2%) pts experienced at least 1 dose modification or treatment interruption due to an adverse event related to treatment. The most common grade 3/4 adverse events were : Hypertension (12.2% of pts), palmar-plantar erythrodysesthesia syndrome (10.2%), and hypophosphatemia (8.2%). No death was related to the treatment. Among the 42 (29 ADK and 13 SCC) pts who had at least one imaging tumor assessment, 8 (19.1%) achieved a partial response, 5 (17.2%) and 3 (23.1%) in the ADK and SCC group respectively. 12 pts (28.6%) demonstrated stable disease and 22 pts (52.3%) had progressive disease. The median PFS and OS were 1.9 months (95%CI 1.8 – 3.5) and 7.5 months (95%CI 4.5 – 15.7) respectively. **Conclusions:** The R+A combination is associated with encouraging antitumor activity in patients with OGC. Full Biomarkers analyses will be presented at the meeting. Clinical trial information: NCT03475953. Research Sponsor: Bayer/ Merck.

4061 **Poster Session**

Impact of immune-related adverse events (irAEs) on PD-1/L1 inhibitors efficacy in advanced esophageal cancer. *First Author: Wenru Qin, Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China*

Background: The recent development of Immune checkpoint inhibitors (ICIs) has improved treatment outcomes for patients with esophageal cancer, although it may initiate autoimmune-related disorders in some patients. Across disease sites, patients who experience irAEs while on therapy with anti-PD-1 and anti-PD-L1 antibodies have been documented to experience improved outcomes as measured by overall response rate (ORR), progression-free survival (PFS) and overall survival (OS). **Methods:** We reviewed the medical records and the following characteristics of patients were collected: age, gender, Eastern Cooperative Oncology Group performance status (ECOG PS), stage, histology, history of surgery, metastatic sites, therapy line, presence of target lesion according to the response evaluation criteria in solid tumors (RECIST) version 1.1, LDH level before initiating ICIs treatment. We divided the patients treated with ICIs into two groups based on occurrence of irAEs. We compared the efficacy between the irAE - and irAE + groups. **Results:** There were total 295 patients. Of all the patients, 143 patients (50.2%) suffered from irAEs. The median patient age was 60 years (range, 36–84). Baseline characteristics including gender, ECOG PS, tumor location, history of surgery, histology, number of organs with metastases, site of metastases, therapy line, history of drinking, history of smoking between patients with or without irAE were not significantly different. The most frequent irAEs were Anemia(71/295, 24.07%), Pneumonitis (55/295, 18.64%), Cardiovascular toxicities (35/295, 11.86%). There were no grade 5 adverse events related to immunotherapy. Objective response was observed in 92 patients (31.19%), 54 of the 143 patients with irAEs had objective response (37.76%) in contrast with 38 of the 152 cases without irAEs (25.00%). Median PFS in patients with irAEs was 10.27 months and 6.2 months in those without irAEs (p<0.001). Median OS in patients with irAEs was 15.4 months and 9.2 months in those without irAEs(p<0.001).Multivariate analyses identified an ECOG PS ≥2, cycles ≤8, and without irAEs as independent poor prognostic factors (p=0.003, p <0.001 and p=0.011). Multivariate analysis demonstrated that ECOG PS ≥2, Therapy line≥22nd ,without radiation and absence of irAEs were associated with a poor overall survival(p=0.022, p=0.006, p. <0.001 and p=0.002). Multivariable analysis also revealed that Cycles>8, Radiation and Anti-angiogenic therapy were positively associated with occurrence of irAEs(p<0.001, p=0.002, p=0.025). **Conclusions:** In advanced esophageal cancer treated with PD-1/L1 inhibitors., patients with irAEs showed a markedly improved efficacy over patients without irAEs. Research Sponsor: None.

4062 **Poster Session**

A phase I study of TST001, a high affinity humanized anti-CLDN18.2 monoclonal antibody, in combination with capecitabine and oxaliplatin (CAPOX) as a first-line treatment of advanced G/GEJ cancer. *First Author: Jifang Gong, Department of Gastrointestinal Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/ Beijing), Peking University Cancer Hospital and Institute, Beijing, China*

Background: TST001 is a recombinant humanized IgG1 antibody specifically against human Claudin 18.2 (CLDN18.2) with high affinity and enhanced FcR engaging of NK cells, which can induce strong antibody-dependent cellular cytotoxicity (ADCC) activities. TST001 monotherapy dose-escalation study has been completed (IGCC2022-ABS-1152) and promising anti-tumor activities were observed in advanced gastric cancer patients with CLDN18.2 overexpression who had failed multiple lines of prior therapies. The current study is an open-label, multi-center, multiple cohorts, phase I clinical trial of TST001 monotherapy or in combination with standard treatments in Chinese patients with advanced or metastatic solid tumors (NCT04495296). **Methods:** This cohort is aimed to determine the recommended phase II dose, evaluate safety, tolerability and preliminary efficacy of TST001 in combination with CAPOX as a 1st line treatment of advanced G/GEJ cancer. A 3+3 design was utilized in the dose escalation phase with treatment naïve advanced G/GEJ cancer patients regardless of Claudin18.2 expression. Claudin 18.2 positive G/GEJ cancer patients were planned to be enrolled in the dose expansion phase in selected dose cohorts. **Results:** The TST001/CAPOX combination cohort was initiated in August 2021 and is ongoing in multiple sites in China with a data cutoff date of January 27, 2022. 12 subjects were dosed with TST001 with a dose range from 1 to 8mg/kg Q3W in combination with the standard dose of CAPOX in the dose escalation phase and one subject with central lab tested Claudin 18.2 overexpression was dosed in the expansion phase of TST001 at 6mg/kg Q3W with CAPOX. There was no subject experienced dose-limiting toxicity . Treatment-emergent adverse events (TEAEs) were mostly grade 1-2, including nausea (76.9%), anemia (69.2%), vomiting, AST increased (63.8% respectively), hypoalbuminemia, ALT increased (46.2%, respectively). Treatment related grade 3 AEs were hypertension **(** 15.4%**)** , anemia, hypoproteinemia, WBC count decreased, hypocalcemia aggravated (7.7%, respectively). Among the eight patients from the dose escalation part (with no CLDN18.2 expression selection yet with measurable disease) with at least one post-treatment tumor assessment, four had achieved partial response, three had achieved stable disease and one had progressive disease as the best tumor response per RECIST1.1. **Conclusions:** Conclusion: TST001 in combination with CAPOX in first line gastric cancer patients is safe and encouraging anti-tumor activities have been observed. Additional data from the 6 mg/kg dose expansion cohort will be updated at the meeting. Clinical trial information: NCT04495296. Research Sponsor: None.

4063 **Poster Session**

SCALE-1: Safety and efficacy of short course neoadjuvant chemo-radiotherapy plus toripalimab for locally advanced resectable squamous cell carcinoma of esophagus. *First Author: Ning Jiang, Department of Radiation Oncology, The Affiliated Cancer Hospital of Nanjing Medical University, Jiangsu Cancer Hospital, Jiangsu Institute of Cancer Research, Nanjing, China*

Background: Adding PD-1 inhibitors to neoadjuvant chemoradiotherapy have shown promising results in treatment of locally advanced esophageal squamous cell carcinoma (ESCC). However, there is a need to explore more effective and safe treatment doses and schedules. The aim of this single arm phase Ib trial is to determine the safety and efficacy of short course neoadjuvant chemo-radiotherapy plus toripalimab following by esophagectomy in patients with locally advanced resectable ESCC. **Methods:** Patients (pts) with histopathologically confirmed thoracic ESCC, diagnosed as clinical stage of cT3-4aN0M0/cT1-4aN+M0 per AJCC 8th and ECOG PS of 0-1 were eligible. Toripalimab (240mg) was given with paclitaxel (135 mg/m^2) and carboplatin (AUC=5) on D1 every 3 weeks for two cycles. Short course neoadjuvant radiotherapy (3000 cGy in 12 fractions on 5 days per week) was administered from D3 to D18. Esophagectomy was scheduled 4 to 6 weeks after the completion of neoadjuvant therapy. Target total enrollment was 20 pts. The primary endpoint was treatment safety. Pre- and post-treatment specimens were collected for PD-L1 expression assay and gene expression profiles (GEPs) analysis using the nCounter platform. **Results:** From Jan 29, 2021 to Nov 3, 2021, 26 patients were screened and 23 met the inclusion criteria. The majority of them were diagnosed with clinical stage of cT3-T4 (95.6%), cN1-2 (62.5%), and cTNM III-IVA (78.2%). All 23 pts finished neoadjuvant radiotherapy, while two of them didn't receive or received reduced dose of the second cycle chemotherapy or toripalimab due to toxicity. Notable grade 3 or higher AEs included leukopenia (n=21), neutropenia (n=21), anorexia (n=19) and nausea (n=18). No treatment related oesophagitis, pneumonia and gastrointestinal hemorrhage above Grade 3 were observed. 20 pts underwent surgery after a median of 7 weeks post neoadjuvant therapy. Reasons for not undergoing surgery were patients' choice (n=2) and tuberculosis reactivation (n=1). 3 pts with Grade III surgical complications were observed during the perioperative period. 11/20 (55%) complete pathological responses (ypT0N0) were observed, 16/20 (80%) pts were major pathologic response (MPR) and the remaining 4 pts achieved partial response. Pre-treatment GEP analysis revealed significantly higher expression levels of CXCL10, CXCL11, OAS2, and lower level of CD209 and KLRB1 in pCR (n=6) than in Non-pCR group (n=4). Moreover, pCR group showed a trend of upregulated signatures of tumor infiltrating leukocytes, cytolytic activity, cytotoxic T cell, T cell markers and Teff score (P= 0.062) after treatment. **Conclusions:** Combining short course nCRT with toripalimab is feasible and effective in patients with locally advanced resectable ESCC, and might be a promising approach for neoadjuvant treatment. Clinical trial information: ChCTR2100045104. Research Sponsor: None.

4064 **Poster Session**

Cellworks singula therapy response index (TRI) predicts clinical outcomes for esophageal adenocarcinoma: MyCare-004. *First Author: Elizabeth Catherine Smyth, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom*

Background: Computational biological modeling reveals many dysregulated signaling pathways responsible for hallmark behaviors of cancer and variable drug response in the population. A mechanistic model created for each patient using comprehensive genomic inputs can biosimulate downstream molecular effects of cell signaling and drugs for each patient's personalized *in silico* virtual disease model. Singula TRI is designed to predict the outcome of specific therapies with a continuous TRI Score, 0 to 100, for each patient's unique genomic network. **Methods:** TRI's ability to predict Overall Survival (OS), Disease Free Survival (DFS) and Mandard – tumor regression grade (TRG) was prospectively evaluated in a retrospective cohort of gastro-esophageal adenocarcinoma (GEA) from UK OCCAMS consortium. Random sampling stratified by clinical factors was used to split the data into independent training (N = 140) and validation (N = 131) subsets. Multivariate Cox Proportional Hazard (PH) and Proportional Odds models were used to predict survival and pathological response as a function of the pre-defined TRI and clinical thresholds compared with standard clinical factors. **Results:** 271 GEA patients were selected who had pre-chemo treated biopsies with 50x whole genome sequencing from the OCCAMS International Cancer Genome Consortium study. The median age was 65.6 years, 234 male and 30 female, with deceased median OS of 21.9 months and living of 49.9 months. There were 35 T2, 215 T3, 70 N0, 126 N1, 62 N2 and 266 M0. Patients were treated with physician prescribed chemotherapy treatments (PPT) according to UK clinical guidelines (SC). Biosimulation revealed that 99% of these tumors had deficiency in DNA repair genes. Other pathways included amplification of multi-drug resistance pumps, TP53 mutations and aberrations of the PI3K/AKT pathway genes. The table shows that TRI provides additional predictive information for OS and DFS beyond PPT and standard clinical factors. TRI was also predictive of TRG in univariate analysis. TRI scores were also generated for 82 alternate therapies for each patient enabling selection of optimal therapies with estimates of improvements in median OS and DFS compared to SC. **Conclusions:** In this cohort of patients, Cellworks Singula TRI was predictive of survival and TRG beyond clinical factors. These positive results suggest the utility of biosimulation-informed therapy selection to improve survival of GEA and validation in prospective clinical studies is warranted. Research Sponsor: None.

Cohort and summary validation results for Singula TRI.[1]

Outcome		**Multivariate**		
	Likelihood Ratio χ_1^2	*p*-value	Hazard Ratio per 25 units TRI	Median TRI
OS[1]	4.2788	0.0386	0.603 (0.360, 0.975)	42.8
DFS[1]	5.7472	0.0165	0.082 (0.008, 0.668)	55.4
		Univariate		
	Likelihood Ratio χ_1^2	*p*-value	Odds Ratio per 25 units TRI	
TRG[2]	4.3644	0.0367	16.300 (1.192, 331.026)	

Adjusted for: [1] age sex T-stage N-stage TRG & PPT; [2] age sex & PPT.

4065 **Poster Session**

Phase III randomized controlled trial comparing chemotherapy to best supportive care in advanced esophageal and gastroesophageal junction cancer. *First Author: Vanita Noronha, Tata Memorial Centre, Mumbai, India*

Background: Patients with advanced esophageal/gastroesophageal junction (GEJ) cancer have a dismal outcome. No study has unequivocally proven that systemic chemotherapy prolongs survival. Current NCCN guidelines recommend palliative/best supportive care as a first-line option for patients with unresectable locally advanced, recurrent, or metastatic esophageal/GEJ cancers. **Methods**: Phase III randomized controlled study conducted in the Department of Medical Oncology at the Tata Memorial Hospital (Mumbai, India) in patients with advanced unresectable or metastatic esophageal or GEJ cancer, planned for palliative intent therapy. Patients aged 18 to 70 years, with a performance status < 2, were stratified based on histopathology, presence of metastatic disease and receipt of prior curative therapy, and randomized 1:1 to best supportive care alone, or best supportive care with chemotherapy consisting of intravenous paclitaxel 80 mg/m^2 once-a-week, continued until disease progression or intolerable toxicity. Best supportive care consisted of patient education and counselling, non-chemotherapeutic palliative measures like radiation, or stenting, placement of feeding tube, analgesia, antiemesis and other supportive medications, nutritional support, and referral to a patient support group. Primary endpoint was overall survival (OS); secondary endpoints included progression free survival (PFS), response rate, adverse events, and quality of life. **Results**: Between May 2016 and Dec 2020, we recruited 281 patients; 143 to chemotherapy and 138 to best supportive care. Histopathology was squamous in 269 (95.7%) patients. In the 143 patients in the chemotherapy arm, median number of paclitaxel cycles was 12 (IQR, 7-23). The response rate was 32%. Grade > 3 toxicities occurred in 82 (57%) patients who received paclitaxel; commonly hyponatremia (18%), anemia (11%), fatigue (10%), peripheral neuropathy (10%), infection (9%), and neutropenia (7%). Median PFS was 2.1 months (95% CI, 1.98-2.23) in the best supportive care arm, and 4.1 months in the chemotherapy arm (95% CI, 3.54-4.74); HR, 0.51 (95% CI, 0.39-0.64); $P < 0.001$. The 1-year OS was 11.6% in the best supportive care arm, versus 30.8% in the chemotherapy arm. Median OS was 4.2 months (95% CI, 2.93-5.42) in the best supportive care arm, and 8.6 months in the chemotherapy arm (95% CI, 7.56-9.66); HR, 0.52 (95% CI, 0.40-0.66); $P < 0.001$. **Conclusions**: Systemic chemotherapy significantly prolongs survival and should be considered the standard of care in patients with advanced esophageal and GEJ squamous cell carcinoma. Metronomic weekly paclitaxel is an attractive option, especially in LMICs with limited access to newer immunotherapy-based combination regimens. Clinical trial information: CTRI/2016/01/006474. Research Sponsor: Indian Cooperative Oncology Network.

4066 **Poster Session**

Outcomes in patients undergoing curative surgery for gastric cancer by facility type and socioeconomic factors: An analysis of the National Cancer Database (NCDB). *First Author: Ali Alqahtani, Ruesch Center for the Cure of Gastrointestinal Cancers, Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC*

Background: Surgical and medical treatment for resectable gastric cancer is complex, and multidisciplinary team involvement is essential to provide optimal treatment outcomes. However, socioeconomic disparities influence the quality of medical care patients receive. We hypothesized that facility type, median income, insurance type, and location would impact patients' overall survival (OS). **Methods:** In a retrospective analysis of NCDB data, we identified patients with stage II and III gastric adenocarcinoma who underwent curative-intent surgical resection and chemotherapy between 2004-2018. Demographic and socioeconomic factors were studied, including treatment facility type, median household income, urban/rural residence, and insurance status. Multivariate Cox proportional hazard model was used to evaluate the impact of these variables on overall survival (OS). The Kaplan-Meier method was used to estimate OS. Log-rank test was used to compare the OS between groups. **Results:** Based on the criteria listed above, 36,318 patients were identified: 76.3% were Caucasian, 14.4% black, 7.2% Asian, and 2.0% other. 56.4% lived in large metropolitan areas (LM), 29.9% in small/medium metropolitan areas (SM), and 14.2% in rural areas (RA). Patients who were treated in academic/research programs had significantly better OS (mOS 40.5 months) compared to integrated-network cancer programs (mOS 34.0 months, HR 0.897, $p < 0.0001$), comprehensive community cancer programs (mOS 31.0 months, HR 0.89, $p < 0.0001$), and community cancer programs (mOS 29.5, HR 0.881, $p < 0.0001$). Patients from LM had better OS compared to those from SM and RA (mOS 39.0, 32.1, 29.9 months respectively, $p < 0.0001$). Privately insured patients had improved OS compared to Medicare-insured patients (mOS 40.8 vs 29.7 months, HR 0.758, $p < 0.0001$). Higher annual income (≥ $63,000) was positively associated with improved OS ($p < 0.0001$). **Conclusions:** Outcomes for patients with gastric cancer treated with surgery and chemotherapy are strongly influenced by socioeconomic variables, including place of residence, treatment setting, insurance, and income level. We highlight improved outcomes in patients who resided in LM and were treated at academic/research centers. A potential hypothesis for this trend is increased access to specialized, multidisciplinary care and clinical trials. Research Sponsor: None.

4067 **Poster Session**

Non-invasive detection of esophageal carcinoma by integrative analysis of low-pass whole methylome sequencing of plasma cell-free DNA. *First Author: Dan Liu, Genecast Biotechnology Co., Ltd., Beijing, China*

Background: Cell-free DNA (cfDNA) methylation, fragmentation patterns, chromosome instability, and chromatin accessiblity have been previously shown to be valid plasma biomarkers for non-invasive cancer detection. However, conventional whole-genome bisulfite sequencing (WGBS) is unable to simultaneously profile all these biomarkers due to bisulfite-induced DNA damages. Here we developed a machine learning approach to comprehensively integrate multiple types of cancer genomic markers from enzyme-conversion-based low-pass whole-methylome sequencing (WMS) of plasma cfDNA to non-invasively detect esophageal carcinoma. **Methods:** Plasma cfDNA sampels from 85 patients and 568 healthy individuals were collected and were split into the discovery and independent testing cohort. The discovery cohort includes 60 cancer patients and 398 healthy individuals and the independent testing cohort includes 25 cancer patients and 170 healthy individuals. Whole methylome sequencing (WMS) libraries were generated from enzymatically converted cfDNA and were subsequently paired-end sequenced at ~2X coverage. The genome-wide methylation density, fragmentation fingerprints, chromosome instability, and chromatin accessibility were extracted from the WMS data and individually modelled via machine learning methods such as SVM, LR, GBDT, random forest. The final predictive model is an ensemble model integrating all uni-modal models. All models were trained and fitted on the discovery cohort. **Results:** Data of different modalities provide complementary information in separating the cancer patients from the healthy individuals. Unsupervised clustering of the individuals showed clear separation between cancer patients and healthy individuals. The final predictive model achieved AUC =96.25% in the discovery cohort and AUC =91.15% in the independent testing cohort. Under a specificity of 95.29% (CI: 87.64% - 100.00%), sensitivity was 72.00% (CI: 56.00% - 92.00%) in the independent testing cohort. Separating the cancer patients into different stages, we found that the detection power is usuaul lower for early-stage cancer patients. **Conclusions:** These results demonstrate the first proof of principle on the feasibility of integrating multiple genomic cancer markers to non-invasively detect esophageal carcinoma from WMS plasma cell-free DNA. A large prospective cohort study is planned to further validate its clinical performance. Research Sponsor: None.

4068 **Poster Session**

TACE with idarubicin-eluting beads compared with TACE with epirubicin-eluting beads in BCLC B-stage HCC: Interim results of a randomized, double-blind, parallel-controlled, phrase IV multicenter study. *First Author: Jiaping Li, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China*

Background: The lack of effectiveness of a cytotoxic agent for intra-arterial use in HCC has been a major limitation for improved outcomes. Idarubicin, an anthracycline-based drug, is currently used as the first-line treatment option for acute myeloid leukaemia. Incredibly, a previous study showed that idarubicin has better anti-tumor effects on HCC compared with oxaliplatin and 5-fluorouracil in vitro, and two single-arm studies of idarubicin lipiodol TACE reported good therapeutic outcomes and acceptable adverse drug reactions. **Methods:** This randomized, double-blind, parallel controlled, phrase IV, multicenter trial was conducted from July 2020. Patients with BCLC stage B HCC were randomly assigned in a 1:1 ratio to receive TACE loaded with 10 mg idarubicin (IT group) or 40 mg epirubicin (ET group). The sample size of 120 was needed in each group according to calculation. The primary endpoint was progression-free survival (PFS, defined as the time from randomization until progression or death from any cause). The secondary endpoints were overall survival (OS, defined as the date of randomization to death from any cause), objective response rate (ORR, the proportion of patients with complete response or partial response according to mRECIST), and adverse events. A single interim analysis was planned when appropriately 1/3 (33.3%) of the required 240 patients. To control the type I error rate at the interim analysis, superiority boundaries that were based on Pocock spending function 24 were a P value of less than 0.022 for PFS. The deadline for interim analysis of data is October 1, 2021. **Results:** Overall, 103 patients (mean age: 56.6 years±11.4; 12 women and 91 men) were randomly assigned to receive either TACE with Idarubicin-eluting beads (n = 50) or TACE with Epirubicin-eluting beads (n = 53). The PFS and OS were not mature on October 1, 2021. The median PFS was significantly longer in the IT group than in the ET group (HR [hazard ratio] = 0.32, P < 0.001). PFS rates were 82.4% and 43.9% at 6 months, and 53.7% and 18.9% at 12 months in IT and ET groups, respectively. The median OS was longer but not significant in the IT group than in the ET group (HR = 0.52, P = 0.058). OS rates were 90.2% and 76.5% at 6 months, and 61.6% and 47.3% at 12 months in IT and ET groups, respectively. TACE with Idarubicin-eluting beads did not improve ORR compared to TACE with Epirubicin-eluting beads according to mRECIST (80.0% vs. 62.3%, P = 0.048). The incidence of myelosuppression was higher in the ET group than in the IT group (22.6% vs. 6.0%, P = 0.024). No difference was observed in other treatment related adverse events. **Conclusions:** This study proved that Idarubicin could be a good safety profile and superior PFS and ORR than Epirubicin when used as part of a TACE regimen for BCLC B stage HCC. Longer follow-up is needed to confirm this conclusion. Clinical trial information: ChiCTR2000034758. Research Sponsor: None.

4069 **Poster Session**

Atezolizumab plus bevacizumab versus lenvatinib or sorafenib in non-viral unresectable hepatocellular carcinoma: An international study. *First Author: Andrea Casadei-Gardini, San Raffaele Hospital, Milan, Italy*

Background: Recently, several evidences have suggested that patients with a no-viral hepatocellular carcinoma (HCC) might be less responsive to immunotherapy and more response to Lenvatinib. **Methods:** The study population derived from prospectively collected retrospectively analyzed data of patients treated with atezolizumab plus bevacizumab (AB) or lenvatinib (L) or sorafenib (S) as first-line treatment for advanced HCC or intermediate HCC deemed not eligible for loco-regional therapies. The overall cohort included Western and Eastern patient populations from 36 centers located in 4 countries(Italy, Japan, Republic of Korea, and United Kingdom) undergoing treatment with L or AB or with S. The primary endpoint was OS of AB versus L; the secondary endpoints were OS of AB versus S. **Results:** 569 patients received L, 190 patients received AB and 210 received S. In the whole population OS was 17.8 months (95%CI:15.8-43.8) for patients receiving L, and 12.1 months(95%CI:11.1-16.8)for patients treated with AB (HR 0.71; 95% CI:0.50-1.06; p=0.1028); multivariate analysis for imbalance patients characteristic highlighted that L is an independent prognostic factor for OS (HR 0.65; 95% CI:0.44-0.95; p=0.0268), compared AB. In the population affected by NASH/NAFLD, 254 patients were treated with L and 82 patients were treated with AB. OS was 21.2 months (95% CI:18.4-30.6) for patients receiving L, and 12.2 months (95% CI:10.0-16.8) for patients treated with AB (HR 0.46; 95% CI:0.25-0.88; p = 0.0181); multivariate analysis for imbalance patients characteristic highlighted that L is an independent prognostic factor for OS (HR 0.46; 95% CI:0.26-0.84; p=0.031),compared AB. In the cohort of no viral and no NASH/NAFLD patients, no statistically significant differences were reported in terms of OS between patients treated with L versus AB. All these results were confirmed following propensity score matching analysis. By comparing patients receiving AB versus S, no significant differences were found in terms of OS in the whole population, in the NASH/NAFLD population and in no viral/no NASH/NAFLD population. **Conclusions:** The present analysis conducted on a large number of non-viral HCC patients showed for the first time a significant survival benefit from lenvatinib over atezolizumab plus bevacizumab, in particular in patients with NAFLD/NASH-related HCC. Research Sponsor: None.

4070 **Poster Session**

Patient-reported outcomes for the phase 3 TOPAZ-1 study of durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer. *First Author: Howard A. Burris III, Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN*

Background: TOPAZ-1 (NCT03875235) is a randomized, double-blind, global, Phase 3 study evaluating the efficacy and safety of durvalumab (D) in combination with (+) gemcitabine and cisplatin (GC) as first-line treatment for patients (pts) with advanced biliary tract cancer (BTC).[1] D + GC significantly improved overall survival (OS) versus placebo (PBO) + GC and represents a new treatment option. **Methods:** A pre-planned secondary objective of TOPAZ-1 was to assess pt-reported outcomes (PROs) for pts receiving D + GC versus PBO + GC. Pts with BTC were randomized 1:1 to D (1500 mg) or PBO, + G (1000 mg/m^2) and C (25 mg/m^2), for up to 8 cycles, followed by D or PBO monotherapy until disease progression, unacceptable toxicity, or other discontinuation criteria were met. PROs were assessed with the European Organisation for Research and Treatment of Cancer 30-item Quality of Life (QoL) Questionnaire, EORTC QLQ-C30 (C30), and the BTC 21-item module, EORTC QLQ-BIL21 (BIL21). Time to deterioration (TTD) was the primary assessment of PROs; defined as the time from randomization to the date of the first pre-specified, clinically meaningful deterioration (e.g. disease progression). The PRO analysis set included all pts from the full analysis set who completed a questionnaire. **Results:** Compliance rates for PROs were high at baseline (>81%) and remained high (majority >70% over 28 cycles) for both treatment groups. Baseline scores were comparable between treatment groups. Addition of D was well tolerated, with no significant difference in TTD in D + GC versus PBO + GC for pt-reported symptoms or functioning using either C30 or BIL21 (Table), or Global Health Status/QoL (hazard ratio [HR], 0.87; 95% confidence interval [CI], 0.69–1.12; p=0.279). **Conclusions:** Addition of D to GC improved OS (Oh D-Y, et al. *J Clin Oncol* 2022;40(suppl 4). Abs 378) and was well tolerated with no difference in TTD of QoL for pts, supporting D + GC as a new treatment option for pts with BTC. Clinical trial information: NCT03875235. Research Sponsor: AstraZeneca.

HRs for median TTD (HR [95% CI)/p-value; HR <1 favors D + GC).

C30 functioning:	Physical	Role	Cognitive	Emotional	Social
	1.05 [0.83–1.35]/ 0.678	1.08 [0.85–1.36]/ 0.558	1.09 [0.86–1.39]/ 0.487	0.98 [0.75–1.30]/ 0.914	0.98 [0.77–1.25]/ 0.865
C30 symptom scales:	**Fatigue**	**Pain**	**Nausea/vomiting**		
	0.97 [0.78–1.20]/ 0.759	0.98 [0.77–1.25]/ 0.848	0.95 [0.74–1.21]/ 0.645		
C30 single symptoms:	**Dyspnea**	**Insomnia**	**Appetite loss**	**Constipation**	**Diarrhea**
	0.93 [0.71–1.22]/ 0.606	0.87 [0.67–1.14]/ 0.307	1.24 [0.96–1.60]/ 0.097	1.09 [0.86–1.39]/ 0.476	0.86 [0.63–1.16]/ 0.315
BIL21 symptom scales:	**Eating**	**Jaundice**	**Pain**	**Anxiety**	**Tiredness**
	1.09 [0.84–1.42]/ 0.512	1.00 [0.76–1.32]/ 0.966	0.93 [0.70–1.25]/ 0.637	0.99 [0.74–1.32]/ 0.941	1.04 [0.82–1.31]/ 0.767
BIL21 single symptoms:	**Abdominal pain**	**Pruritis**	**Jaundice**	**Weight loss**	
	0.92 [0.69–1.23]/ 0.575	1.00 [0.75–1.33]/ 0.991	0.88 [0.62–1.25]/ 0.474	1.11 [0.82–1.50]/ 0.522	

4071 **Poster Session**

A phase II study of stereotactic body radiotherapy (SBRT) combined with sintilimab in patients with recurrent or oligometastatic hepatocellular carcinoma (HCC).

First Author: Yixing Chen, Department of Radiation Oncology, Zhongshan Hospital, Fudan University, Shanghai, China

Background: SBRT is an emerging treatment option for oligometastatic cancer disease. Preclinical studies have shown the synergistic effects between the radiotherapy and immunotherapy. Early clinical data also suggested that immunotherapy might augment the local effects of radiotherapy and decrease metastatic recurrence. This study aimed to evaluate the efficacy and safety of SBRT combined with sintilimab (a PD-1 antibody) in patients with recurrent or oligometastatic HCC. **Methods:** In this single arm, phase II study (NCT03857815), eligibility criteria included Pts with recurrent or oligometastatic HCC (defined as ≤5 metastatic/recurrent lesions), Child-Pugh class A, ECOG PS ≤ 1. Pts received sintilimab 200 mg IV Q3W for up to 12 months, progressive disease, unacceptable toxicity, or withdrawal. SBRT to all lesions was started at cycle 1 day 1. Primary endpoint was progression free survival (PFS) per RECIST 1.1. Secondary endpoints included safety, objective response rate (ORR), disease control rate (DCR) and overall survival (OS). **Results:** At data cutoff (Dec 28th, 2021), 25 pts with 32 lesions were treated with SBRT + Sintilimab. SBRT was delivered at a median dose of 54 Gy (range 48-60) in 6 fractions (range 6-10) and the median follow-up time was 16.9 months (range 3.9-32.1). In those 25 evaluable pts, median age was 64 years (range 37-77), 24 (96%) were male, 24 (96%) were HBV+, 6 (24%) had extrahepatic metastasis, most pts had prior ≥2 local therapies. The confirmed ORR was 96% (24/25) according to RECIST 1.1 with 18pts CR and 6pts PR. 6-mo and 12-mo PFS rate was 100% and 70% (95%CI, 52.3%-93.6%), respectively.12-mo local control rate was 100%. Median PFS and OS was still not mature. Treatment-related adverse events (TRAEs) occurred in 14 pts (56%). Most common TRAEs were rash (16%), platelet count decreased (12%), myositis (8%). Grade 3 TRAEs (myositis) occurred in 1pt (4%). There were no grade 4-5 TRAEs. TRAEs led to discontinuation in 6 pts (24%). SAE were myocarditis (1pt Grade1), viral hepatitis (1pt Grade 3, treatment-independent) and upper gastrointestinal haemorrhage (1pt Grade 3, PD related). **Conclusions:** The combination of SBRT with Sintilimab was tolerable and showed an encouraging ORR of 96% in pts with recurrent or oligometastatic HCC. Longer follow up is required to further evaluate the efficacy and safety. Clinical trial information: NCT03857815. Research Sponsor: Innovent.

4072 **Poster Session**

Clinical outcomes associated with tislelizumab in patients (pts) with advanced hepatocellular carcinoma (HCC) who have been previously treated with sorafenib (SOR) or lenvatinib (LEN) in RATIONALE-208.

First Author: Julien Edeline, Department of Medical Oncology, Eugene Marquis Center, Rennes, France

Background: Tislelizumab, an anti-PD-1 monoclonal antibody, demonstrated clinical activity and was well tolerated in pts with previously treated advanced HCC in the Phase 2 RATIONALE-208 study (NCT03419897). At the time of this study, SOR and LEN were recommended first-line treatments for pts with advanced HCC and continue to have an important role in the first-line treatment of HCC despite the recent approval of new immuno-oncology-based combinations (atezolizumab and bevacizumab) in some regions. We report the clinical outcomes of pts with advanced HCC who were previously treated with SOR/LEN. **Methods:** Pts who had received ≥ 1 prior line of systemic therapy for advanced HCC received tislelizumab 200 mg intravenously once every three weeks. Objective response rate (ORR) by independent review committee (IRC) (ORR_{IRC}), duration of response by IRC (DOR_{IRC}), progression-free survival by IRC (PFS_{IRC}), overall survival (OS), and safety were evaluated in pts who had been previously treated with SOR/LEN. **Results:** As of February 2020, 249 pts were enrolled and 235 pts had received prior treatment with SOR/LEN, of whom 126 and 109 pts had received 1 or ≥ 2 prior lines of systemic therapy, respectively. At study entry, 211 (89.8%) pts had BCLC stage C and 187 (79.6%) pts had extrahepatic spread. Median follow-up duration for pts previously treated with SOR/LEN was 12.5 months and ORR_{IRC} was 13.6% (95% CI: 9.5, 18.7), including 2 complete responses and 30 partial responses. Median DOR_{IRC} was not reached. Median PFS_{IRC} and OS of pts previously treated with SOR/LEN was 2.7 months (95% CI: 1.6, 2.8) and 13.5 months (95% CI: 10.9, 15.8), respectively. Tislelizumab was generally well tolerated in pts previously treated with SOR/LEN (Table), and the most common treatment-emergent adverse events were increased aspartate aminotransferase (n=70; 28.1%) and alanine aminotransferase (n=52; 20.9%). **Conclusions:** Tislelizumab was investigated beyond the first-line setting, as effective second- and third-line treatment options are limited for pts with advanced HCC and there is an unmet medical need. This analysis indicates that tislelizumab is clinically active and well tolerated in pts with advanced HCC who have received prior systemic treatment with SOR/LEN. Clinical trial information: NCT03419897. Research Sponsor: This study was sponsored by BeiGene, Ltd. Medical writing support for the development of this abstract, under direction of the authors, was provided by Claire White, PhD, of Ashfield MedComms, an Ashfield Health company, and was funded by BeiGene, Ltd.

Summary of AEs in pts previously treated with SOR/LEN.

	TEAE	TRAE
	N=235	
≥ 1, n (%)	223 (94.9)	147 (62.6)
≥ Grade 3	116 (49.4)	32 (13.6)
Serious	87 (37.0)	15 (6.4)
Leading to discontinuation	26 (11.1)	12 (5.1)
Leading to dose delay	72 (30.6)	40 (17.0)
Leading to death	24 (10.2)	0 (0)

AE, adverse event; TEAE, treatment-emergent AE; TRAE, treatment-related treatment-emergent AE.

4073 **Poster Session**

Hepatic artery infusion chemotherapy (HAIC) combined with sintilimab and bevacizumab biosimilar (IBI305) for initial unresectable hepatocellular carcinoma (HCC): A prospective, single-arm phase II trial.

First Author: Dongming Liu, Liver Cancer Research Center for Prevention and Therapy, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin's Clinical Research Center for Cancer, Tianjin, China

Background: Sintilimab plus IBI305, a bevacizumab biosimilar, showed a significant overall survival and progression-free survival benefit versus sorafenib in the first-line setting for patients with unresectable hepatocellular carcinoma. Hepatic arterial infusion chemotherapy is an intraarterial procedure that has been widely used in Asia, with high response rate. This trial was designed to assess the feasibility and efficacy of HAIC combined with sintilimab and IBI305 in advanced unresectable hepatocellular carcinoma. **Methods:** This is a prospective, single-arm phase II study. Patients with histologically or cytologically diagnosed or clinically confirmed hepatocellular carcinoma, China liver cancer staging (CNLC) stage IIb-IIIb, no previous systemic treatment, Child-Pugh classification A or B, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 were eligible for inclusion. Patients received FOLOFOX-HAIC, followed by intravenous sintilimab (200 mg every 3 weeks, four cycles) and intravenous IBI305 (7.5 mg/kg every 3 weeks, three cycles). The primary endpoint was objective response rate (ORR) per mRECIST. Secondary endpoint were surgical conversion rate, pCR rate and R0 resection rate. The study is registered with Clinicaltrials.gov: NCT05029973. **Results:** Between May, 2021 to Sep, 2021, a total of 30 eligible patients were enrolled: median age 54.5 years (range 37-73); M:F 27:3; CNLC stage IIb/IIIa/IIIb: 3/16/11; Child-Pugh class A/B: 28/2; ECOG PS 0/1: 26/4. There were 23(76.7%) patients with hepatitis B and 5(16.7%) with hepatitis C. The median tumor size was 8.75 cm (interquartile range [IQR], 4.9-10.5), 60.0% pts present vascular invasion, and 36.7% had extrahepatic metastasis. Of 30 pts evaluable for response, 20 (66.7%; 95% CI: 47.2%-82.7%) achieved confirmed partial response, and became eligible for surgical resection. Finally, 14 of them received surgical resection and all (100%) achieved R0 resection, 3 pts completed radiofrequency ablation (RAF), 3 pts refused resection or RFA. The pCR rate in the patients completed pathological examination was 52.6% (95% CI: 28.9%-75.6%). The most common TRAEs included hypertension (23.3%), rash (16.7%), and abnormal liver function (10.0%). No grade 3-4 TRAEs were observed. Of note, in patients received surgery, 1 developed grade 1 biliary fistula, 1 developed hepatic failure and finally lead to death **Conclusions:** HAIC Combined With sintilimab and IBI305 resulted in a promising ORR, R0 surgical conversion rate and pCR rate with a manageable safety for initial unresectable advanced hepatocellular carcinoma. Further follow-up is ongoing. Clinical trial information: NCT05029973. Research Sponsor: National Natural Science Foundation of China (Grant Nos. 81502019).

4074 **Poster Session**

Patient-reported outcomes from the phase 3 HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma.

First Author: Bruno Sangro, Liver Unit and HPB Oncology Area, Clínica Universidad de Navarra and CIBEREHD, Pamplona, Spain

Background: In the Phase 3 HIMALAYA study (NCT03298451) of patients (pts) receiving first-line treatment for unresectable hepatocellular carcinoma (uHCC), a single priming dose of tremelimumab (T; anti-CTLA-4) plus durvalumab (D; anti-PD-L1) in the STRIDE regimen significantly improved overall survival (OS) vs sorafenib (S), and D monotherapy was noninferior to S for OS (Abou-Alfa et al. *J Clin Oncol* 2022;40[suppl 4]. Abs 379). **Methods:** A pre-planned secondary objective of HIMALAYA was to assess pt-reported outcomes (PROs) in pts receiving STRIDE (T 300 mg plus D 1500 mg [one dose] plus D 1500 mg once every 4 weeks [Q4W]; N=393) or D (1500 mg Q4W; N=389) vs S (400 mg twice daily; N=389). The European Organisation for Research and Treatment of Cancer (EORTC) 30-item Quality of Life (QoL) Questionnaire and the EORTC 18-item HCC QoL questionnaire were used to assess disease-related symptoms, physical functioning (PF), and Global Health Status (GHS)/QoL. Time to deterioration (TTD), defined as time from randomization to first clinically meaningful deterioration (worsening ≥10 points) confirmed at a subsequent visit or death, was assessed in pts with baseline scores ≤90 for symptoms or ≥10 for PF and GHS/QoL. **Results:** Across treatment arms, compliance rates for PROs were >77% at baseline and >70% overall. Baseline scores were comparable across treatment arms. TTD in fatigue, appetite loss, abdominal pain, PF, and GHS/QoL were significantly longer for both STRIDE and D vs S (Table). TTD in nausea and abdominal swelling were significantly longer for STRIDE vs S. **Conclusions:** The positive OS outcomes for STRIDE and D in pts receiving first-line treatment for uHCC in HIMALAYA were associated with clinically meaningful, pt-centered benefits, demonstrated by delayed worsening of disease-related symptoms, PF, and GHS/QoL vs S. Median TTD in months (95% CI) in PROs for STRIDE and D vs S. Clinical trial information: NCT03298451. Research Sponsor: AstraZeneca.

	STRIDE	STRIDE vs S HR (95% CI)/p-value	D	D vs S HR (95% CI)/p-value	S
Fatigue	7.4 (5.6–9.4)	0.71 (0.57–0.89)/ 0.003	6.9 (5.6–7.5)	0.75 (0.61–0.93)/ 0.016	5.4 (3.8–6.3)
Appetite loss	12.6 (9.3–20.9)	0.59 (0.46–0.75)/ <0.0001	11.1 (8.9–16.8)	0.60 (0.47–0.77)/ <0.0001	6.9 (5.6–7.6)
Nausea	25.0 (16.0–NR)	0.65 (0.49–0.87)/ 0.003	16.8 (10.5–NR)	0.81 (0.62–1.06)/ 0.163	11.0 (9.2–13.7)
Shoulder pain	12.6 (9.2–19.6)	0.82 (0.63–1.06)/ 0.109	16.0 (9.0–22.3)	0.81 (0.63–1.05)/ 0.155	9.4 (7.5–13.4)
Abdominal pain	16.8 (11.2–NR)	0.61 (0.47–0.80)/ 0.001	14.1 (9.5–24.4)	0.67 (0.52–0.87)/ 0.002	8.9 (7.2–11.1)
Abdominal swelling	20.9 (12.9–36.0)	0.74 (0.56–0.97)/ 0.043	16.7 (9.5–24.9)	0.88 (0.68–1.14)/ 0.366	11.1 (9.3–13.7)
PF	12.9 (9.2–16.8)	0.68 (0.53–0.87)/ 0.002	14.1 (9.2–8.5)	0.66 (0.51–0.83)/ 0.001	7.4 (5.7–10.2)
GHS/QoL	7.5 (5.8–10.8)	0.76 (0.61–0.96)/ 0.031	7.4 (5.7–9.3)	0.77 (0.62–0.96)/ 0.030	5.7 (4.8–7.4)

CI, confidence interval; HR, hazard ratio; NR, not reached.

4075 **Poster Session**

Regional subgroup analysis of the phase 3 TOPAZ-1 study of durvalumab (D) plus gemcitabine and cisplatin (GC) in advanced biliary tract cancer (BTC).

First Author: Arndt Vogel, Hannover Medical School, Hannover, Germany

Background: TOPAZ-1 (NCT03875235) is a randomized, double-blind, global, Phase 3 study evaluating the efficacy and safety of D + GC as first-line treatment for patients (pts) with advanced BTC. D + GC significantly improved overall survival (OS) versus placebo (PBO) + GC (Oh D-Y, et al. *J Clin Oncol* 2022;40[suppl 4]. Abs 378). **Methods:** A pre-specified subgroup analysis was performed for efficacy outcomes including OS for pts enrolled in Asia (China, Hong Kong, India, Japan, South Korea, Taiwan, Thailand) or the rest of the world (RoW; Europe [Bulgaria, France, Italy, Poland, Russia, Turkey, United Kingdom], North America [NA; USA], and South America [SA; Argentina, Chile]). Post hoc country level analyses were also performed to better characterize outcomes in different countries and regions. Pts with BTC were randomized 1:1 to D (1500 mg once every 3 weeks [Q3W]) or PBO, + G (1000 mg/m^2) and C (25 mg/m^2) on Days 1 and 8, Q3W, for up to 8 cycles, followed by D (1500 mg Q4W) or PBO monotherapy until disease progression or unacceptable toxicity. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated from a Cox proportional hazards model. **Results:** Pt numbers were balanced across regions (Asia, n=374 [54.6%]; RoW, n=311 [45.4%]). Baseline characteristics were balanced between regions with the exception of modest differences in important pre-defined prognostic factors, including disease status: recurrent disease (Asia 23%; RoW 14.5%), ECOG performance status 1 (Asia 59.1%; RoW 41.2%), and metastatic disease (Asia 89.3%; RoW 82%). In the PBO arm, more pts in Asia received subsequent anticancer therapies than pts in RoW (53.6% vs 43.9%). Median duration of follow-up in censored pts was about 2 months (mo) longer in Asia versus RoW (14.8 vs 13.0 mo in D + GC; 13.8 vs 12.1 mo in PBO + GC). Regional level analysis (Table) showed outcomes were similar and approximated the overall population for Asia, Europe, and NA. Grade 3/4 adverse events were similar for Asia (D + GC 78.5%; PBO + GC 78.6%) and RoW (D + GC 72.7%; PBO + GC 76.7%). **Conclusions:** Despite some regional differences in prognostic characteristics, OS trends favored D + GC versus PBO + GC for pts enrolled in both Asia and RoW, supporting the use of D + GC as a potential new treatment option for all pts with BTC. Country-specific and regional outcomes continue to be explored. Clinical trial information: NCT03875235. Research Sponsor: AstraZeneca.

OS outcomes per arm, by region.

Region	D + GC, n/N (%)	PBO + GC, n/N (%)	HR (95% CI)
Overall	198/341 (58)	226/344 (66)	0.80 (0.66–0.97)
Asia	103/178 (58)	137/196 (70)	0.72 (0.56–0.94)
ROW	95/163 (58)	89/148 (60)	0.89 (0.66–1.19)
ROW w/o SA	84/145 (58)	85/135 (63)	0.82 (0.60–1.11)

4076 **Poster Session**

Organ-specific responses to atezolizumab plus bevacizumab in patients with advanced hepatocellular carcinoma.

First Author: Jaekyung Cheon, Department of Medical Oncology, CHA Bundang Medical Center, Seongnam, South Korea

Background: Anti-PD-1 monotherapy elicits various organ-specific immune responses. Although advanced hepatocellular carcinoma (aHCC) showed 20–40% objective response rates (ORR) for cases of extrahepatic lesions in sites such as the lungs or lymph nodes (LNs), only 10% of intrahepatic lesions responded to the monotherapy. The organ-specific responses were due to tumor heterogeneity and differential microenvironments, and may have contributed to the failure of the phase III trials of anti-PD-1 monotherapy for aHCC. Recently, the combination of atezolizumab and bevacizumab (Ate/Bev) as first-line systemic treatment has resulted in survival benefits for patients with aHCC. However, the organ-specific response for this treatment has not been explored. We aimed to evaluate the organ-specific response to Ate/Bev combination therapy in patients with aHCC. **Methods:** We enrolled patients who received first-line Ate/Bev treatment for aHCC. Eligible patients included those with Child-Pugh A liver function, measurable tumor lesions, and serial image studies available for response evaluation. An independent radiologist reviewed the tumors located in the liver, lungs, LNs, and other sites. Organ-specific response criteria, adapted from RECIST 1.1 and immune-related RECIST, were used. **Results:** Between May 2020 and June 2021, 124 patients from two Korean cancer referral institutions received first-line Ate/Bev treatment for aHCC. The patient baseline characteristics included: hepatitis B (n = 85, 68.5%), hepatitis C (n = 6, 4.8%), non-viral (n = 33, 26.7%); BCLC stage A/B/C (n = 2, 1.6%/n = 19, 15.3%/n = 103, 83.1%); macrovascular invasion (n = 39, 31.5%); extrahepatic metastasis (n = 75, 60.5%); and AFP >400 ng/ml (n = 39, 31.5%). The median age was 62 years (range: 34–90). With median follow-up duration of 10.1 months, median progression-free survival was 6.8 months (95% CI, 3.6–10.0) and median overall survival was 16.9 months (95% CI, range not available). The ORR was 29.8%. For 260 individual tumor lesions, the liver was the most commonly involved organ (n = 152, 58.5%), followed by the LNs (n = 42, 16.2%) and lungs (n = 24, 9.2%). Ate/Bev treatment induced potent tumor shrinkage in both intrahepatic and extrahepatic lesions: ORR for hepatic lesions was 28.3%; LN lesions, 40.5%; lung lesions, 29.1%; and other metastatic lesions, 19.0%. Further, the organ-specific response rate for intrahepatic tumors decreased as the tumor size increased (36.7%: ≤50 mm, 13.0%: >50 mm). **Conclusions:** Unlike anti-PD-1 monotherapy, Ate/Bev combination therapy showed favorable responses even in intrahepatic lesions, which are comparable to those in extrahepatic lesions. As such, Ate/Bev may overcome an immune-tolerant hepatic microenvironment in patients with aHCC. (NCT04862949). Research Sponsor: Roche.

4077 **Poster Session**

A phase II study to evaluate the safety and efficacy of anlotinib combined with toripalimab for advanced biliary cancer.

First Author: Jie Shen, The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China

Background: To evaluate anlotinib combined with toripalimab for advanced biliary cancer that failed or without the will of standard first-line treatments. **Methods:** Open single arm phase II study were conducted, eligible patients (pts) were advanced biliary without the chance of operation and failed or without the will of standard first-line treatments. Pts received anlotinib 12mg po qd in 21-day cycles and toripalimab 240mg i.v. every 3 weeks. The main outcome measure was the objective response rate (ORR) of the target lesions evaluated by researchers based on the RECIST 1.1 standard, the secondary outcome measures were progress free survival (PFS) and treatment-related adverse event (TRAE). **Results:** As of Jan, 2022, 15 pts were enrolled including 9 the intrahepatic cholangiocarcinoma, 3 hilar Cholangiocarcinoma, and 3 the gall bladder carcinoma. 11 (73.3%) pts failed standard first-line treatments, and 4 pts were without the will of standard first-line treatments. The median follow-up was 254 days and 15 pts were all evaluated. 4PR, 9SD and 2PD were achieved. The ORR and DCR for irradiated target lesions was 26.7% and 86.7%, respectively. PFS for first line treatment was 139 days, and for second line treatment as 171 days. By this strategy, 1 ps was successfully transferred to operation after 3 cycle treatment. TRAEs (all grades) occurred in 14 (93.3%) pts. Grade 3 related AEs were fatigue (13.3%). Grade 1-2 related AEs were white blood cell count decreased (53.3%), hypertension (20.0%), thrombocytopenia (60.0%), fatigue (13.3%), hypothyroidism (6.7%), and fever asthenia (6.7%). **Conclusions:** The combination of anlotinib and toripalimab were demonstrated promising anti-tumor activity in advanced biliary cancer. Clinical trial information: ChiCTR2000037847. Research Sponsor: None.

4078 **Poster Session**

Characterization of tumor responses in patients (pts) with unresectable hepatocellular carcinoma (uHCC) treated with lenvatinib in REFLECT.

First Author: Masatoshi Kudo, Kindai University Faculty of Medicine, Osaka-Sayama, Japan

Background: In REFLECT, lenvatinib was noninferior to sorafenib based on overall survival in pts with uHCC (median 13.6 vs 12.3 mos; hazard ratio [HR] 0.92, 95% CI 0.79–1.06). The objective response rate (ORR) with lenvatinib was 18.8% by blinded independent imaging review (IIR) per RECIST v1.1; ORR was 40.6% by blinded IIR per mRECIST. Here we further characterize the tumor responses in pts with uHCC who were treated with lenvatinib in REFLECT. **Methods:** Assessments of ORR included all pts randomly assigned to lenvatinib treatment (12 mg/day for bodyweight ≥60 kg or 8 mg/day for bodyweight <60 kg). Time to first objective response (TTR) and duration of response (DOR) were calculated among pts who achieved a partial or complete tumor response. Tumors were assessed by IIR per RECIST v1.1 or mRECIST. Median DOR was estimated with the Kaplan-Meier product-limit method; 95% CI was estimated with a generalized Brookmeyer and Crowley method. **Results:** 478 Pts were randomly assigned to receive lenvatinib. Among the 90 pts (18.8%) who achieved an objective response by IIR per RECIST v1.1, median TTR was 2.8 mos (range 1–29) and median DOR was 7.4 mos (95% CI 5.6–9.2). Of the 194 pts who had an objective response by IIR per mRECIST, median TTR was 1.9 mos (range 1–15) and median DOR was 7.3 mos (95% CI 5.6–7.4). ORRs by selected baseline characteristics are reported in the Table. Notably, among responders by IIR per RECIST v1.1 (n=90), median overall survival (by Simon-Makuch method) was 23.4 mos (95% CI 17.6–26.3), median duration of treatment was 10.3 mos, and 65.6% of pts experienced grade ≥3 treatment-related adverse events. **Conclusions:** Pts with uHCC treated with lenvatinib achieved objective responses with a similar frequency to those seen with single-agent immune checkpoint inhibitors. These responses occurred irrespective of baseline characteristics. Tumor responses occurred early and were durable. Clinical trial information: NCT01761266. Research Sponsor: Eisai Inc., Nutley, NJ, USA, and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Baseline characteristic	ORR, n/m (%) RECIST v1.1 by IIR	ORR, n/m (%) mRECIST by IIR
Age (years):		
<65	47/270 (17.4)	105/270 (38.9)
≥65-75	28/150 (18.7)	62/150 (41.3)
≥75	15/58 (25.9)	27/58 (46.6)
Sex:		
Male	75/405 (18.5)	163/405 (40.2)
Female	15/73 (20.5)	31/73 (42.5)
Body weight (kg):		
<60	25/153 (16.3)	63/153 (41.2)
≥60	65/325 (20.0)	131/325 (40.3)
ECOG PS:		
0	66/304 (21.7)	129/304 (42.4)
1	24/174 (13.8)	65/174 (37.4)
AFP at baseline (ng/mL):		
< 200	56/255 (22.0)	122/255 (47.8)
≥ 200	34/222 (15.3)	72/222 (32.4)
MPVI, EHS, or both:		
Yes	61/329 (18.5)	113/329 (34.3)
No	29/149 (19.5)	81/149 (54.4)
BCLC staging:		
Stage B	23/104 (22.1)	59/104 (56.7)
Stage C	67/374 (17.9)	135/374 (36.1)
Etiology:		
HBV	44/259 (17.0)	99/259 (38.2)
HCV	27/103 (26.2)	49/103 (47.6)
Alcohol	5/33 (15.2)	11/33 (33.3)

AFP, alpha fetoprotein; BCLC, Barcelona Clinic Liver Cancer; EHS, extrahepatic spread; m, number of patients in category; MPVI, macroscopic portal vein invasion; n, number of patients with complete or partial response.

4079 **Poster Session**

Targeting *HER2* mutation–positive advanced biliary tract cancers with neratinib: Final results from the phase 2 SUMMIT basket trial. *First Author: James J. Harding, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY*

Background: *HER2* mutations are infrequent genomic events in biliary tract cancers (BTCs) and are associated with poor overall survival (OS) in patients with metastatic disease. HER2 overexpression is associated with an increased risk of disease recurrence in patients with resected BTC. There is limited data on targeting HER2 in BTC harboring activating somatic *HER2* mutations. Neratinib, an irreversible, pan-HER, oral tyrosine kinase inhibitor, interferes with constitutive receptor kinase activation and has demonstrated activity in several *HER2*-mutant solid tumors. **Methods:** SUMMIT is an open-label, single-arm, multi-cohort, phase 2, 'basket' trial of neratinib in patients with solid tumors harboring oncogenic *HER2* somatic mutations. The primary objective of the BTC cohort was to estimate objective response rate (ORR). Secondary objectives were clinical benefit rate (CBR), progression-free survival (PFS), OS, response duration, safety, and tolerability. Retrospective central confirmation of locally reported *HER2* mutation (next-generation sequencing on archival or fresh tumor tissue using MSK-IMPACT or in cfDNA extracted from plasma by MSK-ACCESS) and association with outcome was an exploratory endpoint. This trial is registered with ClinicalTrials.gov (NCT01953926). **Results:** 25 treatment-refractory patients with metastatic BTC were enrolled (11 cholangiocarcinoma, 10 gallbladder, 4 ampullary cancers). ORR was 16% (95% CI 4.5–36.1%) and CBR was 28% (95% CI 12.1–49.4%). Median PFS and OS were 2.8 (95% CI 1.1–3.7) and 5.4 (95% CI 3.7–11.7) months, respectively. Median PFS for the gallbladder, cholangiocarcinoma and ampulla cohorts was 3.7 (95% CI 0.8–6.4), 1.4 (95% CI 0.5–9.1), and 1.1 (95% CI 1.1–3.8) months, respectively. Corresponding median OS values in these cohorts were 9.8 (95% CI 2.4–NE), 5.4 (95% CI 0.8–16.2), and 5.0 (95% CI 3.7–10.2) months, respectively. Central mutation confirmation was feasible for 23 of 25 patients; 22 were concordant with enrolment assays. The most common *HER2* mutations were S310F (n = 11; 48%) and V777L (n = 4; 17%). Exploratory analyses suggested worse outcomes for *HER2*-mutant tumors with co-occurring oncogenic *TP53* and *CDKN2A* alterations. Loss of amplified *HER2* S310F and acquisition of multiple previously undetected oncogenic co-mutations were identified at progression in one of four responders. Diarrhea (56% any grade) was the most common toxicity. **Conclusions:** Neratinib is tolerable with modest antitumor activity in patients with BTC harboring *HER2* mutations. Although the primary endpoint was met, future studies should evaluate rational combinations to augment and/or prolong responses. Clinical trial information: NCT01953926. Research Sponsor: Puma Biotechnology, Inc., This work was also supported in part by a Cancer Center Support Grant (P30 CA008748) and Cycle for Survival.

4080 **Poster Session**

Preservation of liver function with local radiation therapy in patients with metastatic intrahepatic cholangiocarcinoma with extrahepatic disease. *First Author: Rituraj Upadhyay, The Ohio State University Wexner Medical Center, Columbus, OH*

Background: Tumor related liver failure (TRLF) is the most common cause of death in patients with metastatic intrahepatic cholangiocarcinoma (mICC) accounting for up to 72% deaths in patients treated with systemic therapy alone. We present our institutional experience of treating mICC patients with local liver-directed radiation therapy (RT). **Methods:** ICC patients with extrahepatic metastatic disease who received radiation therapy at our center with a biologically equivalent dose (BED) of at least 50 Gy from January 1, 2011 to March 31, 2021 were included in our study. Patient, tumor and treatment characteristics as well as the survival outcomes were recorded. TRLF was considered the cause of death if the patient died due to liver failure; and freedom from TRLF (FFTRLF) at 1 year and 2 years after RT was calculated. **Results:** Sixty-seven patients were included in the study. The median age was 63 years (range 29-83 years) and median RT dose was 60 Gy (range, 40-100 Gy). 73.1% patients received a BED > 80.5 Gy. All except 1 patient were treated with upfront induction chemotherapy, followed by RT to the primary lesion in liver with (71.6%) or without (28.4%) concurrent chemotherapy. The most common induction chemotherapy regimen used was gemcitabine and cisplatin (65.7%) followed by gemcitabine, cisplatin and paclitaxel (22.4%), while the most common concurrent systemic therapy was capecitabine. Out of 43 patients with satellitosis, 29 were treated with RT to the dominant liver lesion while 14 received RT to the primary as well as one or more satellites. Overall, 15 patients (22.4%) had local progression of the radiated lesion, 42 patients (62.7%) progressed elsewhere in liver, and 52 patients (77.6%) had a distant progression. TRLF was the cause of death in 28.4% of patients. Median OS from diagnosis was 25 months while median OS after RT was 11.9 months. The 1- and 2-year rates of FFTRLF were 73.1% and 58.2% respectively, which were significantly higher than 1- and 2-year OS after RT (47.1% and 24.7% respectively, $p < 0.005$). Univariate analysis did not identify significant association of FFTRLF or OS with age, sex, performance status, size of liver lesions, T or N stage, satellitosis, vascular thrombosis, TRLF, timing of metastasis, site of metastasis, RT technique and dose and chemotherapy. **Conclusions:** Liver directed radiation therapy in patients with mICC with extrahepatic disease appears to have favorable rates of TRLF and survival times, compared to historical data. Future prospective studies are warranted to define the survival benefit in these patients attributable to radiation therapy. Research Sponsor: None.

4081 **Poster Session**

Toripalimab combined with gemcitabine and S-1 in the first-line treatment of advanced biliary tract cancer. *First Author: Wei Li, Department of Oncology, Cancer center, Zhongshan Hospital, Fudan University, Shanghai, China*

Background: Gemcitabine combined with platinum/fluorouracil drugs is the standard first-line treatment for advanced biliary tract cancers (BTCs), but the overall effect needs to be further improved. This study intended to explore the safety and efficacy of toripalimab combined with chemotherapy in the first-line treatment of advanced BTCs. **Methods:** This single-arm, phase II clinical trial enrolled patients with advanced BTCs who had not received systemic treatment. Toripalimab combined with chemotherapy were applied as first-line treatment: toripalimab (240 mg, iv, d1), gemcitabine (1000 mg/m2, iv, d1&d8), and S-1 (40-60mg bid po, d1-14, Q21d). The primary endpoint was progression-free survival (PFS), and the secondary endpoints included overall survival (OS), objective response rate (ORR) , duration of response (DOR) and safety. The study explored the association between response with PD-L1 expression, tumor mutational burden (TMB) and genetic variations identified by next-generation sequencing (NGS) of peripheral blood. **Results:** 50 patients were enrolled from January 2019 to August 2021 with a median follow-up time of 24.0 months (4.3-31.0). The median PFS was 7.0 months (95%CI: 5.0-8.9 months); median OS was 15.0 months (95%CI: 11.6-18.4 months). Of the 49 patients who completed the evaluation for tumor response, the ORR was 30.6% (95%CI: 17.2%-44.0%), and the disease control rate was 87.8% (95%CI: 78.2%-97.3%). The most common treatment-related adverse events (TRAEs) were leukopenia (98.0%), neutropenia (92%), and anemia (86.0%). Grade III/IV TRAEs included leukopenia (38.0%), neutropenia (32%), skin rash (6%), anemia (2.0%), mucositis (2%) and immune-related colitis (2%) .Among them, the Grade III/IV immune-related adverse events irAEs) worthy of attention included were skin rash and immune-related colitis . There was no significant difference in PFS and OS among intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma and gallbladder cancer. Exploratory study showed that patients with CPS≥1 had longer PFS . However, there was no significant correlation between TMB and PFS. **Conclusions:** Toripalimab combined with gemcitabine and S-1 (GS) has shown good safety in the first-line treatment of advanced BTCs. Although the primary endpoint did not reach the preset goal, toripalimab plus GS as first-line treatment has shown encouraging data of PFS and OS in patients with advanced BTC, which is worthy for further verification. Biomarker analysis showed that the expression level of PD-L1 could predict the curative effect. Clinical trial information: NCT03796429. Research Sponsor: the National Natural Science Foundation of China and the Foundation of Shanghai Science and Technology Committee.

4082 **Poster Session**

The potential use of blood-based tumor fibrosis markers as diagnostic and prognostic biomarkers in patients with biliary tract cancer. *First Author: Troels Dreier Christensen, Department of Oncology, Copenhagen University Hospital, Herlev, Denmark*

Background: Patients with biliary tract cancer (BTC) have a very poor prognosis. A better understanding of the disease and potential novel biomarkers are needed. BTC is characterized by a collagen-rich desmoplastic extracellular matrix (ECM), and tumor fibrosis is linked to cancer progression and treatment resistance. We tested the diagnostic and prognostic use of seven circulating biomarkers associated with ECM remodeling. We evaluated both pro-peptides (propeptide of collagen type III (Pro-C3), VI (PRO-C6), XI (PRO-C11)) and degradation fragments (matrix metalloproteinase (MMP) degraded collagen type III (C3M) and IV (C4M), granzyme B degraded collagen type IV (C4G), citrullinated and MMP degraded vimentin fragment (VICM)). **Methods:** The study included 269 patients with all stages of BTC (intrahepatic cholangiocarcinoma (CC) (n=124), extrahepatic CC (n=89), and gall bladder cancer (n=56)), and 49 patients with benign biliary tract disease. Serum samples were collected from the patients with BTC before surgery (n=36), 1st line (n=199), and 2nd line (n=56) treatment. A total of 22 patients had samples collected at two timepoints. The seven ECM markers and carbohydrate antigen 19-9 (CA19-9) were analyzed using enzyme-linked immunosorbent assay (ELISA) and electrochemiluminescence immunoassay. **Results:** The levels of C3M, C4M, PRO-C3, PRO-C6, PRO-C11, and VICM were significantly elevated in patients with BTC compared to patients with benign disease (Wilcoxon test, adjusted p-value < 0.05). Area under receiver operating characteristics curve (AUC) identified PRO-C3 (AUC=0.87) as the ECM marker that best discriminated between patients with BTC and controls. A model combining PRO-C3 and CA19-9 further improved the diagnostic accuracy (AUC=0.97). Elevated levels of four markers (C3M, C4M, PRO-C3 and PRO-C6) before 1st line treatment for BTC were associated with short overall survival (OS) in separate multivariate cox regression analyses adjusting for CA19-9, performance status, and stage. Similarly, elevated levels of PRO-C3 and PRO-C6 before 2nd line treatment were associated with short OS (Table). **Conclusions:** We identified specific blood-based collagen fragments as potential novel biomarkers for BTC. Our results indicate that patients with BTC have an elevated collagen remodeling, and that increased collagen turnover is associated with a poor prognosis for these patients. Research Sponsor: Nordic Bioscience A/S, Other Foundation.

	1st line HR (95% CI)	2nd line HR (95% CI)
C3M*	1.5 (1.1 - 2.1)	1.4 (0.8 - 2.5)
C4M*	1.5 (1.1 - 1.9)	1.4 (0.9 - 2.2)
PRO-C3*	1.4 (1.2 - 1.7)	1.7 (1.1 - 2.6)
PRO-C6*	1.5 (1.1 - 1.9)	2.1 (1.4 - 3.0)

* Hazard ratio (HR) and confidence interval (CI) for a doubling of serum concentration adjusted for CA19-9, stage and PS.

4083 **Poster Session**

Immunogenomic characterization of biliary tract cancers: Biomarker enrichment for benefit to immune checkpoint blockade. *First Author: Wungki Park, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY*

Background: Several immunomodulatory molecules (PD-L1, B7H4, and CD276) have been associated with biliary tract cancer (BTC) subgroups, suggesting potential value to immune checkpoint blockade (ICB) in this lethal disease. Phase II monotherapy (pembrolizumab or nivolumab), and combination (atezolizumab and cobimetinib) ICB trials reported low response rates in unselected advanced BTC with a wide range of responses. A recent randomized phase III trial (TOPAZ-1) reported an overall survival (OS) benefit among patients (pts) with advanced BTC treated with chemotherapy and anti-PD-L1 ICB. However, no correlation between PD-L1 expression and OS was noted and biomarker enrichment strategy in BTC for immunotherapy remains a key to optimize OS. **Methods**: From our comprehensive clinicogenomic database for BTC at Memorial Sloan Kettering (MSK), a retrospective genomic landscape and neoantigen analysis was performed using MSK-IMPACT. Potential immunogenic subgroups were evaluated: homologous recombination deficiency (HRD) defined by pathogenic alterations in *BRCA1/2, PALB2*, and *BAP1*, microsatellite stability high (MSI-H) defined by MSIsensor score ≥10, and tumor mutation burden (TMB)>10. Clinical outcomes with anti-PD-1 ICB were evaluated. **Results**: Among N=1,190 pts with BTC, N=1,346 samples were sequenced between 03/2014 and 01/2022. Key actionable alterations included (%): IDH1, 2 (13, 3), FGFR2 fusions (9), ERBB2 amplification (5), BRAF V600E (2), RNF43 (2), POLE (2), NTRK1 fusion (<1). There were N=230 (17%) patients with putatively more immunogenic BTC (iBTC) identified by HRD [*BRCA1/2* (1, 2.4), *PALB2* (1), *BAP1* (9)], TMB>10, and MSI-H. Frequency, location (intrahepatic, ICC; extrahepatic, ECC; gallbladder, GBC), TMB, and genomic instability score (GIS) are summarized (Table). Among iBTC subgroup, N=32 pts received ICB. Their median follow up was 29.1 months. Median lines of prior therapy was 3. Median PFS was 5.6 M (95%CI: 1.2-10.1) and OS was 33.4 M (23.1-43.6). **Conclusion**: A subgroup of BTC pts (iBTC) benefit from ICB. Apart from MSI-H and TMB>10, other genomically-defined subgroups such as HRD may benefit from ICB. Prospective studies are needed to evaluate a better biomarker enrichment strategy beyond PD-L1 and TMB, that can represent other immunogenic aspects of tumor neoantigen and microenvironment. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

	iBTC: 207 (17%)			983 (83%)
Pts N=1,190 (100%)	MSI-H	MSS/TMB>10	HRD without TMB>10	Others
16 (1.3)	37 (3)	154 (13)	983 (83)	
ICC:ECC:GBC N (%)	7:5:4 (44:31:25)	11:10:16 (30:27:43)	118:18:18 (66:12:12)	557:182:221 (58:19:23)
Median TMB (min-max)	34 (7–75)	14.5 (10.5–28.3)	3.3 (0.8–9.5)	2.6 (1–8.3)
Mean GIS (min-max)	9.5 (7–17)	17.4 (6–27)	13.5 (3–51)	12.6 (1–46)
No ICB mOS M (95%CI)	10.2 (9.6–NR)	17.3 (6.5–NR)	18 (13–24.1)	13.7 (11.7–15.8)
ICB N=32	N=9	N=8	N=4	N=11
ICB mOS M (95%CI)	69 (11–NR)	42 (35–50)	28 (3–52)	20 (6–35)
ICB mPFS M (95%CI)	20 (11–NR)	14 (6–21)	2 (0–5)	3 (1–4)

4085 **Poster Session**

***FGFR2* fusion detection in plasma: A new era in the clinical monitoring of iCCA.** *First Author: Alberto Gonzalez-Medina, Cancer Genomics Group, Vall dHebron Institute of Oncology (VHIO), Barcelona, Spain*

Background: Actionable genetic alterations can be identified in over 50% of intrahepatic cholangiocarcinoma (iCCA). Since EMA approved Pemigatinib, a selective Fibroblast growth factor receptor 1-3 (FGFR1-3) inhibitor for the treatment of CCA with *FGFR2* fusions or rearrangements, the screening of patients who may benefit from such targeted therapies is especially relevant. In addition, novel FGFR inhibitors that are effective for treatment of resistant mutant clones are under development. In patients with no available tissue for genomic profiling or at different timepoints after targeted therapy, NGS testing of circulating cell-free DNA (ccfDNA) would be the most convenient option. Hence, two important issues must be addressed: i) technical set-up and validation of detection of *FGFR2* rearrangements in plasma, and ii) patient shedding in iCCA, in order to consider liquid biopsy for routine clinical care. **Methods:** We conducted a retrospective study in a cohort of 18 iCCA patients with known *FGFR2* fusion or rearrangement events previously identified in tumor FFPE by NGS (FoundationOne CDx test). A custom-designed capture-based NGS panel for use in plasma or tissue (VHIO-iCCA test) was developed to detect *FGFR2* rearrangements and other common altered genes in iCCA. After validating our VHIO-iCCA panel with fusion positive FFPE samples, a concordance study was conducted to evaluate the detection of *FGFR2* fusion and rearrangements in matched-to-tissue timepoint plasmas. Finally, additional serial plasma samples taken during *FGFR* inhibitor treatment were also analyzed. **Results:** From the 18 rearrangement events previously detected with FoundationOne CDx, we were able to identify all 18 in FFPE samples and 15 in the paired plasma using our VHIO-iCCA panel, representing a 100% and 83% concordance, respectively. In the 3 discordant cases, no additional alterations were detected in plasma, indicating a lack of circulating tumor DNA (ctDNA) shedding. Serial sampling of these patients indicated persistent non-shedding. The analysis of fusion allele fraction (FAF) in serial plasma samples revealed that detection of fusion *FGFR2* changed during treatment and correlated with best response. In general, patients with a stable FAF showed a SD, while patients which reduced FAF presented a PR. **Conclusions:** This extremely valuable set of cases has allowed us to validate our VHIO-iCCA panel to be used in tissue and plasma, and to determine that the sensitivity in plasma is >80%, making this a feasible option to avoid tissue biopsies, whenever patients cannot undergo the procedure and even to aid in cancer monitoring. Patient shedding is high in iCCA, yet a fraction of patients may not find a useful resource in liquid biopsy. For those who shed ctDNA, monitoring through the FAF may guide clinical management of iCCA. Research Sponsor: Incyte, Other Government Agency.

4086 **Poster Session**

Clinical impact of MAPK pathway alterations in advanced biliary tract cancer (BTC): SCRUM-Japan GOZILA and COLOMATE international collaboration. *First Author: Hideaki Takahashi, Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Japan*

Background: Abnormalities in the MAPK pathway are potential therapeutic targets in various cancers. However, the clinical impact of alterations in the MAPK pathway in BTC have not been elucidated, especially outside of canonical mutations in KRAS and BRAF. We investigated the clinical outcomes of advanced BTC with MAPK pathway alterations treated with chemotherapy in Japan and the United States. **Methods:** Patients with advanced BTC who received gemcitabine plus cisplatin as first-line therapy were included from the GOZILA study in Japan and Duke Molecular Registry of Tumors in the US. Genetic abnormalities were detected by Guardant360, a cell-free DNA assay, in Japan and by blood or tissue-based next-generation sequencing (NGS) at Duke University. Two hundred and seven patients with BTC from Japan were included in an exploratory cohort to evaluate the association of MAPK alterations with overall survival (OS) according to MAPK alteration status. One hundred and ten patients with BTC from both Japan and the US harboring oncogenic alterations in the MAPK pathway were included in a biomarker selected cohort to assess the association of specific MAPK alterations with OS. Multivariate analysis was performed using a Cox regression model based on a univariate p-value < 0.2. **Results:** MAPK pathway-related oncogenic alterations detected in each cohort are shown in the table below. In the exploratory cohort, median OS was shorter for patients with MAPK alterations vs. no MAPK alteration (15.9 m vs. 24.9 m, log-rank p = 0.001). Based on univariate analysis, the following covariates were selected for multivariate analyses: age, prior resection, and MAPK pathway alteration in the exploratory cohort; country, the timing of NGS, distant metastasis, KRAS amplification, and BRAF class 2 mutation in the biomarker selected cohort. In the exploratory cohort, multivariate analysis identified MAPK pathway alterations as an independent predictor of shorter OS with a HR of 1.92 (95% CI = 1.28-2.87, p = 0.001). In the biomarker selected cohort, multivariate analysis identified BRAF class 2 mutations and KRAS amplification as independent predictors of shorter OS with a HR of 16.2 (95% CI = 3.26-80.8, p = 0.001) and 5.97 (95% CI = 1.74-19.3, p = 0.002) respectively. **Conclusions:** MAPK pathway alterations, especially BRAF class 2 mutation and KRAS amplification, had a significant negative impact on clinical outcomes in BTC receiving first-line chemotherapy. These results are newly confirmed in BTC. Research Sponsor: SCRUM-Japan Funds.

MAPK pathway alteration	Exploratory cohort (n = 207)	Biomarker selected cohort (n = 110)
SNVs		
KRAS	40 pts (19.3%)	62 pts
NRAS / HRAS	6 / 2 pts (2.9 / 1.0%)	11 / 2 pts
BRAF class 1 / 2 / 3	1 / 1 / 8 pts (0.5 / 0.5 / 3.9%)	3 / 3 / 9 pts
RAF1 / MAP2K1	3 / 1 pts (1.4 / 0.5%)	4 / 1 pts
NF1 / PTPN11 / CBL	6 / 2 / 0 pts (2.8 / 1.0 / 0%)	12 / 3/ 1 pts
Amplifications		
KRAS	2 pts (1.0%)	4 pts
BRAF	5 pts (2.4%)	8 pts

LBA4087 **Poster Session**

Understanding the mechanism behind preoperative exercise therapy in patients with gastrointestinal cancers: A prospective, randomized clinical trial. *First Author: Ahmad Hamad, The Ohio State University Wexner Medical Center, Columbus, OH*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

4088 **Poster Session**

Health-related quality of life (HRQoL) impact of pembrolizumab (pembro) plus best supportive care (BSC) versus placebo (PBO) plus BSC as second-line (2L) therapy in patients (pts) in Asia with advanced hepatocellular carcinoma (HCC): Phase 3 KEYNOTE-394 study. *First Author: Shukui Qin, Jinling Hospital, Nanjing University of Chinese Medicine, Nanjing, China*

Background: In the randomized, double-blind, phase 3 KEYNOTE-394 trial (NCT03062358), pembro + BSC vs PBO + BSC as 2L therapy significantly reduced the risk of death by 21% (HR 0.79, 95% CI 0.63-0.99, *P*= 0.0180), prolonged PFS (HR 0.74, 95% CI 0.60-0.92, *P*= 0.0032), and improved ORR (estimated difference 11.4%, 95% CI 6.7-16.0, *P*= 0.00004) with a manageable safety profile in pts in Asia with advanced HCC and progression on or intolerance to sorafenib or oxaliplatin-based chemotherapy. Here we present the results of prespecified exploratory HRQoL analyses. **Methods:** EORTC QLQ-C30 and EuroQol-5D3L (EQ5D-3L) questionnaires were administered at baseline (BL); wks 3, 6, 9, 12, 18; every 9 wks thereafter up to 1 yr or end of treatment; at treatment discontinuation, and at the 30-day safety follow-up visit. Pts who received ≥1 dose of study treatment and completed ≥1 HRQoL assessment were included in the analyses. Least squares mean (LSM) score changes from BL to wk 12 were compared using a constrained longitudinal data analysis model, including treatment by study visit interaction and stratification factors as covariates. Kaplan-Meier method was used to estimate time to deterioration (TTD) (time to 1st onset of ≥10-point decline from BL/confirmed by a 2nd adjacent ≥10-point decline from BL) for EORTC QLQ-C30 global health status (GHS)/QoL. Stratified Cox proportional hazards model was used to assess the magnitude of the treatment difference (HR) between treatment arms in TTD with nominal, one-sided *P* value calculated. **Results:** The HRQoL population included 450 pts (298 pembro; 152 PBO). HRQoL compliance rate at wk 12 was 95.7% for pembro for both questionnaires and 94.4% for EORTC QLQ-C30 and 95.3% for EQ5D-3L for PBO. There was a statistically significant difference in LSM for change from BL to wk 12, between the two arms for the QLQ-C30 GHS/QoL score and EQ-5D VAS score, with more decline observed in the PBO arm. Difference in LSM for QLQ-C30 GHS/QoL score between pembro (-3.97; 95% CI, -6.38, -1.56) and PBO (-8.40; 95% CI, -11.71, -5.10) arms was 4.43 (95% CI, 0.47, 8.40; *P*= 0.0142). Difference in LSM for EQ-5D VAS score between pembro (-2.74; 95% CI, -4.51, -0.96) and PBO (-6.94; 95% CI, -9.40, -4.48) arms was 4.20 (95% CI, 1.21, 7.19; *P*= 0.0030). GHS/QOL mean scores generally remained stable over time in pembro arm. TTD in EORTC QLQ-C30 GHS/QoL score was similar between arms (HR, 0.85; 95% CI, 0.58, 1.25; *P*= 0.1993). **Conclusions:** Over 12 wks, pts treated with PBO + BSC showed more decline in HRQoL than those receiving pembro + BSC. Combined with the efficacy and safety results from KEYNOTE-394, as well as other global 2L trials with pembro, including KEYNOTE-240 and KEYNOTE-224, our data support the benefit of pembro as 2L therapy for pts with advanced HCC. Clinical trial information: NCT03062358. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

4089 **Poster Session**

Antibiotic therapy and association with oncological outcomes from targeted and immune-based therapy in hepatocellular carcinoma (HCC). *First Author: David James Pinato, Department of Surgery and Cancer, Imperial College, London, United Kingdom*

Background: Immune checkpoint inhibitors (ICI) alone or in combination with tyrosine kinase (TKI) or VEGF pathway inhibitors (VEGFi) are therapeutic options in unresectable HCC (uHCC). Whether exposure to antibiotics (ATB), a consolidated adverse prognostic factor in ICI recipients, affects outcome in HCC remains unclear. **Methods:** FDA analysed patient-level data of 4098 patients receiving ICI (n = 842) either as monotherapy (n = 258) or combinations (n = 584), TKI (N = 1968), VEGFi (n = 480) or placebo (n = 808) as part of 9 international clinical trials submitted to the US Food and Drug Administration in support of marketing applications. Associations for ATB exposure within 30 days before or after initiation of anti-cancer treatment (ATB) with overall (OS) and progression-free survival (PFS) were examined across therapeutic modality. Estimates were weighted by propensity score (PSW) using clinically relevant covariates. **Results:** Out of 4098 patients with uHCC mostly secondary to Hepatitis B (39%) or C (21%) infection, the majority were males (83%) with a median age of 64 (range 18-88), ECOG performance status of 0 (60%) and Child-Pugh A class (98%). Most patients had metastases (68%) but did not have macrovascular invasion (71%). Overall, 620 patients (15%) were ATB+, with comparable rates across placebo (12%), TKI (16%), VEGFi (15%), and ICI (16%). In the overall population, ATB was associated with shorter PFS (2.8 vs 3.9 months [m], HR 1.29, 95%CI 1.22-1.36) and OS (6.4 vs. 8.8 m; HR 1.36, 95%CI 1.29-1.43). In PSW analyses, ATB was associated with shorter PFS in patients treated with ICI (HR 1.52, 95%CI 1.34-1.73), TKI (HR 1.29, 95%CI 1.19-1.39) and placebo (HR 1.23, 95%CI 1.11-1.37). Similar results were observed in PSW analyses of OS in patients treated with ICI (HR 1.22, 95%CI 1.08-1.38), TKI HR 1.40, 95%CI 1.30-1.52), and placebo (HR 1.40, 95%CI 1.25-1.57). Consistent outcomes were observed for ATB+ patients within ICI treatment subgroups, including patients treated with anti-PD-1 monotherapy (PFS HR 1.49, 95%CI 1.22-1.80; OS HR 1.31 1.02-1.68) and ICI combinations (PFS HR 1.50, 95%CI 1.26-1.77; OS HR 1.14 0.99-1.32). **Conclusions:** Unlike other oncological indications where the detrimental effect of ATB may be more prominent in ICI recipients, ATB is associated with inferior outcomes across a broad range of anti-cancer therapies for HCC and placebo. Whether ATB is causally linked to worse outcomes through disruption of the gut liver axis remains to be demonstrated in translational studies. Research Sponsor: None.

4090 **Poster Session**

Health care resource utilization (HCRU) and costs in patients with biliary tract cancer (BTC) treated with systemic therapy in the United States (US). *First Author: Liya Wang, Merck & Co., Inc., Kenilworth, NJ*

Background: BTC is associated with poor prognosis and limited treatment choices. There is limited evidence on HCRU and costs among BTC patients receiving systemic treatments (ST). This study examined HCRU and total direct cost of care among BTC patients treated with ST to understand the disease burden in management of BTC. **Methods:** A retrospective cohort study of BTC patients who received first line (1L) ST was conducted, using US private payer Cancer Care Quality Program data and administrative claims from the HealthCore Integrated Research Database between 07/01/2014 - 03/31/2021. Patients with ampullary cancer, brain/ CNS metastases, other primary cancer before BTC diagnosis were excluded. Per patient per month (PPPM) costs in 2020 USD were calculated during 1L, 2L, and 3L treatments associated with HCRU from inpatient, emergency room, and outpatient visits as well as outpatient pharmacy dispensing. **Results:** Among 298 BTC patients (biliary tract, n=203; gallbladder, n=65; bile duct, n=30; stage IV, n=231; stage III, n=28; stage I/II, n=39) who received ST, mean (SD) age was 61.7 (9) years at 1L treatment initiation, and the majority were female (58%). Following 1L treatment, 44% received 2L treatment, and 16% received 3L treatment. Median follow-up was 7.6 months. Among 201 (67%) patients who had hospitalization in the follow-up period, mean (SD) number of hospitalizations was 2.5 (2), and the average length of stay was 7.0 (5) days. Total PPPM all-cause costs were the lowest during 1L treatment (mean [SD]: $19,589 [$22,603]), and increased as the treatment advanced (2L: $22,617[$19,302]; 3L: $33,534[$40,588]). Similar trend was observed in BTC-related total costs with $16,237 ($22,452) in 1L, $19,083 ($18,670) in 2L and $27,609 ($39,949) in 3L. The table summarizes BTC-related HCRU and PPPM cost during each line of therapy. **Conclusions:** Study findings suggest significant resource use burden and high total direct medical costs for BTC patients receiving ST. Hospitalizations and outpatient visits represent important HCRU and cost for BTC. These data indicate a need for future newer innovative therapies in the management of BTC. Research Sponsor: Merck & Co., Inc.

BTC-related HCRU and PPPM costs.

Description	During 1L Treatment N=298	During 2L Treatment N=132	During 3L Treatment N=49
Duration of treatment, Mean (SD), months	3.8 (3.2)	4.1 (3.9)	4.6 (5.7)
Number of INP visits, mean (SD)	1.5 (0.9)	1.7 (1)	1.8 (1.2)
Number of ER visits, mean (SD)	1.1 (0.4)	1.3 (0.6)	1.4 (0.5)
Number of outpatient visits, mean (SD)	34.4 (31.7)	36.4 (37.1)	41.3 (34.7)
INP costs, mean (SD)	$7,630 ($20,889)	$6,678 ($13,738)	$13,601 ($39,094)
ER costs, mean (SD)	$247 ($921)	$158 ($534)	$240 ($949)
Outpatient visit costs, mean (SD)	$8,255 ($7,612)	$10,724 ($12,361)	$12,329 ($12,521)
Pharmacy costs, mean (SD)	$104 ($440)	$1,523 ($5,348)	$1,439 ($4,383)

Abbreviations: INP= Inpatient hospitalization; ER = Emergency room.

4091 **Poster Session**

Sequential trans-arterial chemoembolization and stereotactic body radiotherapy followed by immunotherapy (START-FIT) for locally advanced hepatocellular carcinoma: A single-arm, phase II trial. *First Author: Chi Leung Chiang, Department of Clinical Oncology, The University of Hong Kong, Hong Kong, Hong Kong*

Background: Previous studies proposed therapeutic synergy between loco-regional therapies and checkpoint inhibitors in hepatocellular carcinoma (HCC). We aimed to study the safety and efficacy of sequential transarterial chemoembolization (TACE) and stereotactic body radiotherapy (SBRT) followed by Avelumab in patients with locally advanced HCC. **Methods:** Patients with locally advanced HCC not suitable for curative resections were eligible. All patients had HCC ≥ 5cm, tumor nodules ≤3, and child-Pugh A5-B7 liver function. Tumors with distant metastasis, main portal vein (VP4) invasion, or inferior vena cava (VV3) invasion were excluded. Patients underwent single episode of TACE followed by 5-fraction SBRT (28 days afterwards), followed by Avelumab (10mg per kg) 14 days afterwards and every 2 weeks thereafter. The primary endpoint was percentage of patients amendable to curative surgery, defined as R0 resection with sufficient remnant liver volume and function. Secondary endpoints were objective response rate (ORR) per modified Response Evaluation Criteria in Solid Tumors (mRECIST) version 1.1, survivals, and treatment-related adverse event (TRAE). The sample size assumed that around 20% patients amendable to surgery after experimental treatment compared to 5% of historical institutional results after TACE. Modified Simon two-stage optimal design was used (power, 80%; a = 0.05; P0 = 0.05; P1 = 0.20; n1 = 10; n = 29 with an additional four patients to allow for drop-out or other reasons). **Results:** Out of 67 patients screened, 33 patients were enrolled. The median sum of diameter of lesion(s) was 15.1cm (range: 5.3-31.1cm), and 21 (63.6%) had marcrovascular invasion (n=13, hepatic vein, n=3 branched portal vein, n=5 both). After a median follow-up of 17.2 months (range: 3.5-31.6 months), 3 (9.1%) patients had tumor downstaged with curative surgery done. The objective response rate was 62.5% (95% CI, 45.3-77.1%), of whom 15 had complete response (CR) (43.8%) and 6 had partial response (18.7%). The median overall survival (OS) and progression-free survival was 30.3 months (95% CI: 22.7-37.8 months) and 20.7 months (95% CI: 14.6-26.8 months) respectively. All three patients with surgery done were alive at 2 years (100%). For 15 patients had CR, the 2-year OS rate was 92.9% without surgery. Ten patients (30.3%) experienced ≥ grade 3 TRAEs, commonly transient increase in alanine / aspartate aminotransferase (n=4, 12.1%) and bilirubin (n=2, 6%) level after TACE. Five patients (15.2 %) developed ≥ grade 3 immune-related adverse events. **Conclusions:** Although merely 9% of patients were downstaged to receive curative surgery, combined locoregional treatment and immunotherapy is safe and resulted in an unexpectedly high CR rate of 43% and median OS of 30 months in patients with locally advanced unresectable HCC. Clinical trial information: NCT 03817736. Research Sponsor: Merck Pharmaceutical (HK) Ltd., Hong Kong.

4092 **Poster Session**

Bortezomib in PTEN-deficient patients with advanced intrahepatic cholangiocarcinoma: An open-label, prospective, phase II trial. *First Author: Zhen-gang Yuan, Department of Oncology, Eastern Hepatobiliary Surgery Hospital, Shanghai, China*

Background: Intrahepatic cholangiocarcinoma (ICC) is the second-most common primary liver malignancy after hepatocellular carcinoma. Prognosis of cholangiocarcinoma is poor and therapy options are limited. Bortezomib in unselected patients with BTC has been failed in previous clinical trial. Our previous research dedicates that PTEN-deficient facilitates sensitivity to proteasome inhibition in intrahepatic cholangiocarcinoma. In this open-label, prospective, phase II trial, we explore the efficacy and safety of bortezomib in PTEN-deficient advanced intrahepatic cholangiocarcinoma patients who have progressed during Gemcitabine based treatment. **Methods:** Between August 1, 2017, and July 31, 2021, A total of 130 patients were under went PTEN immunohistochemical staining for screening and 15 patients enrolled. Patients with PTEN-deficient advanced intrahepatic cholangiocarcinoma who had progressed after GC/Gemox therapies received bortezomib 1.3 mg/m2 days 1, 4, 8, and 11 of a 21-day cycle. The primary endpoint was objective response rate according to Response Evaluation Criteria in Solid Tumors v1.1. **Results:** The overall response rate was 23.1% (3/13) and disease control rate was 53.8% (7/13). The Median time of follow up was 4.2 months (95% CI: 0.7~17.2 months). median progression-free survival was 2.3 months and the median overall survival was 9.6 months. Adverse events of any grade were reported in 14 patients. Thrombopenia was the most common toxicity. **Conclusions:** Bortezomib provided an encouraging objective response and disease control as second-line therapy for PTEN-deficient Patients with advanced intrahepatic cholangiocarcinoma, and improving the overall survival to 9.6 months. Bortezomib would be a promising treatment option in PTEN-deficient selected patients. Research Sponsor: None.

4093 **Poster Session**

Preliminary results from a phase Ib study of neoadjuvant ipilimumab plus nivolumab prior to liver resection for hepatocellular carcinoma: The PRIME-HCC trial. *First Author: Antonio D'Alessio, Humanitas University, Pieve Emanuele, Milan, Italy*

Background: Early-stage hepatocellular carcinoma (HCC) can be treated with liver resection (LR), but up to 70% of patients experience relapse within two years after surgery. Despite their established use in advanced disease, immune checkpoint inhibitors (ICPI) are still under investigation in the peri-operatory setting. **Methods:** PRIME-HCC is a phase Ib study investigating safety and bioactivity of the nivolumab (3 mg/kg, day 1 and day 22) plus ipilimumab (1mg/kg, day 1 only) combination (Nivo+Ipi) prior to LR in early-stage HCC. The primary safety analysis assessed treatment-related adverse events (trAE) and delays to surgery. Secondary endpoint included objective response rate (ORR) by RECIST v1.1 and pathologic response rate on resection specimens. **Results:** At data censoring on the 27th of January 2022, 17 patients were enrolled, of whom 82% (n = 14) were male, with a median age of 64 years (range 47-76). Performance status was 0 in 88% of patients (n = 15) according to the Eastern Cooperative Oncology Group scale. Liver cirrhosis was found in 65% (n = 11) of the patients, mostly secondary to viral hepatitis (41%, n = 7). All patients were Child-Pugh A, with 53% (n = 9) classified as albumin-bilirubin (ALBI) grade 2, and the rest grade 1. Median tumour diameter was 3.4 cm (interquartile range [IQR] 2.4-4.0), and the median number of liver nodules was 1 (range 1-3). Any-grade trAEs were reported by 73% of the patients receiving at least one dose of treatment (n = 11, tot n = 15). Four patients (27%) reported grade 2 trAEs including hypothyroidism (n = 2), diarrhoea (n = 1), and fatigue (n = 1), and one (7%) grade 3 ALT/AST elevation. After a median follow-up of 6.3 months (IQR 1.9-23.0), no deaths had occurred. One patient had experienced relapse 20.8 months after treatment commencement, and he achieved partial response to subsequent treatment with atezolizumab plus bevacizumab. Median time to LR from screening was 2.5 months (IQR 2.3-3.2). Only one patient had a surgery delay due to liver function worsening (ICPI-unrelated) and experienced disease progression 12.4 months post-screening. One patient was found to have cholangiocarcinoma (CCA) on LR specimen and was excluded from efficacy analyses. Of the 13 patients with an available radiological assessment, ORR was 23%, with two partial responses and one complete response. Disease control rate was 92%, with one patient with mixed HCC/CCA histology showing primary progression. Of the nine pathologically evaluable patients, seven (78%) achieved a pathological response, including two (22%) complete responses. **Conclusions:** Nivo+Ipi can be safely administered in the neoadjuvant setting for HCC and does not delay LR. The combination demonstrates promising evidence of anti-tumour efficacy in terms of radiological and pathological response. Clinical trial information: NCT03682276. Research Sponsor: Bristol Myers Squibb.

4094 **Poster Session**

Phase 1b results of a multicenter, randomized phase 1b/2 study of gemcitabine and cisplatin +/- CPI-613 as first-line therapy for patients with advanced biliary tract cancer (BilT-04). *First Author: Vaibhav Sahai, University of Michigan, Ann Arbor, MI*

Background: Patients (pts) with advanced biliary tract cancers (BTC) have a poor prognosis despite systemic chemotherapy. Gemcitabine (G) and cisplatin (C) is a standard first-line systemic therapy with a reported overall response rate (ORR) of 26% and median overall survival (OS) of 11.7 months (mo). CPI-613/Devimistat (D) is a stable intermediate of a lipoate analog that inhibits pyruvate dehydrogenase and a-ketoglutarate dehydrogenase enzymes of the tricarboxylic (TCA) cycle, preferentially within the mitochondria of cancer cells augmenting chemotherapeutic cytotoxicity. **Methods:** An investigator-initiated, multi-institutional phase 1b/2 trial is underway across 10 sites in the US investigating the combination of G 1000 mg/m^2, C 25 mg/m^2 and D (dose levels: (-1) 500, (1) 1000, (2) 1500 and (3) 2000 mg/m^2) (GCD) on days 1 and 8 every 21 days in pts with previously untreated advanced BTC. The primary objective of the phase 1b portion (n = 20 pts; TiTE-CRM methodology) was to determine the recommended phase 2 dose (RP2D). The primary objective of the ongoing phase 2 portion (n = 48-58 pts; 2:1 randomization with Bayesian control arm) is to determine the best ORR with an alternative hypothesis of 43% (null of 25%); with 80% power and one-sided alpha of 0.05. Secondary objectives include evaluation of progression-free survival (PFS), OS, and safety. Exploratory objectives include targeted exome/ transcriptomic analysis using tissue, and metabolomic analysis using plasma (pre-, on- and post-treatment). **Results**: 20 pts were enrolled on phase 1b; median age 65 years (range 43-75), ECOG PS 0/1 (9/11), male/female (11/9), Caucasian (85%), intrahepatic/hilar/distal cholangiocarcinoma and gallbladder (9/5/3/3), and metastatic/locally advanced stage (15/5). CPI-613 dose level assignments were 1 pt each for (-1) and (1), 2 pts on (2), and 16 pts on (3). Median follow-up was 9.4 mos and median number of cycles was 9. Only 1 pt had dose-limiting toxicity (grade 2 creatinine elevation). RP2D for CPI-613 was 2000 mg/m^2. In phase 1b, ORR was 40% (7 PR, 1 CR). Median PFS not estimable (NE) but probability of PFS at 9 months was 68.1% [95% CI, 38.1%-85.8%]. Median OS is 16.3 months [95% CI, 9.1-NE]. One locally advanced pt was resected with pathologic CR. **Conclusions**: The combination of GCD was well tolerated and demonstrates encouraging efficacy with ORR, PFS and OS in phase 1b. The randomized phase 2 portion of the trial is open and accruing patients. Clinical trial information: NCT04203160. Research Sponsor: Rafael Pharmaceuticals, University of Michigan Rogel Cancer Center.

4095 **Poster Session**

A multicenter, non-randomized, controlled trial to evaluate the efficacy of surgery versus radiofrequency ablation for small hepatocellular carcinoma (SURF-Cohort Trial): Analysis of overall survival. *First Author: Tatsuya Yamashita, Kanazawa University Hospital, Kanazawa, Japan*

Background: We conducted a multicenter prospective study (SURF trial) to compare the efficacy of surgery vs. radiofrequency ablation (RFA) for small hepatocellular carcinoma (HCC). SURF trial consisted of a randomized controlled trial (SURF-RCT) and a non-randomized prospective observational study (SURF-Cohort), including patients who did not consent to randomization. The initial report of the SURF-Cohort trial showed that recurrence-free survival (RFS) did not differ significantly between patients undergoing surgery and RFA. The focus of the present report was to assess the efficacy for overall survival (OS). **Methods:** The SURF-Cohort trial was a prospective multicenter study conducted in 49 institutions in Japan. Patients (aged between 29 and 79 years) with Child-Pugh scores ≤ 7, largest HCC diameter ≤ 3 cm, and ≤ 3 HCC nodules were considered eligible. Before the enrollment, both liver surgeons and hepatologists who perform RFA confirm that all the patients can be treated using both surgery and RFA. The co-primary endpoints were RFS and OS. OS was assessed at 5 years after the last accrual as per the protocol. Inverse probability of treatment weighted (IPTW) analysis was used to balance the characteristics of the groups. This trial is registered in UMIN000001796. **Results:** During 2009–2015, 782 patients were enrolled. After excluding ineligible patients, the surgery and RFA groups included 382 and 371 patients, respectively. In the surgery group, median platelet count ($13.7x10^4$ vs. $11.5x10^4$, $P< 0.01$) was significantly greater, and the median largest HCC diameter was significantly greater (2.0 cm vs. 1.8 cm, $P< 0.01$) than in the RFA group. The median (range) follow-up period was 6.8 years in the surgery group and 6.7 years in the RFA group. The IPTW-adjusted OS did not differ significantly between the surgery and RFA groups: the 5-year OS, 79.7% vs. 79.3%; HR 0.98; 95% CI 0.75–1.30; $P= 0.906$. The analysis after long-term follow-up in the current report showed that RFS was not significantly different between the surgery and RFA groups: the 5-year RFS, 44.6% vs. 39.3%; HR 0.86; 95% CI 0.71–1.06; $P= 0.155$. **Conclusions:** SURF-Cohort trial revealed that OS and RFS after the IPTW adjustment were not significantly different between patients undergoing surgery and RFA for early stage HCC (≤ 3 cm and 3 nodules). Clinical trial information: UMIN000001796. Research Sponsor: None.

4096 **Poster Session**

Trastuzumab plus FOLFOX for gemcitabine/cisplatin refractory HER2-positive biliary tract cancer: A multi-institutional phase II trial of the Korean Cancer Study Group (KCSG-HB19-14). *First Author: Choong-kun Lee, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea*

Background: HER2 over-expression/amplification, which accounts for roughly 15% of total biliary tract cancer (BTC) patients, has been identified as a druggable molecular target by recent genomic profilings, Trastuzumab is a humanized monoclonal antibody against HER2 that has been shown to be effective in patients with HER2-positive breast and gastric cancer, but it has not been studied prospectively in HER2-positive BTC. In the phase III ABC-06 trial, the FOLFOX regimen showed survival benefit as a second-line therapy of BTC. We report the result of a multi-institutional phase II trial of Trastuzumab plus modified-FOLFOX as a second- or third-line treatment for HER2-positive BTC (KCSG-HB19-14; NCT04722133). **Methods**: HER2-positive (defined as IHC3+ or IHC2+/ISH+ or ERBB2 gene copy number ≥6.0 by NGS) BTC (intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, gallbladder cancer and ampulla of vater cancer) patients who progressed on gemcitabine/cisplatin containing chemotherapy (1 or 2 previous chemotherapy lines permitted) were enrolled. Pts received trastuzumab 4mg/kg (after 6mg/kg load) D1, oxaliplatin 85mg/m^2 D1, Leucovorin 200mg/m^2 D1, 5-FU 400mg/m^2 bolus D1, and 5-FU 2400mg/m^2 infusion D1-2 every 2 weeks until unacceptable toxicities or disease progression. The primary endpoint was ORR per RECIST v1.1. Secondary endpoints included PFS, DCR, OS, safety, QOL and correlative biomarker exploration. **Results:** Total of 34 pts were treated with median follow up of 9.9 months, and 6 pts remained on treatment (treatment duration range: 1.0 to 14.7 months). The primary endpoint was met, with 29.4% (95%CI 15.1-47.5) ORR (PR n = 10), and 79.4% DCR. Median PFS was 5.1 months (95%CI 3.6-6.7) and median OS was not reached (95%CI 7.1-NR; 12-months OS rate 50.6%, 95%CI 29.3-63.6). Pts with HER2 IHC3+ (n = 23, 67.6%) showed tendency for better PFS compared to pts with HER2 IHC 2+/ISH+ (median 5.5 vs 4.9 months, HR 0.52, 95%CI 0.23-1.16). Pts with HER2 3+ tumor cell proportion ≥30% (n = 10) by an artificial intelligence-powered automated HER2 IHC analyzer (Lunit SCOPE HER2) showed significantly better PFS compared to pts without (median 6.67 vs 4.87 months, HR 0.33 95%CI 0.13-0.88). Targeted-panel sequencings were done with tumor tissues from 32 pts and tissue HER2-amplification by NGS did not confer better survival. Treatment-related AE (≥G3) occurred in 29 pts (85.3%) including 19 pts (55.9%) with neutropenia G3-4 and 4 pts (11.8%) with peripheral neuropathy G3-4. No pt showed cardiac AE nor treatment-related study discontinuation. **Conclusions:** For HER2-positive BTC, 2nd- or 3rd-line trastuzumab plus FOLFOX exhibited a promising efficacy with acceptable toxicity, warranting further investigations. Targeted NGS analyses with ctDNAs from pre-treatment and post-progression liquid biopsies are ongoing. Clinical trial information: NCT04722133. Research Sponsor: Korean Cancer Study Group.

4097 **Poster Session**

NEO-GAP: A phase II single-arm prospective feasibility study of neoadjuvant gemcitabine/cisplatin/nab-paclitaxel for resectable high-risk intrahepatic cholangiocarcinoma. *First Author: Shishir K. Maithel, Winship Cancer Institute, Emory University, Atlanta, GA*

Background: Given a high recurrence rate, surgical resection for localized intrahepatic cholangiocarcinoma (IHCC) is curative in only 30-35% of patients. BILCAP has established a standard of care for adjuvant therapy with monotherapy capecitabine. Gemcitabine, cisplatin and nab-paclitaxel combination chemotherapy (GAP) was associated with a response rate of 45% in biliary cancer and 20% of patients who were previously inoperable underwent margin negative resection. Based on these data, we conducted a neoadjuvant study of GAP for resectable but high-risk IHCC. **Methods:** A multi-institutional prospective single-arm phase II trial was conducted for patients with resectable high-risk disease, as defined by tumor size > 5cm, multiple tumors, presence of radiographic major vascular invasion, and lymph node involvement. Patients were administered 4 cycles (3 months) of preoperative GAP (gemcitabine 800 mg/m2, cisplatin 25 mg/m2 and nab-paclitaxel 100 mg/m2 on days 1 and 8 of a 21-day cycle) prior to an attempt at curative-intent surgical resection. The primary endpoint was completion of all therapy, including both preoperative chemotherapy and resection. Secondary endpoints were toxicity, radiologic response according to Response Evaluation Criteria in Solid Tumor (RECIST) criteria, RFS, and OS. Thirty evaluable patients provided 73% power to reject a null therapy completion rate of 50%, with a target completion rate of 70% using a one-sided exact test with a Type I error of 0.05. **Results:** Thirty-seven patients were screened and 30 evaluable patients were enrolled. The trial was sequentially activated at each of the 4 sites from 09/18-02/21 and the final patient was enrolled in 09/21. Median age was 60.5 years and 40% were female. Twenty-three patients (77%, 90% CI: 60.6-88.5%; p = 0.0026) completed all preoperative chemotherapy and underwent surgical resection. Ten patients (33%) experienced grade 3-4 treatment-related adverse events, the most common being neutropenia and diarrhea; 47% required at least one dose reduction. Partial response rate was 23% and disease control rate was 90% (PD: 10%, PR: 23%, SD: 67%). Of the 23 patients who successfully underwent surgical resection, 2 (9%) had minor postoperative complications. Median size of largest tumor was 5.5cm, median number of tumors was 3, and 39% were lymph node positive. Median length of hospital stay was 4 days. There was zero treatment related mortality. **Conclusions:** This study met its primary endpoint and demonstrated that neoadjuvant gemcitabine/cisplatin/nab-paclitaxel is feasible and safe prior to resection of intrahepatic cholangiocarcinoma and does not adversely impact perioperative outcomes. Continued follow-up for RFS and OS with this treatment strategy is underway and larger validation studies are planned. Clinical trial information: NCT03579771. Research Sponsor: Celgene / BMS.

4098 **Poster Session**

Comparative efficacy of novel combination immunotherapy strategies for unresectable hepatocellular carcinoma (HCC): A network metanalysis of landmark phase III trials. *First Author: Claudia A.M. Fulgenzi, Department of Surgery and Cancer, Imperial College London, Hammersmith Hospital, London, United Kingdom*

Background: After over a decade of stagnation, therapeutic options for unresectable HCC (uHCC) are expanding. In 2020, the results of IMbrave150 established the combination of atezolizumab and bevacizumab (A+B) as the novel standard of care for patients with uHCC. Parallel reporting of novel immunotherapy combinations tested in phase III trials against sorafenib limits therapeutic decision making in clinical practice, given direct comparison between novel first line treatment options does not exist. We conducted a network metanalysis (NMA) to compare A+B with other first line systemic therapies that reached their primary endpoint in phase III trials. **Methods:** After performing a literature review from January 2008 to February 2022, we identified 13709 studies for screening, 70 for revision, and the following 9 phase III trials for the analysis: SHARP, Asia Pacific, REFLECT, CheckMate459, IMbrave150, ORIENT32, HIMALAYA, COSMIC312 and Qin et al.2021, which tested respectively: sorafenib (Sor) vs placebo (SHARP and Asia Pacific), lenvatinib (Len) vs Sor, nivolumab (Nivo) vs Sor, A+B vs Sor, Sintilimab+IBI305 vs Sor, Durvalumab+Tremelimumab (D+T) vs Sor, atezolizumab+cabozantinib (A+C) vs Sor, and Donafenib vs Sor, as first line systemic treatments for uHCC. Hazard ratios(HR) and 95% confidence intervals(95%CI) for overall (OS) and progression free survival (PFS) were extracted for each study. A frequentist network metanalysis, with fixed effect multivariable meta-regression models to estimate the indirect pooled HRs and corresponding 95%CI, was performed. CheckMate459 was the only trial testing PD-1 monotherapy and was included as a reference despite not reaching its primary endpoint. **Results:** In total, 6272 patients were included in the analysis, among them, 5896 received active treatment and 376 had placebo. Amongst analyzed treatment regimens, A+B reduced the risk of death by 60% compared to placebo (HR 0.40; 95%CI 0.28-0.57), and by 42%, 37%, 36% and 32% compared to Sor (HR 0.58; 95%CI 0.43-0.79), Len (HR 0.63; 95%CI 0.45-0.89), A+C (HR 0.64; 95%CI 0.43-0.97) and Nivo (HR 0.68; 95%CI 0.48-0.98), respectively. With regards to OS, D+T was not significantly inferior to A+B (HR 0.74; 95%CI 0.52-1.06) and the efficacy of sintilimab+IBI305 was similar to A+B (HR 1.02; 95%CI 0.67-1.54). Considering PFS, A+B was significantly superior to placebo, Sor, donafenib and Nivo. **Conclusions:** In this network metanalysis comparing 9 landmark phase III trials in uHCC, we confirmed combination of immunotherapy with PD-1 pathway plus VEGF blockade (A+B, sintilimab+IBI305) to be associated to the highest reduction in the risk of death compared to other regimens. Within the methodological limits of this NMA, we provide evidence for the first time of comparable efficacy in terms of OS and PFS for D+T and A+B. Research Sponsor: None.

4099 **Poster Session**

A prospective, multicenter, phase II trial of albumin-paclitaxel plus cisplatin versus gemcitabine plus cisplatin in first-line treatment of advanced biliary tract tumors. *First Author: Xiao Yang, Cancer Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China*

Background: The prognosis of biliary system tumors is poor, Gemcitabine combined with cisplatin has been the standard first-line treatment for advanced biliary system tumors, but its efficacy and adverse effects are unsatisfactory. Albumin-paclitaxel is a novel paclitaxel with a broad-spectrum anti-tumor effect, which has been widely used in the treatment of digestive system malignant tumors. Therefore, we designed this study to investigate the efficacy and safety of the combination of albumin-paclitaxel and cisplatin compared with gemcitabine combined with cisplatin in patients with previously untreated advanced biliary tract tumors. **Methods:** This is a multicenter, randomized, controlled, investigator-initiated Phase II trial designed to enroll patients with unresectable, recurrent, or metastatic cholangiocarcinoma (including intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and gallbladder carcinoma). After enrollment, patients were randomly assigned to the experimental TP group (albumin paclitaxel 125mg/m2 iv, D1, 8 cisplatin 75mg/m2 IV, D1 Q21) or the control GP group (gemcitabine 1000mg/m2 IV, D1, 8 cisplatin 75mg/m2 iv, D1 Q21) and received six cycles of chemotherapy. The primary endpoint was PFS, and the secondary endpoint was OS, ORR, and safety. **Results:** Up to January 2022, 67 patients were enrolled, the 41male and 26 female patients had a median age of 55(range 32-74) years. Of the 67 enrolled patients, 33 were randomly assigned to the TP group and 34 to the GP group. Among the these patients, 47 were diagnosed with intrahepatic cholangiocarcinoma, 7 with extrahepatic cholangiocarcinoma, and 13 with gallbladder cancer. 48 patients had completed at least 2 cycles of chemotherapy and were available for evaluation, mPFS in the TP and the GP groups was 7.7 and 7.5 months, respectively (HR 1.33, CI 0.61 - 2.91,P = 0.469) , mOS in TP and GP groups was 12.1 months and 12.9 months, respectively (HR 1.62, 95% CI 0.67-4.17,P = 0.271). After the first assessment, the ORR was 39.4% and 35.3% in the TP group and the GP group, respectively. In terms of side effects, bone marrow suppression (61% vs 76%) was the most predominant adverse events in both groups, abnormal liver and kidney function (56% vs 67%), gastrointestinal reactions (including nausea, vomiting, diarrhea, constipation, etc.) (46% vs 43%), rash or allergy (44% vs 37%), and other side effects such as fever and influenza symptoms (21% vs 24%) were also observed in the TP group and the GP group. **Conclusions:** The result of this study showed that the regimen of albumin paclitaxel combined with cisplatin was non-inferior to gemcitabine combined with cisplatin in terms of PFS, OS and ORR, and the safety advantages of the combination of albumin paclitaxel and cisplatin make it a potential regiment for first-line treatment of advanced biliary tract tumors. Clinical trial information: ChiECRCT-20180167. Research Sponsor: Beijing Xisike Clinical Oncology Research Foundation.

4100 **Poster Session**

A phase 2, randomized, open-label, multicenter study of sintilimab and anlotinib in combination with gemcitabine plus cisplatin (GemCis) as first-line therapy in patients (pts) with advanced biliary tract cancer (BTC): SAGC. *First Author: Li Jingjing, Department of Hepato-Pancreato-Biliary & Gastric Medical Oncology, Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Institute of Cancer and Basic Medicine (IBMC), Chinese Academy of Sciences, Hanzhou, China*

Background: BTC has a higher incidence in China rather than worldwide, with extremely poor prognosis, and the efficacy of standard first-line therapy (GemCis) is rather limited. TOPAZ-1 study suggested immunotherapy + GemCis as first line in advanced BTC significantly improved OS and PFS vs placebo + GemCis with manageable safety, but the median OS was just 12.8 months. SAGC is the first randomized controlled phase 2 trial to evaluate first-line immunotherapy + antiangiogenic targeted drug + GemCis in advanced BTC. **Methods:** In this randomized controlled study, pts previously untreated for unresectable locally advanced, recurrent, or metastatic BTC were randomized 1:1 to receive sintilimab (200mg every 3 weeks [Q3W]) and anlotinib (10mg po qd, Days 1-14 Q3W) in combination with GemCis (Gem 1000 mg/m2 and Cis 25 mg/m2 on Days 1 and 8 Q3W) for up to 8 cycles, followed by sintilimab (200mg every 3 weeks [Q3W]) and anlotinib (10mg po qd, Days 1-14 Q3W) or GemCis (Gem 1000 mg/m2 and Cis 25 mg/m2 on Days 1 and 8 Q3W) for up to 8 cycles until disease progression or unacceptable toxicity. The primary objective was to assess the 1-year overall survival (OS). Secondary endpoints included OS, progression-free survival (PFS), objective response rate (ORR), and safety. **Results:** At data cutoff for this interim analysis (11 November, 2021), 48 pts were randomized to sintilimab + anlotinib + GemCis (n=26) or GemCis (n=22). The primary objective was not meet: the 1-year OS was 52.5% with sintilimab + anlotinib + GemCis and 36.3% with GemCis (p=0.437), but there was a trend of nominal OS benefit in patients treated with sintilimab + anlotinib + GemCis. PFS was significantly improved with sintilimab + anlotinib + GemCis vs GemCis (6.4m vs 5m; p=0.014). ORR was 37.5% with sintilimab + anlotinib + GemCis and 26.7% with GemCis. Grade 3/4 treatment-related adverse events (TRAEs) occurred in 69.2% of pts receiving sintilimab + anlotinib + GemCis and38.7% of pts receiving GemCis. TRAEs led to discontinuation of any study medication in 7.7% of pts receiving sintilimab + anlotinib + GemCis and 9.1% of pts receiving GemCis. **Conclusions:** In pts with advanced BTC, sintilimab + anlotinib + GemCis could improve OS and PFS vs GemCis with manageable safety, indicating sintilimab + anlotinib + GemCis may be a new first-line standard of care regimen. Research Sponsor: Innoventbio Biologics, Inc, Chia Tai Tianqing Pharmaceutical Group Co., Ltd. Clinical trial information: NCT04300959.

4101 **Poster Session**

Genomic characterization and translational immunotherapy of microsatellite instability-high (MSI-H) in cholangiocarcinoma. *First Author: Xu Yang, Department of Liver Surgery, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: Microsatellite instability-high (MSI-H) status is a unique genomic state with encouraging effects of PD-1-based therapy in patients with advanced cancer. Cholangiocarcinoma is often driven by genetic mutations. However, the genomic characterization and translational medicine of MSI-H are not clear. **Methods:** In this study, 881 Chinese patients with cholangiocarcinoma (582 intrahepatic cholangiocarcinoma and 299 extrahepatic cholangiocarcinoma) were enrolled and their genomes were investigated using panel sequencing or whole-exome sequencing. Clinicopathological and genomic features as well as PD-1 inhibitor-based immunotherapy were analyzed by MSI status in patients with cholangiocarcinoma. **Results:** Overall, 47 (5.3%) cholangiocarcinoma patients were identified as MSI-H patients after enrichment enrollment. Intrahepatic cholangiocarcinoma (ICC) accounted for 74.47% (35/47) of MSI-H patients. Clinicopathological parameters showed younger, ICC-dominated, and more positive PD-L1 expression in MSI-H patients. In the genome of MSI-H cholangiocarcinoma, ACVR2A (75.00%), ARID1A (75.0%), KMT2D (72.2%), TGFBR2 (63.9%), PBRM1 (58.3%), RNF43 (55.6%), TP53 (52.8%)), ARID1B (47.2%) had a higher mutation frequency. Comparing the SNV and INDEL mutation in the genome, the differential genes between MSI-H and MSS were ARID1A, ACVR2A, KMT2D, TGFBR2, PBRM1, RNF43, LRP1B, ARID1B, etc., respectively. In addition, the differential mutation pathways of MSI-H showed that the mutation rate of DDR, SWI/SNF CeIICycle, HRD and other pathways was significantly higher than that of MSS samples. The tumor mutation burden (TMB) in MSI-H patients was significantly higher than that in MSS (P<0.001). In a cohort of 151 CCA patients who received PD-1 inhibitor-based immunotherapy, 19 patients with MSI-H cholangiocarcinoma were found to have a favorable prognosis (1-year survival rate 68.4%). Compared with 132 MSS cholangiocarcinoma patients, Patients with MSI-H cholangiocarcinoma had significantly prolonged OS (Not reach vs. 13.4m, P<0.001, HR=0.17, P <0.001) and high clinical benefit (CBR) (OR=8.16, P <0.001). In this immunotherapy cohort, ≥2 DDR pathway genes and ≥2 SWI/SNF pathway genes mutations, positive PD-L1 expression and TMB-H were also associated with better OS and CBR (both P<0.05). **Conclusions:** MSI-H cholangiocarcinoma has distinct genomic features, and the effect of PD-1 inhibitors immunotherapy is excellent to these patients. Clinical trial information: NCT03892577. Research Sponsor: CAMS Innovation Fund for Medical Sciences (CIFMS) (2021-I2M-1-061).

4102 **Poster Session**

Genomic profile of intrahepatic cholangiocarcinoma with *MTAP* loss. *First Author: Tin-Yun Tang, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Recent data suggests a role for immune-checkpoint inhibition in the management of intrahepatic cholangiocarcinoma (iCCA). Chromosomal 9p21 loss with *CDKN2A/MTAP* co-deletion commonly occurs in iCCA and may correlate with poor response to immunotherapy. **Methods:** 2,508 cases of intrahepatic cholangiocarcinoma underwent comprehensive genomic profiling with the FoundationOne CDx assay. PD-L1 expression was measured with IHC using the Dako 22C3 antibody and measured with the tumor proportion score (TPS) method. Prevalence of different selected genomic alterations in tumors with *MTAP* loss was compared against *MTAP* intact tumors using Fischer's exact test. **Results:** In 2,508 cases analyzed, 15.5% of tumors were found to have *MTAP* loss. Of these, 98.7% had concomitant *CDKN2A* and 9p21 loss. No significant difference in immune biomarkers in *MTAP* loss versus wildtype (WT) was seen. PD-L1 low positive at 13.2% vs 19.2%, PD-L1 high positive at 2.9% vs 6.5%, median tumor mutational burden at 2.5 vs 2.5 and MSI high at 0.0% vs 1.6% in *MTAP* loss vs WT, respectively. There were no significant differences between *MTAP* loss and WT in potentially actionable mutations including *FGFR1/2* mutations (12.4% vs 10.7%), *PIK3CA* (6.40% vs 6.60%), *ERBB2* (4.10% vs 5.30%) and *KRAS* G12C (1.20% vs 1.10%) in *MTAP* loss vs WT, respectively. The table depicts significant genomic differences between these subgroups. **Conclusions:** This represents the largest iCCA cohort with *MTAP* loss to our knowledge. Given the historical data regarding 9p21 loss and poor response to immunotherapy, efforts targeting *MTAP* loss through synthetic lethality or other novel combinational therapeutics are justified. Research Sponsor: Foundation Medicine.

Genomic differences between *MTAP* WT and loss in iCCA.

	MTAP Wildtype	*MTAP* Loss	P Value (Fischer's exact)
Number of Cases	2119 (84.50%)	389 (15.50%)	
CDKN2A	19%	99%	<.0001
TP53	36%	31%	0.07
SMAD4	6%	11%	<.0001
BRAF	5%	9%	0.003
IDH1	15%	7%	<.0001
MYC	0%	5%	<.0001
BRCA2	2%	5%	0.001
TERT	7%	4%	0.03

4103 **Poster Session**

Discovery and clinical validation of cost-effective noninvasive early detection of hepatocellular carcinoma (HCC) through circulating tumor DNA (ctDNA) methylation signature. *First Author: Xin-Rong Yang, Liver Cancer Institute and Zhongshan Hospital, Fudan University, Shanghai, China*

Background: Hepatocellular carcinoma (HCC) is one of the most common and lethal cancers worldwide, especially in Asian counties. Patients can be treated more effectively if detected earlier, however the current screening strategies with alpha-fetoprotein (AFP) or ultrasound it is largely suboptimal. We aimed to develop non-invasive and cost-effective assay to improve HCC early detection. **Methods:** HCC-specific DNA methylation markers were screened from tissue and plasma samples through a modified reduce representation bisulfite sequencing assaay,and optimized by a targeted methylation sequencing assay. The most informative markers were then integrated in a multi-locus qPCR assay, HepaQ. **Results:** Profiling DNA methylation pattern on 61 tissue samples (31 HCC tumor and 30 normal tissues) and 663 plasma samples (276 HCC and 393 control plasma samples) achieved an AUC of 0.99, which corresponds to 91% sensitivity at 94% specificity. The best-performance markers were further screened and analytically verified in additional tissues and plasmas after several rounds of marker selection. A multi-locus qPCR assay, designated as HepaQ, was then developed to incorporate the most effective markers. A cohort of 559 plasma samples including 293 HCC (84% of them at stage 0/A), 60 liver cirrhosis (LC), 36 chronic hepatitis B (CHB) and 170 healthy controls (CTRL), were used to train a classifier for HCC early detection. HepaQ classifier enables to detect 85.3% of HCC under a specificity of 88.3%, 91.7% and 92.4% in LC, CHB and CTRL, respectively. Finally, HepaQ classifier was validated in 374 plasma samples independently collected from multiple clinical centers to confirm its performance of 87.2% sensitivity in HCC and 86.8%,90.5% and 93.4% specificities in LC, CHB and CTRL respectively. **Conclusions:** We have developed and demonstrated a blood-based ctDNA methylation assay, HepaQ, that can detect early-stage HCC at high sensitivity and specificity. We proposed that HepaQ assay, a cost-effective qPCR assay, has the great potential to benefit the population at-risk for HCC early detection and screening. Research Sponsor: National Key Research and Development Program of China.

4104 **Poster Session**

Efficacy and safety of low-dose apatinib in advanced hepatocellular carcinoma. *First Author: Lingbin Meng, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

Background: Apatinib, a tyrosine kinase inhibitor, has shown promising effects on advanced hepatocellular carcinoma (HCC) recently. However, studies on its efficacy and safety are limited with controversial findings. Therefore, this study aimed to reveal the efficacy and safety of low-dose apatinib for the treatment of advanced HCC in the real world. **Methods:** Between January 2017 and August 2020, 178 patients with advanced HCC treated with apatinib at three different institutions were included for the present study. 174 patients received oral apatinib 250 mg daily and 4 received 500 mg daily until disease progression. 25 and 103 patients were also treated with immunotherapy and transcatheter arterial chemoembolization (TACE) at least once, respectively. Tumor response and adverse reactions were evaluated according to RECIST 1.1 and CTCAE 5.0 respectively. Survival curves were analyzed using the Kaplan-Meier method. Cox proportional hazards model was used to determine the prognostic value of variables in a univariate and multivariate setting. **Results:** During the 24-month follow-up period, 0 (0%), 28 (15.73%), 103 (57.87%) and 47 (26.40%) patients achieved a compete response (CR), partial response (PR), stable disease (SD), and progressive disease (PR), respectively. The overall response rate (ORR) and disease control rate (DCR) were 15.73% and 73.60% respectively. Interestingly, among the 28 patients with PR, 27 received apatinib as the first or second line treatment and 21 received immunotherapy or TACE as a combined treatment, indicating early application of apatinib and combination treatment could provide better efficacy. Kaplan-Meier analysis revealed the median overall survival (OS) and progressive-free survival (PFS) were 16.0 and 7.0 months respectively, which are significantly higher than previously reported survival of sorafenib in advanced HCC. Univariate Cox analysis indicated medication lines, distant metastasis, aplpha fetoprotein (AFP) level, portal vein tumor thrombus (PVTT) and combination therapy significantly affected OS and PFS. Multivariate Cox analysis confirmed third-line treatment (HR = 3.21; 95%CI = 1.54–6.68; p= 0.002), and PVTT (HR = 1.75; 95%CI = 1.13–2.70; p= 0.011) were independently associated with worse PFS. In contrast, apatinib combined with immunotherapy (HR = 0.52; 95%CI = 0.32–0.83; p= 0.008) or TACE (HR = 0.27; 95%CI = 0.18–0.40; p< 0.001) were independently associated with better PFS. Similar findings were also present on OS. The most common treatment-related adverse events were hypertension (29.21%), fatigue (16.85%), hand and foot syndrome (16.29%), vomiting (14.04%), liver dysfunction (6.18%), and proteinuria (6.74%). No severe (grade ≥3) adverse events were observed. **Conclusions:** Low-dose apatinib is able to provide effective and safe treatment for advanced HCC. Early application of apatinib and combination treatment could provide even better efficacy. Research Sponsor: the National Natural Science Foundation of China[-grant number 82170369].

4105 **Poster Session**

High atezolizumab antidrug antibody levels are associated with unfavorable clinical outcomes and diminished T cell responses following atezolizumab and bevacizumab treatment in advanced hepatocellular carcinoma. *First Author: Hong Jae Chon, Department of Medical Oncology, CHA Bundang Medical Center, Seongnam, South Korea*

Background: Systemic administration of humanized monoclonal antibodies can be immunogenic and trigger unwanted anti-drug antibody (ADA) responses. In the IMbrave 150 study, 29.6% of advanced hepatocellular carcinoma (HCC) patients developed atezolizumab ADAs after atezolizumab and bevacizumab (atezo/bev) treatment. ADAs could impair the action of the therapeutic antibody by reduction of serum concentration or neutralization. We determined the clinical and immunological implications of high ADA levels in advanced HCC patients after atezo/bev treatment. **Methods:** Advanced HCC patients (n = 132) treated with first-line atezo/bev were prospectively enrolled (discovery cohort: 50 from an institute; validation cohort: 82 from four institutes). Serum levels of atezolizumab ADA at baseline and three weeks (C2D1) and atezolizumab concentrations at C2D1 were measured by competitive ELISA. The effects of ADA on T cell immunity were examined by multiplex flow cytometry. **Results:** Strong ADA (≥ 1000 ng/ml) responses at C2D1 were observed in 17.4% of advanced HCC patients. ADA elevation after atezo/bev at C2D1 was evident in non-responders but not significant in responders. In the discovery cohort, patients with high ADA at C2D1 showed a decreased response rate (ADA-high: 11% and ADA-low: 34%) and shorter progression-free survival (PFS) and overall survival (OS) with atezo/bev compared to those with low ADA levels (P = 0.004 for PFS; P = 0.009 for OS). In the validation cohort, patients with high ADA at C2D1 showed reduced response rate than those with low ADA (ADA-high: 7% and ADA-low: 29%). PFS and OS were worse in ADA-high group than in ADA-low group (P = 0.001 for PFS; P < 0.001 for OS). In multivariate Cox regression analysis, the clinical significance of high ADA levels was independently associated with shorter PFS and OS after adjustment for age, sex, ECOG performance status, Child-Pugh score, AFP, macroscopic vascular invasion, extrahepatic spread, and neutrophil-to-lymphocyte ratio (PFS: HR 2.27, P = 0.006; OS: HR 3.04, P = 0.006). The atezolizumab serum concentrations were 29.8% lower in patients with high ADA levels than in ADA-negative patients. Atezolizumab concentration at C2D1 was inversely correlated with ADA levels. Moreover, patients with high ADA lacked $CD8^+$ T cell proliferative responses to atezo/bev treatment. Furthermore, patients with high ADA had decreased secretion of effector cytokines such as IFN-γ and TNF-α from $CD8^+$ T cells compared to those with low ADA. **Conclusions:** Highly elevated ADA at C2D1 is associated with unfavorable clinical outcomes in advanced HCC patients treated with atezo/bev. High ADA levels were associated with reduced atezolizumab exposure and could limit the drug's anti-cancer efficacy. Research Sponsor: Korea government.

4106 **Poster Session**

Hepatic artery infusion chemotherapy (HAIC) combined with apatinib and camrelizumab for hepatocellular carcinoma (HCC) in BCLC stage c: A prospective, single-arm, phase II trial (TRIPLET study). *First Author: Yang-Kui Gu, Department of Minimally Invasive Interventional Radiology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, China*

Background: The combination of anti-angiogenesis and immune checkpoint blockade has been proven to improve clinical outcomes of advanced HCC. We assessed the efficacy and safety of HAIC combined with apatinib and camrelizumab for BCLC stage C HCC. **Methods:** Consecutive treatment-naive patients with BCLC stage C HCC were enrolled in this phase II trial (NCT04191889). Eligible patients were administrated with HAIC (oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2 and fluorouracil 2500 mg/m^2; q3w), combined with apatinib (250 mg qd) and camrelizumab (200 mg q3w) for 6 cycles, followed by maintenance therapy with apatinib and camrelizumab until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR). Following an optimal Simon 2-stage design, 26 eligible patients needed to be included in the first stage, of whom at least 11 patients had to achieve objective responses to warrant further investigation in the second stage. **Results:** In the first stage, confirmed ORR was achieved in 16 and 20 patients per RECIST v1.1 and mRECIST, respectively, therefore enrollment of the second stage continued. From 4/13/2020 to 1/31/2022, 31 eligible patients were enrolled and 29 evaluable for efficacy analyses. The 31 patients were characterized with median age 45 years (range 30-67), men 96.77%, Child-Pugh A 100%, portal vein tumor thrombus Vp 1-2/Vp 3-4 25.81%/45.16%, and extrahepatic metastasis 12.90%. As of 1/31/2022, with a median follow-up of 18.07 months (95% CI 14.10 to 22.04), the confirmed ORR was 70.96% (95% CI, 53.41%-83.91%) with 22 partial responses (PR) per RECIST v1.1,while 87.10% (95% CI, 71.15%-94.87%) with 3 (9.68%) complete responses (CR) and 24 (77.42%) PR per mRECIST. The disease control rate (DCR) was 87.10% (95% CI, 71.15%-94.87%) whether per RECIST v1.1 or mRECIST. The median time to response (TTR) was 2.67 months (interquartile range (IQR), 1.43-2.96) per RECIST v1.1 and 2.03 months (IQR, 1.37-2.80) per mRECIST. The median progression-free survival (PFS) time was 9.37 months (95% CI 7.00 to 11.73) per RECIST v1.1 and 9.63 months (95% CI 5.82 to 13.44) per mRECIST, in particular, the liver-specific median PFS time was 10.80 months (95% CI 5.88 to 15.72) per mRECIST. The 6-month, 12-month, and 18-month overall survival rate were 93.1%, 85.8%, and 65.8%, respectively. Grade ≥3 adverse events (AEs) occurred in 74.19% of the patients, of which the most common AEs were decreased neutrophils (52.17%), decreased lymphocytes (43.38%), and increased ALT and AST (30.43% and 43.48% for each). **Conclusions:** The triplet treatment of HAIC, apatinib and camrelizumab showed promising clinical benefits and acceptable safety for BCLC Stage C HCC. Further confirmatory randomized controlled trial is about to get underway. Clinical trial information: NCT04191889. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

4107 **Poster Session**

IMMUNIB trial (AIO-HEP-0218/ass): A single-arm, phase II study evaluating safety and efficacy of immunotherapy nivolumab in combination with lenvatinib in advanced-stage hepatocellular carcinoma (HCC). *First Author: Arndt Vogel, Klinik für Gastroenterologie, Hepatologie und Endokrinologie, Medizinische Hochschule, Hannover, Germany*

Background: The field of systemic options in HCC therapy has significantly evolved in recent years, and first line options now include sorafenib, lenvatinib and bevacizumab plus atezolizumab. Nivolumab is a recombinant human IgG4 mAb targeting PD-1 with clinically meaningful activity in about 15-20% of HCC patients, but the confirmatory phase III trial Checkmate 459 failed to demonstrate superiority over sorafenib. VEGF signaling is not only a driver of tumor angiogenesis, but also contributes to the formation of an immunosuppressive microenvironment. Combinations of anti-angiogenic multikinase inhibitors, specifically lenvatinib, and PD-1/PD-L1 inhibitors have demonstrated remarkable antitumor activity and manageable toxicity in several tumor types, including HCC. We therefore aimed to evaluate the efficacy of nivolumab in combination with lenvatinib as first line treatment in patients with advanced HCC. **Methods:** This investigator-initiated single-armed phase II trial (NCT03841201) recruited 50 patients (pts) at 8 sites in Germany between 07/2019 and 05/2021. Primary endpoints were objective response rate (ORR) according to investigator assessed RECIST 1.1 and safety/tolerability. Secondary endpoints included ORR according to iRECIST, time to progression (TTP), progression free survival (PFS) and overall survival (OS). Recruitment of the trial was completed in 05/2021. At the time of analysis, 4 patients remained on treatment. **Results:** 50 pts (24 BCLC B, 24 BCLC C, 2 not evaluable) were enrolled and received at least one dose of the combination treatment. ORR by RECIST 1.1 was 28% (CR: 6.0%, PR: 22.0%, SD: 46.0%, PD: 12.0%). Median PFS was 9.0 mo (26 events). Median TTP was 11.5 mo (0.69 at 6 mo, 0.45 at 12 mo, 0.36 at 18 mo) and median OS was 27.1 mo (8 events). 45 (91.8%) pts experienced at least one TRAE, of which 29 pts (59.1%) encountered at least one TRAE ≥ grade 3. 17 (34.7%) pts had one or more SAE related to the study medication, whereof 15 pts (30.6%) experienced at least one treatment related SAE ≥ grade 3. **Conclusions:** No new safety signals were observed for the combination of nivolumab and lenvatinib. Although the study failed to reach its prespecified ORR of at least 40%, the high activity in all efficacy endpoints with a mOS of 27.1 mo supports the further investigation of the combination in HCC. Clinical trial information: NCT03841201. Research Sponsor: EISAI GmbH and Bristol-Myers Squibb GmbH & Co. KGaA.

4108 **Poster Session**

Durvalumab (D) plus tremelimumab (T) immunotherapy in patients (Pts) with advanced biliary tract carcinoma (BTC) after failure of platinum-based chemotherapy (CTx): Interim results of the IMMUNOBIL GERCOR D18-1 PRODIGE-57 study. *First Author: Matthieu Delaye, Medical Oncology Department, Curie Institute, Saint-Cloud, France*

Background: D (anti-PDL1) plus T (anti-CTLA-4) combination immunotherapy showed encouraging results in hepato-biliary cancers. Its efficacy in non-Asian Pts with pretreated BTC is unknown. **Methods:** IMMUNOBIL GERCOR-D18-1 PRODIGE-57 was initially a 2-arm, open-label, randomized non-comparative phase II study. Pts with recurrent/advanced pathologically proven BTC (intrahepatic cholangiocarcinoma [iCCA]/extrahepatic CCA [eCCA]/gallbladder cancer [GC]), ECOG PS 0-1, pre-treated with platinum-based CTx were randomized (1:1) to D (1500 mg Q4W) plus T (75 mg Q4W x 4 cycles [T75]) (Arm A) or D plus T in combination with weekly paclitaxel (Arm B). Arm B was closed prematurely for toxicity after inclusion of 10 Pts. The study continued with Arm A only. It was further amended to modify the T schedule (300 mg at cycle 1 [T300], amended Arm A) due to higher efficacy reported in other tumors as compared to T75 mg x 4. The new primary endpoint was the overall survival (OS) rate at 6 months (M6) in amended Arm A (D + T300) with a Fleming two-stage design (H0: 50%, H1: 65%, one-sided alpha: 5%, power: 90%). A total of 100 evaluable Pts were required (efficacy threshold: 59%). We present here the efficacy data of Arm A (D + T75). **Results:** From 12/2018 to 12/2020, 106 Pts were included in Arm A; 103 were evaluable for OS at M6. Median age was 66 years, 47% were male, 46% had ECOG PS 0, 69%/18%/13% had iCCA/eCCA/GC, 76% had metastatic disease, and 28% had prior tumor resection. First-line CTx was GEMCIS/GEMOX/5-FU-based/other in 63%/22%/4%/11%. The M6-OS rate was 59.2%. With a median follow-up of 12 months (95% CI 11.4-14.9), the median OS was 8.0 months (95% CI 5.7-11.7) and median PFS was 2.5 months (95% CI 2.0-3.2). Complete response (CR) was observed in 2 (1.9%) Pts, partial response (PR) in 8 (7.8%), and stable disease (SD) in 32 (31.1%), resulting in an objective response rate of 9.7% and a disease control rate of 40.8%. Absence of progression (PD, iRECIST) after 2 cycles (M6-OS rate: 84% vs 41%, median OS: 17.9 months vs 4.4 months) and CR/PR as a best overall response (M6-OS rate: 100% vs 84% and 39% for SD and PD, respectively) were associated with markedly prolonged OS. 65 (63.1%) Pts had ≥1 grade 3-4 (G3-4) adverse event (AE) and 22 (21.4%) had ≥1 G3-4 treatment-related AE (TRAE). The most commonly reported G3-4 AEs were fatigue (12.6%), abdominal pain (5.8%), and aspartate aminotransferase increase (5.8%) and G3-4 TRAEs were fatigue (4.9%) and diarrhea (2.9%). One death was possibly related to treatment. **Conclusions:** Although no statistical conclusions can be drawn from this exploratory analysis of Arm A, D+T75 reached the pre-defined threshold for efficacy, with no unexpected toxicity. Results from amended Arm A (D+T300, N = 106 additional Pts), quality of life, and ancillary studies are pending. Clinical trial information: NCT03704480. Research Sponsor: Astra Zeneca, GERCOR.

4109 **Poster Session**

Pembrolizumab monotherapy for previously untreated advanced hepatocellular carcinoma (aHCC): 3-year follow-up of the phase 2 KEYNOTE-224 study. *First Author: Ivan Borbath, Cliniques Universitaires Saint-Luc and Université Catholique de Louvain, Brussels, Belgium*

Background: Pembrolizumab monotherapy showed durable antitumor activity and a manageable safety profile in patients with sorafenib-treated (cohort 1) and treatment-naive (cohort 2) aHCC in the open-label, phase 2 KEYNOTE-224 (NCT02702414) study. Longer term data from KEYNOTE-224 after ~3 years of follow-up for patients with treatment-naive aHCC are reported. **Methods:** Eligible patients in cohort 2 had histologically, cytologically, or radiologically confirmed aHCC, Barcelona Clinic Liver Cancer stage C or B not amenable or refractory to locoregional therapy and not amenable to curative treatment, Child-Pugh A liver function, measurable disease per RECIST v1.1 by blinded independent central review (BICR), and ECOG PS 0 or 1. Patients received pembrolizumab 200 mg intravenously every 3 weeks for ≤35 cycles (~2 years). Primary end point was ORR assessed per RECIST v1.1 by BICR. Secondary end points included DOR, DCR, TTP, and PFS, all assessed per RECIST v1.1 by BICR, OS, and safety/tolerability. **Results:** All 51 patients enrolled in cohort 2 received ≥1 dose of pembrolizumab. Median follow-up, defined as the time from first dose to the data cutoff (October 1, 2021), was 35 months (range, 31-37). ORR was 16% (95% CI, 7-29). Median DOR was not reached (NR; range, 3 to 24+ months); 58% of responders were estimated to have a response duration ≥18 months. Best overall response was 8 (16%) PRs, 21 (41%) SDs, and 17 (33%) PDs; no CRs were observed and response was not evaluable for 2 patients (4%) and not assessed for 3 patients (6%). DCR was 57% (95% CI, 42-71). ORR was generally consistent among patients with a viral and nonviral etiology for HCC, although sample sizes were small. The median TTP was 4 months (95% CI, 3-9). Median PFS was 4 months (95% CI, 2-8). Estimated PFS rate at 24 months was 15%. Median OS was 17 months (95% CI, 8-23). Estimated OS rate at 24 months was 34%. No new or unexpected adverse events (AEs) occurred. Treatment-related AEs were reported in 28 patients (55%; grade 3-5, 8 [16%]). **Conclusions:** Updated results from cohort 2 of the KEYNOTE-224 study continued to demonstrate durable antitumor activity, promising OS, and manageable safety for pembrolizumab monotherapy in patients with aHCC and no prior systemic therapy. These data, together with recent positive results from KEYNOTE-394, underscore the broad applicability of pembrolizumab in patients with aHCC both as monotherapy and in combination with other therapies. Clinical trial information: NCT02702414. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

4110 **Poster Session**

Next-generation sequencing (NGS) of circulating cell-free DNA (cfDNA) in patients (pts) with advanced hepatocellular carcinoma (HCC). *First Author: Darren Cowzer, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: HCC is often diagnosed based on high-quality cross-sectional imaging, and when a biopsy is pursued, acquisition of tissue may be of limited quantity and quality or complicated by underlying medical comorbidities. NGS of tumor derived circulating cfDNA represents an investigational tool for non-invasive molecular profiling, that has the potential to aid in diagnosis, prognosis, and in monitoring disease status. Although prior reports have evaluated such technologies, few studies have included tumor tissues to confirm histology and to explore plasma-tissue gene concordance. **Methods:** The primary objective of this retrospective cohort study was to define genomic alterations in circulating cfDNA and to explore plasma-tissue genotype concordance in HCC pts. HCC pts underwent collection of cfDNA for NGS using the MSK-ACCESS 129-gene assay between August 2019 and February 2021. Matched tissue-based NGS with the FDA authorized MSK-IMPACT gene assay was completed when tumor tissue was available. Clinical actionability of sequence variants was annotated by OncoKB, an FDA recognized knowledge base. Clinicopathologic characteristics were extracted, and all data were reported with descriptive statistics. **Results:** 51 unique patients with 53 plasma samples had an HCC histological diagnosis. Pts were male (39, 76%), median age 69 (42-87), viral hepatitis-related (24, 47%), and advanced stage (Stage III:9, 18%; Stage IV:38, 74.5%). Extrahepatic disease and macrovascular involvement were observed in 28 (55%) and 19 (38%) pts, respectively. 22 (43%) pts had AFP ≥400 ng/mL. 49 (92.5%) of 53 plasma samples had detectable genomic alterations. Median cfDNA yield after extraction was 39.43 ng (range: 7.93-287.68). The most frequently mutated genes occurring in > 10% of patients were *TERT* (57%), *TP53* (47%), *CTNNB1* (37%), *ARID1A* (18%) and *TSC2* (14%). The most common oncogenic pathways that contained alterations were WNT-β-Catenin (45%) and PIK3-AKT-TOR (25%). 37 (73%) pts underwent tissue sequencing with MSK-IMPACT with a median time of 9.0 months to the time cfDNA testing. MSK-ACCESS identified mutations observed in tumor in most cases: *TERT* (20/22; 91%), *TP53* (16/17; 94%), *CTNNB1* (11/12; 92%), *ARID1A* (6/6; 100%) and *TSC2* (6/7; 86%). In 18 (49%) of 37 paired samples, additional mutations in cfDNA not seen in tumor were detected and included *KRAS*, *EGFR*, and *TP53* alterations. Potentially actionable mutations were identified through cfDNA in 37% of cases including *TSC1/2* (18%), *BRCA1/2* (8%) and *PIK3CA* (8%). **Conclusions:** Circulating cfDNA genotyping with MSK-ACCESS identifies previously reported HCC tumor genomic profiles and revealed tumor-associated mutations in 92.5% of plasma samples. Ongoing efforts will explore predictive and prognostic implications of NGS at different HCC stages as well as kinetics of treatment response. Research Sponsor: Society of MSKCC.

4111 **Poster Session**

Nivolumab and lenvatanib combination for fibrolamellar carcinoma. *First Author: Paul Kent, Rush University Medical Center, Chicago, IL*

Background: Fibrolamellar Carcinoma (FLC) is a rare form of primary liver cancer affecting children and young adults that often presents at an advanced stage and even with surgery has an 80% relapse rate. Unresectable FLC patients are considered incurable and have short life expectancy. Effective neoadjuvant and adjuvant systemic therapies are needed to increase chances at remission and protect against relapse. Because of success as single agents in HCC, we tried the combination of nivolumab (NIV) and lenvatanib (LEN) in FLC patients who had exhausted more common therapies. Our objective is to describe our experience using combination NIV-LEN in FLC patients. **Methods:** Over the last 5 years we have seen over 90 patients with FLC at our institution. After securing IRB approval, (ORA Number: 19071603-IRB01), we collected data in a de-identified fashion for all patients who had received NIV-LEN. **Results:** Twenty patients (6M/14F), median age at diagnosis/start of NIV-LEN 17/20 (7-52) have received at total of 349 cycles of NIV-LEN (NIVO 3mg/kg IV q2 weeks) and lenvatanib 8mg po daily, 5 adjuvant, 14 neoadjuvant and one both. All had cross sectional imaging every 3 months with independent review. The median number of cycles/months of follow up was 19.5 (3-43)/13.5 (3-31) respectively. The median number of prior relapses, systemic therapies, prior abdominal surgeries, and prior radiation (IR ablations, TARE, TACE, SBRT) were 3.5 (0-7), 3 (0-11), 2 (0-6), and 2.5 (0-13) respectively. Three patients had gemcitabine added to NIVO-LEN for part (< 1/3) of their regimen. The best response by RECIST 1.1 of the 14 neoadjuvant patients was 3 CR, 3 PR, 7 SD and 2 PD, for an overall response rate (PR + CR) of 40% and overall control rate (CR + PR + SD) of 87%. Seven of 20 (30%) stopped NIVO-LEN [PD (3), infection (2), or patients' wishes (2)] while 14 (70%) continue, including all adjuvant patients who remain in CR (median follow-up of 10 months). The 6-, 12-, and 24-month progression free survival (PFS) and overall survival (OS) were: (70%,49%,49%) and (94%,94%,73%) respectively. For 14 of 17 (82%) relapsed patients, the PFS was longer than the patients' most recent PFS, and longest ever in 9 (53%). Six of the 14 initial non-surgical candidates (43%) either had surgery (2), or avoided surgery (3 CR, 1 ablation). There were 2 grade 3 toxicities (both infections) and no grade 4 toxicities. The most common toxicities were hypertension and fatigue in 25% and 20% respectively. One patient, after 5 relapses, had more than 120 lung nodules > 1cm that after 14 months of NIVO-LEN achieved CR and has remained in CR for another 14 months. **Conclusions:** Our retrospective experience with the novel immune-chemotherapy combination of NIV-LEN for FLC in an extremely rare disease with no proven systemic therapies is encouraging, especially for those who are not surgical candidates or in a surgical remission. We hope this report can inform future prospective trials in treating this deadly disease. Research Sponsor: None.

4113 **Poster Session**

Early detection of hepatocellular carcinoma using cfDNA signatures from cirrhotic patients with nodules. *First Author: Rong Fan, Department of Infectious Diseases, State Key Laboratory of Organ Failure Research, Guangdong Provincial Key Laboratory of Viral Hepatitis Research, Nanfang Hospital, Southern Medical University, Guangzhou, China*

Background: Hepatocellular carcinoma (HCC) is the fourth most common cause of cancer-related death worldwide. Early detection of HCC patients is related to favorable survival. Nodules in liver cirrhosis (LC) are at higher risk of developing into HCC. There is an urgent clinical need for development of an accurate and affordable non-invasive method for early HCC diagnosis among LC patients with nodules. **Methods:** We have previously shown that the genome-wide HIFI (5-Hydroxymethylcytosine/motIf/ Fragmentation/nucleosome footprInt) method held a solid diagnostic value in differentiating HCC from LC. In this study, we leverage this knowledge to diagnose early HCC (BCLC 0/A) in cirrhotic nodules using copy number variation (CNV) to replace 5-Hydroxymethylcytosine to simplify NGS protocol and decrease cost. The updated method generates a score that reflects the presence of tumor-derived cfDNA in 10 ml blood via low coverage (2x) whole-genome sequencing (WGS). We applied it in a retrospective cohort (validation set 1, n = 171) and a prospective cohort (validation set 2, n = 156), both of which involved patients with newly diagnosed early stage HCC (BCLC 0/A) as well as individuals with cirrhotic nodules. **Results:** The updated method showed excellent performance for early HCC detection both in the validation set 1 (84 HCC and 87 cirrhotic nodules; AUC: 0.951, 82.1% sensitivity at 90.8% specificity) and validation set 2 (71 HCC and 85 cirrhotic nodules; AUC: 0.958, 81.7% sensitivity at 91.8% specificity) (Table). The AUC values for distinguishing early HCC from cirrhotic nodules could reach 0.951 (80.9% sensitivity at 91.0% specificity) and 0.947 (74.7% sensitivity at 92.1% specificity) among patients with AFP < 400 μg/L and those with nodular size < = 2 cm, respectively. More importantly, our model also maintained consistent performance in detecting very early stage HCC (BCLC 0) with AUC of 0.941 (74.7% sensitivity at 91.3% specificity). **Conclusions:** These findings provide an accurate, affordable, excellent clinical potential model integrating four cfDNA molecular signatures for detecting early stage HCC from cirrhotic nodules using low-coverage WGS of plasma cfDNA samples. Research Sponsor: None.

		Validation Set 1		Validation Set 2	
		HCC (N = 84)	Nodular cirrhosis (N = 87)	HCC (N = 71)	Nodular cirrhosis (N = 85)
Age (year)		56 (50–62)	51 (46–56)	55 (50–65)	51 (45–57)
Gender (male)		68 (81.0%)	72 (82.8%)	55 (77.5%)	63 (74.1%)
BCLC	0	52 (61.9%)	-	43 (60.6%)	-
	A	32 (38.1%)	-	28 (39.4%)	-
Nodular size (cm)	< = 2	52 (61.9%)	83 (95.4%)	43 (60.6%)	81 (95.3%)
	2-3	32 (38.1%)	4 (4.6%)	28 (39.4%)	4 (4.7%)
Etiology	HBV	65 (77.4%)	70 (80.5%)	57 (80.3%)	73 (85.9%)
	Others	19 (22.6%)	17 (19.5%)	14 (19.7%)	12 (14.1%)
AFP (μg/L)	< 400	76 (90.5%)	86 (98.9%)	60 (84.5%)	82 (96.5%)
	> = 400	7 (8.3%)	1 (1.1%)	10 (14.1%)	1 (1.2%)
	NA	1 (1.2%)	-	1 (1.4%)	2 (2.3%)
Performance of the cfDNA noninvasive model					
Sensitivity			82.1%		81.7%
Specificity			90.8%		91.8%
PPV			89.6%		89.2%
NPV			84.0%		85.7%
AUC			0.951		0.958

4114 **Poster Session**

Clinical and genomic characterization of *ERBB2*-altered gallbladder cancer. *First Author: Sebastian Mondaca, Department of Hematology and Oncology, Faculty of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile*

Background: Gallbladder cancer (GBC) is a molecularly distinct entity among biliary tract tumors. *ERBB2* amplification and mutation have been described in GBC, however, clinical and genomic characterization of the *ERBB2*-altered subgroup has been limited. **Methods:** Patients with GBC treated at Memorial Sloan Kettering and Pontificia Universidad Católica de Chile with genomic tumor profiling between 2014 and 2021 were included. Clinical information was retrieved from electronic medical records. Categorical data were analyzed by Fisher exact test and time-to-event data were analyzed by Cox proportional hazards models. **Results:** During the study period 260 GBC patients underwent genomic profiling. The prevalence of *ERBB2* alterations was 14% including 8% with *ERBB2* gene amplification, 4.2% with *ERBB2* mutation, 1.5% with concurrent amplification and mutation and 0.4% with *ERBB2* fusion. There was no age difference between GBC patients with and without *ERBB2* alterations (63.6 vs. 65.4; p = 0.36) and in both subgroups there was a majority of female patients (75% vs. 84%; p = 0.44). Patients with *ERBB2*-altered tumors had a different genomic profile with lower concurrent *KRAS* alterations (2% vs. 12%; p = 0.14) and higher prevalence of *TP53* alterations (81% vs. 59%; p = 0.01). There was no difference in the prevalence of *PIK3CA* mutations (13% vs. 9%; p = 0.38). GBC patients with *ERBB2* alterations had a longer overall survival (22.3 vs. 12.1 months; HR 0.54 95% CI 0.3 to 0.98). **Conclusions:** *ERBB2* amplification and mutation are the most frequent potentially targetable alterations in GBC (14%). *ERBB2*-driven GBC has higher concurrent alterations of *TP53*, while *KRAS* alterations appear to be less frequent. While no particular clinical feature was associated with this subgroup, overall survival was longer. Research Sponsor: U.S. National Institutes of Health, Conquer Cancer Foundation of the American Society of Clinical Oncology, Other Foundation.

4115 **Poster Session**

A phase II study combining KN046 (an anti-PD-L1/CTLA-4 bispecific antibody) and lenvatinib in the treatment for advanced unresectable or metastatic hepatocellular carcinoma (HCC): Updated efficacy and safety results. *First Author: Baocai Xing, Beijing Cancer Hospital, Beijing, China*

Background: PD-1 inhibitor with Lenvatinib were reported to improve ORR in patients with metastatic HCC. KN046 was a bispecific antibody that target both PD-1/PD-L1 and CTLA-4/B7 immune checkpoints pathway. Preliminary report already showed good efficacy and tolerable safety of the KN046+Lenvatinib regimen. Here we updated the efficacy and safety results with more enrolled patients and longer follow-up duration. **Methods:** This is an open-label, single-arm, multicenter, phase II trial in pts with unresectable or metastatic HCC. Enrolled patients (pts) with Barcelona Clinic Liver Cancer (BCLC) stage B or C who were not suitable for curative surgery or local therapy had received Lenvatinib 12 mg/day (bodyweight [BW] ≥60 kg) or 8 mg/day (BW<60 kg) orally and KN046 5 mg IV on Day 1 of a 21-day cycle until disease progression or intolerable toxicity or 2-year treatment. Primary endpoints were safety and ORR by RECISTv1.1 per investigators. **Results:** As data cutoff (January 7, 2022) date, 55 enrolled pts received combination treatment with median duration of 25 weeks. For 52 evaluable pts, ORR was 51.9% (95% CI 37.6-66.0) (RECIST v1.1) and DCR was 86.5% (95% CI 74.2-94.4) (RECIST v1.1). Median PFS was 9.3 months (95% CI 7.0–not estimable [NE]), The median OS and DOR of pts were not reached. The overall incidence of KN046 related treatment-emergent adverse events(TRAEs) was 98.2%, with 27.3% Gr3. The most common Grade ≥ 3 TRAEs included platelet count decreased (7.3% of pts) and aspartate aminotransferase increased (3.6% of pts). The immune related adverse events (irAE) occurred in 14.5% of pts (grade ≥3 5.5%). 3 pts discontinued KN046 treatment due to ≥3 Gr TRAE, which was infusion related reaction, platelet count decreased and interstitial lung disease. 4 (7.2%) pts died from KN046 TRAEs (Hyponatremia, n=1; Interstitial lung disease, n=2; Cause of death unknown, n=1). **Conclusions:** KN046+Lenvatinib demonstrated a promising efficacy in ORR and PFS and the manageable safety profile in the first-line advanced unresectable or metastatic HCC treatment. These result support the KN046 plus Lenvatinib as a potential new treatment option for this population. Clinical trial information: NCT04542837. Research Sponsor: None.

4116 **Poster Session**

IMMUTACE: A biomarker-orientated phase II, single-arm, open-label AIO study of transarterial chemoembolization (TACE) in combination with nivolumab performed for intermediate-stage hepatocellular carcinoma (HCC; AIO-HEP-0217)—Updated efficacy results. *First Author: Anna Saborowski, Hannover Medical School, Hanover, Germany*

Background: Immunotherapy based combinations recently revolutionized the treatment of patients (pts) with advanced HCC, but its significance in earlier stages remains to be determined. TACE is commonly used as first line treatment in intermediate HCC, but outcome of patients treated with TACE in real-life cohorts is still poor with a median overall survival (OS) below 20 months. The aim of this study was to determine the safety and efficacy of TACE combined with nivolumab. **Methods:** This is a phase II trial, that recruited 59 patients at 10 sites in Germany between 06/2018 and 06/2020. Pts received up to two TACE treatments followed by nivolumab (240 mg/ Q2W), initiated on day 2-3 after the first TACE session and continued until progression for a maximum treatment duration of two years. Primary endpoint was ORR (mRECIST; with ORR exceeding 55% (power = 80%; actual beta 0.17) as promising for further investigations). Secondary endpoints include mPFS, mTTFS (median time to failure of strategy), mOS, QoL, and safety/tolerability. Tumor tissue was obtained at baseline and blood samples were collected longitudinally for translational research. **Results:** 49 pts (14.3% HCV and 8.2% HBV) were enrolled and received at least one dose of nivolumab, median tumor size was 4.5 cm (0.9 – 15 cm) and median number 3 (1 – 12). ORR by mRECIST was 71.4% (CR: 16.3%, PR: 55.1%, SD 4.1%, PD: 14.3%). At a median follow-up of 20 months, mPFS was 7.2 mo (95% CI; 5.3 – 11.2; 40 events), mTTFS was 11.2 mo (95% CI; 7.2, 13.5; 42 events) and mTTSST (median time to subsequent systemic therapy) was 24.9 mo (95% CI; 12.2, - ; 21 events). Median duration of Nivolumab was 8.3 months and mOS was 28.3 mo (95% CI; 20 – not estimable; 23 events). Grade ≥3 treatment-related adverse events occurred in 34.7% of patients. Correlative analysis of efficacy with genetic alterations, gene expression signatures and changes of immune cell populations will be reported soon. **Conclusions:** The study met its primary endpoint and provides evidence for the efficacy of TACE in combination with nivolumab without new safety signals in pts with intermediate HCC and no prior systemic therapy. Our findings support further evaluation of nivolumab-based combinations for the treatment of intermediate HCC. Disclaimer: This study was supported with drug and funding by Bristol-Myers-Squibb. Clinical trial information: NCT03572582. Research Sponsor: BMS.

4117 **Poster Session**

Health-related quality of life in patients treated with gemcitabine/cisplatin and durvalumab ± tremelimumab in chemotherapy-naïve advanced biliary tract cancer. *First Author: Jin Won Kim, Seoul National University Bundang Hospital, Seongnam, South Korea*

Background: In the phase 2 (NCT03046862), gemcitabine/cisplatin (GemCis) and durvalumab (D) ± tremelimumab (T) in chemotherapy-naïve advanced biliary tract cancer (BTC) showed a high objective response rate and durable clinical benefit. Based on this study, phase 3 trial (TOPAZ-1, NCT03875235) has been conducted and the positive result for adding D to GemCis has been reported. Health-related quality of life (HRQoL) for adding immunotherapy to cytotoxic chemotherapy in BTC has not been reported yet. We present HRQoL results from the phase 2 study. **Methods:** In this study, treatment-naïve patients with unresectable or recurrent BTC were enrolled into three cohorts. Patients received one cycle of GemCis followed by GemCis plus D and T (cohort 1) or, starting with the first cycle, received GemCis plus D (cohort 2) or GemCis plus D and T (cohort 3). The EORTC Quality of Life Questionnaire (QLQ)-C30 and BIL21 were administered at baseline and every cycle throughout treatment. Change from baseline to post-2 cycles and deterioration of HRQoL (≥10 points change) were analysed. **Results:** At data cut-off (March 22, 2021), 126 patients (32 in cohort 1, 47 in cohort 2, 47 in cohort 3) were included for this analysis. Compliance for QLQ was very high (> 90 %) at all time points. C30 global health status (GHS) scores remained stable at all time points and from baseline to post 2 cycles (mean [95% CI] change, 2.66 [-1.10–6.42]), with greater improvements observed in patients with responder (a best response of complete response (CR) or partial response (PR)) (3.60 [-1.27 to 8.47]) compared to non-responder (stable disease (SD) or progressive disease (PD) (0.66 [-5.19 to 6.51]). For the overall cohort, functioning scales also remained stable from baseline to post 2 cycles. Nausea/vomiting (8.4 [4.45 to 12.36]), dyspnea (7.28 [2.17 to 12.4]), constipation (9.24 [3.35 to 15.13]), financial difficulties (5.53 [1.65 to 9.41]) in C30 and eating (5.53 [1.65 to 9.41]), tiredness (5.42 [1.23 to 9.6]), treatment side effects (7.98 [1.15 to 14.81] in BIL21 were worse at post 2 cycles. However, pain (-7.14 [-12.24 to -2.04]), diarrhea (-4.48 [-8.86 to -0.1]) in C30 and jaundice (-5.51 [-9.26 to -1.76]), pain (-6.02 [-9.7 to -2.34] in BIL21 were improved and more improvement was shown in responder compared to non-responder. Regarding deterioration of C30 GHS, median deterioration-free survival (months [95% CI]) was 4.14 (2.66-6.47) in all cohorts and there was no difference between responder (3.68 [2.27-7.92]) and non-responder (5.59 [2.73-9.46], Hazard ratio = 1.00 [95% CI, 0.62-1.61], p = 0.997). There was no difference among 3 cohorts. **Conclusions:** GemCis plus D ± T in chemotherapy-naïve advanced BTC generally preserved HRQoL and improved some symptom scales such as jaundice and pain although chemotherapy related symptom scales were worse. Research Sponsor: Astrazeneca.

4118 **Poster Session**

Impact of metformin on clinical outcomes in advanced hepatocellular carcinoma treated with immune checkpoint inhibitors. *First Author: Lana Khalil, Emory University Hospital, Atlanta, GA*

Background: Non-alcoholic steatohepatitis (NASH) is an emerging etiology for hepatocellular carcinoma (HCC) and contributes to the increasing incidence of HCC worldwide. Patients with NASH often have risk factors of metabolic syndrome including hypertension, obesity, and type 2 diabetes (T2DM). NASH induced HCC has been shown to be associated with less response to immune check point inhibitors (ICIs) in HCC. Anti-diabetic agent metformin has been shown to be associated with improved outcomes in patients treated with ICIs in melanoma and non-small cell lung cancer. However, the impact of metformin on the efficacy of ICIs is not well defined in HCC. The main purpose of this study was to examine the effect of metformin on clinical outcomes in patients with advanced HCC treated with ICIs. **Methods:** We performed a retrospective analysis of patients with advanced HCC treated with ICIs in first and later-line settings between 2015 and 2021. The primary endpoints were overall survival (OS), progression free survival (PFS), and objective response rate (ORR) as assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Patients were stratified based on their usage of metformin. OS and PFS were analyzed using Cox proportional hazard models and Kaplan-Meier analysis with log-rank test. **Results:** A total of 111 patients met inclusion criteria, 18 patients in the metformin group and 93 patients in the non-metformin group. Most common cause of HCC was viral hepatitis (52%), followed by NASH (29%), alcohol (8%) and other (11%). Baseline characteristics between the two groups were similar except all patients in the metformin group had a diagnosis of T2DM. ORR was 5.6%. (1 partial response) in the metformin group vs 22.6% (5 complete responses, 16 partial responses) in the non-metformin group. Median OS was 45.9 months in the non-metformin group vs 10.8 months in metformin group (HR 1.99, 95% CI 0.95-4.21, p = 0.064). Median PFS of 6.6 months vs 2.5 months (HR 1.75, 95% CI 0.93-3.29, p = 0.077). Moreover, metformin usage was associated with shorter median OS of 10.8 months (HR 1.96, 95% CI 0.75-5.09, p = 0.16) vs 20.9 months among patients with T2DM. OS was significantly worse in patients with poor ECOG performance status 2-3, MELD score 10-23, higher grade tumor histology, AFP > = 400, and use of IO in later lines of therapy. **Conclusions:** In this retrospective study metformin use was associated with worse clinical outcomes in advanced HCC patients treated with ICIs. Research Sponsor: None.

4119 **Poster Session**

Quantitative analysis of spatial distribution of lymphocytes in hepatocellular carcinoma: A biomarker correlated with survival and gene expression in cancer immune system. *First Author: Hong-Seok Lee, VUNO Inc., Seoul, South Korea*

Background: Tumor microenvironment (TME) is known to impact prognosis in hepatocellular carcinoma (HCC). Although digital pathology and artificial intelligence have been adopted in modern medicine and oncology, few quantitative biomarkers have been identified to predict the prognosis and guide treatment for HCC via an automated analysis of TME at the cellular level. **Methods:** Histopathological images and clinical data of 365 cases with HCC were obtained from TCGA (The Cancer Genome Atlas), and 60 of HCC pathology images and cancer lesion annotations were collected from PAIP2019 [1]. DenseNet-based HCC segmentation model (F1-score, 0.904) and Hover-Net-based cell detection model (F1-score, 0.914) were developed using PAIP2019 and MoNuSac datasets, respectively [2,3,4]. Each histopathology image of TME was segmented via the segmentation model into two areas: 1) non-tumoral regions that include the stroma; 2) tumoral regions where HCC cells are concentrated. The cell detection model recognized individual cells on images, specified lymphocytes, and calculated ratios of lymphocyte to total cell count (RLTCC) in segmented regions. RLTCC was then correlated with clinical survival outcomes, HCC primary risk factors, and RNA expression profiles. **Results:** RLTCC in tumoral regions was not significantly associated with prognosis. Patient groups with higher RLTCC in non-tumoral regions (RLTCC in NT) showed better overall survival (OS) than those with lower RLTCC in NT regardless of HCC risk factors (median OS 45.7 vs 18.6 months; log hazard ratio of -1.6 ± 1.1, p=0.006). These patients had significantly enriched expression of genes (p<0.05) related to cancer antigen presentation (higher gene expression by +33.7%), recognition of cancer cells by T-cell (+32.0%), T-cell priming and activation (+32.2%), immune cell localization to tumors (+31.9%), and killing of cancer cells (+24.7%). Those with HCC etiology of hepatitis B and C had more patients in the higher RLTCC in NT (17/21 patients, 81.0%; 23/29, 79.3%, respectively). In comparison, those with alcohol consumption showed equal distribution (26/53, 49.1%). The RLTCC in NT in hepatitis B/C groups was statistically higher than alcohol consumption group (p<0.05). **Conclusions:** A digital prognostic biomarker, RLTCC in NT of TME was identified as a significant prognostic indicator, and it was shown to correlate with RNA gene expression related to T-cell mediated cancer immunity. A retrospective analysis of clinical response from systemic therapy in relation to digital biomarkers is underway and will be reported. References: [1] Kim et al. Med. Image Anal. 67 (2021). [2] Riasatian, Abtin, et al. Med. Image Anal. 70 (2021). [3] Graham, Simon, et al. Med. Image Anal. 58 (2019). [4] Verma, Ruchika, et al. IEEE Trans Med Imaging 39.1380-1391 (2020). Research Sponsor: Hepatocellular Carcinoma SPORE Grant.

4120 **Poster Session**

Comparative genomic analysis and its prognostic impact on survival between viral hepatitis-related and non-viral hepatitis intrahepatic cholangiocarcinoma. *First Author: Nai-Jung Chiang, National Institute of Cancer Research, National Health Research Institutes, Tainan, Taiwan*

Background: Intrahepatic cholangiocarcinoma (IHCC) is hard-to-treat cancer with a high mortality rate worldwide. Hepatitis B virus (HBV) or hepatitis C virus (HCV) is involved in the development of IHCC, especially in Asian countries. Despite rapidly growing genomic profiling studies of IHCC in Western and Eastern populations in recent years, less on genomic heterogeneity of viral hepatitis-related and non-viral hepatitis IHCC been reported. This study aims to provide a comprehensive genomic analysis of IHCC and its prognostic value in IHCC populations with or without viral hepatitis infection. **Methods:** FFPE tissues from 157 patients with IHCC were subject to next-generation sequencing using the FoundationOne CDx (n = 52) or ACTOnco + comprehensive genomic profiling panels (n = 105). Genomic alterations and features, including single nucleotide variations (SNVs), short insertions and deletions (InDels), copy-number variations (CNVs), fusion genes (only FoundationOne CDx), tumor mutations burden (TMB), and microsatellite instability (MSI) status, were analyzed. The prevalence of genetic mutations and their prognostic values were compared between patients with a history of hepatitis B/C infection (BC; n = 71, 45.2%) and those without hepatitis B/C infection (NBNC; n = 79, 50.3%). Seven patients had no medical record of HBV or HCV infection. **Results:** The most frequently mutated genes in BC- and NBNC-related IHCC populations were TP53, KRAS, and IDH1. The genetic alternations related to PI3K/AKT/mTOR signaling pathway and copy number gain of receptor tyrosine kinase were relatively dominant in BC-related IHCC. In contrast, the Ras/Raf/MAPK pathway alterations were frequently common in NBNC-related IHCC. In addition, we investigated the correlation between commonly altered genes or pathways and overall survival (OS). Interestingly, the prognostic biomarkers in BC- and NBNC-related IHCC were significantly different. The results showed that TP53 DNA-binding domain (DBD) and TET2 mutations were associated with poor prognosis in BC-related IHCC. On the contrary, CDKN2A deletion and Ras/Raf/MAPK pathway alteration were associated with inferior prognosis in NBNC-related IHCC. However, neither the PI3K/AKT/mTOR signaling alteration nor IDH1/2 mutation affected the OS in BC- or NBNC-related IHCC. Notably, we found that SWI/ SNF complex involved in ARID1A, ARID1B, ARID2, PBRM1, and SMARCA4 alterations exhibited a beneficial prognosis in BC-related IHCC patients, which has not been discussed in previous studies. **Conclusions:** This study provides comparative genomic profiling between BC- and NBNC-related IHCC and shows genomic heterogeneity and different dominant prognostic biomarkers and activated signaling pathways. Different treatment strategies should be considered in these two subpopulations based on these results. Research Sponsor: National Institute of Cancer Research, National Health Research Institutes, Pharmaceutical/Biotech Company.

4121 **Poster Session**

Efficacy of nivolumab and temozolomide in advanced neuroendocrine neoplasms (NENs) in a phase 2 clinical trial.

First Author: Dwight Hall Owen, Division of Medical Oncology, Department of Internal Medicine, Ohio State University, Columbus, OH

Background: Treatment options are limited in patients with metastatic NEN. Temozolomide (TEM) alone and in combination with capecitabine is active in NEN and has been shown to have immunomodulatory impact. Here we present the final results for the NEN cohort of a phase 2 trial of combination nivolumab and TEM in patients with advanced NEN along with observed peripheral immune changes. **Methods:** NCT03728361 is a non-randomized, two-cohort, open-label phase 2 trial of nivolumab and TEM in patients with metastatic NEN and small cell lung cancer. The NEN cohort enrolled patients with tumors of any WHO grade, location, and line of therapy; all patients had evidence of progression prior to study. Prior immunotherapy was not allowed. Treatment consisted of nivolumab 480 mg IV on day 1 and TEM 150 mg/m2 on days 1-5 of a 28-day cycle. The primary objective was efficacy measured as response rate (RR) by RECIST v1.1. Secondary objectives were progression free survival (PFS) and overall survival (OS), by the method of Kaplan–Meier. The translational objective was to analyze peripheral blood mononuclear cells (PBMCs) collected at screening (baseline) and on cycle 1, day 15 (C1D15) via mass cytometry. **Results:** The RR was 36% (n=10/28, 95% CI: 18.6%-55.9%), including 10 patients (36%) with PR, 16 (57%) with SD, and 2 (7%) with PD (Table). The disease control rate was 93%. Responses occurred across all WHO grades; 44% of patients with tumors with Ki-67 >20% had PR. There was a significant difference in ORR by primary tumor location (bronchial vs pancreas vs other, p=0.004). There was no significant difference in response by Ki-67% (p=0.872), or in patients treated as first line (31%) or beyond (40%, p=0.706). The median PFS was 8.9 months (95% CI: 3.9 – 11.1 months), and median OS was not reached (95% CI: 20.7 – NR months). Two immune related SAE's occurred: myocarditis and diarrhea in one patient each; gr4 toxicities included neutropenia (10%) and thrombocytopenia (7%). Profiling of PBMCs revealed no correlation of baseline MDSC levels with clinical benefit, however significant changes within the T cell landscape, including a decrease in CD4+ T cells (59.6% ±13.08 vs. 56.5% ±13.01, p=0.001) and increase in CD8+ T cells (27.9% ±13.36 vs. 31.7% ±14.57, p=0.03) were observed. **Conclusions:** Combination nivolumab and TEM demonstrated promising efficacy in patients with NENs; median OS has not been reached. Clinical trial information: NCT03728361. Research Sponsor: OSU-BMS Collaborative Research Grant.

Characteristics and efficacy.

Patient Characteristics (N=28)	N (%)	Response Rate (n, %)	PFS (95% CI), months	OS (95% CI), months
Primary Location:				
All patients	28	10 (36%)	8.9 (3.9, 11.1)	NR (20.7, NR)
Bronchial	11 (39%)	7 (64%)	11.1 (3.0, 29.0)	NR (8.8, NR)
Pancreas	3 (11%)	2 (67%)	28.3 (3.8, 28.3)	NR (NR, NR)
Other	14 (50%)	1 (7%)	6.7 (3.6, 10.0)	20.8 (16.8, NR)
Tumor Ki-67%:				
<3%	5 (18%)	1 (20%)	10.0 (3.0, NR)	NR (3.0, NR)
3-20%	14 (50%)	5 (35%)	9.1 (3.6, 20.8)	NR (8.8, NR)
>20%	9 (32%)	4 (44%)	8.8 (1.4, 28.3)	23.0 (16.8, NR)

4122 **Poster Session**

Australasian Gastrointestinal Trials Group (AGITG) CONTROL NET Study: ^{177}Lu-DOTATATE peptide receptor radionuclide therapy (PRRT) and capecitabine plus temozolomide (CAPTEM) for pancreas and midgut neuroendocrine tumours (pNETS, mNETS)—Final results.

First Author: Nick Pavlakis, Northern Cancer Institute, St. Leonards, Sydney, Australia

Background: CAPTEM is an accepted regimen for patients (pts) with advanced pNETs. Single agent PRRT is now a standard of care for progressive WHO Grade 1/2 mNETs. High activity was seen with PRRT/CAPTEM in a single arm Phase I/II trial. This study aims to determine the activity of combining CAPTEM with PRRT in mNETs and pNETs pts. **Methods:** Non-comparative randomised open label parallel group phase II trial with 2:1 randomisation to PRRT/CAPTEM (experimental arm) vs. PRRT (mNETs control) and CAPTEM (pNETS control). PRRT/CAPTEM: 7.8GBq ^{177}Lu Octreotate (Lutate) given intravenously (IV) on day 10 every 8 weeks for 4 cycles, with concurrent oral capecitabine 750mg/m^2 b.i.d. days 1-14 and temozolomide 75mg/m^2 b.i.d. days 10-14 every 56 day cycle, up to 4 cycles. PRRT alone: 7.8GBq ^{177}Lu Octreotate (Lutate) given intravenously (IV) on day 1 every 8 weeks for 4 cycles. CAPTEM alone: Oral capecitabine 750mg/m^2 b.i.d. days 1-14 and days 29-42; Oral temozolomide 75mg/m^2 b.i.d. days 10-14 and 38-42 every 56 day (8w) cycle. Primary endpoint: Progression free survival (PFS). mNETS: At 15 months, assuming PFS 66.4% in control arm; target PFS ^{3} 80%; pNETS: At 12 months, assuming PFS 60% in control arm; target PFS ^{3} 75%. Secondary endpoints: Objective tumor response rate (complete or partial) (OTRR), overall survival (OS), adverse events (AEs). **Results:** 75 pts enrolled (Dec 2015 – Nov 2018): mNETs 33 PRRT/CAPTEM, 14 PRRT, median follow up (mFU) 60.3 months; pNETS 19 PRRT/CAPTEM, 9 CAPTEM, mFU 57.5 months (mo). Late Grade 3/4 haematologic AEs: mNETS: 2/32 (6%) PRRT/CAPTEM pts and 4/13 (31%) PRRT pts. Events included myelodysplastic syndrome (40 mo), leukaemia (60 mo), pancytopenia (50 mo), anaemia (32 mo), thrombocytopenia (7 mo). No late haematologic G3/4 AEs were reported in the pNETS cohort. No late renal toxicity was identified in all study arms. **Conclusions:** CONTROL NETs is the first randomized trial to demonstrate efficacy for PRRT in pNETs, in addition to a standard of care. Extended follow up confirms durable CAPTEM/PRRT activity, with superior PFS in pNETs. Late haematologic toxicity was seen in both mNET PRRT arms but was not higher with additional CAPTEM. The activity of CAPTEM/PRRT in pNETs should be tested in the phase III setting. Clinical trial information: ACTRN12615000909527. Research Sponsor: NeuroEndocrine Cancer Australia, University of Sydney, Tour de Cure, Australasian Gastrointestinal Trials Group.

	mNETS PRRT/CAPTEM (95% CI)	mNETS PRRT (95% CI)	pNETS PRRT/CAPTEM (95% CI)	pNETS CAPTEM (95% CI)
PFS	90.4% (73.1-96.8) 15 mo	92.3% (56.6-98.9) 15 mo	83.3% (56.8-94.3) 12 mo	88.9% (43.3-98.4) 12 mo
OTRR	34.4 % 15 mo	23.1 % 15 mo	72.2 % 12 mo	33.3 % 12 mo
PFS	60.4% (40.8-75.3) 36 m	61.5% (30.8-81.8) 36 mo	61.1% (35.3-79.2) 27 mo	33.3% (7.8-62.3) 27 mo
PFS HR	HR 1.17 (0.51—2.68 p=0.71) 36 mo		HR 0.41 (0.15—1.12 p=0.08) 27 mo	
OS HR	HR 0.61 (0.19—1.94; p=0.40) PRRT/CAPTEM vs PRRT at 36 mo		HR 1.28 (0.33—4.95; p=0.72) CAPTEM vs PRRT/CAPTEM at 27 mo	

4123 **Poster Session**

Association of LAG-3 expression in circulating T cells and response to combination temozolomide (TMZ) and nivolumab (NIVO) in advanced neuroendocrine neoplasms (NENs): Results from an investigator-initiated phase 2 trial.

First Author: Vineeth Sukrithan, Ohio State University Comprehensive Cancer Center, Columbus, OH

Background: LAG-3 is an immune checkpoint present on NK cells, activated T cells and myeloid cells that inhibit T cell responses. Recent evidence demonstrating the safety and efficacy of LAG-3 inhibition has increased interest in this pathway for the treatment of multiple malignancies but the role in NEN is unclear. We present results from correlative peripheral blood mass cytometry (CyTOF) performed in a phase 2 trial (NCT03728361) of the combination of NIVO and TMZ in pts with advanced NEN. **Methods:** Patients (pts) with progressive NEN of any grade or primary location and any line of therapy were eligible. Small cell lung cancer was excluded. Clinical results from NCT03728361 will be presented in a separate abstract. Study treatment consisted of NIVO 480 mg IV every 4 weeks and TMZ 150 mg/m2 for 5 consecutive days out of a 28-day cycle. Peripheral blood mononuclear cells (PBMCs) were available from 16 out of 28 patients at screening (baseline) and cycle 1, day 15 (C1D15) and analyzed via CyTOF. Antibody labelling was performed using a 37 marker Maxpar Direct Immune Profiling Assay (Fluidigm). Immune cell populations were compared using two sample t-tests between pts with partial response (PR) and non-partial response (non-PR). **Results:** At screening, no differences were observed in PD-1, TIM3, or KLRG1 positive T-cell populations between pts with PR or non-PR. Patients with a PR had a significantly lower % of LAG-3 expressing T cells (p=0.029). There was a trend towards a lower % CD8+LAG-3+ T cells in pts with PR (p=0.086). At C1D15: The % of CD8+ LAG-3+ T cells were significantly higher in PRs vs. non-PR (p = 0.015). In matched samples comparing T cell populations at screening to C1D15, LAG-3+ CD8+ T cells increased significantly in PRs when compared to non-PRs (p=0.021). **Conclusions:** The % of LAG-3+ T cell population at baseline associates with non-response to TMZ/NIVO in NENs. Among responders, there was a significant increase in CD8+ LAG-3+ T cells by Day 15 compared to baseline indicating a potential mechanism of immune escape and eventual resistance. Clinical trial information: NCT03728361. Research Sponsor: Ohio State University-Bristol Myers Collaborative Research Grant.

Percentage LAG3+ T cell population at screening and during treatment in NEN patients treated with TMZ/NIVO comparing responders (PR) and non-responders (Not PR).

Population	Total (n=16)	Not PR (n=11)	PR (n=5)	P-value
		Mean (SD, min-max)		
1. Screening: Total LAG-3+ (PR=5, not-PR=9)	0.6% (0.55, 0.01–1.98)	0.83% (0.55, 0.13–1.98)	0.18% (0.24, 0.01-0.6)	0.029
2. Screening: CD8+ LAG-3+ (PR=5, not-PR=9)	1.07% (1.04, 0.12-3.66)	1.42% (1.16, 0.12-3.66)	0.43%(0.18,0.14-0.61)	0.086
3. C1D15: CD8+ LAG-3+ (PR=3, not-PR=8)	0.99% (0.72, 0.19–2.57)	0.69% (0.48, 0.19- 1.42)	1.78 % (0.71, 1.2-2.57)	0.015
4.Change from screening to C1D15: CD8+ LAG-3+ (PR=3, not-PR=6)	0.46% (1, –0.7–2.13)	–0.03% (0.73, –0.7–1.3)	1.45 % (0.67, 0.8–2.13)	0.021

4124 **Poster Session**

Genomic correlates of response to capecitabine and temozolomide (CAPTEM) in pancreatic neuroendocrine tumors.

First Author: Patrick Lee, Cedars-Sinai Medical Center, Los Angeles, CA

Background: Despite the frequent use of capecitabine and temozolomide (CAPTEM) to treat metastatic, well-differentiated pancreatic neuroendocrine tumors (PNETs), no reliable genomic predictors of response currently exist. PNETs commonly harbor mutations in *MEN1*, *ATRX*, *DAXX*, and the PI3K/AKT/mTOR pathway. We sought to determine whether the mutational status of these genes correlates with response to CAPTEM. **Methods:** A retrospective cohort of PNET cases seen at Cedars-Sinai Medical Center or from Perthera's Real-World Evidence Database included 23 patients who were treated with CAPTEM in 1st or 2nd line and had targeted next-generation sequencing (NGS) of their tumors available. Genomic alterations were correlated with progression-free survival (PFS) using multivariate Cox regression analysis. **Results:** We analyzed 23 PNET patients, 4 (17.4%) of whom had documented functional tumors. We identified *MEN1* mutations as positively associated with CAPTEM response, but this effect was less pronounced for the subset with co-occurring *DAXX* mutations, which are commonly found alongside *MEN1* alterations. With and without accounting for line of therapy, we found that PFS on CAPTEM was significantly longer in *MEN1*-mutated, *DAXX*-wildtype tumors compared to other mutation profiles ($P < 0.01$, see Table). *ATRX* (67%) and *PTEN* (33%) alterations were also enriched in the *MEN1*-mutated/*DAXX*-wildtype subset; however, other PI3K/AKT/mTOR alterations were common across all *MEN1*-mutated cases. **Conclusions:** We describe a novel genomic signature (*MEN1* mut/*DAXX* wt) that correlates with PNET response to CAPTEM therapy and is exploratory in nature. Prospective validation of these associations is warranted while taking into account other therapies, histopathologic factors, and other genomic correlates. Research Sponsor: Know Your Tumor PANCAN.

Exploratory PFS analyses on 1st/2nd line CAPTEM comparing *MEN1*-mutated/*DAXX*-wildtype PNETs versus other genomic profiles.

PNET Subset	mPFS (95% CI)	Univariate p-value (HR (95% CI))	Multivariate p-value (HR (95% CI))	Line of Therapy p-value (HR (95% CI))
***MEN1*-mutated & *DAXX*-wildtype (n=9)**	16.3m [12.6-N/R]	0.009932 (0.16 [0.04-0.64])	0.009722 (0.14 (0.03-0.63))	0.6245 (0.75 (0.24-2.33))
***MEN1*-wildtype or *DAXX*-mutated (n=14)**	7.4m [7.1-N/R]			

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4125 **Poster Session**

REGOMUNE: Phase II study of regorafenib plus avelumab in solid tumors—Results of the gastroenteropancreatic neuroendocrine carcinomas (GEP-NEC) cohort. *First Author: Sophie Cousin, Early Phase Clinical Trials Unit and Thoracic Unit, Institut Bergonié, Bordeaux, France*

Background: There is no standard treatment for patients (pts) with advanced extra-pulmonary neuroendocrine tumors (NET) and carcinomas (NEC) after failure of chemotherapy in the metastatic setting. PD-1/PD-L1 expression is frequent in these tumors. Combining anti-PD1/PDL1 agents with anti-angiogenics has been shown to be synergistic in several tumor models. **Methods:** This is a single-arm open-label multicentric phase II trial assessing the efficacy and safety of regorafenib (R) (160 mg QD 3weeks/4) + Avelumab (A) (10 mg/kg every 2 weeks) combination in pts with advanced or metastatic grade 2 or 3 (G2/3) gastroenteropancreatic (GEP)-NET or GEP-NEC. The primary endpoint was the confirmed objective response rate, based on central review according to RECIST 1.1. Secondary endpoints included: 1-year progression free survival (PFS), 1-year overall survival (OS), and Safety using NCI-CTCAE v5.0. Correlative studies were planned from pts tumor samples obtained at baseline. **Results:** Between May 2019 and Apr. 2021, 46 pts were enrolled in 6 centers. Median age was 63 (range 31 – 80). 10 pts presented with a NEC and 36 pts with a G2/3 NET. Median follow-up was 6.5 months (95% CI: 5.3 - 9.6). Median number of previous treatment lines was: 2 (range 0 – 8). 39 (84.8%) pts experienced at least 1 dose modification or treatment interruption. The most common grade 3/4 adverse events were : Hypertension (13% of pts), fatigue (13%), and diarrhea (11%). One death was related to the treatment. Among the 42 assessable pts, 7 (16.7%) achieved a partial response: 6 pts with a G2/3 NET and 1 patient with a NEC. 22 (52.4%) pts demonstrated stable disease, 22 (52.4%) pts had tumor shrinkage and 10 (23.8%) pts had progressive disease. 3 (7.1%) pts were inevaluable as per RECIST. The median duration of response was 15.5 months (95%CI: 3.7 - not reached (NR)). The median PFS and OS were 5.5 months (95% CI: 3.6 – 9.2) and NR respectively. One year OS rate was 69.4 % (95% CI: 45.1 % – 84.5 %). **Conclusions:** REGOMUNE is the largest prospective study ever conducted in pts with grade 2/3 GEP-NET or GEP-NEC refractory to cytotoxic chemotherapy. The R+A combination has significant clinical activity in pts with refractory disease. Full Biomarkers analyses will be presented at the meeting. Clinical trial information: NCT03475953. Research Sponsor: Bayer, Merck.

4126 **Poster Session**

A pooled analysis of surufatinib safety from phase 3 trials in advanced NETs. *First Author: Jie Li, Department of Gastrointestinal Oncology, Key laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital & Institute, Beijing, China*

Background: Surufatinib is a small-molecule inhibitor of VEGFR1, 2, & 3, FGFR1, and CSF-1R. Surufatinib demonstrated prolonged PFS and tolerable safety in two phase 3 studies in advanced neuroendocrine tumors (NETs) of pancreatic (SANET-p; NCT02589821) and extrapancreatic (SANET-ep; NCT02588170) origin (Xu, 2020 Lancet Oncology). Detailed outcomes on safety from these 2 studies are reported here as a pooled analysis. **Methods:** Data is pooled from SANET-p and SANET-ep studies which have similar designs including a 2:1 randomization of surufatinib to placebo in patients ≥18 years with advanced, well differentiated NETs, progressing on or after ≤2 prior therapies. Surufatinib 300 mg or placebo, was administered once daily until disease progression or unacceptable toxicity. Safety outcomes for each pooled treatment group are reported as treatment-emergent adverse events (TEAE) assessed by NCI-CTC 4.03. Patients were included if they had received study treatment during the double-blinded phase of the studies. **Results:** As of 30th June 2020, 396 patients were assigned to the surufatinib (n = 263) and placebo (n = 133) groups. Median treatment duration was longer with surufatinib 7.4 months (range 0.1–41.4) compared with placebo 4.6 months (range 0.1–39.9). 29% of patients reached more than 12 months of treatment with surufatinib group compared to 11% with placebo. The mean relative dose intensity was 87.56% in the surufatinib group and 97.01% in the placebo group. Most common TEAEs (surufatinib vs placebo) were proteinuria 68.8% vs 54.9%, hypertension 68.4% vs 27.1%, and diarrhea 49% vs 22.6%. Most common grade ≥3 TEAE were hypertension 38.8% vs 13.5%, proteinuria 14.8% vs 0.8% and hypertriglyceridaemia 5.3% vs 0%. Deaths due to TEAEs were comparable between groups 2.7% vs 2.3%. TEAEs led to dose reductions in 43.0% vs 6.8% of patients and dose interruptions in 47.1% vs 29.3% of patients. The majority of patients (83.3% vs 93.2%) were managed without discontinuation because of TEAE. Median onset of proteinuria and hypertension were < 1 month in both groups. Median (range) onset was 0.95 months (0.16–30.36) vs 0.95 months (0.23–16.95) for proteinuria and 0.49 months (0.03–31.18) vs 0.89 months (0.03–14.75) for hypertension. Among patients with hypertension, 59% (n = 111) vs 28% (n = 11) received antihypertensive medication. **Conclusions:** Surufatinib was generally well tolerated in this pooled analysis and the safety profile was consistent with its previously reported data. The monitoring and management of hypertension and proteinuria are important for patients receiving surufatinib. Clinical trial information: NCT02589821; NCT02588170. Research Sponsor: HUTCHMED Limited.

	S (N = 263)		P (N = 133)	
Most frequent TEAEs (PT≥30%), %	**Any**	**Gr.≥3**	**Any**	**Gr. ≥3**
Proteinuria	68.8	14.8	54.9	0.8
Hypertension	68.4	38.8	27.1	13.5
Diarrhea	49.0	2.3	22.6	0.8
Blood thyroid stimulating hormone increased	42.6	0	9.8	0
Blood bilirubin increased	37.6	1.9	19.5	0
Hypertriglyceridemia	35.7	5.3	12.0	0
Occult blood positive	33.1	0	21.8	0
AST increased	30.8	3	30.8	3

4127 **Poster Session**

Molecular correlates of Delta-like-ligand 3 (DLL3) expression in neuroendocrine neoplasms (NENs). *First Author: Justin Hwang, Division of Hematology, Oncology and Transplantation, Department of Medicine, University of Minnesota, Minneapolis, MN*

Background: NENs can occur in many locations but have limited precision therapy options. DLL3 is a cell surface protein that is emerging as a promising therapeutic target in NENs including neuroendocrine prostate cancer (NEPC) and small cell lung cancer (SCLC). Our recent study indicated that ~77% of NEPCs expressed DLL3, with expression in circulating tumor cells being highly concordant with matched biopsies. While there are ongoing clinical trials of drugs targeting DLL3, the repertoire of clinical and genomic features shared across other DLL3-expressing NEN cancers is ill-defined. **Methods:** We analyzed WES and WTS data from NENs identified across 29 different sites of origin using the Caris Life Sciences platform, excluding SCLC and including neuroendocrine carcinomas and neuroendocrine tumors. We used values above or below median DLL3 expression of all NEN samples to define DDL3-High/Low (H/L). Significance of molecular alterations in DLL3-H vs L was determined using Fisher's-Exact/Mann Whitney/X^2 test with Benjamini-Hochberg correction. **Results:** DLL3 expression across all 2672 NEN samples was observed in 27 of 29 NENs after excluding SCLC. NENs of anus, prostate, lung, bladder, and bile duct exhibited the greatest median DLL3 expression, whereas adrenal gland, small bowel, and nervous system displayed the lowest. Certain tissues of origin displayed more robust DLL3 expression, with 71% (50/66) of NEPC, 75% (87/122) of lung, and 77.3% (51/66) of bladder being DLL3-H compared to 14.4% (13/90) of adrenal and 7.9% (12/151) of small bowel NENs. DLL3-H NENs were associated with TMB-high status (> 10 muts/Mb; 12.1% vs 4.5%, OR 2.7, q < 0.001) and more genomic alterations in several driver genes, including tumor suppressors TP53 (51% vs 23%, OR 2.3, q < 0.001) and RB1 (42% vs 10%, OR 4.2, q < 0.001), and oncogenes KRAS (14% vs 5.4%, OR 2.5, q < 0.001), MYC (5.7% vs 0.9%, OR 6.3, q < 0.001) and CCNE1 (5.3% vs 1.3%, OR 4.0, q = 0.001). Conversely, DLL3-L NENs exhibited more alterations in CTNNB1 (2.2% vs 5.2%, OR 0.42, q = 0.04), MEN1 (3.3% vs 11%, OR 0.30, q < 0.001), and BCOR (1.3% vs 4.1%, OR 0.32, q = 0.02). DLL3-H NENs also had significantly more alterations in PIK3CA (6.4% vs 3.0%, OR 2.1, q = 0.04), chromatin remodeling genes KMT2D (6.7% vs 2.6% OR 2.6, q = 0.005) and CREBBP (3.2% vs 0.9%, OR 3.6, q = 0.03), and WNT signaling gene APC (9.7% vs 5.2%, OR 1.9, q = 0.02). **Conclusions:** We confirmed DLL3 expression in NENs across different tissues of origin, with highest expression in poorly differentiated NENs. DLL3-H expression was associated with genomic features considered "undruggable" based on current precision therapy approaches. Therefore, DLL3-targeted therapies may serve as a promising strategy for NEN patients with functional loss of tumor suppressors TP53 and RB1, as well as increased activity of KRAS, WNT and MYC signaling. Research Sponsor: None.

4128 **Poster Session**

Targeted alpha-emitter therapy with ^{212}Pb-DOTAMTATE in neuroendocrine tumor subjects who progressed following prior ^{177}Lu/^{90}Y-PRRT. *First Author: Ebrahim Delpassand, Excel Diagnostics and Nuclear Oncology Center, Houston, TX*

Background: Targeted Alpha-Emitter Therapy (TAT) with ^{212}Pb-DOTAMTATE has been shown to be safe and effective in subjects with neuroendocrine tumors (NET) who have not received previous PRRT, however, data is lacking for the use of TAT once progression occurs. Herein, we present the safety and efficacy of ^{212}Pb-DOTAMTATE in subjects with recurrent NETs following prior ^{177}Lu/^{90}Y-PRRT. **Methods:** Subjects with biopsy-proven unresectable or metastatic SSTR expressing NETs from different primary sites with at least one measurable lesion who had received progressed after receiving prior PRRT were enrolled and received up to four 8-week cycles of ^{212}Pb-DOTAMTATE at 67.6 μCi/kg/cycle. Response to treatment was measured per RECIST 1.1 criteria and by ^{68}Ga/^{64}Cu-DOTATATE PET/CT. Safety parameters were also obtained. **Results:** A total of 11 PRRT subjects were enrolled regardless of primary tumor location (pancreas (4), small bowel (3), midgut (1), ileum (1), thymus (1), and lung (1)). 8/11 subjects (73%) completed all four cycles. The mean cumulative dose was 20.9 mCi. As of January 2022, an objective radiological response (ORR) was demonstrated in 30% of evaluable subjects (1CR, 2PR, and 7 SD). In addition, 70% (7/10) evaluable subjects demonstrated a response per ^{68}Ga/^{64}Cu-DOTATATE PET/CT SSTR imaging. One hundred forty-five AEs were reported, with Grade 1 (79%). There were 23 (16%) Grade 2 AEs and 5 (3%) Grade 3/ 4 AEs. Of the AEs reported, 84 (58%) were considered possibly related, and 61 (42%) were considered not related or unlikely related. The most frequent AEs (reported in ≥ 4 subjects) include: alopecia (100%), fatigue (100%), nausea (91%), anemia (36%), alanine aminotransferase increased (36%), aspartate aminotransferase increased (36%) and lymphopenia (46%). Three SAEs were reported (achalasia, asthma exacerbation, and septic shock) one of which resulted in the death of the subject (septic shock). No SAEs were considered related to study drug. **Conclusions:** This is the first clinical trial of ^{212}Pb-targeted alpha-emitter therapy in subjects with NETs who progressed following prior PRRT. The use of ^{212}Pb-DOTAMTATE in the recurrent setting is highly effective with manageable toxicity and warrants further investigation. Clinical trial information: NCT03466216. Research Sponsor: NCI SBIR direct to Phase II 1R44CA265421, Pharmaceutical/Biotech Company.

4129 **Poster Session**

Analysis of molecular characterization: Pancreatic ductal adenocarcinoma with hepatic metastases. *First Author: Yonggang He, Department of Hepatobiliary, The Second Affiliated Hospital of Army Medical University, Chongqing, China*

Background: Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal solid tumors. Distant metastasis is the leading cause of cancer death. Approximately 50% of PDAC patients are discovered to have distant metastases, mainly in the liver. Chemotherapy is the main recommended treatment for metastatic PDACs, with a median survival time of only 4-6 months and the 5-year survival of 1%. Therefore, deciphering the molecular mechanisms of metastatic PDAC is urgently for exploring effective therapeutic targets. **Methods:** 93 normal-paired samples from patients with PDAC were analyzed using hybridization capture-based next generation sequencing. Somatic and germline mutations were identified including 500 genes associated with tumor development. Sequencing data were analyzed to call tumor specific single nucleotide variants (SNV), small insertions and deletions (InDels), copy number alterations (CNA) and gene fusions and rearrangements. **Results:** A total 93 patients with PDAC were analyzed, including hepatic metastases (15/93), lymph node metastases (1/93), colon metastases (1/93), pelvic metastases (1/93), and no distant metastasis (75/93). In PDAC patients without distant metastasis, the most frequent mutated gene was *KRAS* (72%), followed by *TP53* (60%), *CDKN2A* (21%), *SMAD4* (17%), *ARID1A* (11%), *RNF43* (9%), and *RBM10* (8%). In PDAC patients with hepatic metastases, we found that the most frequent one was *KRAS* (100%), followed by *TP53* (87%), *CDKN2A* (40%), *SMAD4* (40%), *RNF43* (13%), and *RBM10* (6%). Furthermore, four PDAC patients occurred KRAS copy number amplification, including 2 cases of hepatic metastases. And a hepatic metastases PDAC patient had *ERBB2* and *MET* copy number amplification. We also found that seven no-metastasis patients carried pathogenic or likely pathogenic germline variants, including *BRIP1*, *PALB2*, *RECQL*, *ATM*, *RAD50*, *FANCM* and *BRCA1*. **Conclusions:** High frequency mutation genes in PDAC patients with hepatic metastases were highly consistent with those of no-metastasis patients. *KRAS* and *TP53* gene co-mutations were extensively mutated in hepatic metastases patients. Our results revealed the molecular mechanisms driving PDAC hepatic metastases should be considered in further study. Research Sponsor: None.

4130 **Poster Session**

KRAS wild-type pancreatic ductal adenocarcinoma: Molecular and therapeutic opportunities. *First Author: Aakash Desai, Mayo Clinic Rochester, Rochester, MN*

Background: *KRAS* is mutationally activated in over 90% of pancreatic ductal adenocarcinoma (PDAC). Compared to pts with *KRAS* mutation, *KRAS* wild-type (wt) PDAC seem to have better response to therapy and may harbor potentially actionable molecular alterations. Here, we analyze the molecular profile and clinical outcome of a cohort of pts with *KRAS* wt PDAC. **Methods:** A retrospective review was conducted on pts with PDAC who underwent CLIA-certified Next Generation Sequencing (NGS) testing at Mayo Clinic between December 1, 2018 and December 1, 2021. Pts with *KRAS* wt PDAC with available reports were included. Their genomic drivers, RNA expression, demographics, disease characteristics, therapies offered, and clinical outcome data were collected. The study was approved by the institutional IRB. **Results:** Of the 241 eligible pts, 8% (19) has *KRAS* wt PDAC. Among those, 2 pts had no mutation identified by the gene/molecular panel used. Of the 17 pts (89%) with identified alterations, mutations found in ^{3} 2 pts were TP53 (53%), CDKN2A (16%) and CDKN2B/ERBB2/PTEN/MSH3/RNF43/FBXW7/KMT2D/GNAS (11% each). Chromosomal rearrangements were identified in 5 (26%): CADPS2-BRAF, GP2-ERBB2, PTPRK-RSPO3, EML4-NTRK3 and TFG-MET. RNA expression results were available in 12 pts: common overexpression were ERBB2 (27%) and MET/NRAS/MYC/CCDN1/CCNE1/AR (18% each); and the under-expression MGMT (18%). Among the 13 pts with available MSI status via NGS, 2 (11%) were MSI-high (both had high TMB [28.4 and 23.7 m/MB]) while all others were TMB < 10 m/MB. The median age at diagnosis was 61 years (68% males). 8/19 (42%) were Stage IV at diagnosis with 15/19 (79%) pts ultimately diagnosed with metastatic disease. Among metastatic pts, median lines of treatment received was 2.5 (range:0-4). 4 pts received FOLFIRINOX (FFX), 2 gemcitabine/*nab*-paclitaxel (GP) and tumor response were comparable to previously reported results. 1 received 1st-line pembrolizumab and remained on therapy at the time of analysis. The median length of follow up from diagnosis was 29 months. A patient with TFG-MET re-arrangement previously progressed on FFX and GP was treated using a MET inhibitor, and achieved significant CA19-9 drop and pancreas tumor shrinkage at 1st restaging, with ongoing response. **Conclusions:** The molecular profile of *KRAS* wt PDAC is highly heterogeneous and difficult to generalize. Novel approaches (e.g., basket trials) are needed to develop therapy for this rare PDAC subgroup. Research Sponsor: None.

4131 **Poster Session**

A descriptive study on the treatment and outcomes of patients with platinum-sensitive, advanced, *BRCA*- or *PALB2*-related pancreatic cancer who have progressed on rucaparib. *First Author: Timothy J Brown, Abramson Cancer Center, Hospital of the University of Pennsylvania, Philadelphia, PA*

Background: We recently reported the results of a single arm phase II study of maintenance rucaparib in patients with platinum-sensitive advanced pancreatic cancer and a pathogenic variant in *BRCA1, BRCA2*, or *PALB2* (NCT 03140670; Reiss, JCO 2021). However, optimal treatment following progression on PARP inhibitors (PARPi) has not been defined. Here, we report a descriptive study of post-progression treatment and outcomes of this patient population. **Methods:** Patients with advanced pancreatic cancer and germline or somatic *BRCA1, BRCA2*, or *PALB2*mutations treated with at least 16 weeks of platinum-based chemotherapy without progression were enrolled and treated with rucaparib until progression or unacceptable toxicity. At the time of progression, patients were treated with physician-choice chemotherapy. Here we evaluate the objective response rates (ORR) by RECIST 1.1. Overall survival (OS) and time to second progression (PFS2) calculated from trial enrollment and progression free survival on chemotherapy (PFS) by regimen were secondary endpoints. Time-to-event was analyzed by the Kaplan-Meier method and censored at date of last clinic visit, with a cutoff date of 12/10/21. **Results:** The trial enrolled 42 patients; 31 patients had progressed. Of these, 22 received second-line chemotherapy: nine were treated with an oxaliplatin-based regimen, nine were treated with a cisplatin-based regimen, and four were treated with non-platinum regimens. Demographics were balanced between those who received platinum versus non-platinum. All patients who received second-line chemotherapy regimens met the PFS2 endpoint and all but one patient had died at time of data cutoff. No patients had a complete response, five patients had a partial response (PR). By regimen, 1/9 patients treated with cisplatin had a PR, 3/9 treated with oxaliplatin had a PR, and 1/4 patients treated with non-platinum had a PR. OS, PFS2, PFS, and ORR results by regimen are shown in the table. **Conclusions:** In this small sample of patients with advanced pancreatic cancer with progressive disease on PARPi, chemotherapy retains some activity. Further study to identify predictors of response and/or resistance to post-PARPi treatment are underway. Research Sponsor: U.S. National Institutes of Health.

Comparison		OS (months)	PFS2 (months)	PFS (months)	ORR (%)
Platinum vs Non-platinum	Platinum (n=18)	14.8 (9.3-21.5)	9.1 (5.4-15.1)	2.9 (2.0-5.9)	22.2 (6.4-47.6)
	Non-platinum (n=4)	20.3 (14.4-NR)	6.6 (5.5-NR)	3.9 (1.0-NR)	25.0 (0.6-81.0)
Platinum Type	Cisplatin (n=9)	13.8 (5.8-21.5)	9.1 (3.1-15.1)	2.9 (1.5-7.4)	11.1 (0.3-48.2)
	Oxaliplatin (n=9)	19.0 (5.0-23.0)	9.4 (3.8-20.7)	3.7 (1.6-8.4)	33.3 (7.5-70.0)

OS is defined from study enrollment until death. PFS2 is time from study enrollment until second progression. PFS is defined as time from chemotherapy initiation (after rucaparib) and progression. NR= not reached.

4132 **Poster Session**

The impact of HRD in patients with pancreatic adenocarcinoma undergoing surgical resection: An updated analysis. *First Author: Gudbjorg Jonsdottir, University of Iowa Hospitals and Clinics, Department of Internal Medicine, Division of Hematology, Oncology, and Blood & Marrow Transplantation, Iowa City, IA*

Background: Limited data is available regarding which mutations in the homologous recombination repair (HRR) pathway beyond BRCA can be targeted with platinum-based chemotherapy in the perioperative setting in patients with pancreatic ductal adenocarcinoma (PDAC). In this updated analysis, we assess the outcome of patients with homologous recombination deficiency (HRD) in response to platinum vs. non-platinum based perioperative chemotherapy in resected PDAC and have included additional variants linked to HRD. **Methods:** Patients with resectable PDAC, diagnosed between 1999-2020 from the participating members of the Oncology Research Information Exchange Network (ORIEN) were included in the study. Patient's germline and somatic whole exome sequencing (WES) data were analyzed for known pathogenic and likely pathogenic variants according to ClinVar for the following HRR pathway genes: *BRCA1, BRCA2, PALB2, BRIP1, BRAD1, BLM, BAP1, ATM, RAD51C, RAD51, RAD50, RAD54B, CHECK2, NBN, FANCA/B/C/D2/E/F/G, ARID1A, MRE11 and XRCC2.* The Kaplan Meier method was used to compare median overall survival (mOS) between patients with and without HRR pathway mutations in response to perioperative platinum vs non-platinum-based chemotherapy. Multivariate cox proportional hazard model was used to calculate HR and 95% CIs adjusting for age, sex and pathologic stage. **Results:** The ORIEN cohort included 311 patients with resectable PDAC and available WES data. A total of 22 patients (7%) had an HRR pathway mutation. Of these, 8 (36%) received perioperative platinum-based chemotherapy and 9 (41%) a non-platinum based regimen, 4 patients (23%) received no perioperative systemic treatment. Frequency of HRR variants detected: BRCA2 n=8 (2.6%), BRCA1 n=3 (1%), ATM n=2 (0.6%), ARID1A n=1 (0.3%), BRIP1 n=1 (0.3%), CHECK2 n=1 (0.3%), FANCG n=1 (0.3%), PALPB2 n=1 (0.3%), RAD50 n=4 (1.3%), RAD51C n=1 (0.3%). The mOS for patients with HRR mutations exposed to perioperative platinum-based chemotherapy was 3.5 years (95% CI 3.4-NA), patients with HRR mutation but no platinum exposure had a mOS of 1.2 years (CI 0.9-NA). In patients with no HRR mutation exposed to platinum-based chemotherapy mOS was 2.7 years (CI 2.3-3.9) and in those without exposure mOS was 2.9 years, p=0.43. Comparison of risk of death between the 4 groups is demonstrated in the table. **Conclusions:** There was a trend towards improved survival in patients with PDAC who harbored a HRR pathway mutation and were treated with perioperative platinum-based chemotherapy compared to those with no platinum exposure. Our results highlight the importance of identifying patients with HRD beyond BRCA and the need for large prospective studies in the perioperative setting to further assess their predictive role. Research Sponsor: None.

	HR	95% CI	P-value
HRD-, non-platinum	Reference	-	-
HRD+, non-platinum	2.53	0.99-6.5	0.05
HRD-, platinum	1.06	0.69-1.6	0.81
HRD+, platinum	0.78	0.26-2.3	0.65

4133 **Poster Session**

Perioperative or adjuvant nab-paclitaxel plus gemcitabine for resectable pancreatic cancer: Updated final results of the randomized phase II AIO-NEONAX trial. *First Author: Thomas Jens Ettrich, Ulm University Hospital, Department of Internal Medicine I, Ulm, Germany*

Background: Perioperative chemotherapy (CTX) in resectable pancreatic ductal adenocarcinoma (PDAC) is still not considered standard of care and data are limited. The NEONAX trial examined gemcitabine (Gem) plus nab-paclitaxel (nab-P), in the perioperative or adjuvant therapy of resectable PDAC (NCCN criteria). **Methods:** NEONAX is a prospective, randomized phase II trial with two independent experimental arms. 127 resectable PDAC patients in 22 German centers were randomized 1:1 to perioperative (2 pre- and 4 postoperative cycles, arm A) or adjuvant (6 cycles, arm B) of Gem (1000mg/m2) and nab-P (125mg/m2) on days 1,8,15 of a 28-day cycle. **Results:** We previously reported the primary endpoint disease free survival (DFS) at 18 mo. in the modified intention-to-treat (ITT)-population (defined as R0/R1 resected pts. that either started neoadjuvant (A) or adjuvant (B) CTX. The pre-defined DFS rate of 55% at 18 mo. was not reached in both arms (A: 32.2%, B: 41.4%). Here we present the final results of the secondary endpoints median overall survival (mOS), pN0-resection rate, perioperative morbidity/mortality and safety in the ITT-population. Most common grade ≥3 treatment emergent adverse events in the safety population were neutropenia (arm A 21.1%, arm B 12.3%), fatigue (arm A 8.8%, arm B 5.3%) and anemia (arm A 10.5%, arm B 1.8%). The most frequent post-/perioperative complications of all grades in pts. undergoing resection were infections (arm A: 24.4%, arm B: 8.8%), pancreatic fistulas (arm A: 14.6%; arm B: 13.3%) and bleedings (arm A: 9.7%; arm B: 6.7%). Perioperative mortality was 2.4% in the neoadjuvant and 6.7% in the upfront surgery setting. The median number of resected lymph nodes was comparable in both arms (A: n = 21, B: n = 26). The pN0-resection rate was 33.3% in the neoadjuvant/perioperative arm A and 29.5% in the upfront surgery arm B. R0 resection rates were 87.8% in arm A and 67.4% in arm B, respectively. Median OS as a key secondary endpoint in the ITT population was 25.2 mo. in arm A and 16.7 mo. for upfront surgery, a difference of 8.5 mo. This difference corresponds to a mDFS of 11.5 mo. in arm A and 5.9 mo. in arm B. 91.5% of pts. in arm A started and 84.7% completed neoadjuvant CTX but only 42.4% of pts. in arm B started adjuvant CTX. **Conclusions:** Perioperative treatment with Gem/nab-P was well tolerated and showed an encouraging mOS of 25.2 mo., this is well in the range of the data in SWOG 1505 (23.6 mo.) or PREOPANC (15.7 mo.). The corresponding mOS in the upfront surgery arm was 16.7 mo. The 8.5 mo. difference may be explained by the fact that many pts. in arm B did not receive adjuvant treatment whereas the vast majority of pts. in arm A completed at least preoperative CTX. Neoadjuvant/perioperative treatment is a promising novel option for pts. with resectable PDAC. The optimal treatment regimen is subject of current clinical trials. Clinical trial information: NCT02047513. Research Sponsor: Bristol Myers Squibb GmbH & Co. KGaA.

4134 **Poster Session**

Resectable pancreatic adenocarcinoma neo-adjuvant FOLF(IRIN)OX-based chemotherapy: A multicenter, non-comparative, randomized, phase II trial (PANACHE01-PRODIGE48 study). *First Author: Lilian Schwarz, Rouen University Hospital, Rouen, France*

Background: Despite the limited number of published RCTs, patients with resectable pancreatic adenocarcinoma (rPAC; NCCN criteria) seem to benefit from neoadjuvant (NAT) with regards to R0 resection rate, downstaging and survivals (PREOPANC-1; Preop-02/JSAP-05; NEONAX, SWOG05-15). Few prospective results are currently available concerning the completion of the full therapeutic sequence and oncological results. **Methods:** In the PANACHE01-PRODIGE48 prospective multicenter controlled non-comparative Phase II trial, 153 patients with rPDAC were randomized 2:2:1 to 4 cycles of NAT chemotherapy (mFOLFIRINOX; Arm1 or FOLFOX; Arm2) or upfront surgery (Ctrl_Arm) in 28 French centers from 02/2017 to 07/2020. Primary objective was to evaluate the safety and efficacy of two regimens of NAT chemotherapy. The main co-primary endpoints were 1y-OS rate after randomization and the rate of patients undergoing the full therapeutic sequence. Event-free survival (EFS) was used to evaluate the time to recurrence between groups. An event being defined as progression before surgery, unresectable or metastatic disease at surgical exploration, recurrence after surgery or death. **Results:** Of the 153 randomized patients, 146 were available for analysis (Arm1,n=70; Arm2,n=50; Ctrl_arm,n=26). In the Arm1 and 2, completion of the 4 planed cycles was 88.6 and 84%, respectively, with a dose reduction in 52% and 24%. The cumulative rates of grade 3/4/5 toxicity were 56.7 and 57.4%, respectively. The resection rates (RR) were 74, 68 and 81% respectively in Arm1, Arm2 and Ctrl_Arm. Respectively, 88.4, 91 and 85.7% of patients started adjuvant chemo. 1y-OS rates were respectively of 84.1, 71.8 and 80.8% in Arm1, Arm2 and Ctrl_Arm with a median follow-up in each group of 25.6, 33, 30.9 months. Following the intermediate analysis, the Arm2 was stopped for lack of efficacy (rejection of the H0 hypothesis for 1yOS). 1y-Event free survival (EFS) rates were 51.4% in Arm1, 43.1% in Arm2 and 41.7% in Ctrl_Arm, with corresponding median EFS of 12.4, 11 and 9.2 months. **Conclusions:** The feasibility and efficacy of the mFOLFIRINOX neoadjuvant chemotherapy is confirmed regarding completion of therapeutic sequence and oncological outcomes. These results confirm the rationale for ongoing clinical trials, PREOPANC3 and Alliance AO21806. Clinical trial information: NCT02959879. Research Sponsor: Programme for Hospital Clinical Research in Cancer - FRANCE.

4135 **Poster Session**

Socioeconomic factors associated with a late-stage pancreatic cancer diagnosis: An analysis of the national cancer database. *First Author: Jillian Gallegos, Creighton University School of Medicine, Omaha, NE*

Background: Pancreatic cancer is an aggressive, lethal cancer that is the 4th leading cause of cancer death in the United States. It is often asymptomatic until later stages, thus it is critical to assess the socioeconomic factors associated with diagnosis at early vs. late stages. Using the National Cancer Database, we aim to identify associations between socioeconomic factors of patients that present with early stage (0-I) pancreatic cancer in comparison to late-stage disease (stage IV) at diagnosis. **Methods:** In this study, 256,822 patients from the National Cancer Database who were diagnosed with NCDB Analytic Stage Group stage 0-I and stage IV pancreatic cancer were analyzed based on age, race, sex, ethnicity, insurance type, income, geographic location, education and Charlson-Deyo score. Demographic factors of patients that presented with early and late-stage disease were analyzed using chi square and multivariate analysis. All patients included in the study were diagnosed with pancreatic cancer between 2004 and 2018. **Results:** We identified significant (P <0.05) associations between race, sex, insurance status, education, income, and geographic location with diagnosis of advanced-stage disease. A greater percentage of males were diagnosed with late-stage cancer than early-stage (52.8% vs 47.9%). Females were more likely to have an earlier-stage diagnosis and were 15% less likely to have late-stage diagnosis than males (p < 0.001 and 95% CI = 0.839-0.875). African Americans were 10% more likely to have a late-stage diagnosis than Caucasians (p < 0.001 and 95% CI = 1.069-1.144). For insurance status, private and Medicaid insurance had higher percentages of late-stage diagnosis than early-stages, and all types of insurance had lower rates of late-stage diagnosis than patients without insurance (p < 0.001). Patients from a zip-code associated with < $38,000 median household income and zip-codes with lower levels of high school diplomas had higher rates of late-stage diagnosis (p < 0.025). **Conclusions:** Factors associated with increased likelihood of pancreatic cancer presentation at advanced stage compared to early stage include race, sex, insurance status, education, median income, comorbidity score, and geographic location. Research Sponsor: None.

4136 **Poster Session**

Phase Ib study of anetumab ravtansive in combination with immunotherapy or immunotherapy plus chemotherapy in mesothelin-enriched advanced pancreatic adenocarcinoma: NCI10208. *First Author: Pavlina Spiliopoulou, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Mesothelin (MSLN) is overexpressed in 80-85% of pancreatic adenocarcinomas (PDAC). Anetumab ravtansine (AR) is a fully human anti-MSLN immunoglobulin G1 antibody conjugated to the anti-tubulin maytansinoid DM4. Through NCI-ETCTN, the North American Star Consortium conducted a phase I study to evaluate the safety/tolerability of AR in various combinations in patients (pts) with PDAC. Here, we report preliminary results of the escalation part. **Methods:** Pts with advanced PDAC after at least one line of treatment were included. AR was combined with nivolumab (ARM1), nivolumab/ipilimumab (ARM 2), or nivolumab plus gemcitabine (Gem) (ARM3), using an integrated biomarker analysis. Two dose levels (DL) of AR were evaluated, DL1=5.5mg/kg and DL2=6.5mg/kg (established RP2D). Key eligibility criterion was MSLN expression in >5% of tumor cells by immunohistochemistry. Pts with prior anti-PD1/anti-CTLA4 treatment were excluded but treatment with prior Gem was allowed. Mandatory blood and paired tumor samples were collected for investigation of the immune microenvironment, genomic/transcriptomic changes and for an in-depth description of AR pharmacokinetics. **Results:** Data cut-off date was 22/01/2022. A total of n=33 pts were enrolled, n=11 (ARM 1), n=13 (ARM 2) and n=9 (ARM3). Median age of pts was 66 (40-83), 33% of PS=0 and 66% of PS=1. Twenty-six pts (79%) had previously been exposed to Gem. Median number of prior lines of treatment was 3 (1-7). Twenty-eight patients were evaluable for DLT. Grade (G)3/4 TRAEs: 0% in ARM1DL1, 5.3% in ARM1DL2, 0% in ARM2DL1, 16.9% in ARM2DL2, 8.6% in ARM3DL1 and 19.5% in ARM3DL2. There were 2 dose-limiting toxicities in ARM2DL2, one G3 upper gastrointestinal haemorrhage, possibly related to AR, and one G3 thrombocytopenia and G3 anaemia, definitely related to AR. Ocular toxicity events were G1/2 blurred vision in 5/33 (15%) and G1 xerophthalmia in 1/33 (3%), related to both AR and anti-PD1; G2 keratitis in 1/33 (3%), related to AR only. Only G1 peripheral neuropathy was observed in 4/33 (12%) pts. Efficacy data is presented in the table. In ARM3, the range of tumor measurement (TM) change was Δ_{TM}=–16.8% to +16.2% and 3/8 (36%) pts with SD had previously been exposed to Gem. **Conclusions:** Based on the observed disease control rate and acceptable toleratbility, ARM3 (both DL1 and DL2) will be tested in the expansion part. A further 20 patients will be recruited for dose confirmation and comprehensive biomarker evaluation. Pharmacokinetic/pharmacodynamic analysis is under way. Clinical trial information: NCT03816358. Research Sponsor: U.S. National Institutes of Health.

Evaluable for response patients (n=25)	ARM1 (n=9)	ARM2 (n=8)	ARM3 (n=8)	
ORR (CR+PR)	0 (0%)	0 (0%)	0 (0%)	
SD	2 (22.2%	2 (25%)	8 (100%)	
PD	7 (77.8%)	6 (75%)	0 (0%)	
Duration of treatment, days (range)	48 (17-230)	42 (13-182)	99 (55-224)	p=0.0023

4137 **Poster Session**

Mutational landscape of pancreatic adenocarcinoma identified by prospective clinical sequencing in a nationwide cancer network. *First Author: Katherine E Poruk, Cancer Treatment Centers of America, Part of City of Hope, Newnan, GA*

Background: Curative treatment of pancreatic adenocarcinoma (PDAC) remains a challenge. Improved understanding of the tumor biology is needed to adequately target therapies for individual patients. Tumor genomic profiling is a critical component of precision medicine for these patients to identify potential genomic alterations that can be targeted for therapy. We present a cohort of PDAC patients who underwent prospective comprehensive genomic profiling (CGP) in a national cancer network. **Methods:** Between 2013 and 2021, 731 patients with PDAC underwent CGP with hybrid capture of up to 406 cancer-related genes on tumor tissue for treatment decision-making. Clinically relevant genomic alterations (CRGA) were defined as associated with targeted therapies or mechanism-driven clinical trials. Patient demographics and outcomes were retrospectively reviewed with IRB approval. **Results:** Median patient age at presentation was 58 years (range, 26-87) and a slight majority were male (54%). Most patients presented with stage IV disease (n=457; 63%). Median overall survival (OS) was 26 months for stages I-III and 15 months for stage IV disease. A majority of patients were treated with first line chemotherapy, predominantly gemcitabine or FOLFIRINOX. Surgical resection was performed in 198 patients (27%). Genomic alterations (GA) were identified in 96% of PDAC patients. The most common GA were in *KRAS* (86%), *TP53* (75%), *CDKN2A* (49%), *SMAD4* (21%), *ARID1A* (7.8%), *RNF43* (5%), *BRCA2* (4%), *and BRCA1* (1%). A mutation in one of the four commonly mutated genes (*KRAS*, *TP53*, *CDKN2A*, or *SMAD4*) was identified in 92% (n=675). Common *KRAS* mutations were G12D(43%), G12V (30%), and G12R(16%). Median OS was significantly worse for patients with mutations in *KRAS*, *TP53* and *CDK2NA*, while wild type *RNF43* demonstrated improved OS (all, P<0.05). 206 patients (28%) had a CRGA based on the Know Your Tumor registry trial, including mutations in *BRCA1*, *BRCA2*, *BRAF*, *ATM*, *CHEK2*, and *ATK*. Tumor Mutational Burden (TMB) was known for 345 patients and included: 292 TMB-low (85%), 49 TMB-intermediate (14%), and 4 TMB-high (1%). PD-L1 status was obtained in 33 patients, with 18 PD-L1 positive (55%). MSI status was noted for 345 patients; only 5 patients (1%) were MSI-high. Of the 39 patients with a *BRCA1* or *BRCA2* mutation, 30 (77%) were treated with Olaparib. Other commonly utilized therapies included Niraparib (n=56), Regorafenib (n=8), Everolimus (n=35), Erlotinib (n=8), and Cetuximab (n=7). **Conclusions:** In a large series of PDAC patients assayed with CGP, GA were identified in 96% but only 28% had an actionable mutation. Access to the TAPUR trial allowed for an increase in the patients identified for targeted immunotherapy between 2013 and 2019, although overall use remained low for PDAC. Further research is needed to identify therapies based on the more commonly mutated genes given their association with overall survival. Research Sponsor: None.

4138 **Poster Session**

A phase I/II study of LOAd703, a TMZ-CD40L/4-1BBL-armed oncolytic adenovirus, combined with nab-paclitaxel and gemcitabine in advanced pancreatic cancer. *First Author: Benjamin Leon Musher, Baylor College of Medicine, Houston, TX*

Background: Due to its low tumor immunogenicity and immunosuppressive microenvironment, pancreatic ductal adenocarcinoma (PDAC) remains an immunotherapeutic challenge. LOAd703, an oncolytic adenovirus with transgenes encoding TMZ-CD40L and 4-1BBL, has been shown to lyse tumor cells selectively, induce anti-tumor cytotoxic T-cell responses, reduce myeloid-derived suppressor cell (MDSC) infiltration, and induce tumor regression in preclinical studies. **Methods:** In this phase I/II trial, patients with unresectable or metastatic PDAC were treated with intratumoral injections of LOAd703 and standard intravenous nab-paclitaxel/gemcitabine (nPG) chemotherapy. Starting on cycle 1 day 15 of nPG, LOAd703 was injected with image guidance into the primary pancreatic tumor or a metastasis every 2 weeks for 6 injections. In the event of sustained tumor control, subjects were eligible to receive up to 6 more injections. Three dose levels of LOAd703 were investigated using a BOIN dose escalation design. Primary endpoints were safety and feasibility. **Results:** Of the 22 subjects enrolled, 21 received at least 1 LOAd703 injection, and 18 received at least 3 LOAd703 injections (the *a priori* definitions of evaluability for dose limiting toxicity [DLT] and efficacy, respectively). Of the 21 subjects injected, median age was 61, 81% had stage IV disease, and 57% had already received chemotherapy for advanced disease. Median CA 19-9 was 1494. Of the 18 response evaluable subjects, 3 were treated at dose level 1 (5x10e10 VP), 4 at dose level 2 (1x10e11 VP), and 11 at dose level 3 (5x10e11 VP). The most common adverse events (AEs) attributable to LOAd703 were fever, chills, nausea, and increased liver enzymes. AEs were short-lived and grade 1/2, except for a grade 3 transaminase elevation in one subject receiving dose level 3 (the only DLT). Objective response rate (ORR) among those treated at the highest dose level was 55% (5/11 subjects), thus meeting the predefined criterion for efficacy. Among all response evaluable patients, overall response rate (ORR) was 44%, and disease control rate (DCR) was 94%. CA 19-9 decreased by ≥50% in 61% of evaluable patients. Median overall survival (OS) among the 21 subjects receiving at least 1 LOAd703 injection was 8.7 months. The proportion of T effector memory cells increased after initiation of on-protocol treatment ($p = 0.0232$) while the proportion of T regulatory cells and myeloid-derived suppressor cells decreased ($p = 0.0410$, $p = 0.0256$, respectively). **Conclusions:** Combining intratumoral injections of LOAd703 with standard nPG chemotherapy was safe and feasible. The target response rate at the highest dose level was met, and treatment-emergent immune responses were observed. A follow-up clinical trial combining LOAd703, nPG, and the anti-PDL-1 inhibitor atezolizumab is underway. Clinical trial information: NCT02705196. Research Sponsor: LOKON Pharma AB, Swedish Cancer Society, Swedish Research Council.

4139 **Poster Session**

Evaluation of stage IV pancreatic adenocarcinomas based on mutational profiling of tumors. *First Author: Katherine E Poruk, Cancer Treatment Centers of America, Part of City of Hope, Newnan, GA*

Background: Curative treatment of pancreatic adenocarcinoma (PDAC) remains a challenge, as most patients present with advanced disease that has spread to other organs. The main opportunity for cure for these individuals remains systemic therapy. An improved understanding of the tumor biology is needed to appropriately target therapies for individual patients. We present cohort of Stage IV PDAC patients who underwent prospective comprehensive genomic profiling (CGP) in a national cancer network to evaluate genomic mutations, treatment patterns and survival. **Methods:** Between 2013 and 2021, 458 patients with Stage IV PDAC underwent CGP with hybrid capture of up to 406 cancer-related genes on tumor tissue for treatment decision-making. Clinically relevant genomic alterations (CRGA) were defined as associated with targeted therapies or mechanism-driven clinical trials. Patient demographics and outcomes were retrospectively reviewed with IRB approval. **Results:** Median patient age at presentation was 59 years (range, 26-84) and a majority were male (55%). Median overall survival was 15 months. Most patients were treated with first line chemotherapy, predominantly gemcitabine or FOLFIRINOX. GA were identified in 98% (n = 447) of PDAC patients. The most common genomic alterations were in *KRAS* (85%), *TP53* (75%), *CDKN2A* (52%), *SMAD4* (21%), *ARID1A* (9%), *BRCA2* (5%), *RNF43* (4%), *and BRCA1* (1%). A mutation in one of the four commonly mutated genes (*KRAS*, *TP53*, *CDKN2A*, or *SMAD4*) was identified in 94% (n = 426). Median overall survival was significantly worse for patients with mutations in *KRAS* or *TP53* (both, $P < 0.05$). 185 patients (40%) had an actionable mutation based on the Know Your Tumor registry trial, including mutations in *BRCA1*, *BRCA2*, *BRAF*, *CHEK2*, *ATM*, *ATK* and *STK11*. MSI status was noted for 226 patients; only one patient was MSI-high. Tumor Mutational Burden (TMB) was known for 228 patients and was split as follows: 199 TMB-low (87%), 27 TMB-intermediate (12%), and 2 TMB-high (1%). TMB status was not associated with OS ($P = 0.21$). PD-L1 status was obtained in 20 patients, with 9 PD-L1 positive (45%); this was not associated with OS ($P = 0.66$). Of the 38 patients with a *BRCA1* or *BRCA2* mutation, 31 (82%) were treated with Olaparib. Other commonly utilized therapies included Niraparib (n = 56), Regorafenib (n = 8), Everolimus (n = 34), Erlotinib (n = 8), and Cetuximab (n = 6). **Conclusions:** In a large series of Stage IV PDAC patients assayed with CGP, GA were identified in 98% of tumors but only 40% had an actionable mutation. Most patients continue to be treated with conventional chemotherapy despite a sizeable group with targetable mutations. Further work is needed to identify targeted therapies for the more common mutations in PDAC given their impact on overall survival. Research Sponsor: None.

4140 **Poster Session**

A study of relacorilant in combination with nab-paclitaxel in patients with metastatic pancreatic ductal adenocarcinoma. *First Author: Erkut Hasan Borazanci, HonorHealth, Scottsdale, AZ*

Background: Pancreatic cancer remains the third-leading cause of cancer-related death in the US. Average overall survival is only one year, and no standard therapies exist beyond second line. Chemotherapy resistance is one reason for the poor outcomes in pancreatic cancer, which can be caused by, among other factors, excess tumor expression of the glucocorticoid receptor (GR). Nonclinical and clinical data indicate that GR antagonism may enhance or restore chemotherapy sensitivity. Here, we report the interim analysis of RELIANT, a trial evaluating the efficacy and safety of relacorilant, a selective GR modulator, with nab-paclitaxel in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC). **Methods:** RELIANT (NCT04329949) was a single-arm, open-label, multicenter study of relacorilant (100 mg QD) + nab-paclitaxel (80 mg/m^2 on days 1, 8, and 15 of each 28-day cycle) in patients with histologically confirmed mPDAC. Based on tolerability, relacorilant doses were escalated up to 150 mg. Patients with 2+ prior lines of therapy, including prior gemcitabine- and fluoropyrimidine-based therapy, were enrolled. Planned enrollment was 80 patients. The study included a planned interim analysis after approximately 40 patients had completed 12 weeks of treatment or discontinued study treatment due to disease progression or toxicity. Objective response rate (ORR) by blinded independent central review was the primary endpoint. At the interim analysis, ORR was assessed by the investigator. **Results:** At the interim analysis, 43 heavily pretreated patients with a median age of 64 years (range: 43–78; 56% male) had been enrolled. 27/43 (63%) patients had received ≥2 prior lines of therapy (range: 2–5), and all but 3 patients had received prior treatment with nab-paclitaxel. Twelve patients (28%) did not have a post-baseline radiographic tumor assessment and were hence not efficacy evaluable. Most common reasons for discontinuation from relacorilant were disease progression (n = 16), adverse event (AE, n = 8), and patient decision (n = 9). Relacorilant + nab-paclitaxel demonstrated antitumor activity with 15/43 (35%) patients showing decreases in target lesion size, 10/43 (23%) achieving disease control for at least 12 weeks, and 17/43 (40%) having decreases in CA 19-9. Of note, one patient has been on study treatment for > 15 months. No confirmed responses by RECIST (CR or PR) were observed, and enrollment was thus stopped after the interim analysis. No new safety signals were identified. The most common AEs were fatigue, nausea, and decreased appetite. Suppression of GR target genes was also observed. **Conclusions:** Modest antitumor activity of relacorilant + nab-paclitaxel was observed in this heavily pretreated patient population, with a safety profile similar to that observed for relacorilant in other oncology studies. Clinical trial information: NCT04329949. Research Sponsor: Corcept Therapeutics.

4141 **Poster Discussion Session**

Phase 1/2a trial of nadunolimab, a first-in-class fully humanized monoclonal antibody against IL1RAP, in combination with gemcitabine and nab-paclitaxel (GN) in patients with pancreatic adenocarcinoma (PDAC). *First Author: Eric Van Cutsem, University Hospitals Leuven, Leuven, Belgium*

Background: Interleukin-1 Receptor Accessory Protein (IL1RAP) is expressed on cancer and stromal cells in PDAC. The IL-1 pathway is active in the pancreatic tumor microenvironment and upregulated in response to chemotherapy. IL1RAP interacts with IL-1R1 and modulates downstream factors (e.g. IL-6, IL-8) and CRP level. Nadunolimab (CAN04), a fully humanized ADCC-enhanced IgG1 antibody, targets IL1RAP and blocks IL-1α and IL-1β signaling. Here, results are reported from the phase 1/2a clinical trial CANFOUR evaluating nadunolimab combined with GN in PDAC. **Methods:** Patients (pts) with previously untreated, unresectable, locally advanced or metastatic PDAC received nadunolimab at 1 (n=20) 2.5 (n=20), 5 (n=28) or 7.5 mg/kg (n=8) Q2W with standard GN. Primary objective was safety; secondary objectives included ORR, iPFS per iRECIST and OS, and exploratory objectives included effects on serum and tumor tissue biomarkers. **Results:** In total, 76 pts were enrolled: median age 63 years (43-89), 42% female, 93% stage IV, 45% PS=0, 9% received adjuvant chemotherapy. Treatment-related adverse events (AE) of grade≥3 were reported in 72% with neutropenia being most frequent. G-CSF prophylaxis was useful in managing neutropenic events. The 7.5 mg/kg dose was above MTD due to neutropenia. Infusion-related reactions were reported in 29% (grade 3 in 3%). Peripheral sensory neuropathy was rare (only two grade 2 events). Common treatment-related grade 3/4 AE are shown below. Seventy-three pts received combination therapy and were included in the efficacy analysis. Three pts did not receive chemotherapy due to consent withdrawal (n=2) or clinical deterioration (n=1). Median iPFS was 7.3 months (95% CI 5.6-8.9) with 15 pts still on treatment, median OS was 13.2 months (10.0-19.1) with 62% of pts alive and 1-year survival of 59% (42-72%). ORR was 33% (22-45), disease control rate 63% (51-74%) and duration of response 5.7 months (3.9-11.1). ORR was similar for all dose levels. Low baseline CRP was favorable for OS; reduction of serum IL-8 and CRP during Cycle 1 correlated with positive impact on OS. Also, neutrophil-lymphocyte ratio was reduced throughout the trial, driven by the reduction in circulating neutrophils. IL1RAP expression on cancer and stromal cells was confirmed in tumor biopsies. **Conclusions:** Nadunolimab combined with GN shows promising iPFS and OS and manageable safety in PDAC pts. A phase 2/3 trial of nadunolimab combined with chemotherapy in PDAC is planned and nadunolimab is also currently evaluated in additional combination trials with chemotherapy or IO. Clinical trial information: NCT03267316. Research Sponsor: Cantargia AB.

% worst grade per patient	1 mg/kg	2.5 mg/kg	5 mg/kg	7.5 mg/kg	Total
	n=20	n=20	n=28	n=8	n=76
Neutropenia	50	60	57	88	59
Leukopenia	20	5	36	25	22
Febrile neutropenia	15	5	18	13	13
Thrombocytopenia	10	10	7	13	9

4142 **Poster Session**

The tumor microenvironment and immune infiltration landscape of *KRAS* mutant pancreatic ductal adenocarcinomas (PDAC) compared to colorectal adenocarcinomas (CRC). *First Author: Emil Lou, Masonic Cancer Center/ University of Minnesota School of Medicine, Minneapolis, MN*

Background: The composition of the tumor microenvironment (TME) in PDACs is more heavily driven by mutant (mt) *KRAS* than any other cancer. How genomic alterations of PDAC including *KRAS* status affect the immune cell (IC) landscape remains unclear. Thus, we characterized IC types and the prevalence of immuno-oncologic (IO) biomarkers in PDAC by genomic and transcriptomic analysis, and investigated associations of mt *KRAS* with IC estimates in the TME. Our findings were compared to our previous study in CRC. **Methods:** A total of 4,142 PDAC and 3,727 CRC with *KRAS-mts* were analyzed using next-generation DNA sequencing (NextSeq, 592 gene panel or NovaSeq, WES), IHC, and whole transcriptome RNA sequencing (NovaSeq) (Caris Life Sciences, Phoenix, AZ). MSI/MMR was tested by FA, IHC and NGS. TMB-H was classified based on a cut-off of >10 mutations per MB. ICs were estimated by QuantiSeq (Finotello 2019, *Genome Medicine*) or MCP counter (Betcht 2016, *Genome Biology*). Significance was determined by X^2 and Fisher-Exact and p-adjusted for multiple comparisons (q<0.05). **Results:** Mutant *KRAS* was seen in 81% of PDAC and in 48% of CRC. The most common variant was *G12D*, comprising 43% and 32% of all PDAC and CRC *KRAS* variants, respectively. The therapeutically actionable *KRAS G12C* variant comprises 2% and 7% of PDAC and CRC in this cohort, respectively. In PDAC, *KRAS* mt was associated with lower prevalence of MSI-H/dMMR than *KRAS*-wildtype (wt); 0.9% vs 1.9%, p=0.027). PDL1 expression was significantly lower in *KRAS* wt (12%) compared to *G12D* (19%) and *G13X* (33%), similar to previous observations in CRC. However, when considering TMB, in PDAC, *G12D* (1%), *G12V* (1%) and *Q61* (1%) mutations had significantly lower TMB-H than *RAS* wt tumors (4%); in contradiction to CRC. The immune cell environment of *KRAS* mt PDAC showed significantly higher infiltration with M1 macrophages and cancer-associated fibroblasts (CAFs), as well as lower M2 macrophages, $CD4^+$ & $CD8^+$ T cells, T-reg, NK, myeloid dendritic and endothelial cells compared to *KRAS* wt. In CRC, a similar pattern was observed but more pronounced in PDAC. Immune-regulatory markers, were among multiple genes downregulated in *KRAS*-mt PDAC, including *CTLA-4* and *LAG3*. Overall changes were most pronounced in cases harboring *KRAS G12D*, *G12V*, *Q61*, and rare *KRAS* variants. **Conclusions:** The TME of *KRAS* mt PDAC shows IC patterns similar to *KRAS* mt CRC. Actionable IO-targets, such as PDL1, are enriched in tumors harboring specific variants of *KRAS* mt PDAC including the targetable *G12C* variant. If *G12D* becomes druggable, it could be targetable in 35% patients with PDAC or 15% in CRC. These results demonstrate that the TME of PDAC and CRC shows immune-cold features. Tailored immunotherapeutic strategies would have to overcome these barriers in *KRAS* mt PDAC and CRC, possibly in combination with molecularly targeted treatment strategies. Research Sponsor: Caris LLC.

4143 **Poster Session**

Gut microbiota composition and outcomes following neoadjuvant therapy in patients with localized pancreatic cancer: A prospective biomarker study. *First Author: Pranav Murthy, Department of Surgery, University of Pittsburgh, Pittsburgh, PA*

Background: The prognostic role of the gut microbiome, which modulates cancer development and therapeutic response, is unknown in patients with pancreatic ductal adenocarcinoma (PDAC). With increasing utilization of neoadjuvant therapy (NAT) prior to pancreatic cancer surgery, identification of patient-specific biologic signatures associated with NAT response *a priori* could help inform PDAC precision medicine. Thus, we assessed the influence of the baseline gut microbiome on clinical outcomes in patients with PDAC receiving NAT. **Methods:** Stool samples were collected at diagnosis from 42 consenting patients with localized PDAC intending to undergo NAT and surgical resection between 2018 and 2020. 16S rRNA sequencing was completed on pre-NAT stool and resected tumor samples. Microbiota alpha diversity and log transformed taxonomic classifications were utilized in multiple regression analyses to predict oncologic outcomes. **Results:** Five patients progressed during NAT and eight of the 37 operated patients were deemed NAT responders, demonstrating pathologic near complete or partial response (CAP 0-2), T1N0 AJCC 8^{th} staging, and ≥ 80% CA 19-9 reduction. Compared to the gut, the tumor microbiota demonstrated remarkably reduced Shannon diversity (2.4±0.5 vs 1.5±0.4, $p< 0.0001$) and distinct taxa (75.2±19.7 vs 8.0±4.5, $p< 0.0001$) and, accordingly, was not associated with clinical outcomes. Overall, several taxa, including *Bacteroides* and *Akkermansia,* were enriched in the gut relative to the tumor ($p< 0.001$). The gut microbiota of NAT non-responders had an increased proportion of the gemcitabine metabolizing *Enterobacteriaceae* (additive log ratio (ALR) -3.4±2.0 vs -8.7±0.8, $p= 0.0004$). NAT responders, by contrast, had an increased proportion of the adaptive immune cell activating *Akkermansia* (ALR -0.9±1.2 vs -6.2±3.3, $p= 0.0004$). The incidence of jaundice or biliary stent placement was associated with relative increases in *Enterobacteriaceae* (+3.3 ALR, $p< 0.01$ and +4.9 ALR, $p< 0.0001$) and decreases in *Akkermansia* (-3.2 ALR, $p= 0.02$ and -2.4 ALR, $p= 0.057$), without altering total gut microbiota diversity. Age, sex, BMI, comorbidities, receipt of pre-NAT antibiotics, diagnostic EUS tumor size, resectability, and pre-NAT CA 19-9 were not predictive of NAT response or survival in a univariate regression model. However, inclusion of gut microbiota data improved the ability of the model to predict NAT response ($p= 0.016$, adjusted R^2 0.76) and survival ($p= 0.001$, adjusted R^2 0.89), with *Enterobacteriaceae* (FDR $p= 0.012$) and *Akkermansia* (FDR $p= 0.015$) being significant negative and positive predictors of NAT response, respectively. **Conclusions:** The baseline gut microbiota could be leveraged as a biomarker of NAT response and prognosis in patients with pancreatic cancer and warrants further investigation. Research Sponsor: University of Pittsburgh Institutional Funds.

4144 **Poster Session**

A clinical study following phase I/IIa trial of STNM01 to investigate the overall survival and tumor microenvironment in patients with unresectable pancreatic cancer. *First Author: Takayoshi Tsuchiya, Department of Gastroenterology and Hepatology, Tokyo Medical University, Tokyo, Japan*

Background: Carbohydrate sulfotransferase 15 (CHST15) is a proteoglycan biosynthetic enzyme and responsible for tumor matrix remodeling. We reported last year the top-line clinical results of Phase I/IIa (PI/IIa) trial of STNM01, a synthetic RNA oligonucleotide to CHST15, as a second-line (2L) therapy in patients with progressive, unresectable pancreatic ductal adenocarcinoma (PDAC). Here we report the final PI/IIa results and follow-up clinical results investigating the changes of tumor microenvironmental parameters and the correlation with overall survival (OS). **Methods:** An additional clinical study was followed by PI/IIa trial (jRCT2031190055), which was a multicenter, open-label study of locoregional injections with STNM01 three times at 2 week-interval in 4 weeks as one cycle. A total of 3 cycles were repeated at maximum in combination with systemic 2L chemotherapy, oral fluoropyrimidine S-1 in the PI/IIa trial. The primary objective of this additional clinical study was OS. The secondary objectives were relations of tumor microenvironmental parameters evaluated by immunohistochemistry with OS. For comparison analyses, two-tailed unpaired t-test was performed. For correlation analyses, the Pearson coefficient analyses were performed. **Results:** A total of 22 patients were enrolled in the study. The average number of tumor-infiltrating $CD3^+$ (13.8/mm^2) and $CD8^+$ T cells (8.0/mm^2) at baseline in the evaluable population (n = 20) was at most one tenth or less, compared to historical data, indicating 2L population contained more T cell-immune suppressive patients. Baseline $CD3^+$ and $CD8^+$ T cells negatively correlated with tumoral CHST15 expression (p = 0.0051, p = 0.0478, respectively). As the final PI/IIa results, the median OS was 7.8 months with 6 and 12 months-survival rates of 68.2% and 31.8%, respectively. Disease control rate was 76.2% including 1 complete response. STNM01 led to a significant reduction in CHST15 at the end of cycle 1 compared to baseline (p = 0.0095, n = 19), and this was associated with increased $CD3^+$ (p = 0.0331) and $CD8^+$ T cells (p = 0.0146) and reduced $CD33^+$ myeloid-derived suppressor cells (MDSCs) (p = 0.0281) in the tumor. Patient subpopulation who survived over 1 year (n = 5) showed a significant fold increase of $CD3^+$ (p = 0.0033) and $CD8^+$ T cells (p = 0.0147) and decrease of $CD33^+$ MDSCs (p = 0.0403) at the end of cycle 1 compared to another subpopulation who survived less than 1 year (n = 13-14). Higher fold increase of $CD3^+$ T cells (p = 0.0035, n = 19) or fold decrease of $CD33^+$ MDSCs (p = 0.0212, n = 15) at the end of cycle 1 significantly correlated with longer OS. **Conclusions:** Locoregional injection of STNM01 was able to reactivate and augment tumor-infiltrating T cells while repress MDSCs. These changes in tumor immune cell profiles correlate with prolong prognosis in patients with first-line refractory, unresectable PDAC. Clinical trial information: jRCT2031190055. Research Sponsor: Japan Agency for Medical Research and Development.

4145 **Poster Session**

Responses to immune checkpoint inhibition among MSI-H pancreatic ductal adenocarcinoma: A multi-institutional case series. *First Author: Tucker Coston, Jacksonville, FL*

Background: Pancreatic ductal adenocarcinoma (PDAC) is the 4th leading cause of cancer death. Outcomes remain poor, due to irresectability at diagnosis for many and sub-optimal responses to systemic therapy. Cytotoxic chemotherapy remains the standard of care. High microsatellite instability (MSI-H) predicts response to immune checkpoint inhibition (ICI) in many cancers. Detecting high MSI is rare in PDAC (incidence <2%), but case reports demonstrate potential therapeutic benefit with ICI. Here, we present multi-institutional data to characterize the clinical behavior of MSI-H PDAC, with special attention to response to ICI. **Methods:** Cases of MSI-H PDAC were obtained by reviewing data of all PDAC patients from our tertiary cancer center who had undergone genomic sequencing by one commercially available platform. The resulting cohort was supplemented with MSI-H PDAC cases identified by GI oncology specialists at multiple institutions. De-identified patient data were compiled and analyzed. **Results:** 15 MSI-H PDAC patients were identified. 20% had stage II disease at diagnosis, 27% stage III, and 53% stage IV. 73% of patients received ICI (n=11); 40% as 1st line and 33% as 2nd line. These patients demonstrated 100% overall response rate; 45% complete response (1 pathologic CR, 4 radiographic CR) and 55% partial response. No patient that received ICI had lost response or died after a median follow-up of 18 months (range 6-89 mos). 1 patient had oligoprogression of a single hepatic lesion after 7 mos that was then irradiated; this patient retained radiographic CR for 17 subsequent mos (ongoing). In this cohort, we observe poor responses to cytotoxic chemotherapy. In total, 12 regimens were trialed among 9 patients. Overall response rate was 0%. 42% achieved disease stability, with median duration of response of 2 mos; only 2 cases maintained disease stability for >5 mos. 4 patients did not receive ICI; all patients died, with a median survival of 7.5 mos. **Conclusions:** MSI-H PDAC represents a rare but important subtype of PDAC with unique clinical behavior. Given its rarity, large-scale analyses and trials are unlikely to be performed, making case series such as ours crucial. In our cohort, we observe impressive, durable responses to ICI, along with very poor responses to cytotoxic chemotherapy. Our data argues for consideration of ICI in any patient presenting with MSI-H PDAC, including in the first-line and neoadjuvant settings. Research Sponsor: None.

4146 **Poster Session**

Phase I dose escalation and expansion study of defactinib, pembrolizumab, and gemcitabine in patients with advanced treatment-refractory pancreatic cancer. *First Author: Andrea Wang-Gillam, Washington University School of Medicine in St. Louis, St. Louis, MO*

Background: Targeting focal adhesion kinase (FAK) renders checkpoint immunotherapy effective in pancreatic ductal adenocarcinoma (PDAC) mouse models. Defactinib is a highly potent oral FAK inhibitor shown to have a tolerable safety profile. We evaluated the safety and recommended phase 2 dose (RP2D) of defactinib in combination with pembrolizumab and gemcitabine for PDAC patients. **Methods:** We conducted a multicenter, open-label, phase I study with dose escalation and expansion phases. In 3x3 dose escalation, patients with refractory solid tumors were treated at five escalating dose levels of defactinib and gemcitabine to identify a RP2D. In expansion phase, patients with metastatic PDAC who progressed on frontline treatment (refractory cohort) or had treatment response or stable disease (SD) on standard gemcitabine/nab-paclitaxel (maintenance cohort) were treated at RP2D. Pre- and post-treatment tumor biopsies were performed to evaluate changes in tumor immunity. **Results:** The triple drug combination was well-tolerated with no dose-limiting toxicities. Among 17 treated patients with refractory PDAC, the disease control rate (DCR) was 58.8% with one partial response (PR) and nine SDs and the median progression-free survival (PFS) and overall survival (OS) were 4.2 months and 9.1 months, respectively. Among the evaluable patients in the maintenance cohort, DCR was 63.6% with one PR and six SD. Three patients with SD came off study due to treatment- or disease-related complications. The median PFS and OS were 5.0 months and 8.3 months, respectively. **Conclusions:** The combination of defactinib, pembrolizumab, and gemcitabine was well-tolerated, had promising preliminary efficacy, and showed increased infiltrative T lymphocytes in post-treatment tumor biopsies. Incorporation of a more potent chemotherapy backbone should be considered to achieve better clinical response in future trial design. Clinical trial information: NCT02546531. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

4147 **Poster Session**

Phase 2 Quilt 88 trial of DAMP inducers combined with IL15 superagonist, N-803, and anti–PD-L1 NK cell therapy more than doubles historical overall survival in patients with third- to sixth-line advanced pancreatic cancer. *First Author: Tara Elisabeth Seery, Chan Soon Shiong Institute for Medicine, El Segundo, CA*

Background: Pancreatic cancer claimed 48,220 lives in the USA in 2021, with an expected median OS of 3 months after 2nd line. We hypothesize that effective response against pancreatic cancer requires a coordinated approach that orchestrates both the innate and adaptive immune system. We further hypothesize that by inducing DAMPs to expose tumor associated antigens and orchestrating the activation of the entire immune system, we could accomplish immunogenic cell death with durable responses in this disease, previously considered immune therapy resistant. We present results of a novel combination immunotherapy protocol, the NANT Cancer Vaccine: DAMP inducing metronomic low-dose chemoradiation, cytokine-induced NK and T cell activation via N-803 (an IL-15 cytokine fusion protein), and overcoming immune evasion with off-the-shelf PDL1-targeted high-affinity NK cell (PDL1 t-haNK) cell therapy infusion. **Methods:** We report data on 65 patients with > 2 prior lines of therapy (cohort B+C: Quilt 88), with 30 patients at 3rd line, 35 patients ≥4th line. Patients were treated every 4 weeks with low dose DAMP inducing chemo modulating therapy including Nab-paclitaxel (100 mg/ m2 IV), Gemcitabine (600 mg/m2 IV), Aldoxorubicin HCl (150 mg/m2 IV), Cyclophosphamide (50 mg PO BID) and low-dose SBRT. This pre-conditioning therapy induces expression of tumor associated antigens including PDL1 and is followed by cytokine stimulus of endogenous NK and T cells and allogeneic off-the-shelf NK cells to initiate immunogenic cell death via the innate and adaptive system. N-803 is administered at 15 μg/kg SC and PDL-1 engineered off-the-shelf NK cells (PDL1-thaNK) are infused weekly, to induce immune memory. All treatment was conducted as outpatients. **Results:** Follow-up 7 days to 18 months. Median age 62, 95% ECOG 0-1. Well tolerated with mainly low grade AEs [fatigue, chills, injection site reaction (> 50%)]. Treatment related grade ≥3 mainly associated with chemotherapy without prophylactic growth factors: anemia 46%, neutropenia 23%, thrombocytopenia 12%, all others < 10%. Patients with at least 1 Treatment related SAE = 6%; edema, pyrexia, anemia, atrial flutter. No treatment related deaths. In all patients (3rd to 6th line, N = 65) median OS is 5.8 months with 40% still alive; median PFS 2.3 months (95% CI: 2.0, 3.6), 32% not having progressed to date. In 3rd line (N = 30), median OS is 6.3 months (95% CI: 5.0, 9.8). Updated data will be presented. **Conclusions:** Early safety and efficacy is seen in QUILT 88 of the novel immunotherapy combination of DAMP inducers, NK and T cell activation, and PDL1 t-haNK cell therapy in Pancreatic Cancer. OS in 3rd line (6.3 months) exceeds historical results of 3 months across 19 trials (Manax ASCO GI 2019) and compares favorably with the 6.1 months in 2nd line patients in NAPOLI-1. Clinical trial information: NCT04390399. Research Sponsor: ImmunityBio.

4148 **Poster Session**

A randomized, non-comparative, phase II study of maintenance OSE2101 vaccine alone or in combination with nivolumab (nivo) or FOLFIRI after induction with FOLFIRINOX in patients (Pts) with advanced pancreatic ductal adenocarcinoma (aPDAC): First interim results of the TEDOPAM GERCOR D17-01 PRODIGE 63 STUDY. *First Author: Marc Hilmi, Medical Oncology Department, Curie Institute, Saint-Cloud, France*

Background: OSE2101 is a multiple neoepitope vaccine restricted to HLA-A2 positive Pts. This study aimed to assess the efficacy and safety of OSE2101 ± anti-PD1 nivo as maintenance therapy in Pts with aPDAC after FOLFIRINOX induction chemotherapy. **Methods:** TEDOPaM-PRODIGE 63 was initially a 3-arm, open-label, randomized, non-comparative phase II study. Pts with aPDAC, HLA-A2 positive (blood) and no progression after 8 cycles of (modified) FOLFIRINOX were randomized 1:1:1 to receive FOLFIRI (standard Arm A), OSE2101 (subcutaneous injection on D1 Q3W x 6 doses then Q8W until M12 then Q12W up to M24, experimental Arm B) or OSE2101 + nivo (360 mg IV on D1 Q3W x 6 then 480 mg Q4W up to M24, experimental Arm C). FOLFIRI was reintroduced at disease progression in Arms B and C. Primary endpoint was overall survival (OS) rate at 12 months (M12) (Fleming two-stage design, H0: 25%; H1: 50%, one-sided alpha: 2.5%, power: 90%). 156 Pts were planned. **Results:** Following the occurrence of 2 tumor flares in Arm C, an Independent Data Monitoring Committee (IDMC) recommended to continue FOLFIRI as backbone in experimental Arm B and stop Arm C. Interim analysis results refer to 29 randomized Pts: 9/10/10 in Arm A/B/C, respectively. Median age was 63 years, 52% were men, 55% had ECOG PS 0, and 83% were metastatic. Best response to induction FOLFIRINOX was partial response in 48% and stable disease in 52%. With a median follow-up of 23 months, M12-OS rate was 44%, 40%, and 30% in Arm A, B and C. Other efficacy results are summarized in Table below. No OSE2101-related toxicity of grade ≥ 3 (G≥3) were observed in Arm B; 1 G3 cytokine-release syndrome (OSE2101-related) and 2 tumor flares (nivo-related) leading to death were observed in Arm C. **Conclusions:** Maintenance OSE2101 monotherapy showed a favorable safety profile and encouraging time to strategy failure warranting further evaluation. OSE2101 + nivo was associated with poorer outcomes leading to close Arm C. Following IDMC recommendation, the study is ongoing with the new design (maintenance FOLFIRI vs. FOLFIRI + OSE2101). Clinical trial information: NCT03806309. Research Sponsor: OSE Immunotherapeutics, GERCOR.

	Arm A Maintenance with FOLFIRI N = 9	Arm B Maintenance with OSE2101 N = 10	Arm C Maintenance with OSE2101 plus nivolumab N = 10
M12-OS rate, % (95%CI)	44.4 (13.6-71.9)	40.0 (12.3-67.0)	30.0 (7.1- 57.8)
Median OS, months (95%CI)	11.5 (7.6-NA)	9.6 (4.1-NA)	7.9 (3.4-13.0)
Median progression-free survival, months (95%CI)	6.3 (1.8-NA)	2.7 (0.9-3.8)	2.2 (1.6-4.0)
Median time to failure of the strategy (maintenance + FOLFIRI reintroduction), months (95%CI)	6.3 (1.8-NA)	8.1 (2.0-NA)	5.7 (1.8-11.6)
Partial response, n (%)	1 (11.1%)	1 (10.0%)	0 (0.0%)

4149 **Poster Session**

Comparison of systematic inflammatory prognostic scores in patients with advanced pancreatic adenocarcinoma. *First Author: Lucy Xiaolu Ma, Princess Margaret Cancer Center, University Health Network, Toronto, ON, Canada*

Background: Systemic inflammatory scores have been developed as tools to aid clinicians in prognostication and patient (pt) selection for clinical trials. We compared the accuracy of five prognostic scores to predict overall survival (OS) in pts with advanced pancreatic adenocarcinoma (PDAC). **Methods:** Pts with advanced PDAC enrolled on the COMPASS trial (NCT02750657) from 2015 to 2020 were included. All pts had biopsies for whole genome and RNA sequencing prior to standard first-line chemotherapy in the advanced setting. Prognostic risk was calculated using: neutrophil-to-lymphocyte ratio (NLR; >5 = high), platelet-to-lymphocyte ratio (PLR; > 150 = high), Prognostic Nutritional Index (PNI = albumin + 5 x lymphocytes. PNI < 45 = high risk), Gustave Roussy Immune Score (GRIm-S; NLR>6 = 1 point, albumin <35 = 1 point, LDH > upper limit of normal [ULN] = 1 point. GRIm-S ≥2 = high risk), and Memorial Sloan Kettering Prognostic Score (MPS; NLR >4 and albumin < 40 = high risk). OS was estimated using the Kaplan-Meier method and compared between risk groups (high vs. not-high) for each scoring system using the log-rank test. Cox proportional hazards models were used to analyze the association between each prognostic score and OS, adjusting for baseline clinical and genomic factors. **Results:** In total, 263 pts with advanced PDAC cancer were included, with median follow up of 32.9 (95% CI 15.9-64.2) months. Median OS in the intention to treat population was 9.3 months (95% CI 8-10.2). PLR and PNI were not prognostic. High risk NLR (N=85, 32%), GRIm-S (N=47, 18%) and MPS (N=46, 17%) identified pts with poor prognosis. The GRIm-S and MPS were most significant: median OS in high vs low risk pts 6.4 vs. 10 months p<0.001 (GRIm-S) and 6.3 vs. 10 months p=0.002 (MPS). On multivariable analyses, high risk NLR, GRIm-Score and MPS were each associated with poor OS after adjusting for baseline clinical and genomic factors (Table). For all models, ECOG ≥1 (N=165, 63%); the basal-like Moffitt RNA subtype (N=49, 20% vs 80% classical) and low HRDetect scores (N=31, 13%) were significantly associated with poor OS. However these scores did not associate with RNA based classifiers or HRD scores and can therefore provide additional prognostic information. **Conclusions:** Both the GRIm-S and MPS are highly prognostic in PDAC and are scores easily used in the clinical setting and may help in clinical trial selection. Genotypic correlates are being explored. Research Sponsor: Government of Ontario, Wallace McCain Centre for Pancreatic Cancer, Princess Margaret Cancer Foundation, Terry Fox Research Institute, Canadian Cancer Society Research Institute, Pancreatic Cancer Canada Foundation.

Multivariable analyses of association between high risk group and OS for each prognostic score.

Model	Adjusted HR[1]	p-value
NLR	1.39 (1.01,1.90)	0.04
PLR	0.89 (0.66,1.21)	0.46
PNI	0.96 (0.67,1.36)	0.80
GRIm-S	1.85 (1.23,2.77)	0.0029
MPS	1.53 (1.05,2.25)	0.028

[1]Multivariable model for each prognostic score adjusted for age, sex, ECOG, Moffitt subtype and HRDetect score.

4150 **Poster Session**

Do we need postoperative chemotherapy after preoperative FOLFIRINOX in resected borderline or locally advanced pancreatic cancer? A retrospective analysis. *First Author: Roxane Mari, Medical Oncology Department, Institut Paoli-Calmettes, Marseille, France*

Background: Pancreatic ductal adenocarcinoma (PDAC) has poor outcome and surgical resection remains the only curative treatment. Post-operative (Post-Op) chemotherapy (CT) improves survival and FOLFIRINOX (FFX) regimen is the standard of care. Increasing number of patients with borderline resectable (BL) or locally advanced (LA) disease are treated with pre-operative (Pre-Op) CT with FFX. However, the benefit of Post-Op CT after Pre-Op FFX remains unclear. The aim of this study was to analyze the impact on survival of Post-Op CT in patients with resected BL or LA PDAC after Pre-Op FFX CT. **Methods:** 116 consecutive patients treated at the Institut Paoli-Calmettes comprehensive cancer center between 2014 and 2020 were retrospectively analyzed. All patients underwent pancreatectomy after Pre-Op FFX for a BL or LA PDAC. Patients who progressed or died within 3 months after surgery were excluded from the analysis. We compared median relapse-free survival (mRFS) and median overall survival (mOS) defined by time from surgery to relapse or death in patients who received or not Post-Op CT. **Results:** 116 patients (80% BL, 20% LA) were included: 82 received Post-Op CT (CT+) and 34 did not (CT-). The median number of Pre-Op FFX cycles was 4 in the CT+ group *vs* 6 in the CT- group. 24 (29.3%) patients received Post-Op FFX, 37 (45.1%) received Gemcitabine, 9 (11%) received Gemcitabine + Capecitabine, and 9 (11%) received a 5FU-based CT. Median time between surgery and first Post-Op CT cycle was 63 days. No difference in mRFS nor in mOS were found between CT+ and CT- groups: mRFS 15.0 vs 13.6 months, HR 1.1 [IC95% 0.69–1.77] and mOS 33.8 vs 36.1 months, HR 0.94 [IC95% 0.55–1.60]. Among patients with pathologic node positive disease (N+) (n = 79), mRFS was 13.9 months in the CT+ group vs 6.9 months in the CT- group (HR 0.68 [IC 0.35 – 1.19]), and mOS was 31.8 months in the CT+ group *vs* 16.5 months in the CT- group (HR 0.96 [IC95% 0.51-1.81]). Patients who received peri-operative (Peri-Op) FFX (n = 24) experienced longer mOS compared to patients who received Gemcitabine Post-Op CT: NR vs 33.8 months, HR 0.45 [IC95% 0.25-1.02]. Patients who received Peri-Op CT for a total of six months or more (n = 31) had increased mOS (55 vs 32 months, HR 0.61 [IC 95% 0.37- 1.11] and mRFS (16 vs 14 months HR 0.80, [IC95% 0.50 -1.31]) than patients receiving less than 6 months Peri-Op CT (n = 85) **Conclusions:** Post-Op CT does not clearly impact survival in BL or LA pancreatic cancer pretreated with Pre-Op FFX. We observed a trend in the N+ population for a survival benefit. Peri-Op FFX was associated with longer survival than Gemcitabine Post-Op regimen. Further randomized data are needed to assess the impact of Peri-Op FFX for these patients Research Sponsor: None.

4151 **Poster Session**

Discrimination of mucinous pancreatic cysts using an enzymatic turnover assay to improve clinical diagnostic accuracy. *First Author: Daniel Sheik, Amplified Sciences, West Lafayette, IN*

Background: One impact of medical imaging technology has been an approximately 3-fold increase in the incidental detection of pancreatic cysts during routine clinical examinations. To reduce burden on the healthcare system and patients, clinicians desire accurate classification of pancreatic cysts into benign non-mucinous or potentially malignant, mucinous populations. Using EUS-FNA, fluid from these cysts can provide molecular biomarkers of predictive value. However, current in vitro diagnostics lack the desired sensitivity and specificity for clinicians to accurately stratify patients for risk of pre-malignant cancers. This situation can be improved by introducing new biomarkers and novel assay platforms. An enzymatic biomarker, pepsin C, has shown high accuracy for diagnosing mucinous cysts. The use of enzymatic activity assays is applicable to clinical workflows without disruption of current standards of care. **Methods:** A pepsin C activity assay using a magnetic bead-based platform was developed, with both fluorescent and surface-enhanced Raman spectroscopy (SERS) readouts. The assay platform utilizes selective peptide substrates, and a dimeric Rhodamine-6G-based dye, which allows ultrasensitive detection and significantly decreases the sample volume requirement for analysis, down to 1 μL of cyst fluid. The dye-labeled substrate is immobilized on magnetic beads and reacted with enzyme-containing samples to produce a quantitative assay signal that is standardized and expressed in true enzyme activity units. **Results:** While both readouts were quantitative and produced linear standard curves, SERS-based analysis was more robust against established biological matrix effects than fluorescence. Nevertheless, both assay modes successfully differentiated mucinous and non-mucinous cysts in a retrospective cohort of 69 cyst fluid samples. Compared with the standard of care CEA assay, this activity-based assay displays much improved sensitivity in diagnosing mucinous pancreatic cysts (Table). **Conclusions:** This pepsin c activity assay differentiates between mucinous and non-mucinous cysts better than the CEA assay and provides a quantifiable standardized readout. This work establishes a path to a true rule-out assay enabling clinicians to better stratify patients into low risk vs. potential malignancy thus impacting treatment and monitoring plans. Research Sponsor: Amplified Sciences.

Assay	Cutoff	Sensitivity	Specificity	AUC	NPV	PPV
CEA	> 192 ng/mL	62%	93%	0.812	62%	92%
PepC ELISA	$\log_2$ > 16.51 pg/mL	77%	93%	0.873	79%	71%
PepC Activity Fluorescence	> 5.79 pmol Product	85%	93%	0.936	82%	94%
PepC Activity SERS	> 15.14 pmol Product	80%	90%	0.873	76%	89%

4152 **Poster Session**

Circulating tumor DNA profile in pancreatic ductal adenocarcinoma (PDAC) and potential targeted therapy. *First Author: Francis Esposito, Hospital Clinic de Barcelona, Barcelona, Spain*

Background: Despite huge efforts patients (pts) with advanced PDAC, still have a dismal long-term prognosis. The lack of available good-quality tissue samples for next generation sequencing (NGS) prevents from finding actionable alterations that could guide personalized treatments. Circulating tumor DNA (ctDNA) provides a non-invasive method for obtaining molecular information with therapeutic potential. Here, we present prospective data of ctDNA sequencing in pts with PDAC. **Methods:** We collected a single blood sample from advanced PDAC pts at any line of treatment (Tx) and at least 10 days apart from their last therapy. The samples were analyzed by Guardant360 plasma-based NGS, a standardized assay which covers microsatellite instability [MSI] evaluation and analysis of all four types of somatic alterations in 74 genes. Alterations were reported either as pathogenic or non-pathogenic. We classified each gene alteration according to the different OncoKB therapeutic levels of evidence [LE]. Additionally, we gathered the dates of both blood collection and molecular report. In case the molecular report showed no tumor-related alterations, it was interpreted as either absence of detectable mutations or low ctDNA levels, which would translate low disease burden or pts responding to therapy. Demographic and clinical data have been accessed from the medical records. **Results:** From 08/2019 to 09/2021 we collected blood samples from 94 PDAC pts. 56% of them were male and 53% were >65 years old. At the time of sample collection, nearly all pts were metastatic (98%). Regarding previous lines of Tx, 57% pts were Tx naïve; 10% were receiving active systemic Tx and 33% had experienced disease progression. Molecular reports were available in an average of 9.1 days. A total of 243 gene alterations were detected, having 94% of pts at least 1 genomic alteration, which was pathogenic in 69% of the cases (see Table). There were no pathogenic alterations ranked as OncoKB LE 1-2 (*MSI* or *NTRK*). Seventy alterations (30%) were ranked as OncoKB LE 3A and 4 (*ARID1A, BRAC2, CDKN2A, KRAS).* Three of these pts were treated with PARP inhibitors due to the presence of *BRCA2* mutations. No ctDNA was detected in 15 pts (16%), despite being the sample collected >10 days from receiving their last Tx. Of these, 11 had low tumor burden (only peritoneal or lung metastases) and 4 had documented response to the Tx by the time the samples were collected. **Conclusions:** Real-time and prospective genomic profiling of pts with advanced PDAC using ctDNA is feasible and conveniently fast, which would allow its role in identifying and developing therapeutic targets for approved Tx or clinical trial treatments. Research Sponsor: None.

Frequency of alterations with OncoKB level of evidence by gene.

	Alterations			
	Pathogenic N	Not pathogenic N	Any gene N	OncoKB therapeutic LE
ARID1A	3	3	6	4
ATM	6	3	9	-
BRCA1	0	4	4	-
BRCA2	5	1	6	3A
CDKN2A	2	2	4	4
GNAS	6	0	6	-
KRAS	60	0	60	4
TP53	48	8	56	-
Other alteration	37	55	92	-

4153 **Poster Session**

Lymphocyte to monocyte ratio in metastatic pancreatic ductal adenocarcinoma as a prognostic factor and its potential role in identifying a subset of patients with a favorable response to therapy. *First Author: Andrea Pretta, Medical Oncology Unit, University Hospital and University of Cagliari, Cagliari, Italy*

Background: Despite the most recent therapeutic achievements, pancreatic ductal adenocarcinoma (PDAC) is characterized by poor prognosis and response to treatments. Among the most investigated prognostic biomarkers, the lymphocyte to monocyte ratio (LMr) is gaining increasing interest in literature, mostly in hematological malignancies, breast cancer, bladder cancer, non-small cell lung cancer, colorectal cancer, and resected pancreatic adenocarcinoma. In these settings, a higher LMr allows identifying a subset of patients with a better prognosis. Our study aimed to evaluate the role of the LMr as a prognostic factor in patients affected by metastatic PDAC and to find a cut-off value able to identify a subset of patients with better prognosis and possibly susceptible to other therapeutic options. **Methods:** Data from 228 patients were collected retrospectively from 2014 to 2021. 175 from the Department of Medical Oncology of the University Hospital of Cagliari and 53 from the Oncology Clinic - University Hospital of Ospedali Riuniti of Ancona. All patients had metastatic PDAC and blood samples were collected before starting first-line chemotherapy. The cut-off value for LMr was calculated according to the ROC curves at 6, 12, and 18 months. Kaplan-Meier curves were then obtained for the evaluation of survivals. Finally, multivariate analysis was performed, taking into consideration the following prognostic factors: sex, ECOG-PS, NL ratio, metastatic sites, Ca19.9 and LDH. **Results:** The median age was 68 y.o. (range 39-84 y.o.), 123 (54%) were males. Cut off value obtained for LMR, was 4. 156 (68,4%) patients had an LMr < 4 and 72 (31,6%) patients had an LMR ≥ 4. Patients with a ratio ≥ 4 showed a statistically significant difference in terms of median overall survival compared to patients with a ratio < 4 (23 months versus 11 months, $p < 0.0001$). First-line median progression-free survival was also different in patients with a value greater than or equal to 4 (11 months versus 6 months, $p = 0.005$), suggesting a better treatment response in the first group of patients. Finally, multivariate analysis showed that LMR ≥ 4 is an independent prognostic factor for OS ($p = 0.0005$). **Conclusions:** The results of our study show that the lymphocyte to monocyte ratio could be an important prognostic factor in patients with metastatic pancreatic ductal adenocarcinoma, although the limitations of a retrospective study should be considered. Furthermore, these findings suggest the active role of the immune response in limiting disease progression, indicating a group of patients who could benefit most from a target or combined immunotherapy treatment. Research Sponsor: None.

4154 **Poster Session**

Supportive care (SC) utilization for patients with locally advanced pancreatic cancer: Review of the National Cancer Data Base (2004-2018). *First Author: Christopher G Cann, Vanderbilt University Medical Center, Nashville, TN*

Background: Pancreatic cancer is a formidable malignancy, with an estimated 62,000 new cases in 2022 and approximately 50,000 deaths. Five-year overall survival remains low at 11%; 14.4% for locally advanced disease. Nearly one-third of newly diagnosed patients (pts) present with locally advanced pancreatic cancer (LAPC) and only a minority of pts (<25%) are eligible for surgical resection. Given the significant morbidity and mortality associated with LAPC, timely integration of SC into the treatment care plan is vital. **Methods:** Pts diagnosed with Stage II-III LAPC (2004-2018) recorded in the National Cancer Data Base were included, stratified by stage and use of SC (defined as procedures or therapy provided for palliative intent symptom control) from time of diagnosis throughout the disease trajectory. Analyses included tumor characteristics, demographics, and socioeconomic parameters. Multivariate logistic regressions were performed on three sets of data: Stage II, Stage III, and Stage II/III combined. **Results:** 158,340 pts were included in the cohort [stage II (70.6%); stage III (29.4%)]. Only a minority of pts (2.9%) received SC treatment despite > 65% of pts receiving care at an academic program; 95% living in or near a metro area, and nearly 60% living < 20 miles of their primary treatment center (p <0.001). Medicare (58%) and private insurance (32.8%) was consistent across both stages and SC use. The table depicts selected significant factors and the respective adjusted odds of receiving SC from the three logistic regressions. **Conclusions:** Our analysis demonstrates the underutilization of SC in LAPC population over the past decade and potential specific demographic/social areas of unmet need. Future work should focus on practice patterns across cancer centers and the significant impact SC has on both survival and quality of life outcomes for LAPC pts. SC should be an integral component incorporated early on in the care of pancreatic cancer regardless of stage. Research Sponsor: None.

Stage	Variable	Effect for Comparison	Odds Ratio (OR)	OR 95% Confidence Interval	Pr>Chi-Square
Stage II	Histologic Grade ≥3	Histologic Grade 1 - 2	1.15	1.04, 1.27	0.008
Stage II	Residence in	Residence in New England/Middle Atlantic	-0.47	-0.40, 0.54	<0.001
	-South		-0.67	-0.58, 0.76	
	-Central				
Stage II	Hispanic	White	0.68	0.52, 0.90	0.006
Stage III	Asian/Pacific Islander	White	1.62	1.14, 2.28	0.007
Stage III	≥ 60 miles from facility	0-20 miles from facility	0.74	0.57, 0.96	0.026
Stage II and III	Remote region	Metro area	-1.64	-1.31, 2.07	-0.013
			-1.53	-1.09, 2.13	-<0.001
Stage II and III	Median Income ≥ $63,000	Median Income < $38,000	-0.75	-0.63, 0.88	-<0.001
				-0.60, 0.95	-0.017
Stage II and III	Mountain/Pacific region	New England/Middle Atlantic region	-0.52	-0.44, 0.6	-<0.001
			-0.74	-0.58, 0.94	-0.014
Stage II and III	Diagnosis 2014-2018	Diagnosis 2004-2008	-0.65	-0.57, 0.74	-<0.001
			-0.80	-0.67, 0.96	-0.018

4155 **Poster Session**

Comparative analysis of the targetable landscape in *KRAS*-mutant and wild-type pancreatic adenocarcinoma. *First Author: Todd C Knepper, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

Background: Pancreatic adenocarcinoma (PC) is the fourth leading cause of cancer deaths, with increased incidence among patients (pts) younger than 50 years old (yo). Small cohort studies suggest early-onset PC (EOPC, diagnosis at < 50 yo) tumors may have a unique biology, harboring a higher proportion of *KRAS* wild-type status ($KRAS^{WT}$) and enrichment of targetable mutations/fusions compared to non-EOPC. In addition, therapy targeting oncogenic fusions in $KRAS^{WT}$ tumors has shown meaningful responses in PC pts. Here, we investigate the prevalence of fusions, mutations, and homologous recombination deficiency (HRD) in $KRAS^{WT}$ PC to identify potential targets for therapeutic intervention, and compare EOPC to non-EOPC to better characterize EOPC differences. **Methods:** De-identified records from 4,956 PC pts with tumor biopsies sequenced using the Tempus xT solid tumor assay (DNA-seq of 595-648 genes at 500x coverage; full transcriptome RNA-seq) were retrospectively reviewed. Fusions were detected from RNA-seq data via the Tempus bioinformatics pipeline. Mutations identified included germline and/or somatic single-nucleotide variants and insertions/deletions. HRD status was determined from RNA-seq data by the Tempus HRD test. Significance was determined as FDR-corrected p-values < 0.05. **Results:** Across the entire cohort, 21% tumors were $KRAS^{WT}$. HRD was more frequent in $KRAS^{WT}$ (7.9%) compared to $KRAS^{MUT}$ (3.1%) tumors (P< 0.001). Significant somatic mutational differences between the $KRAS^{WT}$ and $KRAS^{MUT}$ cohorts included *BRAF* (5.0% vs 0.2%), *CDKN2A* (5.4% vs 25%), *ARID1A* (3.6% vs 8.6%), *CTNNB1* (1.3% vs 0.3%), and *TSC2* (1.2% vs 0.1%) (all P< 0.001). Actionable rearrangements were enriched in the $KRAS^{WT}$cohort (10% vs 2.1%, P< 0.001); the most common fusion partners include *NRG1*, *MET*, *RAF1*, *BRAF*, *NTRK1-3*, *FGFR 1-4*, and *RET*. TMB-high (10 muts/Mb) and MSI-high were more common in $KRAS^{WT}$ (2.9% and 1.0%) compared to $KRAS^{MUT}$ (1.7% and 0.4%) tumors (P= 0.015). Additionally, 382 pts were classified as EOPC. $KRAS^{WT}$ tumors comprised 30% of EOPCs, 22% of the 50-70 yo cohort, and 17% of the > 70 yo cohort. Germline (pathogenic/likely pathogenic) alterations in *BRCA1* and *BRCA2* were more frequent in EOPCs (2.0% and 4.5%) compared to the 50-70 yo (0.4% and 1.7%) and > 70 yo (0.4% and 0.8%) cohorts (P= 0.015 and < 0.001, for *BRCA1* and *BRCA2* respectively). There were no statistical differences in actionable genes detected in EOPC vs non-EOPC. HRD was found at higher frequency in EOPC (5.4%) and decreased in age cohorts 50-70 yo (4.7%) and > 70 yo (2.5%) ($P = 0.047$). Rearrangements were more common in EOPC compared to non-EOPC (10% vs 1.1%, P< 0.001). **Conclusions:** HRD, TMB-H/MSI-H and oncogenic rearrangements are more prevalent in $KRAS^{WT}$ PC when compared with $KRAS^{MUT}$. These molecular analyses may provide additional therapeutic options for PC pts, warranting comprehensive genomic and transcriptomic profiling for this population. Research Sponsor: None.

4156 **Poster Session**

Landscape of homologous recombination reversion mutations in pancreaticobiliary malignancies. *First Author: Brennan James Decker, Foundation Medicine, Cambridge, MA*

Background: Homologous recombination (HR) pathway reversion mutations (REV) are emerging treatment resistance biomarkers for platinum and PARP inhibitor therapy. The wide diversity of REV presents a diagnostic challenge. We implemented an automated computational approach to detect REV and examined the genomic features of REV-positive pancreaticobiliary cancers. **Methods:** Retrospective study of tissue (n = 31,124) and liquid biopsy (n = 3,870) samples from patients undergoing hybrid-capture comprehensive genomic profiling during routine clinical care 11/2012-03/2021. A proprietary algorithm tested samples for seven distinct REV mechanisms in *BRCA1*, *BRCA2*, or *PALB2*. For subjects with multiple samples, the earliest REV-positive sample was used for downstream analyses. **Results:** 5.3% (1,866/34,994) of biliary and pancreatic primary tumors harbored one or more pathogenic variants (PV) in *BRCA1* (1.4%, n = 499), *BRCA2* (3.2%, n = 1,119), or *PALB2* (0.81%, n = 282). Among patients with at least one PV in these genes, 2.4% (45/1,866) had REV. The majority of REV involved *BRCA2* (82%, 37/45), significantly higher than the proportion of *BRCA2* PV in the cohort overall (59%, 1,119/1,900; p = 0.022). The remainder of REV involved either *BRCA1* (8.9%, 4/45) or *PALB2* (8.9%, 4/45). A total of 63 REV pairs were identified. The most frequent REV mechanism was an exonic non-frameshift deletion completely encompassing a PV (36%, 23/63), followed by a frameshift restoring the reading frame of a pathogenic frameshift (23%, 15/63), a benign missense replacing a PV at the same codon (17%, 11/63), and deletion with intronic breakpoints causing loss of a PV (17%, 11/63). REV were approximately equally prevalent in liquid biopsy (2.8%, 5/178) and tissue samples (2.4% 40/1,688; p = 0.72). A range of 1-9 REV were found per sample (liquid biopsy = 1-9, tissue = 1-2), and liquid biopsy samples had a higher median REV per sample compared to tissue (2.0 vs. 1.0; p < 0.001), as well as a higher prevalence of multiple REV per sample (60% [3/5] vs 7.5% [3/40]; p = 0.013). These differences likely reflect stage of disease and sampling of multiple subclones. **Conclusions:** Although REV are uncommonly detected in pancreaticobiliary carcinomas, the presence of REV in *BRCA2*, *BRCA1*, and *PALB2* in patients with pancreaticobiliary neoplasms supports HR as a therapeutic target in these cancers. Diverse REV mechanisms highlight a need for robust detection to incorporate REV in identifying treatment resistance and guiding therapy selection. Research Sponsor: Foundation Medicine.

4157 **Poster Session**

Neoadjuvant chemotherapy is associated with improved outcomes in patients with stage 1A and 1B pancreatic cancer undergoing surgery: An NCDB study. *First Author: Noah Rozich, Aurora St. Luke's Medical Center, Milwaukee, WI*

Background: The use of neoadjuvant chemotherapy (NAC) for pancreatic ductal adenocarcinoma (PDAC) has shown clear advantages in locally advanced and borderline resectable disease. The benefit in upfront resectable PDAC is debated. Moreover, in early clinical stages IA/IB, potential benefits including improved R0 resection rate, decreased tumor upstaging, and survival, are not clear. We hypothesize that NAC will be associated with improved outcomes and survival compared to adjuvant therapy in patients with clinical stage IA/IB PDAC. **Methods:** The National Cancer Database (NCDB) PUFs (2004-2017) were used to perform a retrospective review of patients with clinical stage IA or IB PDAC undergoing surgery. Treatment groups were selected based on timing of chemotherapy. Patients receiving chemotherapy or surgery alone were excluded. **Results:** We identified 6,613 patients with clinical stage IA or IB PDAC who underwent surgery. The neoadjuvant therapy group (NAT) included 1,533 patients who received neoadjuvant or perioperative chemotherapy, and the adjuvant therapy group (AT) contained 5080 patients who received chemotherapy after surgery. Patients in the NAT had higher rates of T1 and T2 disease and lower rates of T3 pathology compared to the AT (pT1: 18.7% vs 7.8%; pT2: 20.1 vs 18.6%; pT3: 59.3% vs 72.1%, p<0.0001). Additionally, the NAT had significantly higher rates of N0 disease and less N1 pathology (pN0: 54.6% vs 37.5%; pN1: 45.4% vs 62.5%, p<0.0001). The R0 resection rate was higher in the NAT (83.2% vs 62.3%, p=0.0197) and there was less lymphovascular invasion (LVI) compared to the AT (34.8% vs 48.1%, p<0.0001). Using Kaplan Meier estimates, the NAT was associated with improved overall survival (OS) compared to the AT (median OS: 33.4 vs 27.5 months, p<0.0001). On multivariable analysis, R0 resection (HR=0.715, CI: 0.619-0.825, p<0.0001), LVI (HR=1.126, 95% CI: 1.038-1.222, p=0.0043) but not receipt of NAC (HR=0.94, 95% CI: 0.852-1.038, p=0.2229) were independent risk factors for OS. **Conclusions:** NAC is beneficial in patients with stage IA/IB PDAC undergoing surgical resection as it is associated with improved oncologic outcomes including increased R0 resection rate, decreased tumor upstaging, lymph node metastasis, and LVI. Furthermore, patients receiving NAC were found to have improved survival over those getting adjuvant therapy. Based on these results, we recommend all patients diagnosed with PDAC be considered for NAC prior to surgery. Research Sponsor: None.

Patient characteristics	AT (5080) n (%)	NAT (1533) n (%)	p-value
Pathologic T stage			<0.0001
pT1	369 (7.8)	248 (18.7)	
pT2	876 (18.6)	267 (20.1)	
pT3	3401 (72.1)	787 (59.3)	
Pathologic N stage			<0.0001
pN0	1751 (37.5)	749 (54.6)	
pN1	2922 (62.5)	622 (45.4)	
R0 Resection	4000 (62.3)	1216 (83.2)	0.0197
LVI	1749 (48.1)	354 (34.8)	<0.0001

LVI = lymphovascular invasion; AT = adjuvant therapy group; NAT = neoadjuvant Therapy group.

4158 **Poster Session**

Phase 2 study of azacitidine (AZA) plus pembrolizumab (pembro) as second-line treatment in patients with advanced pancreatic ductal adenocarcinoma. *First Author: Rachael A Safyan, Columbia University Irving Medical Center, New York, NY*

Background: Pancreatic ductal adenocarcinoma (PDAC) is the third leading cause of cancer-related death with a 5-year survival rate of 10%. Novel strategies for advanced PDAC are a critical need. A DNA hypomethylating agent (HMA) increased tumor-infiltrating effector T cells and significantly prolonged survival in combination with immune checkpoint blockade (ICB) in a PDAC mouse model (Gonda et al 2020). We hypothesized that combining HMA with ICB will lead to therapeutic benefit in pts with advanced PDAC. **Methods:** This is an open-label, single-arm, single-center, Phase 2 trial of AZA plus pembro in pts with unresectable or metastatic PDAC. Pts were treated with AZA 50 mg/m2 subcutaneous daily for 5 days Q4W beginning week 1 day 1 followed by pembro 200 mg IV Q3W starting week 3 day 1. Key eligibility criteria included documented progression on or following first-line systemic treatment, ECOG PS 0-1, and adequate organ function. The primary objective was progression-free survival (PFS). Thirty-one evaluable pts were required to detect an improvement in PFS from 2 mo to 4 mo with a one-sided p-value of 0.05 and 80% power. Secondary endpoints included safety and tolerability, overall response rate (ORR), disease control rate (DCR), and overall survival (OS). Data cut-off was February 10, 2022. **Results:** Between Oct 2017 and Sept 2021, 36 pts were enrolled (median age 62.5, 75% white, 72% male). At data cutoff, 34 and 31 pts received at least 1 dose of AZA and pembro, respectively. Median PFS for ≥1 dose of AZA was 1.48 mo (95% CI: 1.35, 1.74) and for ≥1 dose of pembro was 1.51 mo (95% CI, 1.38, 3.42). The median OS was 4.67 months. Among the 34 pts, 3 (8.8%) experienced a partial response (PR) by RECIST with a DCR of 32.4%. Of the 3 pts with PR, 2 received 35 doses of pembro and continued beyond 2 years with an ongoing PR. One pt remains on pembro 20 months after study completion. None of the pts with a PR were microsatellite instability-high or tumor mutation burden high, and next-generation sequencing of the 3 cancers identified a BRCA1 variant and POLE variant. Treatment-related AEs (TRAEs) occurred in 20/34 pts (59%), the most common of which were diarrhea and fatigue. Grade ≥3 occurred in 7/34 (21%) including 1 immune-related grade 5 event (encephalitis). **Conclusions:** AZA plus pembro demonstrated a tolerable safety profile but no PFS benefit compared to historical controls. Our data suggests combined epigenetic therapy and ICB may expand therapeutic options in a subset of pts with PDAC. Further investigation is needed to identify biomarkers to predict response and elucidate effective timing, sequencing, and combination of epigenetic agents. Follow-up for OS is ongoing. Correlative analysis of epigenetic effects and characterization of the tumor immune microenvironment will be reported. Clinical trial information: NCT03264404. Research Sponsor: Merck & Co.

4159 **Poster Session**

Evaluation of somatic and germline variants in patients with small bowel adenocarcinoma reveals clinically actionable targets. *First Author: Deng Wei, Department of General Surgery, Beijing Friendship Hospital, Capital Medical University, Beijing, China*

Background: Small bowel adenocarcinoma (SBA) is a rare gastrointestinal cancer with a poor prognosis and limited treatment options. Because the treatments for colorectal cancer showed limited efficacy in SBA, the NCCN guide strongly encourages SBA patients to participate in clinical trials. In this study, we aimed to explore clinically actionable variants in a large cohort of patients with SBA to assist oncologists to select the matched trials for patients. **Methods:** To explore therapeutic targets in 84 Chinese SBA patients, a deep sequencing panel (OncoPanscan, Genetron health) was used to characterize somatic alterations including point mutations, indels, copy number alterations, gene fusions as well as pathogenic germline variants. **Results:** Recurrent somatic mutations included *TP53* (57%), *KRAS* (56%), *APC* (31%), *SMAD4* (21%), *MDM2* (13%), *CTNNB1* (12%), *KMT2C* (12%), *SOX9* (12%), *ARID2* (12%), *FAT3* (11%), *FBXW7* (10%), *SPTA1*(10%) and *PIK3CA* (10%). Of the entire cohort, we observed five activating *PIK3CA* mutations (R108H; G364R; E542K; E545K, n = 2) which may be sensitive to FDA-approved PIK3CA inhibitor alpelisib. Additionally, patients with loss-of-function mutation in *NF1* (n = 2), *STK11* (n = 1) and *PTEN* (n = 1) can be targeted with MEK inhibitor selumetinib and mTOR inhibitor everolimus, respectively. Except for one V600E mutation, all mutations in *BRAF* are either type 2 (L597R, n = 1) or type 3 (N581S, n = 1; D594N, n = 4) which were sensitive to MEK inhibitor trametinib. We also found four type 2 MAP2K1 activating mutations (K57E, K57N, and F53L) which can be targeted by trametinib. Furthermore, oncogenic *ERBB2/HER2* mutations were seen in 4 patients including S310F (n = 1), V842I (n = 2) and V777L (n = 1). We also found one patient harbored *ERBB2/HER2* high magnification amplification. These five patients were candidates for HER2-targeted therapy clinical trials. Interestingly, one IDH1 mutation (R132C) carrier in our cohort might benefit from ivosidenib. In addition, we observed targetable gene amplification of *MDM2* (n = 2) and *FGF3/4/19* (n = 2). There were two patients with *MLH1* loss-of-function germline mutations that may benefit from immunotherapy. Among 78 patients with available MSI status, three were designated as microsatellite instability. The median TMB of microsatellite stable patients was 2.82 mutations/Mb. Lastly, we observed five deleterious germline mutations, three for *SBDS*, one each for *APC* and *ERCC5*. Taken together, at least 33 (39%) patients in our cohort harbored actionable genetic alterations. **Conclusions:** Through comprehensive genomic characterization of Chinese SBA patients, we identified actionable variants of multiple signaling pathways in plenty. NGS profiling results can guide physicians to enroll a significant portion of SBA patients in genomically-matched clinical trials. Research Sponsor: None.

4160 **Poster Session**

Patient-derived explant model of appendiceal cancer. *First Author: Madeleine Cornelia Strach, Faculty of Medicine and Health, The University of Sydney, Sydney, Australia*

Background: Appendiceal cancers (AC) are rare with 5-year survival of 15% for high grade (HG) adenocarcinomas and 75% for low grade (LG) mucinous neoplasms. There is limited literature on the AC tumour microenvironment (TME) in disease progression and drug resistance. *Ex vivo* cultures, such as patient derived explants (PDEs), have been used for other solid tumours to test anticancer agents, explore the TME, and are being developed as personalised models. The aim of our study was to develop a PDE model of AC, preserve the TME, study the biological profile of AC and test novel therapies. **Methods:** Fresh tissue was collected during cytoreductive surgery (CRS) from consenting patients with AC with peritoneal disease, Jul 2020-Mar 2021. Tissues from 10 patients were dissected and cultured as PDEs under varying conditions of tissue size, media, matrix support and duration (Table). Uncultured Day 0 tissues and PDEs were fixed in formalin prior to paraffin embedding (FFPE). Immunohistochemical staining was performed on sections of FFPE tissue to assess viability with antibodies against the tumour marker, Cytokeratin-20 (CK20), and cell death marker, cleaved caspase 3 (CC3). Tissue architecture was rated on a 4-point scale (MS, J-SS). Cancer cells were counted in 6 Day 0 samples and PDEs from 3 patients using QuPath v0.3.2. Apoptotic index (AI) was calculated as the proportion of cells positive for CC3 divided by the number of total CK20 positive cells. **Results:** The mean proportion of tumour and mucin in the tissues was 3% (0-60%) and 39% (0-95%) respectively. Day 0 samples were viable with mean AI of cancer cells 7% (0-4%). Tissue architecture was maintained, as compared to Day 0 control, for varying sizes of PDE and culture durations up to 4d. More small or medium-sized PDEs had improved architecture compared to large sized PDEs (Table). PDEs at 4d had poorer architecture compared to at 1-3d. There was improved architecture in PDEs using enriched media with support factors compared to base media, and in specimens with matrix support compared to none. The mean AI of PDE cancer cells was 21% (0-92%) and 51% of PDEs had no cancer cell death. **Conclusions:** This is the first study demonstrating that AC tissue is amenable to *ex vivo* culture as PDEs. The optimal PDE model was <10mm tissue placed on a gelatine sponge in enriched media for 1-3d. PDEs had preserved tissue architecture and viability compared to uncultured tissue. Protein expression was in keeping with the original tumour. We plan to use this model to test anticancer agents and explore the TME of AC. Research Sponsor: Philanthropic funding from Chris O'Brien Lifehouse, Sydney, Australia.

Model of appendiceal cancer patient-derived explants (PDE).		
Conditions	**PDE, N (sections missing)**	**PDE rated as high quality, N (%)**
Day 0	10	10 (100)
Tissue size (mm)Small-medium (<10)*Large (≥10)	210 (2)23	174 (84)14 (61)
MediaBase+support factors*Base†	143 (2)90	118 (84)70 (79)
MatrixGelatine sponge*None	198 (2)35	161 (81)27 (77)
Duration (d)1-3*4	196 (2)37	165 (85)23 (62)

*optimal method †RPMI, 10% FCS, 1% antimicrobial.

TPS4161 **Poster Session**

Phase 2 study of trastuzumab deruxtecan in the neoadjuvant treatment for patients with HER2-positive gastric and gastroesophageal junction adenocarcinoma (EPOC2003). *First Author: Daisuke Takahari, Department of Gastroenterology, The Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan*

Background: Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate consisting of an anti-HER2 antibody, a cleavable tetrapeptide-based linker, and a cytotoxic topoisomerase I inhibitor. DESTINY-Gastric01 study showed significantly higher objective response rate with T-DXd than physician's choice of chemotherapy (51.3%, vs. 14.3%, Shitara K, et al. NEJM 2020) as well as prolonged overall survival (median 12.5 vs. 8.4 months, hazard ratio 0.59). Considering that high response rate or major pathological response (MPR), which is defined as the proportion of subjects with < 10% residual tumor may be associated with favorable survival outcomes after preoperative chemotherapy, T-DXd could be a promising neoadjuvant treatment for patients with gastric and gastroesophageal junction (GEJ) cancer. However, to our knowledge, there is no currently ongoing study of T-DXd as a neoadjuvant setting for patients with gastric and GEJ cancers. **Methods:** This is an open-label, single-arm, multicenter, investigator initiated phase 2 trial to evaluate antitumor activity of T-DXd as the neoadjuvant treatment for patients with HER2 positive gastric and GEJ adenocarcinoma. Eligible patients should have previously untreated locally advanced gastric and GEJ adenocarcinoma with clinical stage of T2-4 and/or N+ without distant metastasis. The main cohort will enroll patients with HER2 overexpression defined as immunohistochemistry (IHC) 3+ or IHC2+/ in situ hybridization (ISH) + by local assessment. According to the results of exploratory biomarker analysis of DESTINY-Gastric01 study (Shitara K, et al. ESMO-GI2021), patients with HER2-low expression (IHC1+ or 2+ with ISH negative) with HER2-extra cellular domein (ECD) higher than 11.6 ng/ml also will be enrolled into the exploratory cohort. Patients will receive 3 cycles of T-DXd (6.4mg/kg) by intravenous infusion every 3 weeks followed by surgery at 3 to 8 weeks after last T-DXd infusion.The primary endpoint is MPR rate. The threshold in the main cohort is defined as 20%, and the expected MPR rate was set at 45%. The minimum sample size of this trial is 23 patients in the main cohort (α- and β-error probabilities, 0.1 and 0.15, respectively). Total number of patients will be increased up to 27 patients depending on the enrollment. In addition, 10 patients will be recruited into the exploratory cohort. Secondary endpoints are pathologic complete response (pCR) rate, curative resection rate, and adverse event rate. Biomarker analyses including whole exome sequencing, RNA sequencing, proteomics, and ctDNA changes will also be conducted using pre- and post-treatment tumor and blood samples. Enrollment is ongoing at six sites in Japan from November 2021. Clinical trial information: NCT05034887. Research Sponsor: Daiichi-Sankyo.

TPS4162 **Poster Session**

EA2183: A phase III study of consolidative radiotherapy in patients with oligometastatic HER2-negative esophageal and gastric adenocarcinoma. *First Author: Nataliya Volodymyrivna Uboha, UW Carbone Cancer Center, Madison, WI*

Background: Advanced esophageal and gastric adenocarcinomas (EGA) have poor prognosis. Doublet chemotherapy with fluoropyrimidine and platinum agents in combination with nivolumab for PD-L1 positive tumors is now the standard first-line approach, but overall survival (OS) remains < 1.5 years. A subset of EGA patients have limited burden of metastatic disease. There is accumulating evidence that patients with oligometastatic states across disease types may benefit from locoregional ablative therapies during the course of their treatment. EA2183 is the first prospective study to evaluate the potential benefits of consolidative radiotherapy (XRT) in oligometastatic EGA. **Methods:** This is a prospective, randomized phase 3 study evaluating the role of consolidative XRT in oligometastatic EGA. Patients with ≤3 metastases at the time of diagnosis of advanced disease are eligible for enrollment. After completion of 4 months of systemic therapy, patients whose disease has not progressed are randomized to consolidation with XRT to all sites of disease followed by continuation of systemic therapy or continuation of systemic therapy alone. Patients are able to enroll in the study at the time of diagnosis of advanced disease or after completion of induction therapy. Systemic therapy is left to the discretion of the treating physician and can include FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) or CAPOX (capecitabine, oxaliplatin) in combination with nivolumab. Unless there are contraindications to immunotherapy or a history of prior treatment with immune checkpoint inhibitors, nivolumab use is mandatory if tumor has PD-L1 combined positive score (CPS) ≥5. The goal of radiation is to consolidate gains made by chemotherapy by delivering the highest dose that maintains the greatest tumor control probability that is also safe to deliver given the anatomic and normal tissue constraints. Specific radiation dose and fractionation are recommended in the protocol but is left to the discretion of the treating radiation oncologist to choose the course that is most suitable. Radiation must be administered over a maximum of 15 treatment days to minimize systemic therapy treatment breaks. Primary endpoint is OS from the time of randomization. Secondary endpoints include progression free survival from the time of randomization and safety and tolerability of consolidative XRT. We hypothesize that consolidative XRT will prolong OS from 10 to 15.6 months (an increase in median OS of 55.6%). The study is planning to enroll 314 patients with the goal of randomizing 204 patients in a 2:1 fashion. Stratification factors include number of metastatic sites, choice of immunotherapy with relation to PD-L1 CPS, as well as time of registration to the protocol (before or after systemic therapy initiation). Enrollment to the study is ongoing. Clinical trial information: NCT04248452. Research Sponsor: U.S. National Institutes of Health.

TPS4163 **Poster Session**

Anti-PD1, capecitabine, and oxaliplatin for the first-line treatment of dMMR esophagogastric cancer (AuspiCiOus-dMMR): A proof-of-principle study (AuspiCiOus). *First Author: Joris Bos, Amsterdam UMC, University of Amsterdam, Department of Medical Oncology, Cancer Center Amsterdam, Amsterdam, Netherlands*

Background: Doublet cytotoxic treatment demonstrates survival benefit over single drug therapies in patients with advanced esophagogastric cancer (EGC). Previous clinical data suggests an improved survival outcome in patients with microsatellite instability (MSI) treated with PD-1 inhibitor monotherapy or in combination with chemotherapy in first line palliative treatment. The positive effect of immunotherapy was only seen after a couple of months of treatment. This suggests that the patient might benefit from a short course of chemotherapy at the start of treatment. However, reports on the effects of cytotoxic treatment in MSI-high tumors range from beneficial to detrimental. Thus, the value of cytotoxic treatment, as well as the effect on the tumor immune microenvironment (TME) in MSI-high tumors is unclear. Therefore, in AuspiCious-dMMR we will study the effect of sequential treatment in patients with mismatch repair deficient (dMMR) EGC on the tumor immune microenvironment and, more specifically, the impact on the infiltration of cytotoxic T cells, before and after a short course of chemotherapy, and during treatment with PD-1 inhibition. **Methods:** AuspiCiOus is a multi-center, open-label, single arm (phase 2) study in patients with dMMR irresectable or metastatic EGC adenocarcinoma (NCT05177133). Patients are treated with Capecitabine and Oxaliplatin for two 3-weekly cycles, after which treatment is continued with retifanlimab (PD-1 inhibitor) for 4-weekly cycles up to progression or unacceptable toxicity, with a maximum of two years. Before treatment, after chemotherapy and after two cycles of immunotherapy fresh tumor biopsies are collected to study the primary outcome (T cell infiltration and the interferon-γ signature) as well as for translational research purposes (flow cytometry, nanostring profiling, (multicolor) immunohistochemistry and organoid culturing). Blood is collected at the same time points and on day 3 after the first course of immunotherapy for isolation of peripheral blood mononuclear cell, and determination of cytokine/chemokine profile, circulating stromal markers, and circulating tumor DNA. Also, fecal samples are collected to determine changes in the intestinal microbiome and patient reported outcome measures are used to determine quality of life. (s)AEs are assessed according to CTCAE v5 and tumor response is determined according to (i)RECIST 1.1. Key eligibility criteria are 1) histological confirmed diagnosis of untreated metastatic or irresectable HER2- adenocarcinoma of stomach or junction and 2) dMMR determination by IHC. Study is open for inclusion and three of planned 25 patients have been enrolled. Clinical trial information: NCT05177133. Research Sponsor: Incyte.

TPS4164 **Poster Session**

Trial in progress: Phase 3 study of bemarituzumab + mFOLFOX6 versus placebo + mFOLFOX6 in previously untreated advanced gastric or gastroesophageal junction (GEJ) cancer with FGFR2b overexpression (FORTITUDE-101). *First Author: Elizabeth Catherine Smyth, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom*

Background: Fibroblast growth factor receptor 2b (FGFR2b) is overexpressed in approximately 30% of non-human epidermal growth factor receptor 2 (non-HER2) positive gastric cancer (Wainberg, 2021). Bemarituzumab is a first-in-class monoclonal antibody that specifically blocks FGFR2b, inhibiting downstream tumor proliferation and enhancing antibody-dependent cellular cytotoxicity (Catenacci, 2020; Xiang, 2021). In the phase 2 FIGHT study (Wainberg, 2021; Catenacci, 2021), bemarituzumab + mFOLFOX6 improved progression-free survival (PFS; HR, 0.68; 95% CI, 0.44–1.04; p = 0.07) and led to a 5.7 month longer median overall survival (OS; 19.2 months vs 13.5 months; HR, 0.60; 95% CI, 0.38-0.94) compared with placebo + mFOLFOX6. **Methods:** FORTITUDE-101 (NCT05052801) is a double-blind, placebo-controlled phase 3 study in patients with untreated, unresectable locally advanced or metastatic gastric or GEJ adenocarcinoma not amenable to curative therapy. Approximately 516 patients aged ≥18 years with IHC-confirmed FGFR2b overexpression by central testing will be enrolled and randomized 1:1 to bemarituzumab + mFOLFOX6 or placebo + mFOLFOX6. Additional key eligibility criteria include Eastern Cooperative Oncology Group performance status 0-1, evaluable disease per RECIST v1.1, adequate hematologic and organ function, and no contraindication to receive mFOLFOX6 chemotherapy. Key exclusion criteria include prior treatment for metastatic or unresectable disease except one dose of mFOLFOX6 during screening, positive HER2 status, untreated or symptomatic CNS metastasis and leptomeningeal disease, history or evidence of ongoing ophthalmologic abnormalities, and prior treatment with any FGF-FGFR pathway inhibitor. Patients randomized to bemarituzumab will receive 15 mg/kg every 2 weeks (Q2W) with an additional 7.5 mg/kg dose on cycle 1 day 8. mFOLFOX6 will be administered at a fixed dose Q2W. Patients will receive treatment until disease progression, unacceptable toxicity, withdrawal of consent, or death. The primary endpoint is OS; secondary endpoints include PFS, objective response (defined as best overall response of complete or partial response), and treatment-emergent adverse events. Tumor responses and PFS will be assessed locally per RECIST v1.1. The concurrent phase 1b/3 FORTITUDE-102 study (NCT05111626) will evaluate the efficacy and safety of bemarituzumab + mFOLFOX6 + nivolumab versus placebo + mFOLFOX6 + nivolumab. Clinical trial information: NCT05052801. Research Sponsor: Amgen Inc.

TPS4165 **Poster Session**

Trial in progress: Phase 1b/3 study of bemarituzumab + mFOLFOX6 + nivolumab versus mFOLFOX6 + nivolumab in previously untreated advanced gastric and gastroesophageal junction (GEJ) cancer with FGFR2b overexpression (FORTITUDE-102). *First Author: Zev A. Wainberg, UCLA School of Medicine, Los Angeles, CA*

Background: Fibroblast growth factor receptor 2b (FGFR2b) is overexpressed in approximately 30% of non-human epidermal growth factor receptor 2 (non-HER2) positive gastric cancer (Wainberg, 2021). Bemarituzumab is a first-in-class monoclonal antibody that specifically blocks FGFR2b, inhibiting downstream tumor proliferation and enhancing antibody dependent cellular cytotoxicity (Catenacci, 2020; Xiang, 2021). In the phase 2 FIGHT study (Wainberg, 2021; Catenacci, 2021), progression-free survival (PFS) was improved (HR, 0.68; 95% CI, 0.44-1.04; p = 0.07) and a 5.7 month longer median overall survival (OS) was observed (19.2 months vs 13.5 months; HR, 0.60; 95% CI, 0.38-0.94) with bemarituzumab + mFOLFOX6 vs placebo + mFOLFOX6. Preclinical studies indicate that bemarituzumab modulates the tumor microenvironment to sensitize tumors to anti-PD1 monoclonal antibodies (Powers, 2016; Xiang, 2021) providing rationale for combination with nivolumab. **Methods:** FORTITUDE-102 (NCT05111626) is a phase 1b/3 study in patients (pts) with unresectable locally advanced or metastatic gastric or GEJ adenocarcinoma not amenable to curative therapy. Part 1 is an open-label safety lead-in; Part 2 is a double-blind, placebo-controlled study to evaluate efficacy and safety. Approximately 702 pts ≥18 years will be enrolled (Part 1, ~20; Part 2, ~682). Key eligibility criteria include Eastern Cooperative Oncology Group performance status 0-1, evaluable disease per RECIST v1.1, adequate hematologic and organ function, and no contraindication to receive mFOLFOX6 chemotherapy or nivolumab; for part 2, IHC-confirmed FGFR2b overexpression by central testing is required and no prior treatment for metastatic or unresectable disease allowed except 1 dose of mFOLFOX6 ± nivolumab. Key exclusion criteria include positive HER2 status and untreated or symptomatic CNS metastasis and leptomeningeal disease. Pts on bemarituzumab will receive 15 mg/kg every 2 weeks (Q2W) with an additional 7.5 mg/kg dose on cycle 1 day 8. mFOLFOX6 + nivolumab will be at a fixed dose Q2W. The dose-limiting toxicity (DLT) period is 28 days; observed safety data will influence additional enrollment to Part 1, de-escalation of bemarituzumab, or the recommended phase 3 dose (RP3D). For Part 1, primary endpoints are DLTs and adverse events; secondary endpoints include OS, PFS, and objective response (OR). For Part 2, pts will be randomized 1:1 to mFOLFOX6 + nivolumab Q2W plus either bemarituzumab at RP3D or placebo. Primary endpoint for Part 2 is OS; secondary endpoints include PFS, OR, and safety. The concurrent phase 3 FORTITUDE-101 study (NCT05052801) will evaluate bemarituzumab + mFOLFOX6 vs placebo + mFOLFOX6. Clinical trial information: NCT05111626. Research Sponsor: Amgen Inc.

TPS4166 **Poster Session**

Blood-borne assessment of stromal activation in esophageal adenocarcinoma to guide tocilizumab therapy: A randomized phase II proof-of-concept study (NCT04554771). *First Author: Benthe Doeve, Department of Medical Oncology, Amsterdam UMC, location VUMC, Cancer Center Amsterdam, Oncode Institute, Amsterdam, Netherlands*

Background: The tumor stroma is increasingly acknowledged to harbor tumor-promoting properties. Recently, we found that stroma activity measured by serum ADAM12 predicts response to chemoradiation in esophageal adenocarcinoma (Veenstra et al., Oncogenesis, 2018). Preclinically, the esophageal adenocarcinoma stroma was found to produce interleukin 6, which causes epithelial-to-mesenchymal transition of tumor cells. These mesenchymal tumor cells have a poor response to chemoradiation (Ebbing et al., PNAS, 2019). Therefore, stroma-derived interleukin 6 provides a potential new target to improve the treatment of esophageal adenocarcinoma. Tocilizumab is an interleukin 6 receptor inhibitor clinically used in rheumatoid arthritis and cytokine-release syndrome. In this phase II proof-of-concept clinical trial, we aim to demonstrate that stroma-targeting by tocilizumab in esophageal adenocarcinoma patients with highly activated stroma increases efficacy of chemoradiation measured by pathological response according to the Mandard criteria. **Methods:** BASALT is a multi-center, randomized, open-label phase II proof-of-concept clinical trial in patients with surgically resectable adenocarcinoma of the esophagus or gastroesophageal junction (NCT04554771). To assess efficacy of tocilizumab in addition to chemoradiation, 48 patients will be grouped for serum ADAM12 level with a cutoff of 203 pg/mL. Patients are then randomized in a 1:1:1:1 ratio to receive three cycles of tocilizumab every two weeks in addition to paclitaxel, carboplatin and radiation (Table). The sample size is based on the rule-of thumb estimate of 12 patients per arm. Tocilizumab will be given intravenously at a dose of 8 mg/kg with a maximum of 800 mg per dose. Efficacy will be assessed by pathological response to chemoradiation according to the Mandard criteria. Secondary endpoints are overall and progression free survival, safety and toxicity, feasibility and efficacy of interleukin 6 inhibition with serum interleukin 6 levels, immunohistochemistry and RNA-sequencing. Currently, 28 out of the 48 planned patients have been enrolled. Clinical trial information: NCT04554771. Research Sponsor: Oncode Institute.

Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 13-15
P	P	P	P	P	Surgery
C	C	C	C	C	
(T)		(T)		(T)	
RT x5	RT x5	RT x5	RT x5	RT x3	

P = paclitaxel 50 mg/m2; C = carboplatin AUC = 2; T = tocilizumab 8mg/kg with a maximum of 800 mg; RT = radiotherapy 1.8 Gy.

TPS4167 **Poster Session**

First-line lenvatinib plus pembrolizumab plus chemotherapy in esophageal squamous cell carcinoma: LEAP-014 trial in progress. *First Author: Jong-Mu Sun, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea*

Background: Recent data from the KEYNOTE-590 study demonstrated the superiority of pembrolizumab plus chemotherapy compared with chemotherapy as first-line treatment for unresectable locally advanced recurrent or metastatic adenocarcinoma or squamous cell carcinoma of the esophagus, or advanced/metastatic Siewert type 1 adenocarcinoma of the gastroesophageal junction. Prior data also suggest promising antitumor activity of lenvatinib plus pembrolizumab in advanced solid tumors. LEAP-014 (NCT04949256) is a randomized, 2-part, open-label, phase 3 study that will evaluate the efficacy and safety of first-line lenvatinib plus pembrolizumab plus chemotherapy versus pembrolizumab plus chemotherapy in patients with metastatic esophageal squamous cell carcinoma (ESCC). **Methods:** Key eligibility criteria include histologically or cytologically confirmed metastatic ESCC, measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), and Eastern Cooperative Oncology Group performance status 0 to 1. In part 1 (safety run-in), ~6 patients will be treated for induction with intravenous (IV) pembrolizumab 400 mg every 6 weeks (Q6W) for 2 cycles plus oral lenvatinib 8 mg daily (QD) plus IV 5-fluorouracil (FU; 4000 mg/m^2 on days 1-5) plus IV cisplatin (80 mg/m^2) (FP) for 4 cycles and treated for consolidation with pembrolizumab 400 mg Q6W for ≤16 doses plus lenvatinib 20 mg QD; patients will be closely monitored for 21 days after the first dose of study intervention for dose-limiting toxicities. In part 2 (main study), approximately 850 patients will be randomly assigned 1:1 to induction with pembrolizumab plus lenvatinib plus chemotherapy (FP or mFOLFOX6 [Q2W for 6 cycles {IV oxaliplatin 85 mg/m^2 plus bolus IV 5-FU 400 mg/m^2 plus continuous IV 5-FU 2400 mg/m^2 plus IV leucovorin 400 mg/m^2 or IV levoleucovorin 200 mg/m^2}]) followed by consolidation with pembrolizumab plus lenvatinib (arm 1) or pembrolizumab plus chemotherapy (FP or mFOLFOX6; arm 2). Randomization will be stratified by PD-L1 combined positive score (CPS; ≥10 vs < 10), region (East Asia vs North America and Western Europe vs rest of world), and chemotherapy backbone (FP vs mFOLFOX6). Treatment will continue until disease progression, unacceptable toxicity, or withdrawal of consent. Tumor imaging assessment will be performed Q6W for ≤1 year and Q9W thereafter. In part 1, the primary end point is safety and tolerability. In part 2, the dual primary end points are overall survival and progression-free survival (per RECIST v1.1 assessed by blinded independent central review [BICR]); secondary end points include objective response rate and duration of response (per RECIST v1.1 assessed by BICR) and safety and tolerability. Enrollment in this trial is ongoing. Clinical trial information: NCT04949256. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and Eisai Inc., Woodcliff Lake, NJ, USA.

TPS4168 **Poster Session**

Phase I trial of CA-4948, an IRAK4 inhibitor, in combination with FOLFOX/PD-1 inhibitor +/- trastuzumab for untreated unresectable gastric and esophageal cancer. *First Author: Haeseong Park, Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO*

Background: Activated NFκB has been linked to aggressive phenotype, poor survival outcomes and resistance to chemotherapy in multiple gastrointestinal cancers including gastroesophageal cancer (GEC). Preclinical studies established that: 1) Genotoxic stress incurred by chemotherapy induces TLR9, which signals through IRAK4 to drive pro-survival NFκB signaling; 2) The survival mechanism through IRAK4 is independent of cancer types and mutational profiles based on colorectal and pancreatic cancer models; and 3) IRAK4 inhibition reduces tumor desmoplasia and revitalizes intratumoral T cells, setting the stage for successful combination with immune checkpoint inhibitors in a highly aggressive autochthonous pancreatic cancer mouse model. These data combined provide a strong rationale to add CA-4948 to systemic therapy for multiple advanced gastrointestinal malignancies, where resistance to chemotherapy is inevitable and benefit of PD-1 inhibitors is limited to small population. CA-4948 is a novel, first-in-class reversible inhibitor of IRAK4. In a phase I trial, patients with relapsed/refractory hematologic malignancies tolerated CA-4948 monotherapy well with mild fatigue, neutropenia, and nausea as most common adverse events. Recommended phase 2 dose (RP2D) was determined as 300 mg orally twice daily. CA-4948 has not been tested in combination with cytotoxic chemotherapy or immune checkpoint inhibitors for solid tumors in clinic. We hypothesize that inhibition of IRAK4 with CA-4948 will potentiate the effect of immune checkpoint inhibitor while deepening the efficacy of cytotoxic chemotherapy in GEC. **Methods:** This is a phase I trial of CA-4948 in combination with FOLFOX/PD-1 inhibitor with or without trastuzumab for unresectable GEC. During Dose Escalation, we will investigate CA-4948 in combination with FOLFOX/nivolumab by BOIN algorithm evaluating 4 different dose levels. Starting dose of CA-4948 for Part A will be 200 mg twice daily. Once RP2D is determined, the study will proceed to Dose Expansion, including Cohorts A and B. Cohort A will enroll up to 12 patients with HER2 negative disease at the RP2D of CA-4948 determined at the Dose Escalation phase. Cohort B will investigate CA-4948 in combination with FOLFOX/pembrolizumab and trastuzumab. The initial 6 patients in Cohort B will be considered safety lead-in to confirm the safety and tolerability at the RP2D, followed by additional patients, up to 12 patients treated at the RP2D. The primary objective is to determine the safety and RP2D of CA-4948 in combination with FOLFOX/PD-1 inhibitor with or without trastuzumab. Secondary objectives are to determine the preliminary efficacy of the combination. Correlative studies to evaluate pharmacodynamic effects and to identify biomarkers associated with disease response are planned. Clinical trial information: NCT05187182. Research Sponsor: None.

TPS4169 **Poster Session**

Multicenter phase II study of abemaciclib and ramucirumab in metastatic esophageal/gastroesophageal junction carcinoma. *First Author: Ronan Joseph Kelly, Baylor University Medical Center, Dallas, TX*

Background: Cyclin dependent kinases (CDKs) are serine/threonine kinases that are responsible for phosphorylating the intracellular proteins that coordinate cell-cycle progression. The Cancer Genome Atlas (TCGA) molecular analysis of esophageal/gastroesophageal junction (E/GEJ) carcinomas has highlighted significant dysregulation of CDKN2A, the gene coding for the tumor suppressor p16, through deletion, mutation or epigenetic silencing in up to 76% of cases and the associated significant upregulation of the CDK4/6-Cyclin D-axis (The Cancer Genome Atlas Research Network. Integrated genomic characterization of oesophageal carcinoma. Nature 2017). Preclinical experiments demonstrated that single agent abemaciclib has potent antitumor efficacy both *in vitro* and *in vivo* in esophageal adenocarcinoma with direct pathway inhibition (Kosovec J et al. CDK4/6 dual inhibitor abemaciclib demonstrates compelling preclinical activity against esophageal adenocarcinoma: a novel therapeutic options for a deadly disease. Oncotarget 2017 Nov 1;8[59]). Significant activity was seen in the OE33 (p=0.048) and FLO1 (p=0.043) esophageal cancer cell lines while western blot revealed downregulation of Cyclin D, phospho-pRb, E2F1, and Cyclin A2 (Kosovec J et al, 2017). *In vivo* experiments, utilizing the Levrat model of end-to-side esophagojejunostomy performed on Sprague-Dawley rats demonstrated that 78.9% of animals given abemaciclib demonstrated >20% tumor volume decrease (placebo 0%). Post treatment comparison between placebo and abemaciclib of qRT-PCR gene expression demonstrated downregulation of pathway correlates, including CDK4 (p=0.023), CDK6 (p=0.068), E2F1 (p=0.005), Rb1 (p=0.067), Cyclin D (p=0.031), and Cyclin A (p=0.039) (Kosovec J et al, 2017). The JPBJ phase 1b study has previously demonstrated the safety of combining abemaciclib with ramucirumab in NSCLC. **Methods:** Subjects with previously treated metastatic esophageal or gastroesophageal junction adenocarcinomas are eligible for this study which is currently open and enrolling patients. Squamous cell and mixed histology with neuroendocrine features are excluded. A total of 30 patients will be enrolled across 3 sites at Baylor University Medical Center in Dallas, The Allegheny Health Network in Pittsburgh and at Johns Hopkins Hospital in Baltimore. The primary objective is to describe the safety profile of abemaciclib (150mg po bid) and ramucirumab (8mg/kg iv every 2 weeks) in this patient population as assessed according to Common Terminology Criteria for Adverse Events version 4.0. Secondary objectives are to assess response rate, progression free and overall survival. In addition, we will determine the rate of stable disease at 3 months post targeted therapy. Correlative studies investigating changes in the expression of selected serum/tissue genomic markers of interest will be performed. Clinical trial information: NCT04921904. Research Sponsor: Eli Lilly.

TPS4170 **Poster Session**

ACCRU-GI-2008: A phase II randomized study of atezolizumab (Atezo) plus a multi-kinase inhibitor (MKI) versus MKI alone in patients with unresectable advanced hepatocellular carcinoma (aHCC) who previously received atezolizumab plus bevacizumab (Bev). *First Author: Wen Wee Ma, Division of Medical Oncology, Mayo Clinic, Rochester, MN*

Background: IMbrave150 is the first study demonstrating the benefit of anti-PDL1 in the frontline treatment of aHCC, and established Atezo/Bev as a new 1st line standard for aHCC. There is currently limited evidence to guide subsequent therapy for aHCC patients progressing on Atezo/Bev. ACCRU-GI-2008 is designed to determine the benefit of continuing Atezo into 2nd line and the safety of Atezo plus a MKI in patients with aHCC who previously received Atezo/Bev. The study is being conducted across 12 centers in the United States (ClincalTrials.gov#: NCT05168163). **Methods:** This study utilizes a 2:1 randomized phase II design where eligible patients will receive either Atezo/MKI (experimental arm) or MKI alone (control). Patients will be stratified according to the MKI choice (cabozantinib or lenvatinib, per physician's decision), etiology of HCC (viral vs. non-viral) and alpha-fetoprotein level (< 400 vs. > = 400 ng/mL). The major eligibility criteria are histological/cytological diagnosis or clinical diagnosis of HCC per the AASLD or WASL 2018 guidelines, has advanced disease not amendable to curative treatment, previously received and progressed on Atezo/Bev, has received only 1 previous line of systemic therapy (2nd line only), ECOG PS 0-1, Child Pugh Class A, adequate organ reserves and RECIST v1.1 measurable disease; previous MKI for advanced disease is excluded. The primary endpoints are overall survival (OS) and progression free survival (PFS). A total sample size of 122, with 89 PFS events, we will have 80% power to detect an improvement in median PFS from 4 to 7 months, assuming a one-sided significance level of 0.05. With approximately 84 deaths, we will have 80% power to detect an improvement in median OS from 10 to 18 months, assuming a one-sided significance level of 0.05. The overall one-sided significance level, for the study, is 0.1. An OS interim analysis will be conducted at 89 PFS events. Secondary endpoints include objective response, duration of response, and adverse events. Archival tumor and serial blood samples will be collected to evaluate for potential prediction biomarkers and mechanisms of sensitivity/resistance. Baseline and on-treatment tumor biopsy specimens will also be collected from the initial 10 patients of each arm. The study is approved by the ethics committee and enrollment to the study will be underway by Q2/3 2022. Clinical trial information: NCT05168163. Research Sponsor: Genentech.

TPS4171 **Poster Session**

PROOF 301: A multicenter, open-label, randomized, phase 3 trial of infigratinib versus gemcitabine plus cisplatin in patients with advanced cholangiocarcinoma with an *FGFR2* gene fusion/rearrangement. *First Author: Ghassan K. Abou-Alfa, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY*

Background: First-line treatment options are limited for patients with advanced cholangiocarcinoma (CCA). Genetic alterations in the fibroblast growth factor receptor (*FGFR*) gene play an important role in CCA. *FGFR* gene fusions/rearrangements are present in 10–16% of intrahepatic CCA and may predict tumor sensitivity to FGFR inhibitors. Infigratinib (BGJ398) is a potent, orally bioavailable, selective, ATP-competitive, small-molecule tyrosine kinase inhibitor of FGFRs that showed promising clinical activity and a manageable adverse event profile in a phase 2 study in patients with previously treated, unresectable locally advanced/metastatic CCA with an *FGFR2* gene fusion/rearrangement. The multicenter, open-label, randomized, controlled phase 3 PROOF 301 trial is evaluating infigratinib vs standard-of-care gemcitabine + cisplatin as first-line treatment for patients with advanced/metastatic or inoperable CCA with an *FGFR2* gene fusion/rearrangement. **Methods:** Approximately 300 patients ≥18 years of age with histologically or cytologically confirmed, advanced/metastatic or inoperable CCA with an *FGFR2* gene fusion/rearrangement (confirmed by central laboratory) are randomized 2:1 to oral infigratinib 125 mg once daily for the first 21 days of a 28-day treatment cycle vs intravenous standard gemcitabine (1000 mg/m^2) + cisplatin (25 mg/m^2) on days 1 and 8 of a 21-day cycle. Randomization will be stratified by unresectable locally advanced vs metastatic disease, geographic region, prior neoadjuvant/adjuvant treatment vs none, and receipt of up to 1 cycle of gemcitabine-based chemotherapy for unresectable locally advanced/metastatic disease prior to randomization vs none. Treatment will continue until confirmed progressive disease by blinded independent central review (BICR), intolerance, withdrawal of informed consent, or death. Patients on the gemcitabine + cisplatin arm who develop disease progression, confirmed by BICR, can cross-over to receive infigratinib. The primary endpoint is progression-free survival (PFS, RECIST v1.1), confirmed by BICR. Secondary endpoints include overall survival, PFS (investigator determined), overall response rate, best overall response, disease control rate, duration of response (BICR and investigator determined), and the type, frequency, and severity of adverse events (AEs) and serious AEs. PFS after subsequent therapy (PFS2), quality of life, pharmacokinetics and other exploratory genetic alterations/biomarkers will also be evaluated. Trial enrollment is ongoing in the US, EU, and APAC (including Australia). The Data Monitoring Committee last reviewed the trial in December 2021. Clinical trial information: NCT03773302. Research Sponsor: QED Therapeutics, Inc., and Helsinn Healthcare SA.

TPS4172 **Poster Session**

AdvanTIG-206: Anti-TIGIT monoclonal antibody (mAb) ociperlimab (BGB-A1217; OCI) plus anti-programmed cell death protein-1 (PD-1) mAb tislelizumab (TIS) plus BAT1706 versus TIS plus BAT1706 as first-line (1L) treatment for advanced hepatocellular carcinoma (HCC). *First Author: Jia Fan, Fudan University Zhongshan Hospital, Shanghai, China*

Background: Treatment with PD-1/programmed death ligand 1 (PD-L1) inhibitors and anti-angiogenic agents has demonstrated significant survival improvements in patients with untreated HCC. T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain (TIGIT) is a co-inhibitory immune checkpoint receptor upregulated on T cells and natural killer cells in multiple solid tumors. OCI is a novel, humanized mAb that binds TIGIT with high specificity and affinity, blocking interaction with its ligands on tumor cells. TIS is an anti-PD-1 mAb that has demonstrated clinical activity in patients with previously treated, unresectable HCC (NCT03419897). BAT1706 is a similar biological product to the anti-angiogenic agent bevacizumab. OCI combined with TIS and BAT1706 could further enhance both anti-angiogenic and anti-PD-1 therapies for patients with HCC. **Methods:** AdvanTIG-206 is a Phase 2, randomized, open-label clinical study (NCT04948697). Patients aged ≥ 18 years with histologically confirmed advanced HCC that is not amenable to a curative treatment approach are eligible. Patients must have a Child-Pugh A score, ECOG PS ≤ 1, and have received no prior systemic therapy for HCC. Approximately 90 patients will be randomized 2:1 to OCI 900 mg combined with TIS 200 mg plus BAT1706 15 mg/kg (Arm A) or TIS 200 mg plus BAT1706 15 mg/kg (Arm B), all administered intravenously (once every 3 weeks [Q3W]). The primary endpoint is objective response rate as assessed by the investigator (RECIST v1.1). Radiological assessment of tumor response status will be performed Q6W for the first 48 weeks and Q12W thereafter. Secondary endpoints include duration of response, time to response, disease control rate, clinical benefit rate, and progression-free survival (all by investigator's assessment), overall survival, safety, pharmacokinetics, and immunogenicity. Study enrollment is ongoing. Clinical trial information: NCT04948697. Research Sponsor: This study was sponsored by BeiGene, Ltd. Medical writing support, under the direction of the authors, was provided by Victoria Dagwell, MSc, of Ashfield MedComms, an Ashfield Health company, and funded by BeiGene, Ltd.

TPS4173 **Poster Session**

Phase 2 open-label study of pembrolizumab plus lenvatinib and belzutifan in patients with advanced solid tumors. *First Author: Robin Kate Kelley, University of California San Francisco, San Francisco, CA*

Background: There is an unmet medical need in patients (pts) with advanced/metastatic hepatocellular carcinoma (HCC), colorectal cancer (CRC), pancreatic ductal adenocarcinoma (PDAC), and biliary tract cancer (BTC), that progresses after standard therapy. The combination of pembrolizumab (pembro; anti–PD-1 antibody) and lenvatinib (len; anti-angiogenic multikinase inhibitor) demonstrated antitumor activity and manageable toxicity in many tumor types. Hypoxia-inducible factor-2 alpha (HIF-2α) acts on multiple pathways including cell survival and proliferation, angiogenesis, genomic instability and treatment resistance. Monotherapy with the HIF-2α inhibitor belzutifan (MK-6482) impairs hypoxic signaling in cancer cells and has antitumor activity in clear cell renal cell carcinoma (RCC), von Hippel-Lindau (VHL) disease associated non-RCC tumors such as pancreatic neuroendocrine tumors. Based on the potential role of hypoxia signaling and HIF-2α in tumorigenesis and tumor progression, the combination of belzutifan with pembro and len may improve antitumor activity further in the selected tumor types. **Methods:** This phase 2, single-arm, open-label, multicenter study (NCT04976634) is evaluating pembro 400 mg IV Q6W + oral len 20 mg QD (8 or 12 mg QD for body weight < 60 or ≥60 kg, respectively, for pts with HCC) + oral belzutifan 120 mg QD. Eligible pts: ≥18 y old with histologically confirmed unresectable HCC (Child-Pugh A; 1L); previously treated unresectable, metastatic non–MSI-H/mismatch repair deficient CRC (3L+); metastatic PDAC (2L/3L); or locally advanced/metastatic BTC (includes intra/extrahepatic cholangiocarcinoma and gall bladder cancer; 2L+) with progressive disease (PD); measurable disease per RECIST v1.1 (verified by blinded independent central review [BICR]); ECOG PS ≤1 and archival/new tumor sample for biomarker analysis. All pts should be naïve to prior immune checkpoint inhibitor therapy, len or any HIF-2α inhibitor. The safety lead-in phase is based on the modified toxicity probability interval design with a target dose-limiting toxicity (DLT) rate of 30% and DLT-evaluable period of 21 days (3 wk/1 cycle) in ≤10 HCC pts and ≤15 pts with CRC, PDAC and BTC pooled for each dose level. The study will enroll 120 pts (30/tumor type) to receive triplet therapy for up to 2 y (for pembro) or until PD or discontinuation criteria are met. Enrollment may be expanded by an additional 70 pts/tumor type at the chosen dose level after safety and efficacy review with ≥6 mo follow-up. Primary endpoints are safety (DLTs [safety lead-in], AEs, and treatment discontinuation due to AEs) and ORR per RECIST v1.1 by BICR. Secondary endpoints include DOR, disease control rate and PFS per RECIST v1.1 (and mRECIST for HCC) by BICR, and OS. Efficacy analyses will report binomial proportion or Kaplan-Meier estimates with 95% CIs. Safety analyses will be descriptive. Enrollment began August 2021. Clinical trial information: NCT04976634. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

TPS4174 **Poster Session**

An investigator-initiated phase II trial of a PARP inhibitor niraparib monotherapy for patients with pre-treated, *BRCA*-mutated, unresectable/recurrent biliary tract, pancreatic, and other gastrointestinal cancers (NIR-B trial). *First Author: Yasuyuki Kawamoto, Hokkaido University Hospital, Sapporo, Japan*

Background: Recent comprehensive genomic profiling tests have revealed therapeutic target molecules. However, because many targets are present in only a small fraction of patients, a large number of patients need to be screened for enrollment in a single study. In order to overcome this patient identification barrier, the SCRUM-Japan, nationwide large-scale genomic profiling platform, efficiently has been performed umbrella- and basket-type clinical trials. Among the platforms, we have reported that there are *BRCA1/2*-mutated patients in biliary tract, pancreatic, and other gastrointestinal cancers. Niraparib is an anticancer drug belonging to poly(ADP-ribose) polymerase (PARP) inhibitors. Niraparib has been shown to be selective for PARP1/2, to be more cytotoxic among other PARP inhibitor because of its PARP trapping activity. **Methods:** This is an investigator-initiated, multicenter, three-cohort phase 2 study. Main eligibility criteria are unresectable, advanced or recurrent biliary tract cancers (cohort A), pancreatic cancers (cohort B), and other gastrointestinal cancers (cohort C) with *BRCA1/2* gene mutations identified by germline test or genomic profiling test with either circulating tumor DNA (ctDNA) or tumor tissue, refractory or intolerant to previous treatments, and adequate organ function. Primary endpoint is the investigator-assessed objective response rate in each cohort with a threshold-response rate of 10% and an expected response rate of 35%. Key secondary endpoints are progression-free survival, overall survival, disease control rate, duration of response, and safety. Patients with body weight of 77 kg or more and a platelet count of 150,000 /μL or more receive 300 mg of niraparib, and less than 77 kg or having a platelet count less than 150,000 /μL receive 200 mg of niraparib, orally once daily. Furthermore, pretreatment tumor tissue and serial ctDNA will be collected and analyzed to investigate the resistance mechanisms and provide clinically meaningful biomarker which may be used for identifying and implementing treatment changes. The trial was initiated in January 2021 with enrollment being ongoing. Thirty-three out of planned 60 patients (cohort A/B/C; 25/25/10, respectively) have been enrolled as of December 2021. Funding: Takeda Pharmaceutical Co., Ltd. Clinical trial information: jRCT2011200023. Research Sponsor: Japan Agency for Medical Research and Development, Pharmaceutical/Biotech Company.

TPS4175 **Poster Session**

TALENTop: A multicenter, randomized study evaluating the efficacy and safety of hepatic resection for selected hepatocellular carcinoma with macrovascular invasion after initial atezolizumab plus bevacizumab treatment. *First Author: Hui-Chuan Sun, Liver Cancer Institute and Zhongshan Hospital, Fudan University, Shanghai, China*

Background: Hepatocellular carcinoma **(**HCC) patients with macrovascular invasion are consistently considered to be at an advanced stage of disease. The combination therapy of atezolizumab (atezo) plus bevacizumab (bev) has been the new standard-of-care for those patients. In patients responding to systemic therapy, hepatic resection may provide additional benefit. Here we propose a phase 3 study to investigate whether hepatic resection following atezo/bev can bring more benefits for HCC patients with macrovascular invasion when compared with atezo/bev alone. **Methods:** This is a multicenter, open-label, two-arm, randomized study designed to evaluate the efficacy and safety of surgical resection plus peri-operative atezo/bev compared with regular systemic atezo/bev (Q3W, every three weeks) in HCC patients with macrovascular invasion and without extrahepatic metastasis. Initially eligible patients have enrolled into induction phase, during which they receive 3 cycles of atezo/bev and 1 cycle of atezo alone as primary systemic therapy. Patients who are assessed as partial response or stable disease (RECIST v1.1 criteria) and considered suitable for R0 hepatic resection are randomized in a 1:1 ratio to either Arm A, hepatic resection with post-operative atezo/bev for 1 year (or until loss of clinical benefit or intolerable toxic effects), or Arm B, continuing atezo/bev for 1 year (or until loss of clinical benefit or intolerable toxic effects). The primary endpoint of this study is time-to treatment failure (TTF), defined as time from randomization to the first documented treatment failure (i.e., tumor recurrence or metastasis [Arm A], disease progression [Arm B] according to RECIST v1.1, or death from any cause). We hypothesize that hepatic surgery with peri-operative atezo/bev will improve the TTF from 5.8 months to 9.2 months, with the hazard ratio of 0.63. With 2-sided significance level of 0.05, the sample size for randomization will be 198. The study, registered with clinical trial ID of NCT04649489, started enrollment in Apr 2021. As of Jan 2022, 65 patients have been enrolled and 15 patients have been randomized. Research funding: Shanghai Roche Pharmaceuticals Ltd. Clinical trial information: NCT04649489. Research Sponsor: Shanghai Roche Pharmaceuticals Ltd.

TPS4176 **Poster Session**

Study protocol of an open-label, single-arm, phase II trial investigating the efficacy and safety of trifluridine/tipiracil combined with irinotecan as a second-line therapy in patients with cholangiocarcinoma (TRITICC). *First Author: Linde Kehmann, Charité University Medicine Berlin, Berlin, Germany*

Background: Biliary tract cancers (BTC) currently account for ~15% of all primary liver cancers and ~3% of gastrointestinal malignancies. Gemcitabine/Cisplatin has been the standard of care in the first-line therapy of BTC for a decade. Despite recently some survival benefit has been shown in adding a checkpoint inhibitor, further lines of treatment are only poorly defined. In the ABC-06 phase-3 study, second-line FOLFOX demonstrated a moderate but significant improvement of survival and might be regarded as a standard of care. The combination of liposomal Irinotecan and 5-FU infusion pump also improved survival after first line therapy. Both mentioned second-line regimens are based on limited evidence and questionable generalizability. Thus, there is a high need for novel treatment concepts in patients without targetable genetic alterations. Trifluridine/tipiracil (FTD/TPI) is a orally active, antimetabolite agent comprised of trifluridine, a thymidine-based nucleoside analogue, and tipiracil, a potent thymidine phosphorylase inhibitor. Recent reports provided evidence of an antitumor activity of FTD/TPI plus Irinotecan as well in patients with BTC. Therefore, the TRITICC trial was designed to evaluate the safety and efficacy of FTD/TPI plus irinotecan in patients with BTC refractory to previous Gemcitabine based treatment. **Methods:** TRITICC (NCT04059562) is an interventional, prospective, open-label, non-randomized, exploratory, multicenter, single-arm phase IIA clinical trial that evaluates the safety and efficacy of FTD/TPI (25 mg/m^2 body surface area (BSA), BID, orally on days 1-5 followed by a 9-days recovery period from day 6 trough day 14 of each 14-days treatment cycle) plus irinotecan (on day 1 of each cycle at a dose of 180 mg/m^2) in adult patients with histologically verified locally advanced or metastatic BTC (including cholangiocarcinoma and gallbladder or ampullary carcinoma) with documented radiological disease progression to first-line gemcitabine based chemotherapy. A total of 28 patients is planned to be enrolled in 6 sites across Germany. Study treatment will be continued until disease progression according to RECIST 1.1 criteria or occurrence of unacceptable toxicity. The effect of FTD/TPI plus irinotecan on progression-free survival will be analyzed as primary endpoint. Safety (according to NCI-CTCAE), response rates and overall survival are secondary endpoints. In addition, a comprehensive translational research program is part of the study and might provide findings about predictive markers with regard to response, survival periods and resistance to treatment. Currently, 3 out of the planned 6 German study sites are opened for recruitment and 6 patients have been enrolled. The primary study endpoint is estimated to be evaluated in 2023. Clinical trial information: NCT04059562. Research Sponsor: Servier.

TPS4177 **Poster Session**

An open-label, multicenter, randomized phase II study of atezolizumab and bevacizumab with Y90 TARE in patients with unresectable hepatocellular carcinoma (HCC). *First Author: Aiwu Ruth He, Georgetown University Lombardi Comprehensive Cancer Center, Washington, DC*

Background: The anti–PD-L1 antibody atezolizumab (ATEZO) prevents PD-L1 from interacting with PD-1 and B7.1, thus reinvigorating antitumor T cell activity. Anti-VEGF bevacizumab (BEV) increases dendritic cell maturation, enhances T cell infiltration, and reduces myeloid-derived suppressor cells and regulatory T cells in tumors. ATEZO + BEV is FDA approved for first-line treatment of advanced HCC based on the IMbrave 150 study. Locoregional radiotherapy (e.g., Y90 TARE) enhances the diversity of the intratumoral T cell receptor repertoire and increases tumor antigen release. We hypothesize that the Y90 TARE + BEV + ATEZO combination induces synergistic tumor killing and prolongs progression-free survival in patients (pts) receiving Y90 TARE (HR = 0.6 when compared to Y-90 TARE alone). **Methods:** Eligible pts have HCC that cannot be surgically resected (confirmed by pathology review), is at least BCLC stage B, and is outside Milan criteria. Other requirements include ECOG PS of 0-1 at screening, measurable disease by RECIST 1.1, no prior systemic therapy, and FLR estimated at ≥ 40% post local therapy. Pts must have a pretreatment liver biopsy taken and then be randomized 1:1 to TARE (Arm A) or TARE + ATEZO + BEV (Arm B). Pts will have TARE mapping followed by TARE treatment. In Arm B, pts will begin TARE treatment followed by BEV + ATEZO (4 wks [± 1 wk] later). Pts will have abdominal MRI or CT scans every 12 weeks and CT scans of the chest every 24 wks. The primary study objective is to assess and compare pts' progression-free survival (per mRECIST 1.1) in each study arm. The main secondary objective is to determine the safety and tolerability (CTCAE v5) of pts in Arm B. Exploratory objectives are to define the use of cellular and circulating biomarkers in the prediction of improved clinical outcomes of pts in Arm B. Symptoms experienced by pts in both arms using patient-reported outcomes will be assessed. Disease progression will be captured by both RECIST 1.1 and mRECIST. We plan to assess the safety of Y90 TARE + BEV + ATEZO in the first 10 pts randomized to Arm B for two cycles, and if there are no grade ≥ 3 unexpected toxicities possibly, probably, or definitely related to combined TARE + BEV + ATEZO, continue to accrue 128 pts in total (current enrollment n- = 5). Pts will continue study treatment (Arm B) for a total of 24 months from initiation of TARE or until intolerable toxicity or disease progression occur, whichever is earlier. Enrollment began in September 2020. Clinical trial information: NCT04541173. Research Sponsor: Roche/Genentech, Institutional funding.

TPS4178 **Poster Session**

Methodology of the SORENTO clinical trial: Assessing the efficacy and safety of high exposure octreotide subcutaneous depot in patients with GEP-NETs. *First Author: Simron Singh, Sunnybrook Health Sciences Centre, Toronto, ON, Canada*

Background: Somatostatin receptor ligands (SRLs) are first-line standard of care therapies for gastroenteropancreatic neuroendocrine tumors (GEP-NETs), showing efficacy in tumor/symptom control with an established safety profile. Yet, disease progression may occur despite standard-dose SRL treatment, requiring more aggressive and toxic therapies. Retrospective/non-randomized data suggest higher-dose SRLs may benefit patients with GEP-NETs who do not respond to standard-dose treatment and provide improved disease control. Octreotide depot (CAM2029) is a novel high-exposure, subcutaneous (SC) formulation. Clinical trials showed ~500% higher CAM2029 bioavailability versus octreotide long-acting release (LAR) (Tiberg et al. 2015), and maintenance/reduction of NET symptoms (Pavel et al. 2019). Prospective, randomized data are needed to confirm the efficacy/safety of novel SRLs with higher bioavailability such as CAM2029, vs standard-dose SRLs including octreotide LAR and lanreotide Autogel (ATG). **Methods:** SORENTO is a randomized, multi-center, open-label, active-controlled Phase 3 trial, aiming to enroll 302 adults with GEP-NETs. Key eligibility criteria: advanced, well-differentiated NET of GEP/presumed GEP origin; ≥1 measurable SR positive (by nuclear imaging) lesion according to RECIST 1.1; no or < 6 months consecutive treatment with long-acting SRLs. Notably, patients with Grade 3 GEP-NETs (excluded by CLARINET/PROMID trials) are eligible. Patients will be randomized 1:1 to CAM2029 20 mg Q2W, or active comparator (octreotide LAR 30 mg intramuscular or lanreotide ATG 120 mg SC, Q4W). CAM2029 self/carer administration is allowed after ≥3 successful supervised administrations. Randomization stratified by: histological grade, tumor origin, intended comparator. Primary outcome: progression free survival (PFS; time from randomization to date of first documented disease progression [RECIST 1.1] or death), assessed by a Blinded Independent Review Committee. The study is powered to detect a hazard ratio of 0.65. Key secondary outcomes: overall survival; response rate; rescue medication use; patient satisfaction; adverse events. After primary PFS analysis, patient overall survival will be followed for up to 2 years. If CAM2029 displays superiority in the primary analysis, the comparator group may switch to CAM2029 20 mg Q2W. Patients in any treatment group experiencing progressive disease in the randomized part of the study may proceed to an open-label extension with intensified CAM2029 treatment, to investigate effects of higher frequency dosing. First patient randomized in Nov-2021, with readout (following 194 events) expected by 2024 end. This novel head-to-head superiority trial is anticipated to demonstrate the potential benefits of CAM2029 as a first line-therapy in patients with well-differentiated GEP-NETs. Clinical trial information: NCT05050942. Research Sponsor: Camurus AB.

TPS4179 **Poster Session**

SWOG S2012: Randomized phase II/III trial of first line platinum/etoposide (P/E) with or without atezolizumab (NSC#783608) in patients (pts) with poorly differentiated extrapulmonary small cell neuroendocrine carcinomas (NEC). *First Author: David Bing Zhen, University of Washington/Fred Hutchison Cancer Research Center, Seattle, WA*

Background: Poorly differentiated, extrapulmonary small cell NEC are rare cancers with median overall survival (OS) < 1 year. Treatment is extrapolated from small cell lung cancer (SCLC) with use of P (cisplatin or carboplatin) + E. More effective treatment regimens and predictive biomarkers are needed to improve outcomes. In SCLC, induction therapy with combination of P/E + PD-L1 checkpoint inhibitor atezolizumab and maintenance atezolizumab improved OS (12.3 months vs 10.3 months; HR 0.70, 95% CI 0.54 – 0.91, P = 0.007) vs P/E alone (Horn L, et al. N Engl J Med 2018). No study to date has compared PD-1/PD-L1 inhibition during induction only vs during induction and maintenance therapy. In SCLC, distinct molecular subtypes can be identified by the presence of specific transcription factors (e.g., ASCL1, NEUROD1, POU2F3) or an Inflamed gene signature (SCLC-I), with SCLC-I pts more likely to benefit clinically from the addition of immunotherapy (Gay CM, et al. Cancer Cell 2021). In this study we plan to test the benefit of adding atezolizumab to induction P/E plus maintenance vs P/E alone, as well as the role of adding maintenance atezolizumab vs observation after induction chemo-immunotherapy. We also plan to correlate tumor- and blood-based subtype biomarkers with response to therapy. **Methods:** Eligible pts ≥18 years old have evaluable, histologically confirmed extrapulmonary small cell NEC, Zubrod PS ≤2, and are allowed to have up to 1 cycle of P/E prior to enrollment. P (cisplatin 75 mg/m2 or carboplatin AUC 5, iv) on day 1, E 100 mg/m2 iv on days 1-3, and atezolizumab 1200 mg iv on day 1 of q21 day cycles. Treatment consists of an induction phase x 4 cycles, and if no disease progression, a maintenance/observation phase given until disease progression for up to 1 year. Pts are randomized to 1 of 3 arms: A) Induction P/E + atezolizumab → maintenance atezolizumab B) Induction P/E + atezolizumab → observation C) Induction P/E → observation. The primary endpoint is to compare the OS (from randomization) between arms in a fixed sequence: A vs C → B vs C → A vs B. Secondary endpoints include comparing OS (from start of maintenance/observation), progression free survival, response rate, duration of response, and safety/tolerability across arms. Tumor and blood samples will be banked for future biomarker analyses, including immunohistochemistry of transcription factors on tissue and whole exome sequencing on tumor and circulating tumor DNA. With 189 pts, the study is powered to detect an improvement in 12-months OS from 35% to 57.5% (HR 0.53). Both phase 2 and phase 3 portions include interim analyses. Accrual will not pause for phase 2 analysis, expected early 2024. This study was activated December, 2021 and is open to accrual across the NCI National Clinical Trials Network (NCTN). Clinical trial information: NCT05058651. Research Sponsor: U.S. National Institutes of Health.

TPS4180 **Poster Session**

Trial in progress: Phase I study of SY-5609, a potent, selective CDK7 inhibitor, with initial expansion in adults with metastatic pancreatic cancer. *First Author: Manish Sharma, START Midwest, Grand Rapids, MI*

Background: SY-5609 is an oral, selective, potent CDK7 inhibitor that targets two fundamental processes in cancer: transcription and cell cycle control. Early results from the Phase 1 dose escalation portion in patients (pts) with advanced solid tumors reported improved tolerability of the intermittent 7 days on followed by 7 days off (7/7) schedule with ongoing dose escalation beyond the continuous daily dosing maximum tolerated dose. Single-agent clinical activity was demonstrated with durable stable disease, target lesion regressions, and reduction in tumor markers observed in multiple tumor types, notably in pancreatic cancer with a disease control rate (DCR) of 38.5% (Sharma 2021). Pancreatic ductal adenocarcinoma (PDAC) has a 5-year survival rate of 11% (ACS Cancer Facts and figures, 2022) with limited treatment options and therefore, is a disease in need of novel effective therapies. Oncogenic *KRAS* mutations are prevalent in PDAC. Mutant *KRAS* is a potent stimulator of mitogenic MAPK signaling and downstream transcriptional programs for cell proliferation. Preclinical studies have shown that CDK7 inhibition via SY-5609 inhibits tumor growth in *KRAS* mutant PDAC xenograft models, in many cases leading to regressions. SY-5609 also potentiates gemcitabine (gem) activity in PDAC cells *in vitro* and in xenografts *in vivo* (Henry 2021). Therefore, combining SY-5609 with gem +/- nab-paclitaxel (nab-pac) offers a potential new treatment strategy for metastatic PDAC (mPDAC). The expansion portion of this Phase 1 study will evaluate SY-5609 in combination with gem +/- nab-pac in mPDAC pts. Gem +/- nab-pac will be administered on a biweekly schedule as it has shown better tolerability and similar clinical activity compared to the standard of care (SOC) administration schedule (Rehman 2020). **Methods:** This is an ongoing Phase 1, multi-center study in select solid tumors, amended to open expansion cohorts for mPDAC and expected to enroll approximately 80 mPDAC pts who have progressed on SOC treatments. Objectives of the expansion cohorts include evaluation of safety and efficacy of SY-5609 in combination with gem +/- nab-pac. Key objectives of the two parallel safety lead-in cohorts 1) SY-5609 + gem and 2) SY-5609 + gem + nab-pac are safety and determination of the recommended combination dose of the doublet and triplet for subsequent cohort expansions using a 3+3 escalation design. Key objectives of expansion cohorts are to describe efficacy, defined by progression-free survival, overall response rate, and DCR. Additional objectives include evaluation of pharmacokinetics and pharmacodynamics of SY-5609 in combination with gem +/- nab-pac. SY-5609 will be administered orally once daily on a 7/7 regimen and gem +/- nab-pac will be administered intravenously, in a 4-week cycle. The expansion portion is now open to enrollment. Clinical trial information: NCT04247126. Research Sponsor: Syros Pharmaceuticals.

TPS4181 **Poster Session**

A phase 1b/2, dose-escalation, randomized, multicenter study of maintenance (maint) ivaltinostat (ival) plus capecitabine (cap) or capecitabine monotherapy in patients (pts) with metastatic pancreatic adenocarcinoma (PDAC) whose disease has not progressed on first-line FOLFIRINOX chemotherapy (CT). *First Author: Evan Justin Walker, UCSF, San Francisco, CA*

Background: The mainstay of treatment (TX) for pts with advanced or mPDAC consists of CT, with FOLFIRINOX and gemcitabine (gem)/nab-paclitaxel currently representing the front-line standards of care. TX is generally continued until either dis progression (progr) or cumulative toxicity, with pts often reaching a plateau in response after 4-6 mos. For those who have achieved dis control (stable dis or better) on front-line CT, a maint TX strategy that can effectively delay dis progr while preserving quality of life with minimal cumulative toxicity is highly desirable. However, aside from PARP inhibition in the subset of PDAC pts with gBRCA mutated dis, there is no current standard of care in this maint setting. Ival is a pan-HDAC (histone deacetylation) inhibitor that increases histone acetylation (HA), suppresses PDAC cell proliferation, and promotes apoptosis in PDAC cell lines in a dose-dependent manner. It has demonstrated synergy with 5-FU in cholangiocarcinoma cell lines and shows promising antitumor activity when combined with cap in syngeneic PDAC mouse models. On these bases, we are conducting a ph1b/randomized ph2 trial of ival plus cap vs cap alone in the maint setting for pts with mPDAC who have not progressed on front-line FOLFIRINOX. **Methods:** Key eligibility criteria include pts with mPDAC; no evidence of dis progr following at least 16 wks of front-line FOLFIRINOX at full or modified doses; ECOG PS 0-1; and no known gBRCA1/2 mutation. The study includes an initial dose-esc ph1b evaluating 3 dose levels of ival, (60, 125, and 250mg/m^2 iv weekly on days 1 and 8) in combination (comb) with cap (1000mg/m^2 po BID on days 1-14) of a 21-day cycle, using a standard 3 + 3 dose-esc design. Of note, ival 250 mg/m^2 represents the RP2D identified in prior clinical studies of this agent both as monotherapy in solid tumors and in comb with gem/erlotinib in advanced PDAC pts. In the ph2 portion, pts will be randomized 1:1 to receive either ival plus cap or cap alone, in 21-day cycles, until dis progr, with tumor assessments occurring at 6-wk intervals. Blood will be collected at pre-specified serial timepoints for pharmacodynamic assessments, including HA of PBMCs. Primary endpoint for ph2 is investigator-adjudicated PFS. The primary analysis will compare PFS distributions in the ival/cap and cap alone arms using a one-sided log rank test with an alpha = 0.10. The assumed true 6-mo PFS rates are 35% (cap), based on historic data, and 60% (ival/cap), which corresponds to an HR of 0.487. Assuming an accrual duration of 18 mos and a dropout/lost to follow-up rate of 10%, the estimated total number of pts in the randomized ph2 portion is 52 (26 per arm). Enrollment is expected to being in spring 2022 across 25 U.S. sites. Research Sponsor: CG Pharmaceuticals Inc.

TPS4183 **Poster Session**

Phase II study (daNIS-1) of the anti-TGF-β monoclonal antibody (mAb) NIS793 with and without the PD-1 inhibitor spartalizumab in combination with nab-paclitaxel/gemcitabine (NG) versus NG alone in patients (pts) with first-line metastatic pancreatic ductal adenocarcinoma (mPDAC). *First Author: Li-Yuan Bai, China Medical University Hospital, Taichung, Taiwan*

Background: Overall survival remains low for pts with mPDAC despite approved therapies, highlighting the need for further innovative treatment options. Intra-tumoral fibrosis that characterizes PDAC has been associated with a state of immune exclusion and may constitute a mechanical obstacle to the intra-tumoral penetration of chemotherapy as well as contribute to the lack of efficacy of immunotherapy. TGF-β plays a key role in regulating the tumor microenvironment and emerging evidence points to its role as a pivotal activator of cancer-associated fibroblasts, leading to the development of fibrotic networks. Preclinical data in murine models have shown that TGF-β blockade augmented the antitumor activity of both NG and anti-PD-1 therapy, leading to tumor regression. These data provide the rationale for combining TGF-β-targeting agents with immunotherapy and chemotherapy. NIS793 is a human IgG2 mAb that binds to TGF-β. This study investigates NIS793 with and without spartalizumab (PD-1 antagonist) combined with NG in treatment naïve mPDAC. **Methods:** This is a phase II open-label, randomized, multicenter study (NCT04390763) beginning with a safety run-in period followed by randomization. Eligible pts are adults with previously untreated mPDAC and ECOG performance status score ≤1. Pts are excluded if they have a microsatellite-unstable tumor. The safety run-in data will be analyzed after ≥6 pts have received NIS793 (intravenously [IV] 2100 mg Q2W) + spartalizumab (IV 400 mg Q4W) + nab-paclitaxel (IV 125 mg/m^2 on Days 1, 8 and 15) + gemcitabine (IV 1000 mg/m^2 on Days 1, 8 and 15) for 1 cycle (28 days) to assess the safety and tolerability of the combination. In the randomized part, pts will be randomized 1:1:1 to NIS793 + spartalizumab + NG (n = 50) or NIS793 + NG (n = 50) or NG (n = 50). Treatment will continue until unacceptable toxicity, disease progression, discontinuation by investigator's/pt's choice, or withdrawal of consent. The primary objective is to evaluate the progression-free survival per RECIST 1.1, of NIS793 + NG ± spartalizumab versus NG alone . Secondary objectives include safety and tolerability, antitumor activity, overall survival, change in tumoral CD8 and PD-L1 status, and characterization of immunogenicity and pharmacokinetics. Efficacy will be assessed locally per RECIST v1.1 and iRECIST at screening, every 8 weeks for 1 year and then every 12 weeks until disease progression. Blood and tumor samples will be taken at baseline and during study treatment for pharmacokinetic, immunogenicity and biomarker assessments. This study is ongoing and will enroll pts from 31 sites across 14 countries. The first pt was treated on October 22, 2020. Enrollment for the randomized part of the study started on August 09, 2021. Clinical trial information: NCT04390763. Research Sponsor: Novartis.

TPS4184 **Poster Session**

GRECO-2: A randomized, phase 2 study of stereotactic body radiation therapy (SBRT) in combination with rucosopasem (GC4711) in the treatment of locally advanced or borderline resectable nonmetastatic pancreatic cancer. *First Author: Sarah E. Hoffe, H. Lee Moffitt Cancer Center, Tampa, FL*

Background: While treatment of pancreatic cancer has advanced, survival rates remain low. Stereotactic body radiotherapy (SBRT; high dose per fraction radiation) may exhibit improved clinical outcomes in locally advanced pancreatic cancer but carries potential gastrointestinal toxicity risks (Zhong 2017). Rucosopasem (GC4711) is one of a class of investigational selective dismutase mimetics that rapidly and specifically converts superoxide to hydrogen peroxide (Riley 2006). Studies have shown that normal cells tolerate hydrogen peroxide fluxes better than cancer cells (Doskey 2016). As radiation response modifiers, dismutase mimetics have the potential to increase tumor control of SBRT without compromising radiation safety (El-Mahdy 2020, Sishc 2021). In a pilot phase 1/2 trial in patients with pancreatic cancer, avasopasem, a dismutase mimetic related to rucosopasem, nearly doubled median overall survival in patients receiving SBRT vs placebo plus SBRT. Improvements versus placebo were also observed in local tumor control, time to metastases, and progression-free survival. Altogether, these data support the hypothesis that rucosopasem may improve survival and the benefit-risk ratio of SBRT by improving efficacy without increasing gastrointestinal toxicity. **Materials/Methods:** GRECO-2 is a phase 2, multicenter, randomized, double-blind, placebo-controlled study (NCT04698915) to determine the effect of adding rucosopasem to SBRT on overall survival in patients with borderline resectable or locally advanced, unresectable nonmetastatic pancreatic cancer following initial chemotherapy with a FOLFIRINOX-based regimen or a gemcitabine doublet. Approximately 160 patients will be randomized (approximately 35 sites) to receive rucosopasem 100 mg or placebo via IV infusion over 15 minutes, prior to each SBRT fraction (5 x 10 Gy). Patients judged to be resectable will undergo surgical exploration within 8 weeks after SBRT. The primary endpoint is overall survival. Secondary endpoints include progression-free survival, locoregional control, time to metastasis, surgical resection rate, R0 resection rate, best overall response, in-field local response, and safety (acute and late toxicities). Exploratory endpoints include PRO-CTCAE and CA19-9 normalization. This trial is now enrolling. Clinical trial information: NCT04698915. Research Sponsor: Galera Therapeutics, Inc.

TPS4185 **Poster Session**

A randomized phase II study of gemcitabine and nab-paclitaxel compared with 5-fluorouracil, leucovorin, and liposomal irinotecan in older patients with treatment-naïve metastatic pancreatic cancer (GIANT): ECOG-ACRIN EA2186—Trials in progress. *First Author: Efrat Dotan, Fox Chase Cancer Center, Philadelphia, PA*

Background: Evidence-based data is lacking to guide the care of older adults with newly diagnosed metastatic pancreatic cancer (mPCA). As a result, treatment approach and the selection of chemotherapy regimens are often extrapolated from data from younger patients. Furthermore, vulnerable older adults are often treated with dose adjusted regimens with limited data to support this practice. EA2186 is a phase II randomized controlled trial, and the first prospective study aiming to define the optimal treatment approach of vulnerable older adults with newly diagnosed mPCA. **Methods:** Patients aged 70 years and over with histologically confirmed pancreatic adenocarcinoma, evidence of metastatic disease, ECOG PS 0-2 and adequate organ function, who are considered vulnerable are eligible for this trial (accrual target 184). This study utilizes a screening geriatric assessment which characterize patients as fit, vulnerable or frail by evaluating functional status, cognition and co-morbidities. Vulnerable patients according to this screening assessment are those with mild abnormalities in functional status, comorbidities and/or cognition, or older than 80 years of age. Those patients will be randomized to receive either modified Gemcitabine/Nab-Paclitaxel or dose-reduced 5-Fluorouracil Leucovorin and Liposomal Irinotecan every 2 weeks. A comprehensive geriatric assessment (GA) and quality of life (QOL) evaluation are completed prior to initiation of therapy for all randomized patients. Follow up will continue until disease progression or withdrawal, with repeated GA and QOL assessments at each disease evaluation. Overall survival is the primary objective, with secondary objectives including progression free survival, and response rate. Enrolled patients will be stratified by age 70-74 vs ≥75, and ECOG PS 0-1 vs 2. Additional endpoints of interest for older adults include: evaluation of risk factors identified through GA, and capturing toxicities of interest for this patient population (i.e. hospitalization, deterioration in PS, and falls). Correlative studies include assessment of pro-inflammatory biomarkers or aging in the blood (IL-6 and CRP) as well as imaging evaluation of sarcopenia and body composition as predictors of treatment tolerance. Clinical trial information: NCT04233866. Research Sponsor: U.S. National Institutes of Health.

TPS4186 **Poster Session**

Zolbetuximab plus gemcitabine and nab-paclitaxel (GN) in first-line treatment of claudin 18.2-positive metastatic pancreatic cancer (mPC): Phase 2, open-label, randomized study. *First Author: Wungki Park, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY*

Background: GN is a first-line treatment option for patients (pts) with mPC. Poor prognosis and low 5-year survival rate (< 5%) of pts with mPC highlight the need for new therapeutics. Claudin 18.2 (CLDN18.2), a tight junction protein expressed exclusively on normal gastric epithelial cells, is maintained during malignant transformation in gastric cancers and is frequently expressed in some carcinomas from organs that do not normally express it, such as pancreatic cancer. Zolbetuximab, a chimeric IgG1 monoclonal antibody, binds to CLDN18.2 and mediates tumor cell death through antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. **Methods:** This phase 2 study (NCT03816163), expanded to enroll approximately 369 pts, will assess safety and efficacy of GN alone or with zolbetuximab in pts with histologically confirmed mPC and high CLDN18.2 expression (moderate-to-strong IHC staining intensity in ≥75% of tumor cells). The study included a safety lead-in that enrolled 3-12 pts to assess safety/tolerability of zolbetuximab (n = 3 at 1,000 mg/m^2 on Cycle 1 Day 1 then 600 mg/m^2 Q2W, then expand/de-escalate using a 3+3 design) plus GN. Dose-limiting toxicities (DLTs, defined as a specified zolbetuximab-related toxicity that occurs during DLT assessment period) will be assessed after Cycle 1 (28 days). Based on the recommended phase 2 dose (RP2D), confirmed during the safety lead-in, approximately 357 pts will be randomized 2:1 to zolbetuximab Q2W on Days 1 and 15 plus GN on Days 1, 8, and 15 of each cycle (Arm 1), or GN alone on Days 1, 8, and 15 of each cycle (Arm 2). Randomization will be stratified by ECOG performance status (0 or 1) and liver metastasis (yes or no). At sites in Japan, DLTs (assessed from Cycle 1 Day 1 to Cycle 2 Day 1) will be evaluated in ≤6 pts randomized to the RP2D in Arm 1. Pts will undergo imaging (CT/MRI) at baseline and every 8 weeks until investigator-assessed disease progression (RECIST v1.1) or the start of another systemic anticancer treatment, whichever comes earlier. In addition to confirming the RP2D during the safety lead-in, primary objectives are to assess whether treatment with zolbetuximab plus GN, versus GN alone, improves overall survival (randomization phase) and to establish the safety/tolerability profile of zolbetuximab plus GN (across the study). Secondary endpoints include progression-free survival, objective response rate, disease control rate, duration of response, pharmacokinetics, and health-related quality of life (per protocol amendment). Data will be presented using descriptive statistics for continuous endpoints and frequency and percentage for categorical endpoints. At original protocol enrollment completion (October 2021), 84 sites were actively recruiting; sites are currently reopening for screening/enrollment pending protocol amendment approval. Clinical trial information: NCT03816163. Research Sponsor: Astellas Pharma, Inc.

TPS4187 **Poster Session**

PANOVA-3: A phase 3 study of tumor-treating fields with gemcitabine and nab-paclitaxel for frontline treatment of locally advanced pancreatic adenocarcinoma. *First Author: Vincent J. Picozzi, Virginia Mason Hospital and Medical Center, Seattle, WA*

Background: Tumor Treating Fields (TTFields) are a novel, locoregional antimitotic treatment modality approved for glioblastoma and malignant pleural mesothelioma. Continuous, non-invasive low intensity, intermediate frequency (150–200 kHz) alternating electric fields are delivered to the tumor via skin-placed arrays. *In vitro,* TTFields (150 kHz), with or without chemotherapy, induced antiproliferative and anticlonogenic activity on pancreatic cancer cell lines (Giladi M, et al. Pancreatology 2014;14:54–63). The phase 2 PANOVA study (NCT01971281) demonstrated that the combination of TTFields with nab-paclitaxel and gemcitabine (GnP) is well-tolerated, with promising efficacy in metastatic and locally advanced pancreatic adenocarcinoma (LAPC) (Rivera F, et al. Pancreatology 2019;19:64–72). These data indicate that TTFields with GnP warrant phase 3 evaluation. **Methods:** PANOVA-3 (NCT03377491) is a prospective, randomized, phase 3 trial designed to investigate the efficacy and safety of TTFields concomitant with GnP in patients with LAPC. Planned enrollment is 556 patients. Eligibility criteria include unresectable LAPC (per National Comprehensive Cancer Network guidelines), Eastern Cooperative Oncology Group performance status of 0–2, and no prior treatment. Patients will be stratified by performance status and geographical region, and randomly assigned 1:1 to TTFields plus GnP or GnP alone. Based on a recent protocol amendment, a smaller and lighter-weight (reduced from 6 to 2.7 lbs) TTFields device will be used. Standard doses of nab-paclitaxel (125 mg/m^2) and gemcitabine (1000 mg/m^2) will be administered on days 1, 8, and 15 of a 28-day cycle. TTFields (150 kHz) will be delivered ≥ 18 h/day until local disease progression per Response Evaluation Criteria in Solid Tumors V1.1. Follow-up will be performed every 4 weeks and a computed tomography scan of the chest and abdomen every 8 weeks. After local disease progression, patients will be followed every month until death. The primary endpoint is overall survival (OS). Secondary endpoints include progression-free survival (PFS), local PFS, objective response rate, 1-year survival rate, pain- and puncture-free survival rate, rate of resectability, quality of life, and toxicity. The sample size was estimated per log-rank test comparing time to event in patients treated with TTFields plus GnP with published clinical trial data on patients treated with GnP alone. PANOVA-3 is designed to detect a hazard ratio of 0.75 in OS. Type I error is set to 0.05 (2-sided) and power to 80%. The trial is currently recruiting at 106 sites in Austria, Belgium, Canada, China, Croatia, Czech Republic, France, Germany, Hong Kong, Hungary, Israel, Italy, Poland, Spain, Switzerland, and USA. The DMC last reviewed the trial in August 2021, and suggested that the trial continue as planned. Clinical trial information: NCT03377491. Research Sponsor: Novocure Ltd.

TPS4188 **Poster Session**

Precision Promise (PrP): An adaptive, multi-arm registration trial in metastatic pancreatic ductal adenocarcinoma (PDAC). *First Author: Vincent J. Picozzi, Virginia Mason Hospital and Medical Center, Seattle, WA*

Background: The success rate of drug development in PDAC is disappointingly low.PrP is a transformative, adaptive platform clinical trial designed to continuously evaluate many novel therapeutic options while increasing the probability that patients (pts) are randomized to effective experimental therapies. It cultivates enhanced cooperation among groups representing pts advocacy, pharmaceutical companies, academia, and the FDA. This patient-centric study aims to become the largest Phase 3 registrational study in PDAC and represents a fundamental shift in drug development for PDAC in the United States (US). **Methods:** PrP (NCT04229004) is a platform clinical trial sponsored by the Pancreatic Cancer Action Network (PanCAN), developed based on the FDA 2020 guidance document regarding "complex innovative designs" in registration trials https://www.fda.gov/media/130897/download. It utilizes adaptive randomization and other Bayesian statistical innovations provided by Berry Consultants LLC, including the "time machine" which uses all previously randomized controls for each arm, suitably adjusted for line of therapy and the time period of the arm. Focused on 1st and 2nd line treatment of mPDAC, PrP uses an adaptive platform design with randomization to one of 2 control arms (gemcitabine + nab-paclitaxel (GA) or mFOLFIRINOX, 30% of pts) or experimental therapy (70% of pts). Candidate experimental arms are reviewed by an Arm Selection Committee based on validity of the treatment target and strength of the pre-clinical and clinical data. The primary endpoint is overall survival (OS). Pts undergo pre- and on-treatment biopsies with state-of-the-art genomic, transcriptomic, and immune analysis, along with a serial collection of blood-based research samples. Pts are managed using novel supportive care techniques; PrP contains 3 sub-protocols evaluating quality of life, sarcopenia, and actigraphy. PrP launched in 2020 and has enrolled > 130 pts; 30 US sites have been selected with 17 currently active. Current experimental arms include: (i) GA + Pamrevlumab, an anti-CTGF Ab, (ii) Racemetyrosine monotherapy, a cancer metabolism-based therapy (for follow-up of patients) and (iii) an immuno-oncology arm in activation. Other arms are in the planning stages. Compared to traditional designs, PrP offers several advantages: multiple investigational treatments evaluated in parallel over time; ~175 pts per experimental arm required to initiate a regulatory registration; and continuous learning from every patient, resulting in significant savings of time and resources. PrP has created an entirely new learning environment for accelerating drug development in PDAC. Clinical trial information: NCT04229004. Research Sponsor: PanCAN, Pharmaceutical/Biotech Company.

TPS4189 **Poster Session**

A multicenter, randomized, double-blind phase III clinical study to evaluate the efficacy and safety of KN046 combined with nab-paclitaxel and gemcitabine versus placebo combined with nab-paclitaxel and gemcitabine in patients with advanced pancreatic cancer (ENREACH-PDAC-01). *First Author: Gang Jin, Department of Hepatobiliary Pancreatic Surgery, Changhai Hospital, Navy Medical University (the Second Military Medical University), Shanghai, China*

Background: Pancreatic cancer is biologically aggressive, and the majority of pts was diagnosed as locally advanced or metastatic disease. Nab-paclitaxel and gemcitabine is a frequently used regimen for advanced pancreatic cancer, but chemoresistance is unavoidable. The combination of immunotherapy with chemotherapy have shown efficacy for certain types of cancer, but no similar results have been obtained in pancreatic cancer. KN046, a novel recombinant humanized bispecific antibody, can simultaneously block PD-1/PD-L1 and CTLA-4 pathways and restore T-cell immune response to tumor. In a phase II clinical trial (NCT04324307), as of August 10, 2021, 53 pts with unresectable advanced pancreatic cancer had received one cycle KN046 combined AG regimen treatment and 31 subjects had received post-baseline tumor assessment at least once. Objective response rate (ORR) was 45.2% (95% CI: 27.3%, 64.0%) and disease control rate (DCR) was 93.5% (95% CI: 78.6%, 99.2%), excellent preliminary results have been achieved. Based on this, a phase III pivotal study (ENREACH-PDAC-01) is conducting now in China to verify the efficacy and safety of KN046 plus nab-paclitaxel and gemcitabine as first-line treatment for advanced pancreatic cancer (NCT05149326). **Methods:** This nationwide multicenter phase III clinical trial enrolled pts with histologically or cytologically confirmed unresectable locally advanced or metastatic pancreatic ductal adenocarcinomas with a WHO performance score of 0 or 1 and expected survival period of more than 3 months. Eligible pts will be randomized 1:1 to intervention group or control group and receive 4-6 cycles of KN046 (5mpk Q2W) or placebo combined with nab-paclitaxel (initial dose: 125mg/m^2 D1,8,15 Q4W) and gemcitabine (initial dose: 1000mg/m^2 D1,8,15 Q4W) followed by KN046 (5mpk Q2W) or placebo with gemcitabine (QW × 3, 1 week off) maintenance therapy. Treatment will continue until disease progression or intolerable toxicity, withdrawal of consent, loss to follow-up or death, end of study, whichever occurs first. The primary endpoint is overall survival (OS). Key secondary endpoints are ORR and progression free survival (PFS). PFS and ORR will be assessed independently per RECIST v1.1 at screening, every 8 weeks for 1 year and then every 12 weeks until disease progression. Tumor and blood samples will be collected at baseline and during study treatment for pharmacokinetic, immunogenicity and biomarker assessment. The first patient was enrolled in early February 2022. Clinical trial information: NCT05149326. Research Sponsor: Jiangsu Alphamab Biopharmaceuticals Co., Ltd.

TPS4190 **Poster Session**

Sequential first-line treatment with gemcitabine plus nab-paclitaxel (GA) followed by FOLFIRINOX (FFX) versus FFX alone in patients with metastatic pancreatic cancer (PC): GABRINOX-2 randomized phase 2 trial. *First Author: Fabienne Portales, Institut du Cancer de Montpellier (ICM), Univ Montpellier, Montpellier, France*

Background: PC is a major health concern worldwide and a deadly disease due to its high metastatic behavior. In recent years, incremental progresses have been made with the use of new chemotherapy (CT) regimen in the metastatic setting. Thus, both PRODIGE 4/ACCORD11 (Conroy T, et al. 2011) and MPACT (Von Hoff D, et al. 2013) phase III trials established 2 new standard-of-care in the first line treatment of metastatic PC (mPC), demonstrating a survival benefit over gemcitabine monotherapy, with the use of FFX or GA. In the phase I/II GABRINOX trial (Assenat E, et al. ESMO Open 2021), we reported that sequential GA followed by FFX provided a high overall response rate (ORR) (64.9%) and a promising median progression-free survival (PFS, 10.5 months) and median overall survival (OS, 15.1 months), together with acceptable toxicity and remarkably low severe neurotoxicity rate (gr.3: 5.3%). To follow up these encouraging results in a controlled study, we aimed at comparing our experimental GABRINOX regimen to control FFX in the GABRINOX-2 randomized phase 2 trial (NCT05065801). Our primary objective is PFS, and our secondary objectives are tolerance, ORR, disease-control rate, OS, and Quality-of-life. **Methods:** Main inclusion criteria were as follows: Patients (pts) in good condition (ECOG PS $\leq$ 1), aged from 18 to 75 yo, with histologically or cytological proven mPC and at least one measurable metastatic target. Pts should have not been treated with (adjuvant) chemotherapy in the last 6 months. Eligible pts are randomized (ratio 1:1) either in the standard FFX group or in the experimental GABRINOX group where a GA (gemcitabine 1000 mg/m^2 and Nab-paclitaxel 125 mg/m^2, day 1-8-15) cycle alternates after a 2-weeks rest with a FFX cycle. To detect an increase in median PFS from 6.4 to 10.5 months (HR = 0.61) with a 80% power and a 5% α risk, 130 events are required among a total population of 210 pts. PFS was defined as the length of time between randomization and the onset of 1st documented progression (RECIST 1.1 criteria) or death. The study of quality of life will use the EORTC QLQ-C30 and QLQ-PAN26 self-reported questionnaires at baseline and every 2 months up to 12 months and then at 16, 20 and 24 months. Circulating DNA tests will be carried out at baseline and every 2 months until progression. All numerical variables will be expressed as medians and 95% CI, while PFS and OS will be estimated using Kaplan-Meier method. Multivariate analyses will use Cox proportional hazard model. Enrolment started in late 2021 and 3 patients were included so far. Clinical trial information: NCT05065801. Research Sponsor: None.

TPS4191 **Poster Session**

Sequential treatment with gemcitabine/nab-paclitaxel (GA) and FOLFIRINOX (FFX) followed by stereotactic MRI-guided adaptive radiation therapy (SMART) in patients with locally advanced pancreatic cancer (LAPC): GABRINOX-ART phase 2, multicenter trial. *First Author: Fabienne Portales, Institut du Cancer de Montpellier (ICM), Univ Montpellier, Montpellier, France*

Background: LAPC represents a major challenge with no standardized chemotherapy (CT) and radiotherapy (RT) treatment. Phase 2 studies (LAPACT/NEOLAP) indicated efficacy of FFX and GA, although addition of conventionally fractionated RT remains controversial. Phase 3 LAPO7 trial obtained a reduction of progression free survival (PFS), albeit with no overall survival (OS) advantage. Since in metastatic pancreatic cancer we recently attained with GA/FFX sequential combination (GABRINOX) high objective response rate and promising OS with acceptable toxicity and no limiting neurotoxicity, we proposed in LAPC to complement GABRINOX with SMART, recently recognized beneficial in pancreatic tumors by a retrospective multicenter study (OS at 2 years) and our prospective registry study (dosimetric benefit of adaptation). In a first step (SEQ1), we will evaluate GABRINOX efficacy and select patients without progression for a second step (SEQ2), to evaluate feasibility and tolerance in patients without disease progression after SEQ1. Secondarily we will evaluate CT tolerance (SEQ1), acute toxicities and dosimetric results (SEQ2) and for both SEQ1+2, late toxicities, response to treatment, PFS, OS and quality of life (QoL). **Methods:** Naive patients with confirmed non-metastatic unresectable adenocarcinoma by centralized reading (WHO 0/1) and adequate organ function will receive in SEQ1 two cycles of GABRINOX, GA (1000 mg/m^2, 125 mg/m^2) on days 1, 8, and 15 followed by FFX on day 29 and 43. After 3-4 weeks, patients without progression or unacceptable toxicity will benefit from SMART (5 fractions of 10 Gy/day over 5 consecutive days). Specific dummy-run, contouring quality assurance and dosimetric plans will precede post-treatment monitoring every 6 weeks for 6 months for non-progressive patients and then every 2 months until progression: radiological assessment, biological markers (circulating tumor DNA) and QoL evaluation. Co-primary endpoints include success of SEQ1 (non-progression at 4 months, RECIST v1.1) and that of SEQ2 as absence of acute digestive non-toxicity rate > grade 3 (NCI-CTCAE v5.0) within 90 days. Based on Fleming design with maximal inefficacy (p_0) of 70% and 90% (α = 2.5% and β = 5%) we need 98 and 70 patients (SEQ1 and SEQ2), and total of 103 cases considering those entering in SEQ 2 (70%) and non-evaluable patients. Success rate, toxicities (by treatment sequences) and safety (System Organ Class) by patient and cycle will be considered while dosimetry will be correlated with gastro-intestinal toxicities. Median follow-up, OS and PFS will be expressed as medians and rates with 95% CI while QoL will be explored by QLQ-C30 and QLQ-PAN26 analyses using the time to definitive deterioration. From 2021, we included 5 patients (NCT04570943). Clinical trial information: NCT04570943. Research Sponsor: None.

TPS4192 **Poster Session**

Trial in progress: A randomized phase II study of pembrolizumab with or without defactinib, a focal adhesion kinase inhibitor, following chemotherapy as a neoadjuvant and adjuvant treatment for resectable pancreatic ductal adenocarcinoma (PDAC). *First Author: John Davelaar, Samuel Oschin Cancer Center, Cedars-Sinai Medical Center, Los Angeles, CA*

Background: PDAC is an aggressive cancer. It remains refractory to checkpoint inhibition because of its significant desmoplastic and immunosuppressive tumor microenvironment (TME). Focal adhesion kinase (FAK), a non-receptor tyrosine kinase, is involved in tumor progression in many cancers and appears to be a targetable master regulator of the TME in PDAC. FAK inhibition combined with anti-PD1 antibody has been shown to modulate pancreatic stellate cells and decrease immunosuppressive myeloid and T-reg cells, leading to increased CD8 infiltration and improved survival in PDAC mouse models. A recent single arm phase I study of defactinib, a FAK inhibitor, combined with pembrolizumab, an anti-PD1 antibody, and chemotherapy was shown to be safe, and two confirmed partial responses were observed in patients with microsatellite-stable disease. Furthermore, increased CD8 T cell infiltration was observed in metastatic biopsies. Given the promising preclinical data and efficacy signals, as well as safety of the phase I clinical trial, our current study aims to assess the translational and clinical effects of sequentially combined defactinib and pembrolizumab following neoadjuvant and adjuvant chemotherapy in patients with high-risk resectable PDAC. **Methods:** This study is a multi-center, two-arm, randomized, open label, phase II clinical trial of neoadjuvant and adjuvant immunotherapy with defactinib and pembrolizumab, following neoadjuvant standard of care (SOC) gemcitabine and nab-paclitaxel in subjects with high-risk resectable PDAC. The primary objectives aim to assess changes in CD8 T cell intratumoral infiltration utilizing multiplex IHC and the pathologic complete response rate with defactinib and pembrolizumab or pembrolizumab alone, following neoadjuvant chemotherapy. Secondary objectives include assessment of disease-free survival, overall survival, and safety. Translational exploratory objectives include evaluating stromal and immune signatures among treatment groups via multiplex IHC and RNA/DNA sequencing. 36 subjects will be randomly assigned to receive 400 mg defactinib PO BID and 200 mg pembrolizumab IV every 3 weeks (Arm A) or 200 mg pembrolizumab IV alone every 3 weeks (Arm B). After enrollment, subjects will undergo 2 cycles (~2 months) of standard neoadjuvant therapy of gemcitabine and nab-paclitaxel, followed by 2 cycles (6 weeks) of investigational treatment (Arm A or B) before surgical resection. Following surgery, subjects will receive SOC adjuvant chemotherapy followed by investigational treatment (Arm A or B) for 8 cycles (~24 weeks). Key inclusion criteria include: resectable PDAC, CA 19-9>200, no prior systemic treatment for PDAC, and ECOG PS $\leq$1. As of February 2022, 14 patients have been enrolled. Clinical trial information: NCT03727880. Research Sponsor: Merck, Conquer Cancer Foundation of the American Society of Clinical Oncology, U.S. National Institutes of Health.

TPS4193 **Poster Session**

Phase III study (daNIS-2) of the anti–TGF-β monoclonal antibody (mAb) NIS793 with nab-paclitaxel/gemcitabine (NG) versus NG alone in patients (pts) with first-line metastatic pancreatic ductal adenocarcinoma (mPDAC). *First Author: Eileen Mary O'Reilly, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Despite improving outcomes, current therapies for mPDAC have a modest impact on overall survival (OS) and new therapies are needed. PDAC is characterized by an abundance of intratumoral fibrosis, which may contribute to the lack of treatment efficacy and act as a mechanical barrier to effective penetration of therapeutics. TGF-β has a multifactorial role in tumorigenesis and maintaining an immunosuppressive tumor microenvironment (TME). Emerging evidence points to the role of TGF-β as a pivotal activator of cancer-associated fibroblasts that lead to the development of fibrotic networks. In preclinical models, TGF-β blockade alters the TME to facilitate an antitumor response, reduce stromal fibrosis, and augment the benefit of chemotherapy, providing rationale for combining TGF-β–targeting agents with chemotherapy. NIS793 is a potent, selective, human IgG2 mAb antagonist of TGF-β. This study investigates NIS793 in combination with NG vs NG alone in treatment-naïve pts with mPDAC. **Methods:** This is a phase III, randomized, double-blind, multicenter, two-arm study (NCT04935359) consisting of two stages: an initial safety run-in period followed by two-arm randomization. Eligible pts include adults with previously untreated mPDAC and an ECOG performance status $\leq$1. Pts with a tumor histology other than adenocarcinoma or with microsatellite instability-high tumors are ineligible. The aim of the safety run-in period is to assess the safety and tolerability of NIS793 + NG and confirm the recommended dose for the randomized phase of this study. Data will be analyzed once at least six evaluable pts have received NIS793 (intravenous [IV] 2100 mg every 2 weeks) + nab-paclitaxel (IV 125 mg/m^2 on Days 1, 8, and 15) + gemcitabine (IV 1000 mg/m^2 on Days 1, 8, and 15) for one 28-day cycle. Pts (N = 480) will be randomized 1:1 to NIS793 + NG or placebo + NG. Treatment will continue until unacceptable toxicity, disease progression, discontinuation by investigator or pt choice, death, or withdrawal of consent. The primary objective is to evaluate the OS of pts receiving NIS793 + NG vs NG alone; secondary objectives include assessing progression-free survival, the overall response rate, disease control rate, duration of response, and time to response (assessed locally per RECIST v1.1), as well as safety and tolerability, immunogenicity, pharmacokinetics, and patient-reported outcomes such as health-related quality of life. Efficacy will be assessed at screening, every 8 weeks for 1 year, and then every 12 weeks until disease progression. Blood samples will be taken at baseline and during treatment for pharmacokinetic and immunogenicity assessments. This study is ongoing and will enroll pts from approximately 149 sites across 28 countries. The first pt was treated on October 20, 2021. Clinical trial information: NCT04935359. Research Sponsor: Novartis Pharmaceuticals.

TPS4194 **Poster Session**

A phase Ib/II study of sotorasib combined with chemotherapy for second-line treatment of KRAS p. G12C–mutated advanced pancreatic cancer. *First Author: Devalingam Mahalingam, Northwestern University, Chicago, IL*

Background: Kirsten rat sarcoma viral oncogene homolog(*KRAS*) p.G12C mutation is an oncogenic driver mutation in several solid tumors. Sotorasib is a specific, irreversible, small molecule inhibitor of $KRAS^{G12C}$ that has demonstrated durable clinical benefit in NSCLC, with mild and manageable toxicities. Pancreatic ductal adenocarcinoma (PDAC) remains a leading cause of cancer-related death in the world, although recent advances in chemotherapeutic regimens for metastatic PDAC provide better clinical outcomes. *KRAS* p.G12C mutations are found in 1-2% of PDAC. Modest single agent activity of Sotorasib was observed in chemo-refractory PDAC patients (pts). Combination of Sotorasib with approved PDAC chemotherapy regimens is expected to enhance antitumor efficacy. This study is designed to evaluate safety, tolerability and efficacy of Sotorasib in combination with second line chemotherapy in pts with *KRAS*p.G12C mutated advanced PDAC who have progressed on first-line chemotherapy. **Methods:** This investigator initiated study run through Hoosier Cancer Research Network, is a phase Ib/II study evaluating Sotorasib in combination with either Liposomal Irinotecan/5-Fluorouracil/Leucovorin or Gemcitabine/nab-paclitaxel. Physician choice of chemotherapy based on first line chemotherapy regimen used. Histologically confirmed PDAC pts who have *KRAS* p.G12C mutation identified through tumor or blood based testing, progressed on first-line chemotherapy, adequate organ function and performance status are eligible. A safety lead-in will be conducted to evaluate the safety of Sotorasib at a dose of 960 mg in combination with each of the two chemotherapy regimens. A "3+3" dose de-escalation design will be used for each combination separately. All patients treated at the RP2D in the initial safety cohort will be evaluable for response and included in the first stage of Simon's two stage design. The phase II trial conducted at the RP2D follows Simon's two-stage "minimax" design. The trial is designed to test whether addition of Sotorasib to chemotherapy will improve the objective response rate (ORR), from 16% to 31%. In Stage 1, 22 evaluable patients will be enrolled, and the trial will be stopped if 3 or fewer of the 22 evaluable patients respond. If ≥ 4 responses are observed, an additional 28 patients will be enrolled in Stage 2, for a total of 50 evaluable patients. Up to 59 subjects will be enrolled across 15 academic cancer institutions in order to obtain the required number of 50 evaluable subjects, assuming 15% attrition rate. Primary endpoint is to determine the objective response rate (ORR) by RECIST 1.1. The secondary endpoint to evaluate safety, and further evaluate efficacy in terms of disease control rate, duration of response, progression-free survival and overall survival. Correlative endpoints will determine biomarkers based on analysis of blood and/or tumor on study. Clinical trial information: IND 159412. Research Sponsor: Amgen.

TPS4195 **Poster Session**

Phase Ib/IIa trial of CEND-1 in combination with neoadjuvant FOLFIRINOX-based therapies in pancreatic, colorectal, and appendiceal cancers (CENDIFOX). *First Author: Anup Kasi, University of Kansas Cancer Center, Westwood, KS*

Background: The efficacy of chemotherapy is often compromised due to poor penetration of drugs in solid tumors. The tumor microenvironment, which is characterized by dense extracellular matrix-rich stroma that creates a physical barrier to penetration of anti-cancer drugs, is especially pronounced in Pancreatic Ductal Adenocarcinoma (PDAC) and in peritoneal metastases from Colorectal/Appendiceal Adenocarcinoma. CEND-1 is a tumor-penetrating peptide (scientifically also known as iRGD) that has preclinically demonstrated to enhance the tumor penetration of chemotherapy agents through binding and activation of alphav-integrins and neuropilin-1 (NRP-1). The 2-step mechanism leads to a higher delivery and concentration of chemotherapeutics selectively in the tumor, while sparing normal tissue. Hence CEND-1 therapy has the potential to improve the efficacy of anti-cancer therapies and reduce side effects through increased tumor access, specificity, and sensitivity. We hypothesize that CEND-1 may become a powerful adjuvant that safely enhances standard anti-neoplastic therapy in the neoadjuvant setting for the above populations. **Methods:** A safety lead-in 6-9 patients (Phase Ib) will be followed by an open label, single arm, parallel (3 cohorts) Phase IIa study. A total of 50 patients (20 PDAC, 15 colorectal/appendiceal with peritoneal metastases, 15 oligometastatic colorectal) will be enrolled. A starting CEND-1 dose of 3.2 mg/kg in combination with the standard doses of FOLFIRINOX (+/- Panitumumab if RAS/RAF wild type) will be used for the safety lead-in. CEND-1 dose will be lowered for Phase IIa if > 1/6 patients experienced DLTs. Participants enrolled will receive standard doses of FOLFIRINOX q2w +/- Panitumumab q2w 6mg/kg IV q2w (14-day cycles) for Cycles 1-3. After a subsequent research biopsy, the CEND-1 + chemotherapy combo will be continued at RP2D q2w for cycles 4-6, followed by CEND-1 +/- Panitumumab ~72h prior to resection. Assessment of tumor response using RECIST v1.1 will be done every 3 cycles. Up to 10 patients may receive Panitumumab. Eligible Pts are untreated, newly diagnosed, resectable/borderline resectable PDAC or colorectal/appendiceal adenocarcinoma with peritoneal metastases or oligometastases eligible for cytoreductive surgery, as determined by multidisciplinary evaluation. Inclusion criteria also include ECOG PS 0-1, adequate organ function, measurable or evaluable disease. Primary objectives are safety and biological activity of CEND-1. Secondary objectives include ORR, RO resection rate, DFS, OS. Exploratory objectives include pathologic response, tissue immune response, EGFR expression, tumor tissue-to-plasma concentration of Panitumumab pre and post CEND-1 treatment. Enrollment to the CENDIFOX trial is currently ongoing. Clinical trial information: NCT05121038. Research Sponsor: KUCC IITSC EP Pilot Grant, CEND Therapeutics.

TPS4196 **Poster Session**

A phase II, open-label, pilot study evaluating the safety and activity of liposomal irinotecan (Nal-IRI) in combination with 5-FU and oxaliplatin (NALIRIFOX) in preoperative treatment of pancreatic adenocarcinoma: NEO-Nal-IRI study. *First Author: Sherise C. Rogers, Division of Medical Oncology, Department of Internal Medicine, The Ohio State University Comprehensive Cancer Center, Columbus, OH*

Background: Neoadjuvant treatment for potentially curable pancreatic cancer (PDAC) is increasing in acceptability, but a standard regimen has yet to be established. Multiple studies have demonstrated feasibility and effectiveness of the FOLFIRINOX (5-fluorouracil, leucovorin, oxaliplatin and irinotecan) regimen in the perioperative setting. However, FOLFIRINOX often requires dose modifications, delays and growth factor support due to excessive toxicity which can complicate care delivery when given pre-op. Liposomal irinotecan injection (Nal-IRI) is FDA approved in combination with 5-FU/LV with a well-tolerated safety profile in relapsed, refractory metastatic PDAC. The current study aims to substitute Nal-IRI for traditional irinotecan in the standard FOLFIRINOX regimen (NALIRIFOX) and to demonstrate safe and effective neoadjuvant delivery. **Methods:** This phase 2, open-label, multicenter single-arm study focuses on patients (pts) with operable PDAC without metastatic disease. Other key eligibility criteria include age ≥18 years, resectability confirmed by multiD GI tumor board (resectable vs. borderline), adequate cardiac, renal, hepatic function and ECOG performance status of 0 to 1. Pts receive NALIRIFOX regimen as per the table every 2 weeks for four months followed by disease reassessment. Pts who remain surgical candidates will undergo surgical resection within 4 to 8 weeks following last dose of therapy. The primary endpoint is to assess safety and feasibility of regimen in pre-op setting. Secondary endpoints include RO resection rate, clinical, biochemical and radiological response rate and patient-reported quality of life during treatment as measured by the NCI validated FACT-G scale. Enrollment continues to a maximum of 28 evaluable pts to demonstrate a reduction in historical 30-day post-op complication rate. Clinical trial information: NCT03483038. Research Sponsor: University of Florida Health Cancer Center and Ipsen Biopharmaceuticals, Inc.

NALIRIFOX regimen components given intravenously (IV) every 14 days.

Agent	Dose	Infusion Duration
Nal-IRI	50 mg/m2	90 min
Oxaliplatin	60 mg/m2	120 min
Leucovorin	400 mg/m2	120 min
5-fluorouracil	2400 mg/m2	Continuous infusion for 46 hours

LBA4500 **Oral Abstract Session**

EVEREST: Everolimus for renal cancer ensuing surgical therapy—A phase III study (SWOG S0931, NCT01120249). *First Author: Christopher W. Ryan, Oregon Health & Science University, Knight Cancer Institute, Portland, OR*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

4501 **Oral Abstract Session**

Association between depth of response (DepOR) and clinical outcomes: Exploratory analysis in patients with previously untreated advanced renal cell carcinoma (aRCC) in CheckMate 9ER. *First Author: Cristina Suárez, Vall d'Hebron University Hospital, Barcelona, Spain*

Background: Among patients (pts) with untreated aRCC in the CheckMate 9ER trial, superior progression-free survival (PFS; hazard ratio [HR], 0.56) and overall survival (OS; HR, 0.70) were maintained, and objective response and complete response (CR) rates were doubled for nivolumab plus cabozantinib (N+C) vs sunitinib (SUN) with extended 25.4 mo minimum (32.9 mo median) follow-up. This exploratory analysis evaluated the relationship between DepOR and clinical outcomes in CheckMate 9ER. **Methods:** Eligible pts received N (240 mg) every 2 weeks plus C (40 mg) once daily or SUN (50 mg once daily; 4 weeks of each 6-week cycle). In this analysis, DepOR subgroups were based on best overall response (blinded independent central review [BICR] per RECIST v1.1) and best tumor reduction threshold, as follows: CR; partial response subdivided by a tumor reduction of ≥80%–<100% (PR1); ≥60%–<80% (PR2); or ≥30%–<60% (PR3); stable disease (SD); and progressive disease (PD). PFS (per BICR) and OS by DepOR subgroups were analyzed after a 6-mo post-randomization landmark. Treatment-related adverse events (TRAEs) were assessed in DepOR subgroups. **Results:** Of 323 and 328 pts randomized to N+C or SUN, 236 and 157 pts were progression-free and alive and 293 and 253 pts were alive at the 6-mo landmark and were categorized by DepOR subgroup. Overall, greater proportions of pts receiving N+C had deeper responses vs SUN (CR, PR1, PR2; Table). Deeper responses with N+C were associated with improved 12-mo PFS rate vs SUN for CR (94.9% vs 82.4%), PR1 (81.3% vs 37.5%), and PR2 (72.1% vs 53.2%). In both arms, increasingly deeper response led to better OS outcome; yet OS rates and medians were comparable between arms for CR, PR1, PR2, and PR3 (Table). No meaningful patterns for overall TRAE rates by DepOR subgroup were identified in either arm. **Conclusions:** In CheckMate 9ER, more pts receiving N+C achieved deeper responses vs SUN. Deeper responses were generally associated with improved PFS and OS. Clinical trial information: NCT03141177. Research Sponsor: Bristol Myers Squibb.

	N+C						SUN					
	PFS[a] N = 236			OS[a] N = 293			PFS[a] N = 157			OS[a] N = 253		
DepOR	n	12 morate, %[b,c]	Median (95% CI), mo	n	18 morate, %[c]	Median (95% CI), mo	n	12 morate, %[b,c]	Median (95% CI), mo	n	18 morate, %[c]	Median (95% CI), mo
CR	40	94.9	NR(26.0–NE)	40	97.5	NR(NE–NE)	17	82.4	NR(15.9–NE)	17	100	NR(30.2–NE)
PR1	32	81.3	24.3(17.0–NE)	33	97.0	NR(28.9–NE)	8	37.5	6.5(0.9–NE)	9	100	NR(19.7–NE)
PR2	37	72.1	24.8(13.4–NE)	38	83.5	NR(31.7–NE)	18	53.2	12.0(7.9–NE)	18	88.2	NR(NE–NE)
PR3	62	46.7	10.4(5.5–14.0)	69	78.3	NR(30.5–NE)	45	57.0	15.9(6.8–21.6)	49	75.3	NR(25.1–NE)
SD	65	33.5	6.3(4.0–10.6)	99	59.6	28.7(17.8–NE)	69	22.6	5.2(3.7–6.7)	123	68.0	NR(24.6–NE)
PD	0	–	–	14	35.7	10.1(4.8–25.1)	0	–	–	37	39.1	13.7(6.4–18.6)

[a]At the 6 mo landmark. [b]12 mo PFS rate is presented due to low patient numbers at later timepoints. [c]12 mo and 18 mo rates are from 6 mo landmark.
CI, confidence interval; NE, not evaluable; NR, not reached.

4502 **Oral Abstract Session**

The relationship between health-related quality of life (HRQoL) and clinical outcomes in patients with advanced renal cell carcinoma (aRCC) in CheckMate (CM) 214. *First Author: David Cella, Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL*

Background: In CM 214, when compared to sunitinib (S), nivolumab plus ipilimumab (N+I) was associated with both clinical benefit and improved HRQoL as first-line treatment for intermediate/poor (I/P)-risk patients (pts). This analysis investigates the direct association between HRQoL and clinical outcomes in aRCC pts. **Methods:** I/P-risk population included 425 and 422 pts in the N+I and S arms, respectively. HRQoL was assessed using the FKSI-19 (Total Score and Disease Related Symptoms [DRS]). Three separate analyses (A, B, and C) were conducted. A: Changes in individual item scores from baseline to last assessment prior to progression were descriptively assessed. B: For each FKSI-19 score, multivariable Cox regression, adjusted for treatment and stratification factors, was used to evaluate the prognostic significance of baseline and time-dependent HRQoL scores in separate models. Hazard ratios (HR) were calculated based on the risk of death per improvement in HRQoL scores, defined using the clinically meaningful change threshold (5 points for FKSI-19 Total and 3 points for DRS). Pts with overall survival (OS) events were censored if their survival event was not within 12 weeks of the last available HRQoL assessment. C: The association between HRQoL change status (ie, improvement or maintenance vs. worsening from baseline in the FKSI-19 Total Score), irrespective of treatment arm, and OS was further assessed using a landmark analysis at the month 6 (mo-6) landmark. Additional landmark time points were explored in sensitivity analysis. **Results:** Items related to fatigue and perceived bother of the side-effects of treatment had the largest percentage of pts worsening prior to progression. In both baseline and time-dependent HRQoL analyses, OS was independently associated with both HRQoL measures. Higher (better) baseline scores were associated with significantly reduced risk of death (HR [95% CI] for FKSI-19 Total Score and DRS was 0.83 [0.80-0.87] and 0.80 [0.76-0.84], respectively). Every 5-point increase (improvement) in FKSI-19 Total Score and 3-point increase in DRS was associated with a 31% decreased risk of death ($P < 0.01$). At mo-6, 301 pts showed improvement or maintenance in HRQoL. Pts with improved/stable HRQoL had a 52% reduction in risk of death compared to pts who had worsened (HR 0.48 [95% CI: 0.39-0.59]). **Conclusions:** Results demonstrate there is an association between HRQoL and clinical outcomes in CM 214. Baseline HRQoL scores are a potential predictor for survival in aRCC, and HRQoL changes are informative for pts' expected survival. HRQoL change status at mo-6 was significantly and positively associated with subsequent survival. Thus, patient-reported outcomes may be useful for both describing pt experience in clinical trials and providing valuable clinical insights during routine practice. Clinical trial information: NCT02231749. Research Sponsor: Supported by Bristol Myers Squibb in collaboration with Ono Pharmaceutical.

LBA4503 **Oral Abstract Session**

CALYPSO: A three-arm randomized phase II study of durvalumab alone or with savolitinib or tremelimumab in previously treated advanced clear cell renal cancer. *First Author: Thomas Powles, Barts ECMC, Barts Cancer Institute, Queen Mary University of London, London, United Kingdom*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

4504 **Oral Abstract Session**

Cabozantinib (C) in combination with atezolizumab (A) in urothelial carcinoma (UC): Results from Cohorts 3, 4, 5 of the COSMIC-021 study. *First Author: Sumanta K. Pal, City of Hope Comprehensive Cancer Center, Duarte, CA*

Background: C, a multitargeted receptor tyrosine kinase inhibitor (TKI), promotes an immune-permissive environment that may enhance response to immune checkpoint inhibitors (ICIs). COSMIC-021, a multicenter phase 1b study, is evaluating C + A (anti–PD-L1 therapy) in various solid tumors (NCT03170960). C + A demonstrated encouraging clinical activity in cohort 2 of COSMIC-021 in patients (pts) with UC previously treated with platinum-containing chemotherapy (chemo) (Pal S et al. ASCO 2020. Abstract 5013). Outcomes of C + A from 3 other UC cohorts (C3, C4, C5) are presented. **Methods:** Pts with inoperable locally advanced/metastatic UC with transitional cell histology and ECOG PS 0–1 were eligible. Pts enrolled in C3 and C4 had no prior therapy and were cisplatin-based chemo ineligible (C3) or eligible (C4). C5 enrolled pts with one prior ICI and no prior VEGFR-TKI therapy. Pts received C 40 mg PO QD and A 1200 mg IV Q3W. CT/MRI scans were performed Q6W for first year and Q12W thereafter. The primary endpoint is objective response rate (ORR) per RECIST v1.1 by investigator. Other endpoints: safety, duration of response (DOR), PFS, and OS. **Results:** Thirty pts each were enrolled in C3 and C4, and 31 in C5. Baseline characteristics for C3, C4, and C5, respectively: median age, 74 y, 66 y, 68 y; male, 67%, 73%, 55%; ECOG PS 1, 63%, 57%, 74%; lung/liver metastasis; 33%/17%, 40%/20%, 58%/23%; ≥3 tumor sites, 30%, 43%, 45%; bladder as primary site, 67%, 70%, 71%. As of Nov 30, 2021, the median follow-up for C3, C4, and C5 was 27.9, 19.1, and 32.9 mo, respectively, with 1, 6, and 1 pts on treatment. C + A demonstrated clinical benefit across all cohorts (Table). Most common treatment-related adverse events (TRAEs) of any grade across C3, C4, and C5, respectively, were diarrhea (43%, 33%, 35%), nausea (27%, 17%, 26%), fatigue (27%, 27%, 48%), and decreased appetite (33%, 27%, 39%); grade 3/4 TRAEs occurred in 63%, 43%, and 45%, and there was no grade 5 TRAE. **Conclusions:** C + A demonstrated encouraging clinical activity with manageable toxicity in inoperable locally advanced/metastatic UC as first-line systemic therapy in cisplatin-based chemo eligible/ineligible pts and as second- or later line in pts who received prior ICI. Clinical trial information: NCT03170960. Research Sponsor: Exelixis, Ipsen, Takeda.

	C3 (cisplatin ineligible) (N = 30)	C4 (cisplatin eligible) (N = 30)	C5 (received prior ICI) (N = 31)
ORR, % (95% CI)	20 (8, 39)	30 (15, 49)	10 (2, 26)
Best overall response, n (%)			
Complete response (CR)	1 (3)	2 (7)	0
Partial response (PR)	5 (17)	7 (23)	3 (10)
Stable disease (SD)	18 (60)	10 (33)	16 (52)
Progressive disease	3 (10)	7 (23)	8 (26)
Disease control rate, % (95% CI)*	80 (61, 92)	63 (44, 80)	61 (42, 78)
Median DOR, mo (95% CI)	7.1 (2.8, NE)	NE (7.2, NE)	4.1 (2.6, NE)
Median PFS, mo (95% CI)	5.6 (3.1, 11.1)	7.8 (1.6, 13.8)	3.0 (1.8, 5.5)
Median OS, mo (95% CI)	14.3 (8.6, NE)	13.5 (7.8, 23.2)	8.2 (5.5, 9.8)

*CR + PR + SD.

LBA4505 **Oral Abstract Session**

A randomised, double blind, phase II clinical trial of maintenance cabozantinib following chemotherapy for metastatic urothelial carcinoma (mUC): Final analysis of the ATLANTIS cabozantinib comparison. *First Author: Robert J. Jones, University of Glasgow, Glasgow, United Kingdom*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

4506 **Oral Abstract Session**

Cell-free DNA methylation as a predictive biomarker of response to neoadjuvant chemotherapy for patients with muscle-invasive bladder cancer in SWOG S1314. *First Author: Yi-Tsung Lu, Division of Medical Oncology, Department of Medicine, Keck School of Medicine and Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA*

Background: Neoadjuvant chemotherapy is the standard of care in muscle-invasive bladder cancer patients. However, treatment is intense, the overall benefit is small, and there is no established marker to identify patients who benefit most. The aim of the study is to characterize cell-free DNA (cfDNA) methylation from patients receiving neoadjuvant chemotherapy in SWOG S1314, a prospective cooperative group trial, and to correlate the methylation signatures with pathologic response. **Methods:** Blood samples were collected prospectively from 73 patients before and during standard neoadjuvant chemotherapy. At radical cystectomy, pathologic response was documented. Plasma cfDNA was profiled using Infinium MethylationEPIC BeadChip array. Differential methylation between pathologic responders (≤pT1N0M0) and non-responders was analyzed, and a Random Forest model was used to generate a classifier predictive of treatment response. **Results:** Using pre-chemotherapy plasma cfDNA, we developed a methylation-based response score (mR-score) predictive of pathologic response. The mR-score also could be calculated using plasma samples collected after the first cycle of neoadjuvant chemotherapy, resulting in a similar predictive ability. Furthermore, we used cfDNA methylation data to calculate the circulating bladder DNA fraction, which had a modest but independent predictive ability for treatment response. When we combined the mR-score and circulating bladder DNA fraction, we successfully predicted pathologic response outcomes in 79% of patients based on their plasma collected before chemotherapy and after 1 cycle of chemotherapy. **Conclusions:** Our study provides proof of concept that cfDNA methylation may be used to predict treatment response in bladder cancer patients receiving neoadjuvant chemotherapy. Clinical trial information: NCT02177695. Research Sponsor: U.S. National Institutes of Health, Conquer Cancer Foundation of the American Society of Clinical Oncology, Other Foundation, Tower Cancer Research Foundation.

4507 **Oral Abstract Session**

TRUCE-02: An open label, single-arm, phase II study of tislelizumab combined with nab-paclitaxel for high-risk non-muscle-invasive urothelial bladder carcinoma. *First Author: HaiTao Wang, Tianjin Medical University, Tianjin, China*

Background: Pts with multiple or tumors with large invasion areas which are un-completely-resectable through TURBT would be recommended radical cystectomy in the clinical treatment. The KEYNOTE-057 study has illuminated the efficiency of immune checkpoint inhibitors monotherapy in HR-NMIBC pts, with acceptable adverse events (AEs). However, the role of PD-1/PD-L1 inhibitor in combination with chemotherapy in NMIBC pts remains unclear. We report preliminary treatment efficiency, safety data, and exploratory work of TRUCE-02 trial. **Methods:** TRUCE-02 is a phase II study for NMIBC pts with uncompletely resectable tumour by TURBT. The primary endpoint was complete response(absence of non-muscle-invasive bladder cancer or progressive disease). Pts that meet the criteria would receive tislelizumab 200mg on days 1 plus paclitaxel 200mg on days 2 every 3 weeks (Q3W) x 3 or 4 cycles followed by a comprehensive assessment including pathology, urine cytology, and imageology. Meanwhile, biomarker analyses included programmed death-ligand 1 (PD-L1) expression using the combined positive score (CPS; Dako 22C3 pharmDx assay) and whole transcriptome RNA sequencing of the tumor. **Results:** Between July 2020 and January 2022, 54 pts were enrolled. 42 pts have completed whole 3 or 4 treatment cycles and reached the primary endpoint. 23 pts achieved CR condition (56%, 95%CI, 43.6% and 74.4%). ORR of 60% (N=25/42, 95%CI, 45.2% and 74.8%). As a secondary endpoint, 33 pts remain cystectomy-free condition (78.6%, 95%CI, 66.2% and 91%). Grade 3-4 AEs were lower than 2%. Urine cytology showed its diagnostic efficiency of 68.42% (95%CI, 61.3% and 75.6%), urine FISH showed a diagnostic efficiency of 45.71% (95%CI, 37.7% and 53.4%) before pathological assessment. As for PD-L1 expression, 47.3% (N = 9/19) of response pts (CR+PR) showed positive, 50% (N = 5/10) of un-response pts (PD+SD) showed positive. We also found out through sequencing results that AR, TCF7L2 might be underlying markers that predict adverse outcomes for pts in this crew. HRR mutation may predict a positive prognosis and mutations in NMIBC which might predict the prognosis of this treatment plan. **Conclusions:** Tislelizumab with nab-paclitaxel represents a novel treatment option with a satisfactory benefit in treating NMIBC. PD-L1 expression has no obvious correlation with the efficiency of this treatment plan. WGS result also showed that there are mutation markers that may predict whether pts would benefit from this treatment plan. Clinical trial information: NCT04730232. Research Sponsor: The Natural Science Foundation Project of Tianjin (grant no. 18PTLCSY00010), Other Foundation.

	Grade (counts)				
AEs	**1**	**2**	**3**	**4**	**Rate**
Alopecia	25	20			81.82%
Fatigue	23	1			43.64%
Erythra	11	2	1		25.45%
Pyrexia	13				23.64%
Hypothyroidism	1	5			10.91%
Aleucocytosis	3	1			7.27%
Pruritus	2				3.64%

4508 **Oral Abstract Session**

Final clinical results of pivotal trial of IL-15RαFc superagonist N-803 with BCG in BCG-unresponsive CIS and papillary nonmuscle-invasive bladder cancer (NMIBC). *First Author: Karim Chamie, Department of Urology, University of California-Los Angeles, Los Angeles, CA*

Background: Patients with NMIBC CIS unresponsive to BCG have limited treatment options. N-803 (Anktiva) is a mutant IL-15-based immunostimulatory fusion protein complex (IL15RaFc) that promotes proliferation and activation of natural killer (NK) cells and CD8+ T cells, but not regulatory T cells. Phase 1b data in BCG-naïve patients with NMIBC demonstrate that intravesical administration of N-803 with BCG induced complete response in all patients, without recurrences for the study duration of 24 months. Pembrolizumab was approved in 2020 with a 41% complete response (CR) rate in a single arm phase 2 trial of 96 patients. We report data on 160 subjects from an open-label, 3 cohort multicenter study (QUILT 3.032) of intravesical BCG plus N-803 in patients with BCG-unresponsive high-grade NMIBC (NCT03022825). **Methods:** All treated patients received intravesical N-803 plus BCG, consistent with the standard induction/maintenance treatment schedule. The primary endpoint for Cohort A (CIS) is incidence of CR of CIS at any time. The primary endpoint for Cohort B (Papillary) is disease-free rate (DFS) at 12 months. **Results:** To date, we enrolled 160 patients (83 CIS, 77 Papillary). In the overall population, median age is 72.3 years, 81% male, with mean number of prior TURBT = 4. Median number of prior BCG doses = 12. CIS patients have a CR rate of 71% (59/83), with a mediation duration of CR of 24.1 months in responders; 91% avoided cystectomy and 96% 24 month bladder cancer specific progression free survival (defined as progression to MIBC). Papillary patients have a 57% 12 month DFS rate, 48% 24 month DFS rate, and 95% avoided cystectomy. Median time to cystectomy in responders (N = 4) is 12.9 months versus 7.8 in non-responders (N = 8) for a 5.1 month delay in cystectomy. PK data shows no systemic levels of N-803; activity is confined to the bladder. Low grade treatment related AEs (grade 1-2) include dysuria (22%) , pollakiurua (19%), hematuria (18%), fatigue (16%), and urgency (12%), all other AEs were seen at 7% or less. No treatment related grade 4 or 5 AE were seen. No SAE's were considered treatment related. No immune related SAE's have been seen. **Conclusions:** In 160 patients with BCG-unresponsive NMIBC, there is a 99% bladder cancer specific overall survival at 2 years. In CIS patients 71% CR rate with 24.1 months median duration of response, and 53% DFS rate at 18 months in Papillary disease. Cystectomy was avoided in over 90% of patients with 2 years of follow-up. The efficacy and safety profile of N-803+BCG exceeds that of other available intravesical and systemic options for BCG-unresponsive NMIBC. Clinical trial information: NCT03022825. Research Sponsor: ImmunityBio.

4509 **Poster Discussion Session**

Phase 1 LITESPARK-001 (MK-6482-001) study of belzutifan in advanced solid tumors: Update of the clear cell renal cell carcinoma (ccRCC) cohort with more than 3 years of total follow-up. *First Author: Eric Jonasch, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Hypoxia-inducible factor 2α (HIF-2α) is a key oncogenic driver in RCC. Antitumor activity of the HIF-2α inhibitor belzutifan has been observed in RCC and is approved for treatment in patients (pts) with VHL disease who require therapy for associated RCC, CNS hemangioblastomas, or pNETs not requiring immediate surgery. Previous data from the phase 1 LITESPARK-001 trial (NCT02974738) designed to evaluate belzutifan in heavily pretreated RCC showed durable antitumor activity and an acceptable safety profile. After more than 3 years of follow-up for pts with ccRCC still receiving treatment, updated data are presented. **Methods:** Pts enrolled in the ccRCC cohort were previously treated with ≥1 therapy, had RECIST-measurable disease, ECOG PS score of 0 or 1, adequate organ function, and life expectancy of ≥6 months. Pts received oral belzutifan 120 mg once daily. The primary end point was safety. Secondary end points were ORR, DCR (CR + PR + SD), PFS, and DOR per RECIST v1.1 by investigator. The data cutoff date was July 15, 2021. **Results:** Of 55 pts enrolled in the ccRCC cohort, 9 (16%) remain on treatment as of the data cutoff date of July 15, 2021; the primary reason for discontinuation was progressive disease (n = 34; 62%). Pts received a median of 3 prior therapies (range, 1-9); 39 (71%) received prior VEGF and immunotherapy. Pts were followed while on treatment and for 30 days after the last dose for a median of 41.2 months (range, 38.2-47.7). Twenty-two pts (40%) experienced grade 3 TRAEs. The most common (≥10%) grade 3 TRAEs were anemia (n = 13; 24%) and hypoxia (n = 7; 13%). There were no grade 4 or 5 TRAEs. ORR was 25%, with 1 confirmed CR (2%) and 13 PRs (24%); DCR was 80%. Median DOR was not reached (range, 3.1+ to 37.9+ months); 8 of 14 responding pts (57%) remain in response as of the data cutoff date. Per IMDC risk, 4 of 13 pts with favorable risk achieved response (ORR = 31%; all PRs) and 10 of 42 pts with intermediate/poor risk achieved response (ORR = 24%; 1 CR, 9 PRs). DCR was 92% for pts with favorable risk and 76% for pts with intermediate/poor risk. For pts who received prior VEGF and immunotherapy, 8 of 39 pts achieved response (ORR = 21%; 1 CR; 7 PR); DCR was 74%. For the 16 pts who did not receive prior VEGF/immunotherapy, 6 achieved response (ORR = 38%; all PRs); DCR was 94%. Median PFS for the total cohort was 14.5 months (95% CI, 7.3-22.1); PFS rate at 156 weeks (~36 months) was 34%. **Conclusions:** As seen after a median follow-up of > 3 years for pts still receiving treatment, belzutifan monotherapy continued to show a high rate of disease control and durable responses in previously treated pts with advanced ccRCC. Belzutifan exhibited a favorable safety profile, and no new safety signals were observed. In several phase 3 studies, belzutifan is being evaluated as monotherapy and combined therapy for ccRCC. Clinical trial information: NCT02974738. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

4510 **Poster Discussion Session**

Characterization of the microbial resistome in a prospective trial of CBM588 in metastatic renal cell carcinoma (mRCC) offers mechanism for interplay between antibiotic (abx) use and immune checkpoint inhibitor (ICI) activity. *First Author: Nazli Dizman, City of Hope Comprehensive Cancer Center, Duarte, CA*

Background: The negative association between ICI response and abx therapy is well defined (Derosa *et al* Cancer Discov 2021). Paradoxically, a retrospective assessment of the live bacterial product (LBP) CBM588 in patients (pts) with advanced lung cancer showed improved outcome with ICIs when the combination of CBM588 and abx (as compared to CBM588 alone) was employed (Tomita *et al* Cancer Immunol Res 2020). We postulated that the microbial resistome (genes encoding antimicrobial resistance) could shift in a manner with CBM588 therapy that facilitated ICI response. **Methods:** Pts with newly diagnosed mRCC with clear cell and/or sarcomatoid histology and intermediate/high risk disease per IMDC criteria were randomized to nivolumab/ipilimumab (nivo/ipi) or nivo/ipi/CBM588 in a 1:2 ratio. Stool samples were collected at baseline and week 12. Whole-metagenome sequencing was performed to analyze stool microbiome composition. Abx resistance genes (RGs) were inferred using publicly available database (McArthur *et al*. Antimicrob Agents Chemother 2013), and groups of abx RGs for various classes of abx were characterized. Wilcoxon signed-rank test was used for comparison of abx RG abundance between baseline and week 12 in each treatment arm and in responders (R) and non-responders (NR). **Results:** The study enrolled 30 pts, with the final analysis including 29 eligible pts (median age: 66 years, M:F 21:8, nivo/ipi: 19 pts, nivo/ipi/CBM588:10 pts). Objective response was 20% and 58% in nivo/ipi and nivo/ipi/CBM588 arms, respectively. The overall abundance of abx RGs remained unchanged between baseline and week 12 in pts receiving nivo/ipi alone. In contrast, a decrease in abx RGs was observed in pts receiving nivo/ipi with CBM588 arm from baseline to week 12 ($p = 0.042$ in Rs; $p = 0.078$ in NRs). More specifically, nivo/ipi/CBM588 treatment led to a significant reduction in fosfomycin RGs and nitroimidazole (e.g., metronidazole) RGs in both pts with R ($p = 0.019$ and 0.042, respectively) and NR ($p = 0.031$ and $p = 0.031$, respectively). A multitude of other clinically relevant abx RGs were downregulated in pts receiving CBM588, including those mediating resistance to glycopeptide (e.g., vancomycin) and lincosamide (e.g., clindamycin) abx. **Conclusions:** In the first interrogation of the resistome in mRCC, we demonstrate that CBM588 decreases abx RGs associated with multiple commonly used classes of abx. Abx clear commensals and increase pathogenic (abx resistant) bacteria in the gut. Based on our data, we formulate the hypothesis that combining abx with CBM588 may decrease potentially pathobionts and favor butyrogenic species, thereby improving CPI response. Clinical studies using CBM588 with abx priming may be warranted. Clinical trial information: NCT03829111. Research Sponsor: The Gateway Foundation.

4511 **Poster Discussion Session**

A phase 1b/2 study of batiraxcept (AVB-S6-500) in combination with cabozantinib in patients with advanced or metastatic clear cell renal cell (ccRCC) carcinoma who have received front-line treatment (NCT04300140). *First Author: Neil J. Shah, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: AXL is up-regulated by hypoxia-inducible factor-1 signaling in both VHL-deficient and hypoxic tumor cells and plays a critical role in the metastatic phenotype of ccRCC. Batiraxcept is a recombinant fusion protein containing an extracellular region of human AXL combined with the human immunoglobulin G1 heavy chain (Fc), demonstrating highly potent, specific AXL inhibition. **Methods:** Batiraxcept at doses of 15 and 20 mg/kg, plus cabozantinib 60 mg daily, was evaluated using a 3+3 dose escalation study design. The primary objective was safety; secondary and exploratory objectives included identification of the recommended phase 2 dose (RP2D), overall response rate (ORR), and duration of response (DOR). Correlation of serum soluble AXL (sAXL)/GAS6 with ORR was evaluated. Key eligibility criteria include previously treated (2L+) ccRCC patients; prior treatment with cabozantanib was not allowed. sAXL/GAS6 was evaluated at baseline. **Results:** Data as of 4-February-2022, Phase 1b enrolled 26 patients, 16 patients treated with 15 mg/kg and 10 patients with 20 mg/kg dose of batiraxcept. Baseline characteristics: median age 60 (40-81); male 22 (85%); median prior line of therapy 1 (1-5); IMDC risk group of favorable 6 (23%); prior VEGF inhibitor 15 (58%); 100% with prior immunotherapy. At median follow up of 4.9 months, 92% (n=24) patients remained on the study. No dose limiting toxicities were observed at either 15 mg/kg or 20 mg/kg dose. Batiraxcept and cabozantinib related adverse events (AEs) occurred in 17 subjects (65%). Most common related AE include decreased appetite 31% (n=8), diarrhea and fatigue 23% (n=6). Grade 3 related AEs occurred in 4 patients (15%) including diarrhea, thromboembolism, hypertension, small bowel obstruction, and thrombocytopenia (n=1, 4% each) being most common. No grade 4 or 5 related AEs were observed. The ORR was 46% (n=12, partial response [PR]; Table). No patients had primary progressive disease. Among the patients who had baseline sAXL/GAS6 ratio of ≥ 2.3, the ORR was 67% (12/18). Regardless of baseline sAXL/GAS6 ratio, 3-month DOR was 100%; and 6-month progression free survival was 79%. Batiraxcept PK levels were similar across both doses and GAS6 levels suppressed through the dosing period. **Conclusions:** Batiraxcept plus cabozantinib is well tolerated. The RP2D of batiraxcept was identified as 15 mg/kg. Early efficacy signals were observed including 100% DOR at 3 months. Baseline sAXL/GAS6 may serve as a potential biomarker to enrich the population. Clinical trial information: NCT04300140. Research Sponsor: Aravive, Inc.

	Entire cohort N=26 (%)	Batiraxcept 15 mg/kg cohort N=16 (%)	Batiraxcept 20 mg/kg cohort N=10 (%)
ORR (confirmed + unconfirmed)	12 PR (46)	9 PR (56)	3 PR (30)
DOR (3-month)	26 (100)	26 (100)	Not reached
Any grade-related AEs	17 (65)	11 (69)	6 (60)
Grade ≥3 related AEs	4 (15)	2 (13)	2 (20)

4512 **Poster Discussion Session**

Adjuvant pembrolizumab for postnephrectomy renal cell carcinoma (RCC): Expanded efficacy analyses from KEYNOTE-564. *First Author: Toni K. Choueiri, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA*

Background: The randomized, double-blind, phase 3 KEYNOTE-564 study (NCT03142334) met its primary end point of disease-free survival with adjuvant pembrolizumab versus placebo after nephrectomy in patients with localized RCC who are at increased risk for recurrence. Extended follow-up (30-month median follow-up) continued to support the benefit of adjuvant pembrolizumab. We describe additional efficacy analyses of time to first subsequent drug treatment or any-cause death (TFST) and time from randomization to progression on next line of therapy or any-cause death (PFS2). **Methods:** Patients with histologically confirmed clear cell RCC, with intermediate-high or high risk for recurrence (pT2, grade 4 or sarcomatoid, N0, M0; or pT3-4, any grade, N0 M0; or pT any stage, any grade, N+ M0) after nephrectomy, or after nephrectomy and resection of metastatic lesions (M1 NED), were randomly assigned 1:1 to receive pembrolizumab 200 mg IV or placebo Q3W for up to 17 cycles (~1 y). Exploratory analyses of TFST and PFS2 were conducted. The Kaplan-Meier method was used to estimate TFST and PFS2. Hazard ratios (HRs) were estimated using a Cox regression model. **Results:** Of 994 patients, 496 were randomly assigned to receive pembrolizumab and 498 to placebo. Median time from randomization to the data cutoff date (June 14, 2021) was 30.1 months (range, 20.8-47.5). Overall, 67 patients (13.5%) in the pembrolizumab group and 99 patients (19.9%) in the placebo group received ≥1 line of subsequent anticancer drug therapy. Of patients who received ≥1 line of subsequent drug therapy, most in the pembrolizumab group (90.0% [60/67]) and placebo group (85.9% [85/99]) received a VEGF/VEGFR-targeted therapy; 23.9% of patients (16/67) in the pembrolizumab group and 59.6% (59/99) in the placebo group received an anti–PD-1/PD-L1 agent. Seventy-seven TFST events were observed in the pembrolizumab group; 110, in the placebo group. Compared with placebo, adjuvant treatment with pembrolizumab delayed TFST (HR, 0.67; 95% CI, 0.50-0.90; medians not reached). A total of 108 PFS2 events were observed, 40 (8.1%; 12 death events and 28 progression events) in the pembrolizumab group and 68 (13.7%; 14 death events and 54 progression events) in the placebo group. PFS2 was also delayed with pembrolizumab compared with placebo (HR, 0.57; 95% CI, 0.39-0.85; medians not reached). **Conclusions:** Treatment with adjuvant pembrolizumab reduced risk for TFST and PFS2 compared with placebo. Results of this exploratory analyses suggest sustained clinical benefit of adjuvant pembrolizumab and support the use of adjuvant pembrolizumab after nephrectomy as standard of care for patients with localized RCC at increased risk for recurrence. Clinical trial information: NCT03142334. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

4513 **Poster Discussion Session**

Pembrolizumab (pembro) plus axitinib (axi) versus sunitinib as first-line therapy for advanced clear cell renal cell carcinoma (ccRCC): Analysis of progression after first subsequent therapy in KEYNOTE-426. *First Author: Thomas Powles, Barts Health NHS Trust and the Royal Free NHS Foundation Trust, Barts Cancer Institute, and Queen Mary University of London, London, United Kingdom*

Background: The randomized, open-label, phase 3 KEYNOTE-426 study (NCT02853331) met its primary and key secondary end points of improved OS, PFS, and ORR with pembro + axi versus sunitinib as first-line treatment for patients with advanced ccRCC. Extended follow-up (42.8-mo median follow-up) continued to show the superior efficacy of pembro + axi versus sunitinib in this patient population. We describe the results of PFS2 for all randomly assigned patients and across IMDC risk categories. **Methods:** Treatment-naive patients with advanced ccRCC, Karnofsky Performance Status Scale score ≥70% and measurable disease per RECIST v1.1 were randomly assigned 1:1 to receive pembro 200 mg IV every 3 weeks for up to 35 doses (~2 y) + axi 5 mg orally twice daily or sunitinib 50 mg orally once daily on a 4-wk on/2-wk off schedule. The end point of this exploratory analysis was PFS2, defined as time from randomization to progression after first subsequent therapy or any-cause death. The Kaplan-Meier method was used to estimate PFS2 and hazard ratios were estimated using a Cox regression model. **Results:** Of 861 patients, 432 were assigned to receive pembro + axi; 429, to sunitinib. Median time from randomization to the database cutoff date (January 11, 2021) was 42.8 mo (range, 35.6-50.6). Overall, 47.2% of patients (204/432) in the pembro + axi arm and 65.5% of patients (281/429) in the sunitinib arm received ≥1 line of subsequent anticancer therapy. For patients who received subsequent therapy, anti–PD-1/PD-L1 agents were the first subsequent treatment for 11.3% of patients (23/204) in the pembro + axi arm and 54.8% of patients (154/281) in the sunitinib arm. In the pembro + axi arm, 82.8% of patients (169/204) received a VEGF/VEGFR inhibitor as first subsequent therapy, as did 43.4% (122/281) in the sunitinib arm. PFS2 results are displayed in the Table. **Conclusions:** In this exploratory analysis, PFS2 was longer for patients randomized to pembro + axi compared to sunitinib. Results were consistent across IMDC risk groups. These data support use of pembro + axi for the first-line treatment of patients with advanced ccRCC. Clinical trial information: NCT02853331. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

	ITT		IMDC favorable risk		IMDC intermediate/poor risk	
	Pembro + axi N = 432	Sunitinib N = 429	Pembro + axi n = 138	Sunitinib n = 131	Pembro + axi n = 294	Sunitinib n = 298
Received ≥ 1 line of subsequent anticancer therapy, n (%)	204 (47.2)	281 (65.5)	64 (46.4)	87 (66.4)	140 (47.6)	194 (65.1)
Median (95% CI) PFS2, mo	40.1 (34.9-43.8)	27.7 (23.1–29.9)	46.0 (43.8 to NR)	39.9 (33.5 to NR)	32.1 (27.9–39.3)	20.1 (15.9–25.1)
HR (95% CI)	0.63 (0.53–0.75)		0.68 (0.47–0.98)		0.62 (0.51–0.76)	

4514 **Poster Discussion Session**

Impact of subsequent therapies in patients (pts) with advanced renal cell carcinoma (aRCC) receiving lenvatinib plus pembrolizumab (LEN + PEMBRO) or sunitinib (SUN) in the CLEAR study. *First Author: Martin H Voss, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: In the open-label, randomized, phase 3 CLEAR study, LEN + PEMBRO had significant PFS (primary endpoint) and OS (key secondary endpoint) benefits over SUN among pts with aRCC in the 1L setting (Motzer 2021, *NEJM*). We evaluated PFS on next-line therapy ("PFS2") and explored the effect of subsequent anticancer therapy on OS in the LEN + PEMBRO and SUN treatment arms of CLEAR. **Methods:** PFS2 was defined as time from randomization to disease progression (as assessed by investigator) on next-line treatment or death from any cause (whichever occurred first). PFS2 was evaluated in all pts randomly assigned to LEN 20 mg orally QD + PEMBRO 200 mg IV Q3W (n=355) or SUN 50 mg orally QD (4 wks on/2 wks off) (n=357) using Kaplan-Meier estimates, and compared between treatment arms via a log-rank test stratified by geographic region and MSKCC prognostic groups. The HR and corresponding CI were estimated using the Cox regression model with Efron's method for ties, using the same stratification factors. A post hoc analysis accounting for the effect of subsequent anticancer therapy on OS (time from randomization to death from any cause) in the LEN + PEMBRO and SUN arms using 2-stage estimation was conducted. **Results:** Among pts who received subsequent anticancer therapy in the LEN + PEMBRO (n=117 pts) and SUN (n=206 pts) arms (Table), median time to next-line therapy was 12.2 mos (range 1.45–37.36) and 6.4 mos (range 0.39–28.52), respectively. Median duration of first subsequent anticancer therapy was 5.2 mos (range 0.10–30.23) in the LEN + PEMBRO arm and 6.8 mos (range 0.03–30.72) in the SUN arm. Among all pts, PFS2 was longer with LEN + PEMBRO than with SUN (median not reached vs 28.7 mos; HR, 0.50; 95% CI 0.39–0.65; nominal $P<0.0001$); PFS2 rates at 24 and 36 mos are in the Table. The unadjusted OS HR for LEN + PEMBRO vs SUN (from the primary analysis [Motzer 2021, *NEJM*]) was 0.66 (95% CI 0.49–0.88); the HR for OS adjusted for subsequent therapy was 0.54 (bootstrap 95% CI 0.39–0.72). **Conclusions:** LEN + PEMBRO had a statistically significant and clinically meaningful benefit over SUN in the CLEAR study. These findings remained consistent after accounting for subsequent therapies, as evidenced by prolonged PFS2 and adjusted OS. Results further support LEN + PEMBRO as a standard of care in 1L aRCC. Clinical trial information: NCT02811861. Research Sponsor: This study was sponsored by Eisai Inc., Nutley, NJ, USA, and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Parameter	LEN + PEMBRO (n=355)	SUN (n=357)
Pts receiving any subsequent systemic anticancer therapy[a], n (%)		
Anti-VEGF	117 (33.0)	206 (57.7)
PD-1/PD-L1 checkpoint inhibitor	108 (30.4)	120 (33.6)
MTOR Inhibitor	29 (8.2)	154 (43.1)
CTLA-4 Inhibitor	6 (1.7)	17 (4.8)
Other	6 (1.7)	18 (5.0)
	12 (3.4)	20 (5.6)
PFS2, median (95% CI)	Not reached (NE–NE)	28.7 mos (23.0–NE)
PFS2 HR (95% CI)	0.50 (0.39–0.65)	
Nominal *P* value	<0.0001	
PFS2 rate at 24/36 mos, % (95% CI)	72.7 (67.3, 77.4) / 61.9 (53.7, 69.0)	54.2 (48.4, 59.6) / 42.9 (32.8, 52.5)

[a]Monotherapy or in combination. NE, not estimable.

4515 **Poster Discussion Session**

Perioperative chemoimmunotherapy with durvalumab for operable muscle-invasive urothelial carcinoma (MIUC): Primary analysis of the single arm phase II trial SAKK 06/17. *First Author: Richard Cathomas, Division of Oncology, Cantonal Hospital Graubunden, Chur, Switzerland*

Background: SAKK 06/17 investigated the addition of perioperative immunotherapy with the anti-PD-L1 antibody durvalumab (Durva) in the multimodality treatment of resectable MIUC. While most similar trials had a primary endpoint of pathological complete remission rate, this study evaluated the clinically more relevant primary endpoint of event-free survival (EFS) at 2 years (yrs). **Methods:** SAKK 06/17 was an open-label, single-arm phase II study including 61 cisplatin-fit patients (pts) with stage cT2-T4a cN0-1 operable MIUC. Pts received four cycles of neoadjuvant Cis/Gem q3w in combination with 4 cycles Durva 1500mg q3w followed by complete resection. Adjuvant Durva 1500mg q4w was given for 10 cycles or a maximum of 40 weeks. The primary endpoint was EFS at 2 yrs after neoadjuvant trial treatment (NAT) start. An event was defined as progression during NAT, appearance of metastases, locoregional recurrence after surgery or death from any cause. 58 pts were needed based on one-sided type I error 10% and power 80% for H_1 EFS at 2 yrs ≥ 65% compared to H_0 EFS at 2 yrs ≤ 50%. Secondary endpoints included pathological response, recurrence free survival after R0 resection (RFS), overall survival (OS) and safety. We report the primary analysis of the full analysis set (FAS, received at least one dose of Durva). **Results:** 61 pts were included between July 2018 and September 2019 at 12 sites. Median follow up is 28.1 months (95%CI 27.8-28.4). FAS consisted of 58 pts (79% male, median age 68 yrs) with bladder cancer (95%) or upper urinary tract/urethral cancer (5%). Clinical T2, T3, T4 stage was present at diagnosis in 69%, 21%, 10%, respectively, and 17% had cN1. Resection was performed in 53 pts (91%; 4 refused, 1 unresectable) with R0 resection in 52 pts (98%). 48 (91%) of resected pts started adjuvant Durva and 32 (67%) completed it. Pathological response < ypT2 ypN0 was achieved in 32 pts (18 pts ypT0 and 14 pts ypT1/a/is), corresponding to 60% of resected pts and 55% of the FAS. EFS at 2 yrs was overall 76.1% (one-sided 90% CI (lower bound): 67.6%; 95% CI 62.3% - 85.3%), for ypT1/a/is 92.9% and for ypT0 100%. RFS at 2 yrs after R0 resection (N=52) was 83.5% (95% CI 69.6% - 91.4%) and OS at 2 yrs for the FAS population was 87.3% (95% CI 73.8% - 94.1%). Grade 1, 2, 3, 4 adverse events attributed to Durva during overall treatment were 14%, 35%, 19%, 7%, respectively. **Conclusions:** The addition of perioperative Durvalumab to the standard of care for pts with resectable MIUC results in a high EFS, RFS and OS at 2 yrs, especially for pts with downstaging to <ypT2. The null hypothesis for the primary endpoint was clearly rejected. More in-depth analyses for biomarkers (PD-L1, ctDNA) will be presented at the meeting. Clinical trial information: NCT03406650. Research Sponsor: Astra Zeneca, SERI: Swiss State Secretariat for Eduction Research and Innovation.

4516 **Poster Discussion Session**

Long-term outcomes in EV-301: 24-month findings from the phase 3 trial of enfortumab vedotin versus chemotherapy in patients with previously treated advanced urothelial carcinoma. *First Author: Jonathan E. Rosenberg, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Enfortumab vedotin (EV), an antibody-drug conjugate directed against Nectin-4, demonstrated longer overall survival (OS) and progression-free survival (PFS) in the confirmatory phase 3, randomized, open-label EV-301 trial at the prespecified interim analysis. The longer-term clinical profile of EV is unknown. Data from 12 additional months of follow-up in EV-301 are presented. **Methods:** In EV-301 (NCT03474107), patients with locally advanced or metastatic urothelial carcinoma (la/mUC) who had received a prior platinum-containing chemotherapy and had disease progression during or after PD-1/L1 inhibitor treatment were randomized 1:1 to receive either EV 1.25 mg/kg on Days 1, 8, and 15 of each 28-day cycle or investigator-chosen standard chemotherapy with docetaxel, paclitaxel, or vinflunine. The primary endpoint was OS; secondary endpoints included investigator-assessed PFS per RECIST v1.1, as well as safety and tolerability. Efficacy and safety findings from July 30, 2021, approximately 1 year after the interim analysis (July 15, 2020), are reported. **Results:** Overall, 608 patients with la/mUC were randomly assigned to EV (n = 301) or chemotherapy (n = 307). As of July 30, 2021, 444 deaths had occurred (EV, n = 207; chemotherapy, n = 237). After a 23.75-month follow-up, median OS was significantly prolonged by 3.97 months with EV compared with chemotherapy (median OS: 12.91 vs 8.94 months, respectively; HR = 0.704 [95% CI: 0.581-0.852], 1-sided P= 0.00015). Additionally, the OS benefit of EV was retained in the majority of prespecified subgroups. PFS also was improved with EV (median 5.55 months) vs chemotherapy (median 3.71 months) (HR = 0.632 [95% CI: 0.525-0.762]; 1-sided P< 0.00001). Rates of treatment-related adverse events (TRAEs; 93.9% vs 91.8%), including serious TRAEs (22.6% vs 23.4%), were comparable between the EV and chemotherapy groups. Rates of grade ≥3 TRAEs were ~50% in both groups. **Conclusions:** EV continues to show significant and consistent survival advantage over standard chemotherapy in patients with treatment-experienced la/mUC. No new safety signals were identified. With robust clinical benefit and a tolerable safety profile, EV maintains its place as a standard of care for this aggressive disease. Clinical trial information: NCT03474107. Research Sponsor: Astellas Pharma, Inc.

4517 **Poster Discussion Session**

Avelumab as the basis of neoadjuvant regimen in platinum-eligible and -ineligible patients with nonmetastatic muscle-invasive bladder cancer: AURA (Oncodistinct-004) trial. *First Author: Nieves Martinez Chanza, Medical Oncology Department, Jules Bordet Institute, Université Libre de Bruxelles, Brussels, Belgium*

Background: Nearly half of the patients (pts) diagnosed with non-metastatic muscle invasive bladder cancer are unfit for cisplatin therapy and no alternative options of neoadjuvant treatment exist. Avelumab (A), a monoclonal antibody directed against PD-L1, showed efficacy in advanced urothelial cancer. We report preliminary data assessing preoperative avelumab associated with paclitaxel and gemcitabine or avelumab alone in the cisplatin ineligible cohort. The results of the cisplatin eligible cohort were reported at ESMO 2021. **Methods:** AURA is a prospective, multicenter, randomized, phase II trial for pts with cT2-4aN0-2M0 bladder carcinoma. Pts were enrolled in two separated cohorts based on eligibility for cisplatin chemotherapy. Cisplatin ineligible pts received 4 cycles of paclitaxel-gemcitabine (PG) plus A every 2 weeks or 4 cycles of A every 2 weeks (1:1). Primary endpoint was pCR rate (ypT0/isN0) with the objective, in each arm, to show pCR rate > 5% (90% power reached in case of pCR rate > 25%). Two-step design was used with planned interim analysis after 12 evaluable pts per arm. Secondary endpoints were pathologic downstaging rate (< ypT2N0) and safety. **Results:** A total of 56 cisplatin-ineligible pts were evaluable. For PG + A arm (n = 28): median age was 72 years (41-80), 93% male. For A alone arm (n = 28): median age was 75 years (49-89), 93% male. One patient did not undergo surgery due to progression in the A arm but was included in intention to treat analysis. Five pts did not receive the 4 cycles of treatment; reasons included toxicity (n = 3) for PG + A arm and patient/physician decision (n = 2) for A arm. pCR was achieved in 5 pts (18%; 95%CI 6%-37%) treated with PG + A and 10 pts (36%; 95%CI 19%-56%) treated with A. Downstaging to < ypT2N0 was achieved in 6 pts (21%; 95%CI 8%-41%) and 11 pts (39%; 95%CI 22%-59%), respectively. Median time from treatment initiation to surgery was 82 days (55-144) for PG + A arm and 67 days (38-89) for A arm. Most common irAEs of any grade were asthenia (15%), skin toxicity and myalgia/arthralgia (each 5%). There were 2 pts in the PG + A arm with grade 3 irAEs (hepatitis and pneumonitis) that caused A discontinuation for 1 patient. No treatment-related deaths were reported. **Conclusions:** Neoadjuvant single agent avelumab resulted in high pCR and was safely administered without compromising surgical resection. Our results suggest that the addition of taxane-gemcitabine regimen to avelumab may reduce avelumab efficacy with low pCR rate. Survival analysis and correlative studies are underway. Clinical trial information: NCT03674424. Research Sponsor: This study is financially supported by Amis de l'Institut Bordet and Merck N.V.-S.A., Overijse, Belgium, an affiliate of Merck KGaA, Darmstadt, Germany, as part of an alliance between Merck KGaA and Pfizer.

4518 **Poster Discussion Session**

Preliminary results of a phase Ib/II combination study of RC48-ADC, a novel humanized anti-HER2 antibody-drug conjugate (ADC) with toripalimab, a humanized IgG4 mAb against programmed death-1 (PD-1) in patients with locally advanced or metastatic urothelial carcinoma. *First Author: Xinan Sheng, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Genitourinary Oncology, Beijing Cancer Hospital, Beijing, China*

Background: RC48-ADC has shown promising data in HER2-positive and even negative patients with metastatic urothelial carcinoma (mUC) who failed with platinum-based chemotherapy. RC48-ADC combined with anti-PD-1 antibody may have a synergistic antitumor effect. **Methods:** This is an open-label, multicenter, phase 1b/II trial to evaluate the safety and activity of RC48 combined with toripalimab in mUC. Patients received RC48-ADC at 1.5 or 2 mg/kg, in combination with 3mg/kg toripalimab every two weeks in a dose-escalation and expansion cohort until confirmed disease progression, unacceptable toxicity, or voluntary withdrawal. The key primary endpoint was safety; secondary endpoints included efficacy and tumor tissue biomarkers. **Results:** As of 17 Jan 2022 (data cutoff), 41 la/mUC pts (19 males; median age 66 y [42-76]) were enrolled since 20 Aug 2020. 61% patients were systemic treatment naïve, and 54% had visceral metastases (mets), including 24% with liver mets. The primary site was in upper tract UC in 54%. HER2 expression was positive (IHC 2+ or 3+) in 59% patients, and PD-L1 positive (CPS ≥ 10) in 32%. No dose-limiting toxicity was observed. The recommended dose was RC48-ADC 2mg/kg + toripalimab 3mg/kg every 2 weeks. With a median follow-up of 8.0 mos, 36 patients had at least one tumor assessment, the best ORR was 83.3%, and the confirmed ORR was 76.7% (95%CI: 57.7, 90.1), including 10% CR. The cORR was 82.4% for 1L previously untreated mUC patients, 100% for patients with HER2 IHC (2+ or 3+) & PD-L1 (+), 92.3% for HER2 (2+ or 3+) & PD-L1 (-), 50% for HER2 (0 or 1+) & PD-L1 (+), and 50% HER2 (0 or 1+) & PD-L1 (-). DCR was 96.7% (95%CI: 82.8, 99.9). The median PFS was immature and 9.2 mos (95%CI: 5.49, 10.32) by the time and the median OS was not reached. The most common treatment-related AEs were ALT/AST increase (65.9%), peripheral sensory neuropathy (58.5%), appetite decrease (56.1%), asthenia (56.1%), hypertriglyceridemia (48.8%). Grade ≥3 TRAEs included γ-glutamyl transferase increase (12.2%), ALT/AST increase (7.3%), asthenia (7.3%), hypertriglyceridemia (4.9%), and neutropenia (4.9%). 9 pts had irAEs (22.0%, 7.3% ≥ G3), including immune-related pneumonitis, hepatitis, and myositis. **Conclusions:** RC48-ADC in combination with toripalimab demonstrated promising efficacy in patients with mUC and a manageable safety profile. A randomized study of RC48-ADC and toripalimab vs. platinum-based chemotherapy in previously untreated la/mUC patients is ongoing. Clinical trial information: NCT04264936. Research Sponsor: Remegen.

Stratification	cORR
HER2 IHC (2+/3+) PD-L1 (+)	100% (5/5)
HER2 IHC (2+/3+) PD-L1 (-)	92.3% (12/13)
HER2 IHC (1+) PD-L1 (+)	50% (2/4)
HER2 IHC (1+) PD-L1 (-)	50% (3/6)
HER2 IHC (0) PD-L1 (+)	-
HER2 IHC (0) PD-L1 (-)	50% (1/2)
Total	76.7% (23/30)

4519 **Poster Discussion Session**

A phase II study of RC48-ADC in HER2-negative patients with locally advanced or metastatic urothelial carcinoma. *First Author: Huayan Xu, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education, Beijing), Department of Genitourinary Oncology, Peking University Cancer Hospital & Institute, Beijing, China*

Background: RC48-ADC is a novel humanized anti-HER2 antibody-drug conjugate (ADC). A phase II clinical study showed that RC48-ADC has a good effect on locally advanced or metastatic urothelial carcinoma with HER2-positive expression that failed standard chemotherapy. In the study, some patients with HER2-postive immunohistochemistry (IHC 2+) but negative FISH test still benefited from the treatment of RC48-ADC.This study was to evaluate the activity and safety of RC48-ADC in HER2-negative patients with locally advanced or metastatic urothelial carcinoma. **Methods:** This study is an open-label, single-center, single-arm, phase II trial. Eligibility criteria include: histologically confirmed urothelial carcinoma, HER2-negasitive (IHC 0 or 1+), ECOG PS 0-1,and treated with ≥1 prior systemic treatment. Patients received RC48-ADC 2mg/kg q2w until disease progression, unacceptable toxicity, withdrawal of consent, or study termination. The primary objectives were activity (ORR) and safety. Second objectives included progress-free survival, disease control rate and overall survival. **Results:** As of February 2022(date cutoff),19 patients were enrolled. The median age was 64 years old(-range:36-77). At baseline, there were 6 patients with HER2(IHC 0), and 13 patients with HER2(IHC 1+).Most patients (13/19) had visceral metastasis. 15(79%) patients had received≥2 lines treatment.At date cutoff, 19 patients were assessable for response. The objective response rate was 26.3% (95% CI:9.1%,51.2%) and the DCR was 94.7% (18/19). The mPFS was 5.5months (95% CI:3.9,6.8) and mOS was 16.4months (95% CI:7.1,21.7) .All of the 6 patients with HER2(0) were SD in the study. The ORRs were 38% (5/13) in patients with HER2(IHC 1+),31% (4/13) in visceral metastasis,17% (1/6) in liver metastasis patients,27% (4/15) in patients post to ≥ 2 lines of treatment. Common treatment-related AEs were leukopenia (52.6%), hypoesthesia (47.4%),alopecia (47.4%), AST increase (42.1%), ALT increase (42.1%), and neutropenia (42.1%), fatigue (42.1%),nausea (26.3%), vomiting (15.8%).Most of these AEs were Grade 1 or 2. The AE of Grade 3 was neutropenia (10.5%). The SAE was CPK increased (5.3%). **Conclusions:** This study showed that RC48-ADC was safe and the ORR was 26.3% in HER-negative patients with locally advanced or metastatic urothelial carcinoma. The enrollment was completed and data will be updated later. Clinical trial information: NCT04073602. Research Sponsor: RemeGen,Ltd.

4520 **Poster Discussion Session**

RC48-ADC for metastatic urothelial carcinoma with HER2-positive: Combined analysis of RC48-C005 and RC48-C009 trials. *First Author: Xinan Sheng, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Genitourinary Oncology, Beijing Cancer Hospital, Beijing, China*

Background: RC48-ADC (Disitamab Vedotin) is a novel humanized anti-HER2 antibody-drug conjugate (ADC). RC48-ADC demonstrated a promising efficacy with a manageable safety profile in HER2-positive locally advanced or metastatic UC patients who failed to platinum based chemotherapy in RC48-C005 and RC48-C009 trials. Here are the pooled results of the two studies with the supplementary efficacy, safety and updated OS data. **Methods:** Both of the two trials are single-arm, multi-center, phase II trials. Eligible patients were 18~80 years old, with central-laboratory confirmed, histologically HER2-postive (IHC2+,3+), unresectable mUC. Patients had at least one line of systemic chemotherapy. The primary endpoint was objective response rate (ORR). Progress-free survival (PFS), overall survival (OS), and safety were also assessed. **Results:** RC48-C005 and RC48-C009 enrolled HER2-positive locally advanced or metastatic UC patients from Nov 2017 to Sep 2020. 107 mUC patients (80 males; median age 63 y [40-79]) were enrolled. 64.5% patients had received ≥ 2 lines systemic chemotherapy. 90.7% patients had visceral metastases. As of 04 Sep 2021 (data cutoff), The overall confirmed ORR as assessed by the BIRC was 50.5% (95% CI: 40.6%, 60.3%). Similar responses were observed in prespecified subgroups. cORR was 52.1% (25/48) for patients with liver metastasis and was 55.6% (15/27) in patients with previous PD-1/L1 treatment. The cORR was 62.2% (28/45) for HER2 IHC2+&FISH+ or IHC3+ patients, 55.6% (5/9) for HER2 IHC2+&FISH unknown patients, and 39.6% (21/53) for HER2 IHC2+&FISH- patients respectively. DCR was 82.2% (95% CI:73.7%, 89.0%). The mPFS was 5.9 (95% CI:4.2, 7.2) months. The mOS was 14.2 (95% CI:9.7, 18.8) months. The median OS follow up time was 19.1 months. Most common treatment-related AEs were hypoaesthesia (50.5%), Leukopenia (49.5%), aspartate aminotransferase increased (43.0%), neutropenia (42.1%), alopecia (40.2%), asthenia (39.3%), alanine aminotransferase increase (35.5%), decreased appetite (31.8%). The grade ≥3 TRAEs (≥5%) only included hypoaesthesia (15.0%), neutropenia (12.1%) and r-GT increased (5.6%). **Conclusions:** RC48-ADC showed continuously a promising efficacy with a manageable safety profile in HER2-postive mUC patients who had failed at least one line systemic chemotherapy. Clinical trial information: NCT03507166, NCT03809013. Research Sponsor: Remegen Ltd.

4521 **Poster Session**

Association of DNA damage repair (DDR) mutations (mts) and clinical outcomes in CALGB 90601 (Alliance). *First Author: Gopa Iyer, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Platinum-based chemotherapy is the standard 1st-line therapy for metastatic urothelial cancer (mUC). C90601 was a randomized phase III trial testing gemcitabine and cisplatin (GC) with bevacizumab (B) or placebo (P) in patients (pts) with untreated mUC. Median overall survival (OS) for GCB vs GCP was 14.5 months (mo) vs 14.3 mo (p=0.14) and median progression-free survival (PFS) was 8 vs 6.7 mo, respectively. DDR mts have been implicated in response and survival in mUC and were investigated in this negative trial. **Methods:** C90601 enrolled 506 pts randomized 1:1 to GCB or GCP from 7/15/09-12/2/14, with stratification for prior chemotherapy and visceral metastases. Consenting pts submitted archival FFPE tumor specimens and blood for matched germline (g)DNA. Tumor and gDNA were sequenced by MSK-IMPACT, a 468-gene exon capture assay, to detect mts in select DDR genes. The proportional hazards model was used to correlate mts in the DNA helicase ERCC2 (pre-specified hypothesis) and additional DDR gene panels being explored in prospective trials in muscle-invasive disease with OS and PFS, adjusting for tumor mt burden and stratification factors. Mts were categorized as deleterious (del) or non-del using pre-defined published criteria. **Results:** 208 pts underwent DNA sequencing. Clinical features and PFS/OS were comparable to the 506-pt cohort. Median sequencing coverage was 497X. Median mutation count was 13.2 and 8.8 for DDR mt and wild-type tumors, respectively. A non-significant improvement in OS and PFS was seen in pts with ERCC2 mts (HR 0.70), but the 5.3% frequency of ERCC2 mts was lower than in historical series. Neither del mts (table) nor any mts in DDR genes were associated with PFS/OS. **Conclusions:** DDR mts were not associated with improved outcomes in C90601. The reliance on archival specimens, lower-than-expected ERCC2 mt frequency, small sample sizes, and tumor genomic heterogeneity may have influenced the predictive capacity of DDR mts in this cohort. Similar analyses are underway in pts who received neoadjuvant chemotherapy prior to cystectomy from completed prospective trials. Support: U10CA180821, U10CA180882, Genentech. Research Sponsor: U.S. National Institutes of Health, Department of Defense grant funding.

Median OS and PFS by del DDR gene mts status.

Gene	# Mts out of 208	Median OS, mo (95%CI) Mts	Median OS, mo (95%CI) No Mts	Hazard Ratio (HR;95% CI)	Median PFS, mo (95%CI) Mts	Median PFS, mo (95%CI) No Mts	HR (95% CI)
ERCC2	11	18.8 (12.8–NR)	14.3 (12.4–16.2)	0.7 (0.3–1.5)	12.8 (6.7–NR)	6.9 (6.4–8.0)	0.7 (0.3–1.4)
Any Del mts in ERCC2, FANCC, ATM, RB1	49	14.3 (12.3–20.5)	14.8 (12.2–16.3)	1.0 (0.7–1.5)	6.9 (6.2–10.4)	7.0 (6.4–8.2)	1.1 (0.7–1.5)
Any Del mts in ERCC2, ERCC5, BRAC1, BRAC2, ATM, ATR, RECQL4, FANCC, RAD51C	29	18.0 (12.8–42.1)	14.3 (12.2–16.2)	0.8 (0.5–1.3)	8.3 (6.4–14.7)	6.9 (6.4–8.0)	0.8 (0.5–1.2)
Any Del mts	71	14.2 (11.7–18.9)	15.2 (12.5–16.5)	1.1 (0.8–1.5)	6.7 (5.9–8.9)	7.4 (6.6–8.4)	1.1 (0.8–1.6)

NR=Not reached.

4522 **Poster Session**

Association of DNA damage response (DDR) gene mutations (mts) and response to neoadjuvant cisplatin-based chemotherapy (chemo) in muscle-invasive bladder cancer (MIBC) patients (pts) enrolled onto SWOG S1314. *First Author: Gopa Iyer, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Neoadjuvant cisplatin-based chemo followed by radical cystectomy (RC) is a standard of care treatment for pts with MIBC. DDR gene mts, including within ERCC2, a DNA helicase implicated in cisplatin sensitivity in MIBC, have been associated with higher pathologic (path) downstaging (< pT2) and complete response (pT0) at RC and improved overall survival (OS) in retrospective series. S1314 randomized pts to one of 2 chemo regimens (dose dense MVAC or Gem/Cis) followed by RC. We sought to correlate ERCC2 and other DDR gene mts with response and survival in MIBC pts enrolled onto this prospective trial. **Methods:** Tumor and matched germline DNA from evaluable pts enrolled onto S1314 underwent exon capture sequencing of 505 cancer-associated genes (MSK-IMPACT). Both deleterious (del) mts and any mts in 9 DDR genes (ERCC2, ERCC5, BRCA1, BRCA2, RECQL4, ATM, ATR, RAD51C, FANCC) were correlated with clinical outcomes. The prespecified analyses included the association of mts with < pT2 and pT0 by logistic regression analysis and with progression-free survival (PFS) and OS by Cox proportional hazards regression. **Results:** 179 patients (median 61 years, 85% male, 87% white, and 87% clinical stage T2) who received >2 cycles of chemo and were evaluable for path response were included in the analysis. The pT0 rate was 28% and < pT2 was 41%. Del mts in ERCC2 were detected in 26 (14%) pts followed by ATM (n = 12, 7%), ATR (n = 3) and BRCA2 (n = 2). ERCC2 mts were associated with statistically significantly higher path responses with a 54% pT0 rate and 62% downstaging rate. Patients with any del mts had higher path response rates (51% pT0, 56% < pT2) and better PFS (Table) with a median follow-up of 53 months. There was a non-significant trend towards improved OS. **Conclusions:** In pts managed with neoadjuvant chemo and RC on S1314, both ERCC2 mts and del DDR gene mts correlated with pathologic response. Any del DDR gene mt was associated with improved PFS. These results are in line with retrospective analyses displaying a correlation between DDR gene mts and neoadjuvant chemosensitivity in MIBC and support ongoing genomically-informed organ sparing trials. Research Sponsor: U.S. National Institutes of Health.

Mutation	pT0 OR (95% CI) p-value	< pT2 OR (95% CI) p-value	PFS HR (95% CI) p-value	OS HR (95% CI) p-value
ERCC2 (Y vs N)	3.50 (1.48, 8.30)	2.51 (1.06, 5.95)	0.64 (0.31, 1.33)	0.57 (0.23, 1.44)
N = 26	p = 0.005	p = 0.037	p = 0.23	p = 0.23
Any Deleterious Mutation (Y vs N)	3.78 (1.81, 7.90)	2.17 (1.07, 4.41)	0.54 (0.29, 1.01)	0.53 (0.25, 1.13)
N = 41	p = 0.0004	p = 0.033	p = 0.053	p = 0.10

p-values are two-sided, adjusted for stratification factors (clinical stage and performance status)
OR: Odds Ratio HR: Hazard Ratio

4524 **Poster Session**

Landscape analysis of urothelial carcinoma (UC) by telomerase reverse transcriptase (*TERT*) alterations. *First Author: Tyler F. Stewart, University of California San Diego Health, La Jolla, CA*

Background: TERT is a catalytic subunit of telomerase, the unique enzyme that confers immortality to cells and is expressed in >90% of cancer cells. Mutations in the *TERT* promoter region (pTERTmut) are the most prevalent noncoding mutations in cancer. Recent data suggest pTERTmut are associated with improved outcomes in patients with UC treated with immune checkpoint inhibitors. We evaluated the molecular and immune landscape of UC with and without pTERTmut. **Methods:** UC tissue samples were analyzed for DNA alterations (NextSeq, 592 Genes; NovaSeq, WES) and mRNA expression (NovaSeq, WTS). Immune cell fraction was calculated by QuantiSeq (Finotello 2019, Genome Medicine). PD-L1 expression was assessed by immunohistochemistry (IHC) (Caris Life Sciences, Phoenix, AZ). MSI/MMR was tested by fragment analysis, IHC and NGS. TMB-H was based on a cut-off of > 10 mut/MB. We compared alterations between samples with and without detected pathogenic pTERTmut. Significance was determined by Mann–Whitney U, X^2, and Fischer-Exact and p adjusted for multiple comparisons (q) was < 0.05 using Benjamini-Hochberg. **Results:** Overall, 1686 UC samples were analyzed, 1166 from primary lesions and 499 from a lymph node or metastatic site. pTERTmut was present in 68% of primary and 61% of metastatic tumors, and correlated with modest increase of TERT expression (1.18 fold, p=0.015). pTERTmut was associated with less frequent alterations in TP53, KMT2D, CCND1, MYC, KEAP1 and less MSI/dMMR. By contrast, pTERTmut was associated with more frequent alterations in ARID1A, TSC1, PIK3CA and TMB-H (all q<0.05). Over 41% of pTERTmut were TMB-H. TERTp mutations were not associated with FGFR alterations. The frequency of co-occurring mutations was similar by specimen site. In evaluating the immune landscape (Table), pTERTmut was associated with higher expression of PD-L1 (IHC, mRNA), PD-L2 (mRNA) and TIM3 (mRNA) in tumors from primary sites (all p and q<0.05), but not in metastatic sites. Investigation of tumor-associated immune cells demonstrated that pTERTmut correlated with higher percentage of M1-macrophages and CD8+ T cells in primary tumors, and was inversely-correlated with NK cells in metastatic sites (all q<0.05). **Conclusions:** This is the largest analysis looking at the molecular and immune landscape of pTERTmut UC tumors. We observed differential patterns of DNA alterations and tumor immune microenvironment based on pTERTmut status. Further work is needed to understand differences in these molecular cohorts and the association of these data with clinical outcomes. Research Sponsor: None.

Fold change in checkpoint gene expression and immune cell type with/without pTERTmut by specimen site.

	Overall	Primary Site	Metastatic Site
PDL1	1.22*	1.27*	1.04
PDL2	1.11*	1.15*	1.04
TIM3	1.07	1.17*	1.02
M1 Macrophage	1.20*	1.35*	0.99
NK cell	0.93*	0.97	0.83*
CD8+ T cell	1.16	1.71*	0.49
Regulatory T Cell	1.20*	1.21*	1.21

*q<0.05.

4525 **Poster Session**

Monitoring efficacy of neoadjuvant sunitinib in metastatic renal cell carcinoma using a personalized and tumor informed ctDNA assay. *First Author: Christine B. Peterson, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Approximately 30% of renal cell carcinoma (RCC) cases present as stage IV at the time of diagnosis. Metastatic RCC (mRCC) is associated with poor outcomes, with a five-year survival rate below 50%. Tools to evaluate the efficacy of novel systemic regimens are needed. Biomarkers like ctDNA can accurately and non-invasively assess molecular residual disease (MRD) in response to therapy and monitor disease status over time to predict disease progression. Here, we aimed to determine the feasibility of performing personalized and tumor-informed ctDNA testing in mRCC patients enrolled on a study integrating systemic therapy with surgical cytoreduction, as well as to measure patient response to sunitinib by assessing ctDNA dynamics. **Methods:** We analyzed a cohort of 21 mRCC patients with median age of 59.5 (43-76) years who were treated with sunitinib, and had planned cytoreductive nephrectomy during their second cycle of therapy. Baseline and post-first cycle ctDNA levels were measured using a personalized and tumor-informed ctDNA assay (SignateraTM bespoke mPCR NGS assay). Changes in ctDNA levels from baseline to the best response time point were correlated with disease status as assessed by radiological imaging. **Results:** In this cohort, baseline ctDNA was detected in 81% (17/21) of patients, with higher ctDNA concentrations observed in patients who presented with multiple distant metastases (n = 11) compared to the 10 cases with a single metastatic mass (median 5.8 vs 1.3 mean tumor molecules/mL , not statistically significant). Of those with baseline ctDNA measurement, 12% (2/17) cleared their ctDNA, 24% (4/17) had a decrease in ctDNA, and 59% (10/17) had an increase in ctDNA after 4 weeks of sunitinib. During the course of treatment, patients whose ctDNA concentration increased from baseline were more likely to experience a disease progression (HR: 3.9 95% CI 1.13-13.7; p = 0.032) compared to those whose ctDNA decreased. In addition, higher ctDNA concentration before surgery after initial treatment with sunitinib correlated with shorter time to progression (p = 0.04). **Conclusions:** Our results demonstrate the feasibility and prognostic value of personalized and tumor-informed ctDNA testing for determining response to systemic therapy in patients with mRCC. Early signs of unfavorable ctDNA kinetics can provide rationale for modification of systemic therapy in order to enhance response. Future work exploring the clinical utility of ctDNA testing in larger mRCC cohorts is warranted. Research Sponsor: None.

4526 **Poster Session**

Molecular profile and clinical outcomes of renal cell carcinoma brain metastases treated with stereotactic radiosurgery. *First Author: Jennifer Ma, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Molecular profiles of renal cell carcinoma (RCC) tumors are associated with systemic treatment (ST) responses and clinical outcomes. However, the molecular profiles of RCC brain metastases (BM) and their correlation with ST response and clinical outcomes are not well characterized. Effective management of BM with locoregional therapies including stereotactic radiosurgery (SRS) is critical as ST advances have improved overall survival (OS). Therefore, we sought to identify the clinical and genomic features of RCC BM in a large cohort of patients treated with SRS. **Methods:** We performed an institutional retrospective analysis of RCC BM patients treated with SRS and evaluated corresponding genomic next generation sequencing (NGS) data via a targeted sequencing panel (MSK-IMPACT). A comparison cohort of all institutional patients with available NGS data was utilized to investigate genes enriched in our BM cohort using Fisher exact testing. Kaplan Meier analyses were performed for OS and intracranial progression-free survival (iPFS). Clinical factors and genes mutated in ≥ 10% of samples were assessed per patient using Cox proportional hazards models, and per individual BMs using clustered competing risks regression with a competing risk of death. **Results:** From 2010-2021, 91 RCC BM patients underwent SRS for 212 BMs, including 86% clear cell and 14% non-clear cell RCC. NGS data was available for 76 patients (84%), including 18 resected BMs, 26 extra-cranial metastatic lesions (EM), and 32 primary kidney tumors (Table 1). Median follow-up was 3.2 years with median OS of 21 months (m) and median iPFS of 7.8m. Karnofsky performance status ≥80 and extracranial disease control were significantly associated with improved OS on multivariable analyses (MVA; p=0.049 and 0.01, respectively). No clinical variables were significantly associated with iPFS on MVA. At the BM level, *SETD2* alterations approached significance for improved iPFS (HR=0.35; 95%CI 0.11, 1.05; p=0.06). Enrichment in *SMARCA4* alterations was seen in the BM cohort as compared to primary kidney and EM samples from patients without BM (17% vs 1% vs 2%, p<0.05). **Conclusions:** To our knowledge, this is the largest study investigating mutational profiles of RCC BM. *SMARCA4* alterations were enriched in BM samples and a trend towards improved iPFS was seen in *SETD2* variant BMs, warranting further investigation. Research Sponsor: None.

Targeted sequencing results of the five most frequently mutated genes in our BM cohort compared to an institutional cohort of genomic NGS data of all patients with primary RCC or with extracranial lesions without BM.

Gene	Brain Metastases Cohort (n=76)	Non-BM Comparison Cohort: Primary Kidney (n=468)	Non-BM Comparison Cohort: Extracranial Metastases (n=260)
VHL	72%	74%	84%
PBRM1	56%	39%	32%
SETD2	39%	21%	20%
SMARCA4	17%	1%*	2%*
BAP1	22%	16%	8%

*statistically significant (p≤0.05) by Fisher exact testing.

4527 **Poster Session**

Association between decline of neutrophil-to-eosinophil ratio (NER) at week 6 after ipilimumab plus nivolumab initiation and improved clinical outcomes in metastatic renal cell carcinoma (mRCC). *First Author: Yu-Wei Chen, Vanderbilt Ingram Cancer Center, Nashville, TN*

Background: Low baseline NER has been associated with improved response to immunotherapy in mRCC (PMID:34732251). The current study aimed to investigate the early decline of NER at week 6 after ipilimumab/nivolumab (ipi/nivo) initiation and treatment responses in mRCC. **Methods:** Retrospective chart review of ipi/nivo-treated mRCC patients at Vanderbilt-Ingram Cancer Center and Duke Cancer Institute was conducted. Landmark analysis at week 6 after ipi/nivo initiation was performed to assess the association between change in NER and clinical responses [progression-free survival (PFS)/overall survival (OS)]. **Results:** There were 150 mRCC patients included in the analysis: 78% had clear cell histology, 78% were IMDC intermediate/poor risk, and 74% were male. The median follow-up time was 11.9 months. After ipi/nivo initiation, the median NER decreased from 23.8 (interquartile range: 15.0-57.1) at baseline to 19.8 (10.6-40.8) at week 6; 102 (68%) patients had decreased NER. The NER at week 6 was grouped by percent change (≥ 50% decrease vs <50% decrease vs increase). In multivariable regression analysis after adjustment for age, sex, race, IMDC risk group, baseline NER, histology, prior systemic therapy, and prior nephrectomy (Table), decreased NER ≥ 50% was associated with improved PFS [adjusted hazard ratio (AHR): 0.55, p-value: 0.03] and OS (AHR: 0.38, p-value: 0.02) (Table). Stratified analysis was conducted by baseline NER [≥vs < baseline median NER (23.8)]: decreased NER ≥ 50% was associated with improved PFS (AHR: 0.46, p-value: 0.048) and OS (AHR: 0.29, p-value: 0.01) in the subgroup with high baseline NER. These associations were not observed in the subgroup with low baseline NER (p-value for PFS: 0.25; p-value for OS: 0.61). **Conclusions:** The decline of NER ≥50% at week 6 after ipi/nivo initiation was associated with improved PFS/OS in mRCC patients with high baseline NER. Prospective studies are warranted to validate NER change as a biomarker to predict response to ICIs in mRCC. Research Sponsor: U.S. National Institutes of Health.

Association between change in NER at week 6 and clinical responses.

	ORR %	PFS		OS	
		Median (95%), months	AHR (95%)	Median (95%), months	AHR (95%)
All patients (N=150)					
Decreased NER ≥ 50% (N=44)	43%	7.5 (3.7-10.1)	0.55 (0.31-0.95)	NR (15.3-NR)	0.38 (0.17-0.85)
Decreased NER < 50% (N=58)	36%	6.6 (2.5-13)	0.63 (0.38-1.05)	NR (22.5-NR)	0.52 (0.24-1.13)
Increased NER (N=48)	25%	2.5 (1.4-4.2)	Ref	19.5 (7.6-NR)	Ref
Subgroup with high baseline NER (N=75)					
Decreased NER ≥ 50% (N=32)	41%	7.2 (1.8-10.0)	0.46 (0.22-1.00)	25.9 (12-NR)	0.29 (0.11-0.76)
Decreased NER < 50% (N=23)	26%	2.2 (1.2-9.1)	0.59 (0.26-1.31)	28.2 (7.6-NR)	0.48 (0.17-1.41)
Increased NER (N=20)	20%	1.7 (0.4-2.5)	Ref	7.0 (2.6-14.1)	Ref

PFS and OS were estimated by landmark analysis calculating from week 6 after ipi/nivo initiation.
NR: not-reached.

4528 **Poster Session**

Healthcare resource utilization (HCRU) and costs for patients (pts) with metastatic renal cell carcinoma (mRCC) receiving first-line (LOT1) pembrolizumab plus axitinib (P+A) or ipilimumab plus nivolumab (I+N). *First Author: Neil J. Shah, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Approval of immuno-oncology (IO) agents have changed treatment paradigm for mRCC pts. While IO-based therapies have demonstrated improved survival, these can be associated with considerable HCRU and costs necessitating their examination in real-world practice. **Methods:** This retrospective claims analyses utilizing Optum Research Database included adult pts with mRCC diagnosis from July-2017 to Aug-2020 and received P+A or I+N as LOT1 from Jan-2018 to May-2020 (first claim=index date). All eligible pts required continuous enrollment for minimum of 6-months prior and 3-months post the index date unless death occurred. All-cause HCRU counts, and associated costs were examined during the first 90 days (LOT1-90) and entire LOT1 duration and reported as overall and per-pt-per-month (PPPM) estimates. **Results:** The study identified 507 pts (P+A=126, I+N=381). Average age of the entire cohort was 67 years, 71% were male, mean NCI Charlson score was 2.4, and lung (55%) and bone (33%) were the most common metastatic sites. Mean (SD) distance from mRCC diagnosis to index date was 97 (172) days. Pts with P+A and I+N had similar baseline characteristics. Total % of pts with ambulatory visits was similar for P+A and I+N for LOT1-90 and entire LOT1 (99.2 vs. 100.0%, p=0.082 for both). During LOT1-90, we observed a lower % of pts on P+A with ER visits and inpatient (IP) stay compared to I+N (34 vs. 48, p=0.008; 19 vs. 38, p<0.001, respectively). We also observed a shorter mean (SD) IP stay for P+A vs. I+N during LOT1-90 (1.9 (6.5) vs. 5.6 (13.24) days, p<0.001). Similarly, P+A had lower mean PPPM ambulatory visits, IP stay, and ICU stay during both LOT1-90 and entire LOT1 (Table). In addition, mean PPPM total (medical + pharmacy) and mean PPPM medical costs were lower for P+A compared to I+N, but mean PPPM pharmacy costs were higher for P+A for both LOT1-90 and entire LOT-1 (Table). **Conclusions:** This study noted significantly higher HCRU with I+N including higher mean PPPM ambulatory visits, IP stays, and ICU stays compared to P+A. Although, P+A had higher mean PPPM pharmacy costs, the total medical plus pharmacy costs were significantly lower compared to I+N. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

All cause HCRU counts and costs-PPPM mean (SD).

	LOT1-90 P+A	LOT1-90 I+N	p-value	Entire LOT1 P+A	Entire LOT1 I+N	p-value
HCRU Counts						
Ambulatory	6.68(3.37)	7.52(4.52)	0.029	6.28(2.80)	7(4.20)	0.031
ER visit	0.32(0.74)	0.4(0.65)	0.246	0.32(0.76)	0.38(0.58)	0.361
IP stay	0.09(0.22)	0.23(0.38)	<0.001	0.11(0.20)	0.23(0.36)	<0.001
ICU stay	0.05(0.16)	0.1(0.29)	0.015	0.06(0.15)	0.1(0.28)	0.02
HCRU Costs (USD)						
Total (Medical + pharmacy)	36,963 (15,240)	48,939 (37,040)	<0.001	31,868 (14,739)	37,115 (31,993)	0.013
Medical	21,123 (14,737)	48,436 (37,154)	<0.001	19,328 (13,573)	36,645 (32,048)	<0.001
Pharmacy	15,840 (6,150)	502 (2,697)	<0.001	12,540 (5,473)	469 (2,630)	<0.001

4529 **Poster Session**

Phase II randomized double blind trial of axitinib (Axi) +/- PF-04518600, an OX40 antibody (PFOX) after PD1/PDL1 antibody (IO) therapy (Tx) in metastatic renal cell carcinoma (mRCC).

First Author: Sarmad Sadeghi, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA

Background: Immune checkpoint blockade has revolutionized mRCC Tx, but primary and acquired resistance continues to result in poor patient outcomes. OX40 (CD-134) mediates IO resistance. Co-stimulatory OX40 (CD-134) activates exhausted T-cells. OX40 activation in dendritic cells increases the proliferation, effector function, and survival of T cells. PFOX is an agonist for OX40. We hypothesized that PFOX + the VEGFR inhibitor Axi would improve outcomes vs. Axi in patients (pts) with mRCC after IO Tx. **Methods:** Pts with predominantly clear cell mRCC were stratified for MSKCC risk groups then randomized 1:1 to Axi 5mg po bid plus PFOX 0.3mg/kg iv (Arm 1) or placebo (PL) iv (Arm 2) on Day 1 of a 2-week cycle. The primary endpoint was progression free survival (PFS); secondary endpoints included overall survival (OS), objective response rate (ORR), duration of response (DOR) per RECIST v1.1, and safety/tolerability. A prespecified interim analysis (IA) tested PFS at a 1-sided $P < 0.02$ when ≥ 33 events were observed. **Results:** Between February 2018 and October 2021 a total of 59 pts were randomly assigned and treated with Axi+PFOX (N = 29) or Axi+PL (N = 30). Pt and disease characteristics are summarized in the table. As of October 2021, 38 PFS events had occurred, 19 on each arm. The IA rejected the hypothesis of added efficacy for PFOX with a *p* of 0.0089. Subsequently the study was closed to new accrual. At a median follow up of 13.4 mo, median PFS was 13.1 (6-15.8) months (mo) for Arm 1 and 8.5 (5.5-11) mo for Arm 2 (HR = 0.85 [95% CI: 0.45-1.60] p = 0.61). After adjusting by MSKCC risk group and prior lines of Tx, HR = 0.74 [95% CI: 0.38-1.46] p = 0.39. Median OS was not reached (adjusted HR = 0.71 [95% CI: 0.24-2.12] p = 0.54). ORR Arm 1: 31% PR, 52% SD, 14% PD, and Arm 2: 37% PR, 50% SD, 13% PD. Median DOR 9.1 (3.3-23.9) mo for Arm 1, and 7.5 (1.8-32.7) mo. for Arm 2. Rates of any grade Tx related adverse events (TRAEs; 93% vs 100%), including grade 3 or 4 TRAEs (66% vs 47%), in Arm 1 and Arm 2, respectively. 4 pts discontinued Tx due to TRAE, 3 in Arm 1 (1 grade 3 hypertension, 1 grade 2 stroke, 1 grade 3 bullous dermatitis) and 1 in Arm 2 (grade 4 ALT elevation). The most common TRAEs were diarrhea 52%, hypertension 52%, fatigue 41%, nausea 41% for Arm 1 and hypertension 67%, diarrhea 53%, fatigue 50% for Arm 2. **Conclusions:** In IO-pretreated mRCC pts, Axi + PFOX did not improve outcomes compared to Axi alone. Clinical trial information: NCT03092856. Research Sponsor: Pfizer.

	Arm 1	Arm 2
N	29	30
Median Age (Range)	59 (41–85)	64 (35–84)
Female	10 (34%)	7 (23%)
Male	19 (66%)	23 (77%)
ECOG		
0	14 (48%)	10 (33%)
1	14 (48%)	19 (63%)
2	1 (3%)	1 (3%)
MSKCC		
Good	4 (14%)	6 (20%)
Intermediate	21 (72%)	23 (77%)
Poor	4 (14%)	1 (3%)
# of Prior Tx		
1 – 2	16 (55%)	18 (60%)
3+	13 (45%)	12 (40%)
Nephrectomy		
Radical	16 (67%)	17 (63%)
Partial	8 (33%)	10 (37%)
Site of Disease		
Lung	16 (55%)	24 (80%)
Bone	11 (38%)	8 (27%)
Liver	7 (24%)	9 (30%)
Adrenal	5 (17%)	7 (23%)
Pancreas	2 (7%)	7 (23%)
Lymph Nodes	16 (55%)	11 (37%)

4530 **Poster Session**

Impact of steroid use among patients with renal cell carcinoma (RCC) who develop immune-related adverse events (irAE).

First Author: Peter Zang, LAC+USC Medical Center, Los Angeles, CA

Background: Immune checkpoint inhibitor (ICI) therapy has become a standard therapy in the treatment of advanced renal cell carcinomas (RCC). This has led to a proportional increase in the frequency of immune related adverse events (irAE), however. While increasing evidence suggests that irAE may be correlated with benefit from ICI, the impact of steroids to mitigate irAE's remains unclear. **Methods:** We analyzed records of patients with RCC treated with an ICI at the USC Norris Comprehensive Cancer Center, Keck Hospital of USC, and LAC+USC Hospital from 2015-2021. Statistical analysis was performed using R. The Kaplan-Meier model was used to calculate progression free survival (PFS) and overall survival (OS). A log-rank test was used to determine if differences in PFS/OS were statistically significant. **Results:** Out of a total 841 cancer patients treated with ICI, 107 RCC patients were identified. The median age was 60 (range 20-91). The two most common represented ethnicities were 48 Hispanic/Latino (44.9%) and 37 Caucasian (34.6%). The patient population include 64 male patients (59.8%) versus 43 female patients (40.2%). Most had metastatic disease (74.8%) versus local disease (25.2%), and most patients (80.4%) received ICI therapy as initial therapy. Only 6 patients (5.6%) were given combination ICI therapy. The three most common systems affected by irAE were endocrine (18.7%), dermatologic (16.8%), and renal (14.0%). Of the irAE that occurred, 21.5% were categorized as CTCAE grade III or higher. The median PFS of the irAE group was 51.8 months (95% CI 10.0 – 51.8) versus 11.2 months (95% CI 2.7 – 13.8) in the no irAE group. The median OS of the irAE group was 55.0 months (95% CI 23.9 – 55.0) versus 15.6 months (95% CI 13.5 – 23.5). The occurrence of irAE was associated with both statistically significantly increased PFS (p = 0.02) and OS (p = 0.007). The median PFS of patients receiving steroids to treat irAE was 6.5 months (95% CI 3.9 – 9.2) compared to 12.5 months (95% CI 10.4 – 12.5) in the group with irAE who did not receive steroids. The use of steroids was associated with statistically significant worse PFS (p = 0.04) and worse OS but not at statistical significance (p = 0.2). **Conclusions:** The occurrence of irAE was associated with improved PFS and OS in RCC patients treated with ICI. Furthermore, the use of steroids among patients with irAE was associated with worsened PFS, but not OS. Although steroids should still be used as clinically indicated for the management of irAE, clinicians should be judicious as they may blunt tumor response to ICI treatment. Research Sponsor: None.

4531 **Poster Session**

Cross-trial validation of molecular subtypes in patients with metastatic clear cell renal cell carcinoma (RCC): The JAVELIN Renal 101 experience.

First Author: Renee Maria Saliby, Dana-Farber Cancer Institute, Boston, MA

Background: Vascular endothelial growth factor (VEGF) and immune checkpoint inhibitors (IO) combinations are a standard in mRCC. Molecular clusters of patients have been identified and correlated with outcomes in the phase 3 IMmotion151 (IM151) trial of atezolizumab + bevacizumab (IO+VEGF) vs. sunitinib (Sun) (Motzer, *Cancer Cell* 2020 & *JAMA Oncol* 2021). Avelumab+axitinib (AA) is an approved IO+VEGF combination in mRCC. This work aims to evaluate these clusters in patients from the phase 3 JAVELIN Renal 101 (JR101; NCT02684006) trial of AA vs. Sun. **Methods:** Bulk RNA-sequencing of primary and metastatic samples and clinical data (data cutoff: 28 January 2019) from JR101 were obtained. A random forest model designed to predict molecular clusters based on transcriptomic data was trained on the IM151 dataset. Using this model, patients from JR101 study were categorized into previously defined molecular subgroups. We then evaluated treatment outcomes including progression-free survival (PFS), objective response rate (ORR), and overall survival (OS) from JR101 in relation to molecular subgroups. **Results:** The proportion of patients in each molecular subtype and across MSKCC risk groups were largely comparable between the 2 trials (accuracy: 81.6%; p=0.2). AA was generally superior to Sun. for PFS and ORR across all molecular subsets, including angiogenic and immune-based clusters (Table). Combining immune and/or cell cycle-enriched clusters 4+5 resulted in improved PFS (HR: 0.65; 95% CI: 0.44-0.97) for AA vs. Sun. **Conclusions:** We were able to largely validate the molecular clusters classification and some of the associations with survival outcomes from IM151 in the JR101 clinical trial cohort. Biomarkers of specific VEGF+IO combinations in mRCC should be prospectively validated in randomized trials. Research Sponsor: None.

Treatment outcomes from the JR101 trial in relation to previously defined molecular clusters.

Molecular Clusters	N AA/Sun	PFS median AA/Sun	PFS HR (95% CI)	2-year OS AA/Sun	OS HR (95% CI)	ORR % AA/Sun
Overall	356/376	13.3/8	0.69 (0.57–0.83)	0.63/0.62	0.80 (0.62–1.03)	53/27
1-Angiogenic/Stromal	40/41	15.1/7	0.55 (0.31-0.97)	0.75/0.72	0.77 (0.29-2.07)	60/29
2-Angiogenic	113/106	19.4/15.4	0.91 (0.61-1.35)	0.81/0.75	0.75 (0.41-1.35)	60/34
3-Complement/Oxidation	86/89	12.5/7.1	0.65 (0.43-0.97)	0.83/0.69	0.56 (0.28-1.11)	58/32
4-T-eff/Prolif	47/69	20.6/6.9	0.54 (0.32-0.91)	0.63/0.62	0.96 (0.47-1.94)	53/24
5-Proliferative	32/26	5.7/8.4	0.83 (0.44-1.57)	0.43/0.55	0.97 (0.43-2.19)	40/15
6-Stromal/Prolif	38/45	4.2/2.9	0.75 (0.44-1.26)	0.37/0.46	0.95 (0.49-1.86)	44/17
Clusters 1+2	153/147	16.6/11.2	0.78 (0.57-1.08)	0.79/0.74	0.74 (0.45-1.23)	60/33
4+5	79/95	12.5/8.2	0.65 (0.44-0.97)	0.55/0.60	1.11 (0.66-1.87)	48/22

Cluster 7 separately was excluded as it contains 1 patient per treatment arm.

4532 **Poster Session**

First-line therapy for elderly patients with advanced renal cell carcinoma (aRCC): A systemic review and network meta-analysis.

First Author: Yu Fujiwara, Department of Medicine, Icahn School of Medicine at Mount Sinai, Mount Sinai Beth Israel, New York, NY

Background: Multiple regimens incorporating tyrosine kinase inhibitors (TKI) or immune checkpoint inhibitors (ICI), either alone or in combination, confer a significant OS benefit in 1L metastatic clear cell RCC. However, guidance for optimal treatment selection in elderly patients remains limited. A network meta-analysis (NMA) was performed to compare the efficacy of 1L treatments for elderly patients with aRCC. **Methods:** Database search was performed through Pubmed, Embase, Web of Science, and Scopus. Eligible studies were randomized controlled trials (RCTs) evaluating first-line regimens for patients with aRCC older than 65 years old. The primary outcomes were progression-free survival (PFS) and overall survival (OS). Indirect comparisons of available regimens were estimated using a random-effects NMA. **Results:** 14 RCTs with more than 2,100 patients and 5 RCTs with 1,529 patients were eligible for PFS and OS analyses, respectively. Compared with sunitinib (Sun), the pembrolizumab (Pem) + axitinib (Axi) (HR 0.68, 95% CI 0.48-0.97) and Pem + lenvatinib (Len) (HR 0.61, 95% CI 0.4-0.94) regimens were associated with significantly improved OS. In comparing the TKI-ICI combinations with dual ICI nivolumab (Niv) + ipilimumab (Ipi), no significant OS differences were observed (Pem + Len: HR 0.71, 95% CI 0.40-1.27; Pem + Axi: HR 0.79, 95% CI 0.47-1.34; Avelumab (Ave) + Axi: HR 1.03, 95% CI 0.58-1.85; Niv + cabozantinib [Cab]: HR 1.03, 95% CI 0.57-1.93, using Niv + Ipi as a reference). Pem + Len, Niv + Cab, Pem + Axi, and Cab alone each showed improved PFS over Sun (Table). Among these, Pem + Len showed a PFS advantage compared to Pem + Axi (HR 0.58, 95% CI 0.37-0.91), but no PFS difference compared with the other regimens (vs Niv + Cab: HR 0.63, 95% CI 0.39-1.03; vs Cab alone: HR 0.84, 95% CI 0.40-1.77). **Conclusions:** Pem + Len and Pem + Axi provided the largest OS benefit in elderly patients for 1L aRCC. Pem + Len showed improved PFS compared with Pem + Axi, but no difference compared with Niv + Cab or Cab alone. Further validation using real-world data is needed to confirm the efficacy and safety of first-line regimens for the geriatric population with aRCC. Research Sponsor: None.

The HR of OS and PFS using Sun as a reference with treatment rankings.

Treatment	HR (95% CI) of OS vs Sun	Median rank for OS	HR (95% CI) of PFS vs Sun	Median rank for PFS
Pem + Len	0.61 (0.40-0.94)	1	0.43 (0.31-0.60)	1
Pem + Axi	0.68 (0.48-0.97)	2	0.74 (0.55-0.99)	6
Niv + Ipi	0.86 (0.58-1.27)	3	-	-
Ave + Axi	0.89 (0.58-1.37)	4	0.85 (0.63-1.15)	8
Niv + Cab	0.90 (0.56-1.44)	5	0.68 (0.48-0.97)	5
Sun	-	6	-	9
Cab	-	-	0.51 (0.26-0.99)	2
Tivozanib	-	-	0.53 (0.23-1.23)	3
Axi	-	-	0.52 (0.19-1.43)	4
Sorafenib	-	-	0.77 (0.38-1.55)	7
Pazopanib	-	-	1.18 (0.92-1.52)	10
Bevacizumab (Bev) + Interferon α (IFNα)	-	-	1.79 (1.03-3.11)	11
Placebo	-	-	2.27 (1.34-3.86)	12
Temsirolimus + Bev	-	-	2.33 (1.21-4.46)	13
IFNα	-	-	2.33 (1.45-3.72)	14

4533 **Poster Session**

Estimating clear cell renal cell carcinoma transcriptomic signatures using machine learning and histopathology images. *First Author: Saeed Hassanpour, Geisel School of Medicine at Dartmouth, Hanover, NH*

Background: Gene expression signatures derived from RNA sequencing data have been associated with treatment outcomes for renal cell carcinoma (RCC) patients. Incorporating these RNA biomarkers into clinical practice is promising, yet its real-world applicability is heavily limited as RNA profiling is expensive, time-consuming, and requires specialized expertise for data analysis. In this study, we applied a deep neural network framework to identify the correlation between standard pathology images and underlying RNA signatures using hematoxylin and eosin (H&E) stained formalin-fixed paraffin-embedded (FFPE) whole slides of clear cell kidney tumors from The Cancer Genome Atlas (TCGA). **Methods:** We collected 496 H&E stained FFPE clear cell RCC whole-slide images and the RNA gene signatures for 496 patients from the TCGA database. We partitioned 496 slides into training (N = 245, 50%), development (N = 49, 10%), and test (N = 202, 40%) sets. We used this dataset to train and evaluate our weakly-supervised deep learning model. The model was iteratively trained using extracted patches from a slide and processed the patches through a convolutional neural network (CNN), pretrained for the RCC subtypes classification task, to represent features. The features were aggregated and summarized to predict angiogenesis, myeloid infiltration, and adenosine gene signature (AdenoSig) scores. Performance was assessed by computing Pearson's correlation coefficients. 95% confident intervals (CI) are computed using the Fisher Z transformation. **Results:** The median angiogenesis score was 6.98 (range: 1.77-8.40), the median myeloid score was 0.54 (range: -4.59-5.96), and the median AdenoSig score was 268.31 (range: -4988.71-7621.57). A total of 202 slides were included in the test set. On this test set, the results of our weakly supervised method achieved a Pearson's correlation of 0.65 (95% CI: 0.57-0.73), 0.10 (95% CI: -0.04-0.23), and 0.10 (95% CI: -0.04-0.23) with angiogenesis, myeloid, and AdenoSig scores from gold-standard RNA sequencing data, respectively. **Conclusions:** We proposed using deep learning-based AI techniques to process digitized histopathological images and estimate actionable signatures of angiogenesis, myeloid, and AdenoSig from H&E stained slides. Our model showed promising results for predicting angiogenesis scores compared to myeloid and AdenoSig scores. These results suggest the feasibility of this approach for estimating digital biomarkers from H&E histopathology images and offering a rapid and cost-effective alternative to conventional RNA sequencing. Research Sponsor: None.

4534 **Poster Session**

The prognostic value of peripheral blood inflammatory indices early variation in patients (pts) with metastatic renal cell carcinoma (mRCC) treated with nivolumab (Δ-Meet-URO analysis). *First Author: Sara Elena Rebuzzi, Department of Internal Medicine and Medical Specialties (Di.M.I.), University of Genova, Genova; Medical Oncology Unit, Ospedale San Paolo, Savona, Italy*

Background: Immunotherapy has improved the treatment landscape of mRCC pts and identifying biomarkers for patients' selection is clinically needed. Inflammatory indices from peripheral blood showed a prognostic value in different tumors and therapies, including immunotherapy. These biomarkers are inexpensive and readily available in clinical practice. We aimed to assess the prognostic role of the dynamic evaluation of these indices in immunotherapy-naïve pretreated mRCC pts. **Methods:** The Meet-URO 15 multicentric retrospective study enrolled 571 pretreated mRCC pts receiving nivolumab. The Δ-Meet-URO was a secondary analysis on the early variation through the first four cycles of therapy compared with baseline (difference, delta - Δ) of white blood cells, platelets and inflammatory indices, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and systemic immune-inflammation index (SII, platelets x NLR), their comparison with baseline values and correlation with treatment response, overall (OS) and progression-free survival (PFS). The baseline and Δ cut-offs were identified by ROC curves for OS. **Results:** The analysis was performed on 422 mRCC pts (74% of the entire cohort). Patients with ΔNeutrophils < 730 at 2nd, 3rd and 4th cycles were more responders ($p < 0.001$, $p = 0.003$ and $p < 0.001$) with longer mPFS (11 *vs* 6.1 months, $p = 0.033$) and mOS (46.9 *vs* 20.8 months, $p = 0.046$) compared to ΔNeutrophils ≥ 730. There was a significant interaction between baseline and ΔNeutrophils on PFS ($p = 0.047$). Pts with baseline neutrophils ≥ 4330/mm^3 had longer mPFS when ΔNeutrophils < 730 ($p = 0.002$), whilst no difference was observed in those pts with baseline neutrophils < 4330/mm^3 according to ΔNeutrophils ($p = 0.46$). Similar non-significant trends were observed in mOS. Patients with ΔNLR < 0.5 at 3rd and 4th cycles were more responders ($p = 0.004$ and $p = 0.001$, respectively) with doubled mPFS (12.1 vs 6.4 months, $p = 0.007$) and mOS (46.9 vs 21.7 months, $p = 0.062$) compared to ΔNLR ≥ 0.5. No significant interaction between baseline NLR and ΔNLR was observed in PFS and OS, suggesting a similar association between ΔNLR and PFS or OS, regardless of the baseline NLR cut-off of 3.2. The multivariable analyses confirmed all these results. **Conclusions:** The early assessment of NLR and neutrophils variations during immunotherapy for mRCC pts is a promising, affordable and non-invasive prognostic tool. Prospective and external validation analyses are warranted. Research Sponsor: Italian Ministry of Health (Ricerca Corrente 2018–2021 grants).

4535 **Poster Session**

The prognostic role of nephrectomy in patients (pts) with metastatic renal cell carcinoma (mRCC) treated with immunotherapy according to the novel prognostic Meet-URO score: Subanalysis of the Meet-URO 15 study. *First Author: Sara Elena Rebuzzi, Department of Internal Medicine and Medical Specialties (Di.M.I.), University of Genova, Genova; Medical Oncology Unit, Ospedale San Paolo, Savona, Italy*

Background: Most of mRCC pts with favorable and intermediate prognosis, according to the IMDC classification, are offered a nephrectomy. However, in the immunotherapy era, the role of nephrectomy is still unclear. In the Meet-URO 15 study we reported the higher prognostic accuracy of the Meet-URO score compared to the IMDC score, by the addition of the neutrophil-to-lymphocyte ratio (NLR) and the presence of bone metastases to the IMDC score, identifying five categories with progressively worse prognosis. For this reason, we aimed to explore the prognostic impact of the previous nephrectomy (PN) on mRCC pts receiving immunotherapy and according to the Meet-URO score groups. **Methods:** The Meet-URO 15 study was a multicentric retrospective analysis on 571 pretreated mRCC pts receiving nivolumab. Univariable analysis of the correlation between PN and overall survival (OS) and multivariate analysis adjusted for IMDC score, therapy line, NLR and metastatic sites were performed. The interaction of PN with the Meet-URO prognostic groups was then evaluated. **Results:** 503/571 pts (88%) underwent PN. A reduced risk of death (HR = 0.44; 95% CI: 0.32-0.60; $p < 0.001$) and higher mOS and OS rate were observed in pts with PN than without (mOS: 36 vs 13 monhts; 1-year-OS 72% vs 52% and 2-year-OS 57% vs 24%, respectively). The reduced risk of death for pts who underwent PN was confirmed at the multivariate analysis (HR = 0.69; 95% CI: 0.49-0.97; $p = 0.032$). The percentage of pts receiving PN progressively reduced through the five Meet-URO prognostic groups (PN: group 1: 98%, group 2: 95%, group 3: 84%, group 4: 79%, group 5: 59%). No significant interaction was observed between the PN and Meet-URO score when all the five groups were considered ($p = 0.17$). A significant interaction was observed when the Meet-URO groups 1,2 and 3 were taken together (HR = 0.40; 95% CI: 0.25-0.63; $p < 0.001$), highlighting the significant protective role of the PN on OS for these three groups. For the Meet-URO groups 4 and 5, the interaction was indeed not significant (HR = 0.81; 95% CI: 0.51-1.30; $p = 0.39$). **Conclusions:** PN has a favourable prognostic impact on pretreated mRCC pts receiving immunotherapy. This benefit may be limited to mRCC pts with more favorable diseases as belonging to Meet-URO prognostic groups 1, 2 and 3. Further analysis of the type of PN (i.e., radical vs cytoreductive) is ongoing and confirmatory prospective evaluations are warranted. Research Sponsor: Italian Ministry of Health (Ricerca Corrente 2018 - 2021 grants).

4536 **Poster Session**

Progression-free survival after second line of therapy (PFS-2) for metastatic clear cell renal cell carcinoma (ccRCC) in patients treated with first-line immunotherapy combinations. *First Author: Kelly N. Fitzgerald, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Front-line therapy with immunotherapy combinations is standard of care for metastatic ccRCC, with ipilimumab/nivolumab (IO/IO) and several combinations of a VEGFR-targeted tyrosine kinase inhibitor with a PD-1 inhibitor (TKI/IO) showing superior efficacy to TKI monotherapy. PFS-2 evaluates the ability to be salvaged by 2nd line therapy and is a surrogate for overall survival (OS). PFS-2 was compared in patients receiving 1st line IO/IO vs TKI/IO for metastatic ccRCC. **Methods:** A retrospective analysis was performed on patients with ccRCC treated at Memorial Sloan Kettering Cancer Center between 1/1/2014 and 12/30/2020, in cohorts defined by 1st line: IO/IO or TKI/IO. PFS-2 is defined as time from start of 1st line to progression on next therapy, or death. Patients without a PFS-2 event were censored at a prespecified cutoff date. Objective response rate to 1st (ORR_{1st}) and 2nd (ORR_{2nd}) line are compared with the Fisher's exact test. OS, PFS-2, and time on therapy are estimated with the Kaplan-Meier method and compared with the log-rank test. **Results:** One hundred seventy-three patients received 1st line IO/IO (N = 90) or 1st line TKI/IO (N = 83); respectively, 52 and 40 patients had a PFS-2 event. 1st line TKI/IO regimens included: 34% axitinib/pembrolizumab, 29% lenvatinib/pembrolizumab, 25% axitinib/avelumab, 11% other. More IO/IO patients had brain metastases and intermediate/poor MSKCC risk category (respectively $p = 0.007$, $p < 0.001$). ORR_{1st} and median months on 1st line were higher with TKI/IO vs IO/IO (65% vs 39%, $p < 0.001$; 16.1 vs 5.1, $p < 0.001$). ORR_{2nd} was higher with IO/IO vs TKI/IO (47% vs 13%, $p < 0.001$), and median months on 2nd line was not significantly different (7.7 vs 7.1, $p = 0.30$). Median PFS-2 for TKI/IO was 44 months (95% CI: 27, 53) vs 23 months (95% CI: 16, 47) for IO/IO, $p = 0.13$. For TKI/IO and IO/IO groups, respective PFS-2 at 12 months was 86% (95% CI 77, 92) and 74% (95% CI 63, 82); PFS-2 at 36 months was 51% (95% CI 39, 63) and 42% (95% CI 30, 53). OS was not significantly different (p = 0.32; 3 year OS: IO/IO 60%, 95% CI 47, 71; TKI/IO 62%, 95% CI 49, 73). (Table) **Conclusions:** In patients receiving 1st line IO/IO or TKI/IO, ORR_{2nd} was higher with IO/IO and median PFS-2 was numerically higher with TKI/IO, but no statistically significant difference in PFS-2 or OS was seen. These findings suggest that IO/IO and TKI/O are both acceptable 1st line treatment strategies in ccRCC. Research Sponsor: Memorial Sloan Kettering Cancer Center Support Grant/Core Grant P30 CA008748, National Institute of Health Clinical and Translational Science Awards Program, grant number UL1TR00457.

	1st line IO/IO (n = 90)	1st line TKI/IO (n = 83)	P
MSKCC Risk Category Int-Poor	80 (89%)	55 (66%)	< 0.001
Metastases (% brain/liver/bone)	9/16/31	0/21/27	< 0.001/0.43/0.61
ORR_{1st} (95% CI)	39% (29, 50)	65% (54, 75)	< 0.001
ORR_{2nd} (95% CI)	47% (34, 61)	13% (5, 25)	< 0.001
Median PFS-2, months (95% CI)	23 (16, 47)	44 (27, 53)	0.13
12 month PFS-2 % (95% CI)	74% (63, 82)	86% (77, 92)	
36 month PFS-2 % (95% CI)	42% (30, 53)	51% (39, 63)	
Median OS, months (95% CI)	50 (35, NR)	56 (35, NR)	0.32

4537 **Poster Session**

Sequential immunotherapy in rare variant renal cell carcinomafinal report of UNISoN (ANZUP 1602): Nivolumab then ipilimumab + nivolumab in advanced nonclear cell renal cell carcinoma. *First Author: Ciara Conduit, Australian & New Zealand Urogenital and Prostate (ANZUP) Cancer Trials Group, Camperdown, Australia*

Background: Immune checkpoint immunotherapy (ICI) is active against many cancers. Many people are failed by PD1 inhibition alone, but not all patients benefit, nor require combination ICI treatment. UNISoN (NCT03177239) previously reported outcomes in people with nonclear cell renal cell carcinoma (nccRCC) receiving nivolumab (N) monotherapy, and N plus ipilimumab (I) in those whose cancers progressed after N alone. We present the final planned report. **Methods:** Population, Intervention, Analysis: Participants (pts) with advanced nccRCC with good performance status (ECOG 0/1) received N 240mg q2w alone (Part 1). Those with cancers refractory to N at 3 months were offered combination I (1mg/kg) + N (3mg/kg) q3w for up to 4 doses, followed by N 240mg q2w for a maximum total of 12 months of N (Part 2). UNISoN was powered to identify a clinically-relevant objective tumor response rate (OTRR) of 30% (assuming 15% was not relevant) among people receiving I+N in Part 2. **Results:** 85 pts with a representative spectrum of nccRCC histologies were enrolled and received N. Amongst the total population enrolled to UNISoN Part 1/2, mOS was 24 (16-28) months and 12m OS was 65% (54%-74%); of those proceeding to Part 2, the mOS was 10 (6-17) months only. Overall, 17% (10%-27%; 14/83) and 10% (3%-23%; 4/41) of pts experienced a response from N alone or I+N, respectively. 41 pts refractory to N received I+N. Overall in Part 2, the median time on treatment was 2.1 (95% CI 1.8, 2.8) months, the median number of cycles was 3; median follow-up at final analysis was 22 (16-30) months. In this population, the median PFS was 2.6 (2.2-3.8) months and 12m PFS was 11% (4%-23%). 13% (7%-22%) of patients were free of progression or death at 24 months. The primary endpoint was not met; only 80% of pts failed by N were assessable for response in Part 2. Overall tumor responses from N alone or I+N were more common in pts with papillary histology; pts with chromophobe histology had poor outcomes. No late toxicity safety signals were observed. **Conclusions:** Some pts with nccRCC benefit from N alone, or addition of I when disease is inadequately controlled by N alone, however most pts have limited benefit from ICI. More effective therapeutic options are needed for the majority of people with rare variant renal cell carcinomas. Novel markers of response are required to more rapidly predict pts who will progress on N. Translational research to identify predictive biomarkers of response is ongoing. Clinical trial information: NCT03177239. Research Sponsor: Bristol Myers Squibb, Other Government Agency, Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP).

4538 **Poster Session**

Prognostic value of the lung immune prognostic index in patients with untreated advanced renal cell carcinoma (aRCC) receiving nivolumab plus ipilimumab (N+I) or sunitinib (SUN) in the CheckMate 214 trial. *First Author: Lucia Carril-Ajuria, Gustave Roussy, Villejuif, France*

Background: The Lung Immune Prognostic Index (LIPI), defined by lactate dehydrogenase (LDH) and derived neutrophil to lymphocyte ratio (dNLR), has been shown to correlate with outcomes of immune checkpoint inhibitor therapy in patients (pts) with lung and other cancers, including pts with previously treated aRCC receiving nivolumab in the phase 2 NIVOREN GETUG-AFU 26 trial. We report an analysis of LIPI in pts with previously untreated aRCC receiving N+I or SUN in the randomized phase 3 CheckMate 214 trial with 5 years minimum follow-up. **Methods:** Data were used from CheckMate 214 comparing N+I (N 3 mg/kg + I 1 mg/kg) vs SUN (50 mg) for untreated aRCC (N = 1096). Pts with available LIPI data were categorized into 3 LIPI groups (good [LG], dNLR ≤ 3 and LDH ≤ upper limit of normal [ULN]); intermediate [LI], dNLR > 3 or LDH > ULN; and poor [LP], dNLR > 3 and LDH > ULN). This analysis focused on the prognostic value of LIPI using overall survival (OS) outcomes. Univariable analyses (UVAs) were conducted to evaluate LIPI groups alongside known risk factors including age, sex, IMDC risk, baseline PD-L1 status, prior nephrectomy, and baseline tumor burden. Variables that were statistically significant in UVAs ($P < 0.1$) were included in the full multivariable analyses (MVAs), from which a reduced model was generated. **Results:** A total of 1085 pts were evaluable for LIPI (N+I, n = 542; SUN, n = 543). Pts were distributed evenly between treatment arms for all 3 LIPI groups, but distribution between LIPI groups was unbalanced, with most pts grouped as LG (Table). OS outcomes were improved with N+I over SUN across all LIPI groups. Moreover, pts in the LG group had better OS outcomes vs pts in the LI or LP groups regardless of treatment, but with more distinct differences between LIPI groups in the SUN arm (Table). Final MVA results showed the LIPI correlated with OS for LI vs LG in the N+I arm and for LI vs LG and LP vs LG in the SUN arm (Table). **Conclusions:** These results from CheckMate 214 indicate the potential prognostic value of the LIPI in pts with untreated aRCC receiving N+I or SUN. Additional analyses are ongoing to further investigate the prognostic value of LIPI in this pt population and its impact on other clinical outcomes. Clinical trial information: NCT02231749. Research Sponsor: Bristol Myers Squibb.

	N+I (n = 542)			SUN (n = 543)		
LIPI group	**LG**	**LI**	**LP**	**LG**	**LI**	**LP**
n (%)	404 (74.5)	115 (21.2)	23 (4.2)	412 (75.9)	111 (20.4)	20 (3.7)
Median OS (95% CI), months	64.5 (52.7-70.3)	25.8 (16.8-48.1)	23.0 (5.3-32.3)	49.5 (41.9-57.3)	17.0 (12.3-22.7)	4.3 (2.0-6.7)
5-year OS, %	52.0	35.7	25.1	43.6	17.2	0.0
MVA[a] HR LI vs LG (*P* value)	–	1.48 (0.0057)	–	–	2.05 (< 0.0001)	–
MVA[a] HR LP vs LG (*P* value)	–	–	1.49 (0.1436)	–	–	9.26 (< 0.0001)

[a]N+I reduced model included age, LIPI group, IMDC category, and baseline tumor burden; SUN reduced model included IMDC category, LIPI group and baseline tumor burden.
HR, hazard ratio for probability of death.

4539 **Poster Session**

Real-world treatment patterns in von Hippel-Lindau (VHL) disease-associated renal cell carcinoma (RCC): Costs of tumor reduction procedures and their complications. *First Author: Murali Sundaram, Merck & Co., Inc., Kenilworth, NJ*

Background: VHL disease is an inherited condition associated with tumors in multiple organs; RCC may affect up to 70% of patients with VHL. Patients often need many tumor reduction procedures (TRP) to manage renal neoplasms. This study evaluated TRP treatment patterns, costs, and complications among patients with VHL-RCC. **Methods:** Using an algorithm based on VHL manifestations, patients with VHL were identified from the Optum Clinformatics claims database. Patients were then selected with a prior RCC diagnosis. Minimum continuous enrollment of 12 months before and 3 months after first observed RCC diagnosis was required. TRPs for RCC included nephrectomy, renal ablation, and cryotherapy. Time to first TRP from initial observed RCC diagnosis was estimated using Kaplan-Meier analysis. Mean hospitalization costs per TRP type were estimated. Costs associated with TRP complications were estimated via linear regression; the explanatory variable was the presence of a given complication. Short-term complications were evaluated for 4 weeks post-TRP; long-term ones were evaluated over 6 months. Renal function was evaluated using chronic kidney disease (CKD) stages before and after TRPs, using diagnosis codes and eGFR lab values. **Results:** 160 patients with VHL-RCC were identified; mean follow-up time was 34.1 months. 115 (71.8%) patients incurred ≥1 RCC TRP over their study period. 68.4% had a TRP in the first year after RCC diagnosis and 76.5% had TRPs by year 5. Of the 125 observed TRPs, 97 (77.6%) were nephrectomies and 28 (22.4%) were ablation/cryotherapy. The mean costs for nephrectomy were nominally higher vs. ablation/cryotherapy ($29,313 vs. $18,290). The most common short-term complications were respiratory related (20.8%) and vascular injury/anemia (13.6%). The most common long-term complications were CKD stage 1-5 (24.0%) and end-stage renal disease (chronic dialysis dependence) (4.0%). The most expensive complications were related to impaired renal function: acute renal failure ($21,013 over 4 weeks), CKD ($26,032 over 6 months) and end stage renal disease ($65,338 over 6 months). At baseline, the proportion of patients with a diagnosis of CKD ≥ stage 3 was similar between patients who had TRPs (n = 115) and those who did not have TRPs (n = 45): 24.3% and 24.4%, respectively. After the first TRP, the proportion of patients with CKD ≥ stage 3 increased from 24.3% to 41.7%. **Conclusions:** Patients with VHL-RCC incur a significant clinical and economic burden related to TRPs for managing their renal tumors. This is in addition to the burden that VHL-RCC patients incur from the management of other VHL tumors. This study underscores the need for novel effective therapies to prevent or delay the recurrence of VHL-related renal neoplasms to mitigate the burden of morbidity and long-term medical management related to VHL. Research Sponsor: Merck & Co., Inc.

4540 **Poster Session**

Prostate-specific membrane antigen (PSMA) positron emission tomography (PET) compared to computed tomography (CT) for advanced renal cell carcinoma (RCC). *First Author: Shivanshan Pathmanathan, Department of Oncology, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia*

Background: There is emerging role of the use of PSMA PET in RCC. Herein, we report our experience in use of PSMA PET in recurrent or metastatic RCC in Brisbane, Australia. **Methods:** Patients (pts) who underwent PSMA PET and conventional diagnostic CT for metastatic or recurrent RCC between 2015 and 2020 at three institutions were identified. Retrospective chart reviews were conducted using standardized collection template. The outcomes included percentage of patients who had a change in management secondary to PSMA PET findings, comparison of metastasis detection for PSMA PET vs. CT, and biopsy histology of PSMA avid sites. **Results:** 42 PSMA PET were performed in 40 patients. 10 pts (25%) and 30 pts (75%) had PSMA PET in the metastatic disease and recurrent disease setting, respectively. Table 1 highlights demographics. Overall, 12 pts (30%, n=3 metastatic, n=9 recurrent) had a change in management following PSMA PET. In the metastatic disease group, 2 pts (20%) underwent initial systemic therapy (after histological confirmation) due to higher burden of disease shown with PSMA PET than CT, while systemic therapy was changed for 1 pt (10%). In the recurrent disease group, PSMA improved delineation of suspected recurrence (compared to CT) resulting in resection rather than surveillance (n=4; 13%) or change in surgical approach for resection (n=1; 3%). PSMA PET distribution showed more metastatic sites than CT leading to systemic therapy rather than resection of recurrence (n=2; 7%), while absent PSMA activity for suspected recurrence on CT led to surveillance rather than resection (n=2; 7%). PSMA PET detected more sites of metastases compared with conventional scan in 6 pts (60%) with metastatic disease and in 9 pts (30%) with recurrent disease. 26 pts had biopsy of PSMA avid sites. Majority of pts had confirmed recurrence of clear cell renal carcinoma (n= 22; 85%). Other histology included sarcomatoid renal cell carcinoma (n=2; 8%), carcinoid (n=1; 4%), and urothelial cancer (n=1; 4%). In 2 instances, biopsy/resection was performed of a suspected recurrence on CT that was not PSMA avid, and neither showed malignancy. **Conclusions:** PSMA PET detected more accurately metastatic and recurrent disease, with high pathological concordance, to result in change in management for 30% of patients. Prospective study is warranted to further investigate the utility of PSMA PET scan in advanced RCC. Research Sponsor: None.

Baseline characteristics.

	Metastatic N=10	Recurrence N=30
Median Age (yrs)	63	64
Prior nephrectomy	5 (50%)	30 (100%)
Clear cell histology	9 (90%)	29 (97%)
Sarcomatoid histology	1 (10%)	1 (3%)
IMDC favourable risk	2 (20%)	18 (60%)
IMDC intermediate risk	6 (60%)	4 (13%)
IMDC poor risk	2 (20%)	0 (0%)
1L Tyrosine kinase inhibitor	8 (80%)	8 (27%)
1L Immunotherapy	1 (10%)	9 (30%)

4541 **Poster Session**

Association between tumor burden and response to immunotherapy in patients with metastatic renal cell carcinoma. *First Author: Hesham Abdallah Yasin, Vanderbilt Ingram Cancer Center, Nashville, TN*

Background: Immunotherapy (IO) has become the standard of care in patients with metastatic renal cell carcinoma (mRCC), yet clinical biomarkers of outcome remain elusive. Preclinical and clinical studies have demonstrated that a lower tumor volume burden is associated with better response to IO in melanoma and lung cancer. **Methods:** Retrospective chart review of mRCC patients treated with Immunotherapy/Immunotherapy or Immunotherapy/Tyrosine kinase inhibitors (TKI) combinations at Vanderbilt Ingram Cancer Center was conducted. Baseline target tumor lesions including primary kidney tumors and treatment response were assessed by RECIST 1.1 criteria. The association between baseline tumor burden and outcomes of interest [progression-free survival (PFS) and overall survival (OS)] were assessed with multivariable Cox regression model. **Results:** 79 patients with mRCC were included in the cohort. The median age was 64, 80% were male, 82% had clear cell histology, and 73% were IMDC intermediate/poor risk group. 53% received IO/IO and 39% received IO/TKI. 71% had prior nephrectomy and 14% had prior systemic therapy. The median baseline tumor burden was 87 mm (range: 16-363 mm). After adjusting for age, gender, histology, prior nephrectomy/systemic therapy and IMDC risk, baseline tumor burden was not associated with either PFS (p-value: 0.42) or OS (p-value: 0.99). At the initial follow-up scan (median time of 3.1 months from treatment initiation) 22 (28%) patients had an objective response and 41 (52%) patients had stable disease. Among patients with tumor shrinkage, every 10% decrease seen in the sum of the target lesions was associated with improved PFS (AHR: 0.77, 95%CI: 0.63-0.94, p-value:0.009) and OS (AHR: 0.62, 95%CI: 0.42-0.93, p-value:0.02). **Conclusions:** While baseline tumor burden volume was not associated with clinical outcome to immunotherapy-based therapy in patients with metastatic RCC; however, the degree of early tumor shrinkage was significantly associated with better outcomes. Large tumor burden does not preclude response and good outcome to immunotherapies. Research Sponsor: None.

4542 **Poster Session**

Activity of tivozanib in non-clear cell renal cell carcinoma (nccRCC): Subgroup analysis from a phase 2 randomized discontinuation trial. *First Author: Pedro C. Barata, Tulane University Medical School, New Orleans, LA*

Background: Non-clear cell renal cell carcinoma (nccRCC) is a blanket term for a collection of heterogenous and biologically diverse RCC histologies including (but not limited to) papillary, chromophobe and unclassified subtypes. Tivozanib is a selective VEGFR tyrosine kinase inhibitor with demonstrated activity in RCC with clear cell component. Here we report efficacy of tivozanib in a histologically diverse nccRCC subset included in a phase 2 study. **Methods:** We conducted a subgroup analysis of patients with nccRCC enrolled in the study 201 (NCT00502307), a phase 2 randomized discontinuation trial of tivozanib in patients with RCC who had no prior VEGF targeted treatment. Clinical outcomes including overall response rate (ORR), disease control rate (DCR, defined by CR+PR+SD), and progression free survival (PFS) were examined. Safety outcomes for all patients are reported in the original publication (Nosov, JCO 2012). **Results:** Of the 272 patients enrolled, 46 (16.9%) patients had nccRCC. [11 (4%) papillary, 2 (0.7%) chromophobe, 2 (0.7%) collecting duct, and 31 (11.4%) unclassified/mixed]. Of the 46 nccRCC patients, the ORR was 17.4% by investigator (INV) review and 15.2% by independent radiology review (IRR). The DCR was 80.4% by INV and IRR. The median PFS was 6.7 months (204 days) (95%CI: 125-366 days) by IRR (Figure 1). Of note, 14 patients with SD after 16 weeks on tivozanib were randomized to 12 weeks of placebo and may have progressed during that timeframe before unblinding and resuming tivozanib. Safety was not analyzed by histology but there were no new safety signals and was consistent with tivozanib labelling in the ITT population. **Conclusions:** Tivozanib demonstrated activity and a favorable safety profile in patients with nccRCC. This data adds to the body of evidence supporting VEGFR TKI use in advanced RCC including in non-clear cell histologies. Clinical trial information: NCT00502307. Research Sponsor: AVEO Oncology.

Best Response	IRR Assessment, n (%)
Complete Response (CR)	0
Partial Response (PR)	7 (15.2)
Stable Disease (SD)	30 (65.2)
Progressive Disease (PD)	3 (6.5)
Not evaluable/missing	6 (13)
Disease Control Rate (CR+PR+SD)	37 (80.4)
Patients who experienced PFS events	24 (52.2)
Patients who were censored	22 (47.8)
KM PFS estimates, days (95% CI)	
25% PFS	111 (60, 164)
50% PFS	204 (120, 366)
75% PFS	892 (249, NE)

4543 **Poster Session**

Variation in recurrence rate and overall survival (OS) outcomes by disease stage and incremental impact of time to recurrence on OS in localized renal cell carcinoma (RCC). *First Author: Naomi B. Haas, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA*

Background: Prior research shows that post-nephrectomy recurrence is correlated with significantly increased mortality in patients (pts) with intermediate-high (int-high) risk and high risk RCC. However, no study has quantified the incremental OS associated with increased time to recurrence (ToR). Additionally, limited evidence is presented on the variation of recurrence rate and OS by stage of RCC. **Methods:** The SEER-Medicare database (2007–2016) was used in this retrospective observational study. Post-nephrectomy pts with newly diagnosed, int-high risk (pT2 N0 high grade, pT3 N0 any grade) or high-risk (pT4 N0 any grade, pT any N1 any grade) RCC were identified and stratified based on tumor stage and grade. Grade was defined based on Furhman grading system and was reported in SEER Registry. Post-nephrectomy recurrence free rates and OS by disease stage were described using Kaplan-Meier analyses. OS from nephrectomy in pts with recurrence vs pts without recurrence was compared by disease stage. Multivariable regression analysis was used to quantify the incremental OS associated with increased ToR post-nephrectomy in all pts with recurrence. **Results:** 643 pts met the inclusion criteria (269 with vs 374 without recurrence; median follow-up: 23 months). The mean age was 75.5 years (yrs), 61% male, and 86% white. Results presented in the table showed wide variance in 5-yr recurrence-free rate in int-high risk group (28%-63%) and indicated substantial risk of disease recurrence in all subgroups of int-high risk pts. Among those with T3 Grade 1-2, T3 Grade 3, and T3 Grade 4 disease, pts with recurrence had significantly higher risk of death than those without (all ps<0.05;). Results for pts with T2 and T4 disease were not presented due to small sample size. Multivariable regression analysis indicated that 1 additional yr of ToR was associated with 0.73 additional yrs (8.8 additional months) of OS post nephrectomy (95% CI: 0.40, 1.05 yrs; p<0.001). **Conclusions:** The non-trivial recurrence rates observed in pts with T3 Grade 1-2 and T3 Grade 3 RCC highlighted the substantial risk of recurrence and unmet needs in the int-high risk RCC patients. This study also confirms the incremental nature of the association of ToR and OS in patients with int-high and high risk localized RCC. These findings highlight the need for effective early intervention with adjuvant treatments in int-high and high risk post-nephrectomy RCC pts. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Recurrence-free rate and OS by risk groups.

Variable	Int-High N=629	Int-High Subgroups			High N=14
		T3G1-G2 N=297	T3G3 N=250	T3G4 N=64	
Median ToR, yrs	6.57	NR	4.59	1.42	0.74
5-yr recurrence free, %	55%	63%	50%	28%	15%
5-yr OS, %	69%	77%	65%	37%	36%
Median OS, with recurrence, yrs (N)	4.64 (259)	6.47 (101)	4.64 (111)	1.95 (41)	NA
Median OS, without recurrence, yrs (N)	NR (370)	NR (196)	NR (139)	NR (23)	NA

NR: Not Reached NA: Not Available as sample size <11.

4544 **Poster Session**

Prognostic factors for patients with advanced renal cell carcinoma (aRCC) in the era of first-line (1L) treatment with immune checkpoint inhibitors (ICIs). *First Author: Charlene Mantia, Dana-Farber Cancer Institute, Boston, MA*

Background: The most commonly used prognostic models in aRCC, the Memorial Sloan-Kettering Cancer Center (MSKCC) and the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk scores, were developed when cytokines and VEGF targeted monotherapies were standard of care, respectively. aRCC 1L treatment now includes combination therapy with 2 ICIs or ICI+VEGF receptor inhibitor. Re-evaluation of the MSKCC and IMDC prognostic models in the era of ICI therapy and identification of additional prognostic factors are overdue. **Methods:** Data from 1052 patients with aRCC treated on the CheckMate-214 (CM214) clinical trial with 1L nivolumab/ipilimumab (NIVO/IPI) or sunitinib (SUN) were analyzed retrospectively at median follow-up 5 yrs. For each treatment group, multivariable Cox model hazard ratios (HR) were compared to the published MSKCC and IMDC model HRs. Discrimination (c index) was assessed based upon the continuous scores obtained as the weighted combination of regression parameters from the published MSKCC & IMDC models. **Results:** KPS < 80% remained highly prognostic in both treatment groups (HRs > 2.5). With the exception of high calcium, the other factors of time from dx to treatment < 1 yr, hemoglobin < lower limit of normal (LLN), neutrophils > upper limit of normal (ULN), platelets > ULN and LDH > 1.5xULN consistently retained prognostic value for SUN (HRs ≥ published model HRs) but had diminished prognostic value for NIVO/IPI (each HR < published model HR). High calcium had diminished prognostic value for SUN and retained prognostic value for NIVO/IPI. The c-indices for discrimination were 0.61 and 0.64 for the MSKCC model in the NIVO/IPI and SUN treatment groups, respectively, and were 0.63 and 0.67 for the IMDC model in the NIVO/IPI and SUN treatment groups compared to reported IMDC c-index of 0.73 (Heng 2009). (Table) **Conclusions:** The prognostic ability of the MSKCC and IMDC risk models is reduced with combination ICI treatment. Evaluation of additional prognostic factors and development of new risk scores are needed and this work is ongoing. Research Sponsor: BMS.

Factor	IMDC HR (Heng 2009)	CM214 NIVO/IPI	CM214 SUN	MSKCC HR (Motzer 2002)	CM214 NIVO/IPI	CM214 SUN
KPS < 80%	2.5 (1.9-3.3)	2.7 (1.9-3.8)	2.9 (2.0-4.1)	1.5 (1.2-2.0)	2.7 (1.9-3.8)	2.4 (1.7-3.4)
TTT < 1 yr	1.4 (1.1-1.8)	1.1 (0.9-1.5)	1.6 (1.3-2.0)	1.5 (1.2-1.9)	1.2 (0.9-1.5)	1.6 (1.2-2.0)
Hgb < LLN	1.7 (1.3-2.3)	1.4 (1.1-1.9)	1.6 (1.2-2.0)	1.5 (1.2-1.9)	1.4 (1.1-1.8)	1.7 (1.4-2.1)
Ca++ > ULN or Corr Ca > 10 mg/dL	1.8 (1.3-2.5)	2.5 (1.7-3.8)	1.2 (0.8-1.7)	1.9 (1.5-2.6)	1.5 (1.1-2.0)	1.3 (0.9-1.7)
Neutrophils > ULN	2.4 (1.7-3.4)	1.7 (1.2-2.5)	2.1 (1.5-2.9)	X	X	X
Platelets > ULN	1.5 (1.1-2.0)	1.1 (0.7-1.7)	1.7 (1.2-2.3)	X	X	X
LDH > 1.5xULN	X	X	X	3.2 (2.3-4.5)	2.4 (1.5-3.8)	4.8 (2.9-8.0)
C index (95%CI)	.73	.63 (.627-.633)	.67 (.662-.668)	X	.61 (.607-.614)	.64 (.64-.65)

4545 **Poster Session**

Outcomes with novel combinations in nonclear cell renal cell carcinoma (nccRCC): ORACLE study. *First Author: Deepak Kilari, Department of Medicine, Froedtert Cancer Center, Medical College of Wisconsin, Milwaukee, WI*

Background: Despite recent advances in the treatment of clear cell RCC, there is a paucity of data to guide management of nccRCC due to the heterogeneity and rarity of these tumors. The clinical activity of combination therapies (including IO-IO, IO-VEGF, VEGF-mTOR) in subtypes of advanced nccRCC is unknown. **Methods:** In this multicenter retrospective analysis, we evaluated the efficacy of combination systemic therapies in patients with nccRCC. Eligible patients included those with nccRCC as determined by local genitourinary pathology review and receipt of one of three combination regimens during any line treatment (IO-IO, IO-VEGF, mTOR-VEGF). The primary endpoint was objective response rate (ORR) assessed by investigator review. Secondary endpoints were progression- free survival (PFS), disease control rate (DCR), and overall survival (OS). **Results:** Among 128 included patients, median age was 57 years; 66% were male and 65% white. Histologies included papillary (37%), unclassified (33%), chromophobe (16%), translocation (9%), and other (5 %). Among all patients, 69% had prior nephrectomy; 80% were IMDC intermediate/poor risk; 20% had sarcomatoid and/or rhabdoid differentiation, 27% and 29% had liver and bone metastasis respectively and 63% received combination treatment as first line. Comparison of outcomes based on treatment regimen, line of treatment and subtype is shown in the table. Median PFS and OS were longer with IO/IO and IO/VEGF compared to VEGF/ mTOR at 8.5, 9.5 and 3.7 months and 24.4, 18.2 and 15.4 months respectively. **Conclusions:** Antitumor activity was observed with novel combinations in nccRCC in both frontline and later line setting. Optimal management of nccRCC remains an unmet need and prospective data is warranted to guide treatment selection for this population. Research Sponsor: None.

		First line		Second or later line	Papillary	Chromophobe	Unclassified/ other	Sarcomatoid component present	
	n	ORR (%)	Median PFS (mo.)	ORR (%)	ORR (%)	ORR (%)	ORR (%)	ORR (%)	OS (mo.)
IO/IO	68	24	8.5	5	8	20	24	39	24.4
IO/VEGF	44	28	9.5	0	7	0	35	37	18.2
VEGF/ mTOR	16	17	3.7	10	0	33	NA	NA	15.4

n- number of patients; mo.-months; NA-not available. IO/VEGF (pembrolizumab + axitinib/ atezolizumab + bevacizumab /avelumab + axitinib); IO/IO (Ipilimumab and nivolumab); VEGF/mTOR (lenvatinib plus everolimus).

4546 **Poster Session**

LITESPARK-004 (MK-6482-004) phase 2 study of belzutifan, an oral hypoxia-inducible factor 2α inhibitor (HIF-2α), for von Hippel-Lindau (VHL) disease: Update with more than two years of follow-up data. *First Author: Eric Jonasch, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: VHL disease is associated with malignant or benign tumors, including renal cell carcinoma (RCC), pancreatic neuroendocrine tumors (pNETs), and hemangioblastomas. Alterations in the *VHL* gene cause aberrant stabilization and accumulation of HIF-2α, leading to activation of genes associated with tumor growth. Antitumor activity observed in the ongoing open-label phase 2 study, LITESPARK-004 (NCT03401788), led to the approval of belzutifan for the treatment of patients (pts) with VHL disease who require therapy for associated RCC, CNS hemangioblastomas, or pNETs not requiring immediate surgery. Updated results are presented after > 2 years of follow-up. **Methods:** Pts (≥18 years) with germline VHL alterations, ≥1 measurable nonmetastatic RCC tumor, no tumor of > 3 cm that necessitated immediate surgery, no prior anticancer systemic treatment, and an ECOG PS score of 0 or 1 received oral belzutifan 120 mg once daily until disease progression, unacceptable toxicity, or pt withdrawal. The primary end point was objective response rate (ORR) in VHL disease–associated RCC per RECIST v1.1 by independent central review (ICR). Secondary end points were safety, ORR in non-RCC neoplasms, and duration of response (DOR) in renal and nonrenal neoplasms, per RECIST v1.1 by ICR. **Results:** Of 61 pts, 50 were on treatment as of July 15, 2021; the primary reasons for discontinuation were disease progression in RCC neoplasms (n = 4) and pt decision to withdraw (n = 4). Twenty pts (33%) had ≥1 pNET and 50 (82%) had ≥1 CNS hemangioblastoma evaluable by ICR at baseline. At baseline, 97% of pts (n = 59) had prior VHL-related surgery; 38 pts had ≥1 VHL-related surgery within 3 years before starting belzutifan. Median time from first dose to database cutoff date was 29.3 mo (range, 27.6-37.5). ORR in RCC was 59% (n = 36), with 2 CRs (3%) and 34 PRs (56%). Median DOR was not reached (range, 8.3+ to 27.6+ mo). ORR in CNS hemangioblastomas was 38% (n = 19; 3 CRs; 16 PRs); median DOR was not reached (range, 3.7+ to 28.0+ mo). ORR in pNETS was 90% (n = 18; 3 CRs; 15 PRs); median DOR was not reached (range, 11.0+ to 31.0+ mo). Three pts (5%) underwent VHL-related surgeries after starting belzutifan. Grade 3 treatment-related adverse events (TRAEs) were reported in 10 pts (16%); the most common was anemia (n = 6 [10%]). No pt had a grade 4 or 5 TRAE. Two pts (3%) stopped treatment because of TRAEs (grade 1 dizziness and grade 2 intracranial hemorrhage). **Conclusions**: After a median follow-up of 29.3 mo, belzutifan continued to show antitumor activity in VHL disease–related neoplasms, including RCC, pNETs, and CNS hemangioblastomas, whereas the safety profile remained consistent with that of previous reports. These results support the use of belzutifan as a systemic treatment for VHL disease. Clinical trial information: NCT03401788. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

4547 **Poster Session**

Individualized prediction of post-surgical pathologic T3a (pT3a) upstaging risk in localized renal tumors undergoing nephrectomy (UroCCR 15 study). *First Author: Astrid Boulenger de Hautecloque, Bordeaux University Hospital, Bordeaux, France*

Background: Surgery is the standard of care for localized kidney cancer. Diagnostic imaging plays a critical role in disease staging and informs the extent of surgical resection (partial or radical nephrectomy, extended resection). In clinical routine, up to 15% of the tumors initially assessed as T1-T2 on imaging is upgraded to pT3a status post-surgery, implying a higher risk of relapse. The ability to correctly predict pT3a status pre-surgery would inform the surgical approach. An individualized prediction of the risk of clinical T1 or T2 tumors to be upstaged to pT3a is thus of high surgical interest. **Methods:** UroCCR is a French national network of 37 multidisciplinary teams for kidney cancer management that collects longitudinal data on the routine clinical care of its patients. A retrospective cohort of 4,395 cases of clinical T1-T2 kidney tumors was analyzed to develop a machine learning-based algorithm predictive of post-surgical pT3a upstaging risk at the individual patient level. For each patient, pre-surgical data were collected, including gender, age, symptoms, tumor size, tumor location, RENAL score, ECOG performance status, ASA score, and post-surgical pathological status. Sites were randomly assigned to the training or testing cohort, and their respective patient cases split between cohorts in a 60/40 ratio. Missing values were addressed through imputation performed with a k-nearest neighbor algorithm. Algorithms were trained on a data set of 2,636 patients and hyperparameters were optimized using a Bayes cross-validation (10-fold) approach . The area under the precision-recall curve (prAUC) was used as optimization metric. The performance of the algorithms for pT3a status prediction was then evaluated on the test dataset of 1,759 patients using precision-recall curves. **Results:** A logistic regression algorithm reached an AUC of 0.77 and a prAUC of 0.41. Higher values of the tumor size or age at surgery, the hilar location and the presence of symptoms at diagnosis were all associated with an increase of the predicted probability of pT3a upstaging. For each patient, Shapley values graphs were generated to display the pT3a upstaging probability and the relative contribution of each feature to the prediction. Three risk groups were defined based on the relative computed probability of pT3a upstaging, which displayed a statistically significant difference in Disease-Free Survival (DFS) ($p < 0.0001$), suggesting that pre-surgical multimodal data analysis could help predict long-term outcomes. **Conclusions:** This study suggests that machine learning applied to pre-surgical multimodal data can predict the risk of pT3a upstaging of a localized kidney tumor and inform long-term outcomes at the individual patient level. The results have been validated on an external cohort of 1,759 patients with data from the clinical routine. Research Sponsor: None.

4548 **Poster Session**

Racial differences in treatment patterns and outcomes of first-line (1L) therapies for advanced renal cell carcinoma (aRCC) in the real-world (RW) setting. *First Author: Daniel M. Geynisman, Fox Chase Cancer Center, Philadelphia, PA*

Background: In 1L therapy for aRCC, nivolumab plus ipilimumab (NIVO+IPI) and pembrolizumab plus axitinib (PEM+AXI) have demonstrated significantly improved clinical outcomes versus sunitinib in phase III trials. African American/Black (AA) patients are grossly underrepresented in all aRCC trials. Little is known about the impact of racial differences on the use of 1L therapies and clinical outcomes in the RW setting. **Methods:** This retrospective chart review included AA and White American (WA) patients diagnosed with International Metastatic Renal Cell Carcinoma Database Consortium (IMDC)/Memorial Sloan Kettering Cancer Center (MSKCC) intermediate/poor (I/P)-risk aRCC who initiated on 1L NIVO+IPI, PEM+AXI, or tyrosine kinase inhibitor (TKI) monotherapy with sunitinib, pazopanib, or cabozantinib. Patients' demographic/clinical characteristics and outcomes were abstracted from medical charts by treating oncologists. Use of 1L therapy, treatment discontinuation, and clinical outcomes including disease response, landmark progression-free survival (PFS), landmark overall survival (OS), and treatment-related adverse event (TRAE) rates were assessed descriptively by race. **Results:** Of 473 patients, 95 (20.1%) were AA, and 378 (79.9%) were WA patients. Median follow-up was 10.9 months. A higher proportion of AA vs. WA patients had received 1L TKI monotherapy (21.1% vs. 16.1%). Treatment discontinuation rate was higher in AA vs. WA patients (49.5% vs. 43.4%). Treatment response was lower in AA than WA patients (overall response rate [ORR]: 58.8% vs. 74.8%; complete response [CR]: 8.2% vs. 11.4%). The TRAE rate was slightly lower in AA vs. WA patients (25.3% vs. 32.5%). Stratified clinical outcomes including landmark PFS and OS rates at 6 and 9 months are shown in the Table. **Conclusions:** In this RW I/P-risk aRCC cohort, fewer AA patients were treated with standard of care immune-oncology (IO)-based therapy vs. WA patients, which may contribute to differences in therapy discontinuation and survival outcomes. Also, even with short follow-up, clinically meaningful ORR differences are noted in AA and WA patients. Research Sponsor: Bristol Myers Squibb.

Clinical outcomes after 1L therapy, stratified by racial groups.

	Overall		NIVO+IPI		PEM+AXI		TKI mono	
(N)	AA (95)	WA (378)	AA (41)	WA (202)	AA (34)	WA (115)	AA (20)	WA (61)
ORR, %	58.8	74.8[a]	73.0	79.8	56.3	77.6[a]	31.3	54.4
CR, %	8.2	11.4	18.9	16.9	0	4.1	0	7.0
OS, 6M, %	89.7	91.8	91.4	96.4	85.5	90.3	93.3	78.5
OS, 9M, %	81.0	86.5	82.3	93.1	77.2	83.5	85.6	69.1
PFS, 6M, %	79.6	84.4	82.3	89.7	75.9	83.9	79.6	67.7
PFS, 9M, %	73.6	73.5	79.1	81.4	67.9	72.3	70.7	48.4
TRAE, %	25.3	32.5	26.8	26.2	23.5	36.5	25.0	45.9

[a] $P < 0.05$. M, months. Significance tests of ORR, CR, and TRAE were performed with Pearson's chi-squared and Fisher's exact tests. Significance tests of OS and PFS at 6- and 9-month time points were performed with z-tests.

4549 **Poster Session**

Molecular characterization of the tumor microenvironment in chromophobe renal cell carcinoma (ChRCC) and related oncocytic neoplasms. *First Author: Chris Labaki, Dana Farber Cancer Institute, Boston, MA*

Background: ChRCC represents about 5% of all kidney cancer and has a dismal prognosis in the metastatic setting, with limited response to immune checkpoint inhibitors (ICI) and targeted therapy. We evaluated the molecular properties of ChRCC and related oncocytic neoplasms to define the tumor immune microenvironment and identify potential therapeutic strategies. **Methods:** ChRCC, renal oncocytoma (RO) and low-grade oncocytic tumor (LOT) samples with matched normal kidney specimens were evaluated using single-cell RNA sequencing (scRNA-seq) and single-cell T-cell receptor sequencing (scTCR-seq). T-cell antigenic specificities from scTCR-seq were inferred using a comprehensive database of annotated T-cell receptor sequences (VDJdb). The infiltration of CD45+ immune cells in renal oncocytic tumors and ccRCC samples was quantified using immunohistochemistry (IHC). Bulk RNA-sequencing (RNA-seq) data of clear cell RCC (ccRCC) and ChRCC were further analyzed using The Cancer Genome Atlas (TCGA) KIRC and KICH cohorts, respectively, with immune cell fractions calculated using CIBERSORTx. **Results:** After quality-control, 46,817 cells from 5 tumor (ChRCC: n = 3, RO: n = 1 and LOT: n = 1) and 4 normal samples were isolated for scRNA-seq analysis. Renal oncocytic tumors (ChRCC, RO, and LOT) had a low density of CD45+ cells (mean: 739 ± 114 cells/mm^2; n = 5) compared to ccRCC (mean: 3,420 ± 1,979 cells/mm^2; n = 5) ($p < 0.05$). Across all tumors, CD8+ T-cell clusters displayed a low expression of immune exhaustion markers (i.e. *PDCD1* [PD-1], *CTLA4*, *LAG3*, *HAVCR2* [TIM-3], and *TIGIT*). Analysis of TCGA bulk RNA-seq data after adjustment for CD8 T-cell fraction showed no difference in the expression of most immune exhaustion markers (i.e. *PDCD1*, *CTLA4*, *LAG3*) in ChRCC compared to normal samples ($p > 0.05$), contrasting with a substantially higher expression in ccRCC versus normal kidney ($p < 0.05$). Analysis of the T-cell repertoire (scTCR-seq) of ChRCC, RO and LOT samples did not identify a pattern of clonal expansion, and a considerable proportion of clonotypes were inferred to have specificity for viral antigens (range: 1.3 to 34.4% among all samples; 11.3 to 34.4% after filtering out two samples with a low (< 300) number of T-cells). **Conclusions:** Renal oncocytic tumors, including ChRCC, exhibit a low infiltration of immune cells, a non-exhausted immune phenotype and, a lack of clonally expanded tumor-specific T-cells. These findings may partially explain the molecular basis for the lack of response to ICIs in advanced ChRCC and outline the unique exhaustion phenotype of renal oncocytic tumors. Research Sponsor: US DOD Kidney Cancer Research Program KC180079.

4550 **Poster Session**

Comprehensive genomic profiling (CGP) of chromophobe renal cell carcinoma (chrRCC) compared with non-chromophobe RCC (nonchrRCC): Impact of *FLCN* genomic alteration (GA) status. *First Author: Gennady Bratslavsky, SUNY Upstate Medical University, Syracuse, NY*

Background: *FLCN* is a tumor suppressor gene associated with cutaneous hair follicle development. *FLCN* germline mutations are linked to inherited chrRCC in the Birt-Hogg-Dube (BHD) syndrome. We queried whether clinically sporadic chrRCC featured *FLCN* mutations by comparing the genomic profiles of chrRCC with nonchrRCC. **Methods:** 109 chrRCC and 5,862 nonchrRCC underwent hybrid-capture based comprehensive genomic profiling (CGP) to evaluate all classes of genomic alterations (GA). Tumor mutational burden (TMB) was determined on up to 1.1 Mb of sequenced DNA and microsatellite instability (MSI) was determined on 114 loci. PD-L1 expression was determined by IHC (Dako 22C3). **Results:** Patients (pts) with chrRCC were more frequently female (37 [34%] vs. 1,817 [31%]) and younger than pts with nonchrRCC (median age 58 vs 62 years, $p < .0001$). None of the submitted clinical records in the chrRCC cases listed signs of BHD syndrome. *FLCN* GA were identified in the nonchrRCC cases only at 2.3% with 37% of the GA being germline. 1/109 (0.9%) of chrRCC featured a germline *FLCN* GA. GA/tumor were slightly higher in nonchrRCC vs chrRCC (3.6 vs 2.4; NS). There were no significant differences in gLOH, genomic signatures or ancestry between the groups. GA more frequent in chrRCC included *TP53*, *RB1*, *PTEN*. GA more frequent in the nonchrRCC included *VHL*, *BAP1*, *PBRM1*, *SETD2*, *CDKN2A/B*, *ARID1A*, *NF2*, *PIK3CA* and *TERT*. Biomarkers of immune checkpoint inhibitor (ICPI) drug response revealed higher mean TMB, TMB ≥10 mutations/Mb and *PBRM1* inactivating mutation frequencies in the nonchrRCC than the chrRCC indicating possible differences in IO drug response. **Conclusions:** *FLCN* mutations that are associated with familial incidence of chrRCC are rarely associated with sporadic chrRCC. Sporadic chrRCC has a substantially different genomic profile from nonchrRCC and appears to harbor fewer opportunities for both targeted and immunotherapies. Research Sponsor: Foundation Medicine Inc.

	chrRCC (109 cases)	nonchrRCC 5,862 cases)	P Value
FLCN	0.9% (0% germline)	2.3% (37% germline)	NS
TP53	64.8%	18.5%	< .0001
VHL	6.5%	47.4%	< .0001
PBRM1	2.8%	24.8%	< .0001
CDKN2A/B	3.7%/1.9%	25.8%/19.7%	< .0001
PTEN	21.3%	9.7%	= .0005
NF2	0%	10.5%	< .0001
PIK3CA	0%	4.9%	= .009
Mean TMB	1.8	3.3	< .0001

4551 **Poster Session**

Phase Ib trial of selinexor (SEL) in combination with nivolumab (NIVO) alone or nivolumab plus ipilimumab (NIVO+IPI) in patients (pts) with advanced malignancies: The renal cell carcinoma (RCC) experience. *First Author: Omar Alhalabi, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: SEL is a first-in-class nuclear exportin 1 inhibitor, which blocks the transport of several proteins involved in cancer-cell growth from the nucleus to the cytoplasm. A syngeneic RENCA mouse model showed that SEL combined with checkpoint blockade resulted in increased effector and activated T cells, and NKT cells and reductions in myeloid cells and Tregs. We hypothesized that SEL+NIVO and SEL+NIVO+IPI are well tolerated and improve the overall response rate (ORR) observed with anti-PD1/CTLA-4. **Methods**: NCT02419495 is an open label, single center phase IB study of SEL with multiple standard chemotherapy or immunotherapy regimens in pts with advanced malignancies using 3 + 3 design in dose escalation. For SEL+NIVO+IPI, SEL was 60 mg (N = 4) or 80 mg (N = 6) given P.O. weekly with NIVO 3 mg/kg x 4 cycles then 480 mg Q4W plus IPI 1 mg/kg Q3W for 4 cycles only. For SEL+NIVO, SEL was 40 mg twice a week (N = 8), or 60 mg twice a week (N = 11) given with NIVO 240 mg Q2W or 480 mg Q4W. Primary objective was to establish the safety and tolerability of SEL+NIVO and SEL+NIVO+IPI. Secondary objectives included ORR and progression free survival (PFS). **Results**: 29 pts with RCC (25 males) were enrolled (table), including 3 pts with nonclear cell RCC (nccRCC), with a median age of 64 years (IQR 56-69). 21 patients (72%) had prior systemic therapies. Most common SEL or NIVO/IPI treatment-related ≥ grade (G) 3 adverse events (AEs) included endocrine disorders (N = 3), hyponatremia (N = 3), leukopenia (N = 3), transaminitis (N = 3), thromboembolic events (N = 2), asymptomatic lipase increased (N = 2), anemia (N = 1), pneumonitis (N = 1), nephritis (N = 1), colitis (N = 1), fatigue (N = 1). Two pts discontinued therapy due to AEs (G3 pneumonitis from SEL+NIVO+IPI and G3 transaminitis from SEL+NIVO, respectively). At a median follow up of 17.5 months, 5 (17%) pts achieved a PR, and 17 (59%) achieved a stable disease (SD). The median PFS for the entire cohort was 17.5 months (SEL+NIVO+IPI: 7.2 months, SEL+NIVO: 17.5 months). Among the patients with clear cell RCC who received SEL+NIVO+IPI as first line (1L) therapy (N = 4), all (100%) achieved SD as best overall response. Among the patients with ccRCC who received SEL+NIVO as 1L (N = 2), one patient achieved confirmed PR and the other achieved SD. The median overall survival (OS) was 27.8 months (SEL+NIVO+IPI: unreached, SEL+NIVO: 21.3 months). **Conclusions**: Treatment with SEL in combination with NIVO or NIVO+IPI is well-tolerated and shows modest clinical activity as compared to historic NIVO or NIVO+IPI activity. Clinical trial information: NCT02419495. Research Sponsor: Karyopharm.

4552 **Poster Session**

Baseline circulating soluble factors as predictors of response to nivolumab in metastatic clear cell renal cell carcinoma (mRCC): A validation study within the NIVOREN GETUG-AFU 26 translational study. *First Author: Lucia Carril-Ajuria, Gustave Roussy, Villejuif, France*

Background: The NIVOREN GETUG-AFU 26 study launched a translational research program to quantify baseline circulating soluble factors levels and correlate them with outcomes to nivolumab in mRCC pts. We previously identified on a training set (n = 80, 40 responders/40 progressors) several soluble factors significantly associated with worse overall survival (OS), progression-free survival (PFS) and response (IL-8 and VEGF), or with worse OS only (IL-6, IL-7) (Carril-Ajuria et al. ASCO GU. 2022). Our aim was to confirm these findings using an independent validation set. **Methods:** The remaining pts (n = 233) included in the translational-program of the NIVOREN study were included in this validation set. Based on previous results (training set), a panel of 7 different soluble factors (VEGF, VCAM-1, IL-6, IL-7, IL-8, BAFF, CXCL13) were quantified for each plasma sample using the MSD electrochemiluminescence assay. The association between baseline soluble-factors levels and response, PFS and OS was evaluated using previously identified cut-off values. **Results:** Two hundred thirty-three pts were included in the validation set. Baseline characteristics were similar to the overall trial population. The IMDC risk score breakdown was 17.7% good, 57.3% intermediate and 25.0% poor. With a median follow-up of 21.8 months (mo), the OS rate was 69.6% at 12 mo and median PFS was 3.0 mo. IL-8 (cut-off: 17.9 pg/ml) and IL-6 (cut-off: 8.7 pg/ml), involved in inflammation, confirmed an association with worse OS (IL8: HR = 2.57, $p < 0.0001$, IL-6: HR = 3.28,$p < 0.0001$) and worse PFS (IL-8: HR = 1.61,$p = 0.0008$, IL-6: HR = 1.68, $p = 0.0021$). VEGF (cut-off: 48.3 pg/ml) confirmed the association with worse OS (HR = 1.56, $p = 0.0176$), but not with PFS ($p = 0.2068$). IL-7, involved in T and B cells development, did not show a significant association with OS or PFS when using 8.6 pg/ml (training set) as cut-off ($p = 0.0675$ and $p = 0.7818$, respectively). IL-7 was the only cytokine to show an association with response ($p = 0.044$). Interestingly, circulating CXCL13 (cut-off: 106.4 pg/ml) and BAFF (cut-off: 1122.6 pg/ml), involved in B cell differentiation/survival, were significantly associated with worse OS (HR = 2.09, $p = 0.0001$ and HR = 2.34, $p = 0.0001$, respectively); BAFF showed a trend for worse PFS (HR = 1.29, $p = 0.0920$). **Conclusions:** Using the cut-off values previously identified in the training set, we confirmed a significant association between baseline blood concentration of IL-6/IL-8 and worse OS/PFS, and of VEGF with worse OS. Non-responders presented lower baseline circulating IL-7 concentrations. CXCL13 and BAFF were significantly associated with worse OS. Multivariate analyses are ongoing. Research Sponsor: PRT-K16-181 and Bristol-Myers Squibb.

4553 **Poster Session**

Preventing adverse events in patients with renal cell carcinoma treated with doublet immunotherapy using fecal microbiota transplantation (FMT): Initial results from perform a phase I study. *First Author: Ricardo Fernandes, London Regional Cancer Program, Western University, London, ON, Canada*

Background: The treatment landscape of metastatic renal cell carcinoma (mRCC) has evolved with the advent of either dual immune checkpoint inhibition (ICI) or in combination with Vascular Endothelial Growth Factor Receptor Tyrosine Kinase Inhibitor. Gut microbiota plays a central role in developing local and systemic immunity, with potential influence in controlling antitumor immune response in cancer patients treated with ICI. We hypothesize that FMT from healthy donors given before immunotherapy will establish a more resilient gut microbiota, reducing the treatment toxicity and improving response to therapy. PERFORM is an ongoing phase I study evaluating the safety of FMT and immunotherapy combination in first-line (1L) mRCC, and assessing whether FMT will prevent or mitigate immune-related adverse events (irAE). **Methods:** Eligible patients with untreated mRCC received a full dose and 2 supportive FMT procedures prior to the first 3 cycles of doublet ICI or in combination with VEGF-TKI. Primary endpoint is the feasibility and safety of combining FMT using intestinal bacteria existing in the stool of healthy donors with immunotherapy. Secondary endpoints include incidence of irAEs, objective response rate (ORR; RECIST v1.1), and changes in pts microbiome and immune profile post-FMT. We included a preliminary analysis of the first 10 patients. **Results:** 10 patients received FMT and doublet ICI therapy (10 ongoing). 8/10 (80%) patients were male. Median Age: 59.5 (53-71) years-old. Most common histology was clear cell RCC (90%) and all patients had an intermediate or poor-risk disease. 93.3% of planned FMT were administered. No dose-limiting toxicities due to FMT were observed. Median (range) follow-up was 5.5 (1–22) months. 4 patients (40%) discontinued treatment due to irAEs: colitis (n = 3), arthritis (n = 1). IrAEs were reported in 8 (80%) patients, including diarrhea (n = 6; 60%) and skin rash (n = 2, 20%). Grade 3/4 AEs were experienced by 6 (60%) patients, including colitis (n = 4, 40%). ORR was confirmed in 4/9 patients (44%; 95% CI, 30–60); 1 (11%) partial response. Microbiota and immune analysis data to be presented. **Conclusions:** The role of microbiome modification in preventing immune-related toxicities by adding FMT to ICI therapy was associated with a safety profile in unselected 1L mRCC and promising clinical efficacy data. Further prospective studies to examine the changes in the immune and microbiota profiles to determine biomarkers related to healthy outcomes/less frequent toxicities in patients receiving immunotherapy are warranted. Clinical trial information: NCT04163289. Research Sponsor: Medical Oncology Research Funding, Academic Medical Organization of Southwestern Ontario Opportunities Grant and London Regional Cancer Centre Catalyst Keith Samitt Translational Cancer Research Grant.

4554 **Poster Session**

Distinct outcomes in Hispanic/Latinx and non-Hispanic/Latinx patients with metastatic renal cell carcinoma (mRCC) treated with first-line ipilimumab plus nivolumab (ipi/nivo). *First Author: Sana Ali, Harbor-UCLA Medical Center, Torrance, CA*

Background: Subgroup analyses have reported differences in clinical outcomes by ethnicity in patients (pts) receiving immune checkpoint inhibitors (Cheng *et al* Ann Oncol 2019; Peravali *et al* World J Clin Oncol 2021). We sought to compare real-world outcomes between Hispanic/Latinx and non-Hispanic/Latinx mRCC pts treated with first-line ipi/nivo within a safety-net healthcare system and at a tertiary care center in Southern California. **Methods:** We performed a retrospective analysis of mRCC pts who received ipi/nivo within the Los Angeles County Department of Health Services (a safety-net healthcare system) and the City of Hope Comprehensive Cancer Center (a tertiary oncology center) between Jan 1, 2015 and Dec 31, 2021. Pts were identified using institutional databases and clinical data were compiled from electronic health records. Pts with pathologic diagnosis of stage IV mRCC, age > 18 years and receipt of ipi/nivo as first-line therapy were included. Progression-free survival (PFS) was analyzed using the Kaplan-Meier method and covariates were adjusted using multivariate Cox proportional hazards regression. **Results:** Of 96 pts, 67 (70%) were male, 90 (94%) had clear-cell histology, and 89 (93%) had intermediate/poor IMDC risk. Forty-two pts (44%) were Hispanic/Latinx while the remainder were non-Hispanic/Latinx (44 pts [46%] White, 7 pts [7%] Asian, and 3 pts [3%] Other). Fifty (52%) and 46 (48%) pts received their care at a tertiary care center and within a safety-net healthcare system, respectively. Median age, IMDC risk classification, BMI, and number of comorbidities were similar between both groups. Pooled analysis by ethnicity revealed significantly shorter PFS in Hispanic/Latinx vs non-Hispanic/Latinx pts (HR 1.60, 95% CI 1.04-2.48, p = 0.03). At 12 months, 19% of Hispanic/Latinx pts (95% CI, 9-32) and 35% of non-Hispanic/Latinx pts (95% CI, 23-48) were alive and progression-free. There was no difference in PFS between pts at the safety-net hospital system vs tertiary care center (HR 1.32, 95% CI 0.87-2.02, p = 0.19). **Conclusions:** Our real-world analysis of mRCC pts demonstrated poorer outcomes with ipi/nivo in Hispanic/Latinx pts. We are currently interrogating multiple social determinants of health that may contribute to these concerning disparities. Research Sponsor: None.

4555 **Poster Session**

Transcriptomic profiling identifies genomic markers associated with benefit from stereotactic body radiation therapy (SBRT) in oligoprogressive metastatic renal cell carcinoma (mRCC). *First Author: Zeynep Busra Zengin, City of Hope Comprehensive Cancer Center, Duarte, CA*

Background: Addition of SBRT to systemic therapy in oligoprogressive mRCC has been shown to prolong the duration of systemic treatment (Cheung *et al* Eur Urol 2021; De *et al* BJUI 2021). To date, the genomic predictors of benefit are unknown. We hypothesized that hypoxia-related genes would be associated with lesser benefit from SBRT. **Methods:** We retrospectively identified patients (pts) with mRCC who had oligoprogressive disease (progression of < 5 sites) while on systemic treatment and received SBRT without any systemic treatment change or interruption. Clinicopathologic characteristics, whole exome and transcriptome sequencing (Ashion Analytics) data were collected. Duration of systemic therapy (DOT) was quantified as systemic treatment duration prior to oligoprogression (DOT[P]) and after completion of SBRT (DOT[S]). The ratio of DOT[S]/DOT[P] was calculated and patients with a ratio ≥ 1.0 were considered to derive greater benefit from SBRT. The frequency of specific DNA alterations and RNA expression of pts above and below a DOT[S]/DOT[P] threshold of 1.0 was compared using a two-tailed Fischer's exact and student's t-test, respectively. **Results:** In this study, 23 mRCC pts who had oligoprogression during systemic treatment and received SBRT were identified. Within this cohort 16 pts (69.6%; M:F, 12:4) had available genomic data. Median age was 70 years and the most common histology was clear cell (87.5%). At the time of oligoprogression 11 pts (68.8%) were on immunotherapy, 4 pts (25.0%) were on targeted therapy. Median DOT[S] and DOT[P] were 12.6 months (range,0.7-46.3) and 13.4 months (range, 0.5-26.9), respectively, with a median DOT[S]/DOT[P] ratio of 1.4 (range,0.01-3.8). The most commonly mutated genes were *VHL* (56.3%), *PBRM1* (37.5%), and *SETD2* (37.5%). Alterations in *VHL, PBRM1* and *SETD2* were seen in 66.7% vs 42.9%, 33.3% vs 43.9%, and 44.4% vs 28.6% in patients with greater vs lesser benefit from SBRT, respectively (p≥0.05for each). Transcriptomic analysis was available in 9 pts and 1580 genes were noted to be differentially expressed between the groups (p < 0.05). Limiting scope to cancer genes in the COSMIC database, pts with lesser benefit from SBRT had higher expression of *CDKN1B, CNBP*, and *FOXO3* whereas pts with greater benefit had higher expression of *RNF43, POLD1* and *PBRM1* (p < 0.05 for each). Gene set enrichment analysis showed a trend towards increased expression of hypoxia related genes in pts with lesser benefit. **Conclusions:** Our data align with existing studies supporting the role of SBRT in oligoprogressive mRCC. In addition, while clinical benefit from SBRT appears to be independent of DNA-level alterations, transcriptomic analysis revealed significant differences in gene expression. Hypoxia-associated signatures may be associated with lesser benefit from radiotherapy. Research Sponsor: None.

4556 **Poster Session**

Association of antibiotic therapy and treatment efficacy in patients with renal cell carcinoma receiving immune checkpoint inhibitors. *First Author: Avery Braun, Einstein Healthcare Network, Philadelphia, PA*

Background: There is growing evidence indicating that gut microbiome content is associated with the effectiveness of immune checkpoint inhibitory (ICI) therapy in various cancer types. Antibiotic therapy (ABT) induces significant changes in gut microbiota; however, the effects of ABT on oncologic outcomes with ICI therapy has only been explored in small, single-institution studies. We aimed to investigate the relationship between ABT on overall survival (OS) and real-world progression free survival (rwPFS) in subjects with advanced renal cell carcinoma (RCC) treated with ICI utilizing a national database. **Methods:** We queried the nationwide electronic health record (EHR)-derived de-identified FlatIron Health (FIH) database after Institutional Review Board approval was obtained and included a waiver of informed consent to select 1809 subjects who received ICI therapy. Patient characteristics were described and compared between those with known ABT use and without known ABT use (in the 3 months pre/post ICI initiation) using ANOVA and Chi-square tests. rwPFS and OS were calculated from date of initiation of ICI to date of real-world progression/date of death. Three-month landmark Kaplan Meier and log-rank tests were used to compare rwPFS and OS between groups defined by ABT use (any ABT, and ABT in 3 months pre-ICI vs 3 months post-ICI initiation). Cox proportional models were used to investigate the association between rwPFS, OS, and antibiotic use, adjusting for patient characteristics. **Results:** Patients receiving ABT group were younger (p = 0.007) and more likely female (p = 0.024) but similar in other measured demographic variables. rwPFS (median: 9.03 vs 11.6 months; p = 0.015) and OS (median: 23.7 vs 31.8 months; p = 0.019) were significantly shorter in the with-ABT group than in the without-ABT group. When assessing ABT use 3 months prior to initiation of ICI (vs ABT during/no known ABT use), neither rwPFS (median: 9.53 vs 11.66, p = 0.38) nor OS (median: 23.7 vs 22.6 months; p = 0.38) were significantly different. However, rwPFS (median: 23.5 vs 14.0 months vs not reached; p = 0.004) and OS (median: 36.2 vs 22.5 vs 31.8; p = 0.007) were statistically significantly different when stratifying based on exposure and timing of ABT amongst pre-ICI initiation ABT, post-ICI initiation ABT and no ABT groups, respectively. Multivariable analysis identified as a significant predictor of rwPFS (HR = 0.725, CI = 0.579-0.908; p = .005) and OS (HR = 0.722, CI = 0.573-0.911; p = 0.006). **Conclusions:** This study identifies a significant negative prognostic association of ABT administration on survival in advanced RCC treated by ICI in the first line setting. These results are consistent with the growing body of evidence suggesting that alterations in gut microbiome secondary to antibiotics appear to blunt efficacy of ICI treatment and emphasize the importance of antibiotic stewardship. Research Sponsor: None.

4557 **Poster Session**

Maturation of overall survival (OS) in TIVO-3 with long-term follow-up. *First Author: Brian I. Rini, Vanderbilt-Ingram Cancer Center, Nashville, TN*

Background: Maturity of survival data is a consideration in the value assessment and confident clinical application of oncology drugs based on trial evidence. TIVO-3 supported FDA-approval of tivozanib (TIVO) in relapsed/refractory (R/R) advanced RCC, meeting the primary endpoint of significantly improved PFS over sorafenib (SOR) (HR: 0.73, 95% CI, 0.56-0.95). Long-term follow-up analyses demonstrate that the PFS rate at 3-years with TIVO is >5x higher than with SOR (12% vs 2%, respectively), yet a significant OS benefit for TIVO has not been observed to date. Here we report the contribution of event accumulation and data maturation on the stability of KM survival estimates. **Methods:** Intent-to-treat analyses of Cox proportional hazards and log-rank statistics were used to estimate the HR and 95% CI for OS in the TIVO-3 trial at pre-specified (2-years after last-patient-in [LPI]; ≥251 events) and exploratory extended follow-up timepoints (≥270 events; database closure). Patients were followed for survival until death, consent withdrawal, or loss to follow-up. **Results:** 350 patients were randomized 1:1 to TIVO (n=175) or SOR (n=175). 2-years post LPI and a mean follow-up of 17.9 months (data cut-off August 2019), 65% of patients experienced an event (HR: 0.99, 95% CI, 0.76-1.29). Subsequent analyses are reported at 20.3 (May 2020), 21.9 (January 2021), and 22.8 (May 2021) months follow-up. Accumulation of events and HR over time is shown in the Table. After almost 23 months of follow-up and realization of 80% of events, OS HR has decreased to below 0.90, in favor of TIVO. **Conclusions:** Serial OS analyses using KM estimates are subject to increased curve reliability with decreased censoring and limited residual patients at risk for death. Long-term follow-up of TIVO-3 suggests early and consistent PFS benefit with TIVO over SOR is associated with an OS HR decline over-time with more events. Clinical trial information: NCT02627963. Research Sponsor: Aveo Oncology.

TIVO-3 OS HR with extended follow-up.

Data cut-off date	Follow-up, months mean (95% CI)	Events, n	HR (95% CI)
August 2019	17.9 (16.7–19.1)	227	0.99 (0.76–1.29)
May 2020	20.3 (18.8–21.8)	251	0.97 (0.75–1.24)
January 2021	21.9 (20.2–23.6)	270	0.91 (0.72–1.17)
May 2021	22.8 (20.9–24.6)	280	0.89 (0.70–1.14)

4558 **Poster Session**

A robust, trial-agnostic gene signature for response to tyrosine kinase inhibition in ccRRCC. *First Author: Sari Khaleel, Memorial Sloan-Kettering Cancer Center-Fellowship (GME Office), New York, NY*

Background: Combination systemic therapies (ST) including immunotherapy (IO) and Tyrosine Kinase Inhibitors (TKI) have become the standard of care for management of metastatic clear cell carcinoma (ccRCC). Several expression (GE) signatures have been reported to predict TKI response with the aim of identifying the optimal ST regimen (IO/IO or IO/TKI) per patient. However, these gene signatures were developed and evaluated using data from individual trials with clinically distinct patient cohorts, fundamentally impeding their general application to diverse and heterogeneous patient populations. We therefore sought to identify genes consistently and directly associated with progression-free survival (PFS) with TKI ST across several trials. **Methods:** We applied a stratified, weighted concordance model to identify genes consistently demonstrating statistically significant association with PFS in the sunitinib TKI arm in four large randomized controlled trials (RCTs) of ST in ST-naïve ccRCC patients: COMPARZ (Motzer et al, 2013), Checkmate 214 (Motzer et al, 2018), IMmotion 151 (Rini et al, 2019), and Javelin 101 (Motzer et al, 2019). Concordant genes with Benjamini-Hochberg adjusted p-value (pAdj) ≤ 0.01 were selected. Of these, genes significantly associated with PFS on Cox proportional hazard regression (pAdj ≤ 0.05) in at least 3 of the 4 datasets were selected. Ontologic process and pathway enrichment analyses (OPPEA) against several ontologic databases were peformed using Metascape (Zhou et al, 2019). **Results:** We identified 2,794 statistically significant genes demonstrating concordant association with PFS across all 4 datasets (1087 patients); 71 genes were significantly associated with PFS on univariate *post-hoc* analysis in ≥3 of the datasets. OPPEA of these results identified significant enrichment in genes associated with cell cycle, cell division, and VEGFA-VEGFR2 pathways (Table 1). Although 5 genes in our set overlapped with published angiogenesis GES, the majority of these genes constitute entirely novel transcriptomic correlates of response to sunitinib. **Conclusions:** We developed a robust meta-gene signature consisting of genes directly and consistently associated with TKI response using data from several clinical trials. This gene signature is readily applicable to heterogeneous patient populations treated with anti-VEGF therapies. Research Sponsor: U.S. National Institutes of Health.

Top 5 enriched processes on OPPEA using Metascape platform against several ontologic databases including Gene Ontology (GO) and Reactome.

Ontologic Database	Entry ID	Process Description
GO	GO:0000278	Mitotic cell cycle
Reactome	R-HSA-194315	Signaling by Intracellular Rho GTPases
GO	GO:0001944	Vasculature Development
Reactome	R-HSA-1640170	Cell cycle
GO	GO:0010564	Regulation of cell cycle process

4559 **Poster Session**

Avelumab first-line (1L) maintenance for advanced urothelial carcinoma (aUC): Long-term outcomes from JAVELIN Bladder 100 in subgroups defined by response to 1L chemotherapy. *First Author: Begoña Pérez-Valderrama, Hospital Universitario Virgen del Rocío, Seville, Spain*

Background: In the phase 3 JAVELIN Bladder 100 trial (NCT02603432), avelumab 1L maintenance + best supportive care (BSC) significantly prolonged overall survival (OS) vs BSC alone in patients (pts) with aUC that had not progressed with 1L platinum-based chemotherapy. We report exploratory analyses in subgroups defined by response to 1L chemotherapy (complete response [CR], partial response [PR], or stable disease [SD]) after ≥2 years of follow-up. **Methods:** Eligible pts had unresectable locally advanced or metastatic UC without progression with 4-6 cycles of 1L gemcitabine + cisplatin or carboplatin. Pts were randomized 1:1 to receive avelumab + BSC (n = 350) or BSC alone (n = 350), stratified by best response to 1L chemotherapy (CR/PR vs SD) and visceral vs nonvisceral disease at start of 1L chemotherapy. **Results:** At data cutoff (June 4, 2021), median follow-up in both arms was ≥38 months. OS and PFS were longer in the avelumab + BSC vs BSC alone arm in all subgroups (Table). Median duration of study treatment and incidence of grade ≥3 treatment-emergent adverse events (TEAEs) in subgroups are shown in the Table. In the avelumab + BSC vs BSC alone arm, respectively, subsequent second-line anticancer drug therapy was received by: CR subgroup, 50.0% vs 74.2%; PR subgroup, 58.3% vs 71.8%; and SD subgroup, 46.4% vs 70.4%. **Conclusions:** Long-term follow-up from JAVELIN Bladder 100 continues to show prolonged OS and PFS with avelumab + BSC vs BSC alone irrespective of response (CR, PR, or SD) to 1L chemotherapy and despite a higher proportion of pts in the BSC alone arm receiving subsequent therapy. Long-term safety was consistent across subgroups. These findings further support avelumab 1L maintenance as standard of care for all pts with aUC that has not progressed with 1L platinum-based chemotherapy. Clinical trial information: NCT02603432. Research Sponsor: Pfizer, Pharmaceutical/Biotech Company.

Response to 1L chemotherapy	CR (n = 179)		PR (n = 326)		SD (n = 195)	
Arm	Avelumab + BSC (n = 90)	BSC (n = 89)	Avelumab + BSC (n = 163)	BSC (n = 163)	Avelumab + BSC (n = 97)	BSC (n = 98)
Study treatment ongoing, %	13.3	6.7	12.9	0.6	10.3	3.1
Median OS (95% CI), mo	39.8 (28.5-not evaluable)	26.8 (18.5-33.6)	19.2 (16.0-23.8)	12.8 (10.3-14.8)	22.3 (18.2-28.8)	14.0 (10.6-19.6)
HR for OS (95% CI)	0.72 (0.482-1.076)		0.70 (0.541-0.914)		0.84 (0.596-1.188)	
Median PFS by investigator (95% CI), mo	9.5 (5.7-16.6)	5.1 (3.0-5.7)	3.8 (3.7-5.6)	1.9 (1.9-2.1)	5.6 (3.7-7.5)	2.0 (1.9-3.6)
HR for PFS (95% CI)	0.58 (0.410-0.817)		0.47 (0.367-0.607)		0.59 (0.421-0.816)	
Median duration of study treatment (range), wk*	33.8 (2.0-214.4)	24.1 (0.1-168.4)	22.2 (2.0-213.1)	12.3 (0.1-231.7)	25.1 (2.0-216.0)	12.3 (0.1-164.0)
Grade ≥3 TEAE, %*	51.1	16.9	51.9	27.0	59.6	32.0

*In treated pts

4560 **Poster Session**

Long-term outcomes in patients with advanced urothelial carcinoma (UC) who received avelumab first-line (1L) maintenance with or without second-line (2L) treatment: Exploratory analyses from JAVELIN Bladder 100. *First Author: Joaquim Bellmunt, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA*

Background: Avelumab 1L maintenance + best supportive care (BSC) significantly prolonged overall survival (OS) vs BSC alone in patients (pts) with advanced UC that had not progressed with 1L platinum-based chemotherapy (median OS, 23.8 vs 15.0 months; HR, 0.76 [95% CI, 0.631-0.915]; 2-sided p = 0.0036). Avelumab 1L maintenance is now considered standard of care per international guidelines. However, data on outcomes in pts who receive 2L treatment after avelumab 1L maintenance are limited. We report a descriptive analysis of outcomes in pts enrolled in the avelumab + BSC arm of the JAVELIN Bladder 100 trial based on receipt of 2L treatment. **Methods:** In the phase 3 JAVELIN Bladder 100 trial (NCT02603432), eligible pts had unresectable locally advanced or metastatic UC without progression with 4-6 cycles of 1L gemcitabine + cisplatin or carboplatin. Pts were randomized 1:1 to receive avelumab + BSC or BSC alone. Exploratory analyses of time from randomization to end of 2L treatment and OS were performed in the avelumab + BSC arm in subgroups defined by 2L treatment administered by investigators after discontinuation of study treatment. **Results:** In the avelumab + BSC arm (n = 350), median follow-up at data cutoff (June 4, 2021) was 38.0 months. 185 pts (52.9%) had discontinued avelumab 1L maintenance treatment for any reason and received 2L treatment, whereas 122 (34.9%) had discontinued avelumab and did not receive 2L treatment. Median OS (95% CI) in subgroups is shown in the Table. In 43 pts (12.3%) who were still receiving avelumab, median treatment duration was 154.6 weeks (range, 106.7-216.0). Among pts who received 2L treatment, median time from end of avelumab 1L maintenance to start of 2L treatment was 1.35 months (range, 0.3-30.9) and median time from randomization to end of 2L treatment was 11.7 months (95% CI, 9.7-13.8). 2L treatment comprised rechallenge with platinum-based chemotherapy in 75 pts (21.4%) or other 2L treatment in 110 pts (31.4%), including 2L anti–PD-(L)1 therapy in 11 pts (3.1%). Additional data based on different types of 2L treatment will be presented. **Conclusions:** In this exploratory analysis from the JAVELIN Bladder 100 trial with extended follow-up, approximately 60% of pts (185/307 pts) who had discontinued avelumab received 2L treatment. Long-term OS was observed in pts who received avelumab 1L maintenance with or without 2L treatment. Clinical trial information: NCT02603432. Research Sponsor: Pfizer, Pharmaceutical/Biotech Company.

	n	Median OS (95% CI), mo
Avelumab treatment ongoing	43	Not reached
Any 2L treatment post avelumab discontinuation	185	19.9 (18.2-23.0)
No 2L treatment post avelumab discontinuation	122	18.2 (10.0-34.4)

4561 **Poster Session**

Health-related quality of life (HRQoL) for patients with advanced/metastatic urothelial carcinoma (UC) enrolled in KEYNOTE-052 who are potentially platinum ineligible. *First Author: Rafael Morales-Barrera, Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain*

Background: Frontline cisplatin-based chemotherapy improves survival in patients (pts) with UC, but ~50% are cisplatin-ineligible owing to poor performance status or comorbidity. The definition of platinum ineligibility is not standardized; hence, treatment decisions are almost solely made by clinical judgment. Pembrolizumab (pembro) showed antitumor activity and manageable toxicity as frontline therapy in 370 cisplatin-ineligible pts in the single arm, phase 2 KEYNOTE-052 trial (NCT02335424). We present effects of pembro on HRQoL of pts in KEYNOTE-052 who were potentially platinum ineligible in this exploratory analysis. **Methods:** Eligible pts for KEYNOTE-052 were adults with no prior systemic chemotherapy for advanced/metastatic UC, ECOG PS ≤2, and measurable disease per RECIST v1.1 by blinded independent central review. Pembro 200 mg IV was administered Q3W for up to 2 y. Clinical characteristics of frail pts (platinum ineligible) were identified by extensive review of real-world treatment patterns and relevant literature. Consequently, platinum ineligibility was defined as having an ECOG PS ≥2 plus ≥1 of the following: visceral disease, creatinine clearance < 60 mL/min, or age ≥80 y. HRQoL was assessed using the EORTC QLQ-C30 and EQ-5D-3L during the first 4 cycles, then every 2 cycles for 1 year or until treatment discontinuation (whichever occurred first), and at least 30 days after treatment discontinuation. Key end points were change from baseline per the QLQ-C30 global health status (GHS)/QoL score, QLQ-C30 physical functioning subscale, and EQ-5D visual analog scale (VAS). The minimum important difference (MID) was 10 for QLQ-C30 score change (improved: ≥10; stable: −10 to 10; deteriorated: −10 or less); MID for VAS score change was 7 (improved: ≥7; stable: −7 to 7; deteriorated: −7 or less). **Results:** Median age for 143 pts was 75 y (range, 34-91); 129 pts (90.2%) had visceral disease; 142 (99.3%) had ECOG PS 2; 1 had ECOG PS 3 (enrolled in error). Compliance rate for HRQoL questionnaires was 93.7% at baseline. At the prespecified analysis time of week 9, 77.6% of pts had improved (n = 51) or stable (n = 60) QLQ-C30 GHS/QoL scores, 64.3% had improved (n = 35) or stable (n = 57) QLQ-C30 physical functioning scores, and 62.2% had improved (n = 56) or stable (n = 33) EQ-5D VAS scores. These scores were stable throughout the HRQoL assessment period for pts who continued pembro. **Conclusions:** In this exploratory analysis, pembro maintained HRQoL for pts with advanced/metastatic UC in KEYNOTE-052 who were potentially platinum-ineligible per the above criteria. Together with the efficacy and safety data from KEYNOTE-052, these data suggest that pembro monotherapy is a valuable treatment option for select pts with advanced UC who are more senior and/or deemed medically frail. Clinical trial information: NCT02335424. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

4562 **Poster Session**

Association between molecular subtype membership or hypoxia-associated gene expression signatures and clinical outcomes in the CALGB 90601 (Alliance) phase 3 clinical trial of gemcitabine and cisplatin (GC) plus bevacizumab (B) or placebo (P). *First Author: David James McConkey, Johns Hopkins Greenberg Bladder Cancer Institute, Baltimore, MD*

Background: Our previous work showed that basal tumors were associated with the best clinical outcomes in a Phase 2 clinical trial of neoadjuvant dose-dense MVAC plus B, and in other work we showed that basal tumors were enriched with hypoxia-associated gene expression signatures. Here we attempted to validate these findings in the C90601 Phase 3 clinical trial of GC plus B versus GC plus P. **Methods:** Whole transcriptome RNAseq was performed on all available tumors using Ion Torrent's Ampliseq platform (n = 189). Tumors were assigned to molecular subtypes using 3 different classifiers - BASE47 (k=2), MDA oneNN (k=3), and the Consensus classifier (k=6). Tumor hypoxia signature enrichment was determined using 2 different gene expression signatures and gene set variation analysis (GSVA). The proportional hazards model was used to correlate molecular subtype calls and hypoxia signature enrichment with overall survival (OS) and progression-free survival (PFS) adjusting for stratification factors and treatment arm (for PFS). **Results:** The median OS & PFS by different signatures and the hazard ratios (HR) are presented in the Table. **Conclusions:** Predefined signatures associated with clinical benefit in the Phase-2 neoadjuvant clinical trial were not associated with benefit in C90601. Possible explanations include the lack of strong therapeutic effects of the treatments, potential heterogeneity ("subtype plasticity") between the profiled tissue samples and the metastatic lesions under treatment pressure, and differences in biology associated with the disease states (muscle-invasive vs advanced/metastatic disease). Support: U10CA180821, U10CA180882, Department of Defense (CA160312), Genentech; ClinicalTrials.gov Identifier: NCT00942331. Research Sponsor: US Department of Defense Peer-reviewed Cancer Research Program, U.S. National Institutes of Health.

	OS		PFS	
Signature	Median, months (95% CI)	Hazard Ratio (HR; 95% CI)*	Median, months (95% CI)	HR (& 95% CI)*
MDA				
P53-Like (Referent)	15.4 (12.9, 22.0)		8.7 (6.9, 13.3)	
Luminal	15.3 (12.5, 18.8)	1.0 (0.7–1.4)	6.7 (6.3, 8.5)	1.3 (0.9–1.9)
Basal	13.4 (9.46, 16.3)	1.4 (0.9–2.2)	6.2 (4.9, 7.7)	1.5 (1.0–2.3)
Base47				
Luminal (Referent)	15.4 (12.7, 18.8)		6.7 (6.3, 8.4)	
Basal	14.2 (11.1, 17.3)	1.2 (0.9–1.7)	7.4 (6.6, 9.5)	0.8 (0.6, 1.1)
Consensus Classifier				
LumP (Referent)	16.4 (12.3, 21.7)		6.9 (6.4, 8.7)	
LumU	14.5 (12.5, 18.8)	1.4 (0.9–2.0)	6.7 (6.4, 8.9)	1.0 (0.7–1.5)
Ba/Sq	13.7 (9.4, 17.8)	1.6 (1.0–2.4)	5.8 (4.8, 9.2)	1.1 (0.7–1.6)
Other	13.5 (9.9, 27.0)	1.4 (0.9–2.4)	10.7 (7.0, 15.0)	0.8 (0.5–1.4)
HIF scores				
West		1.0 (0.7–1.5)		0.9 (0.6–1.3)
#x2264; −0.16	15.2 (12.3, 17.3)		7.1 (6.6, 8.4)	
> -0.16	14.5 (12.7, 19.6)		6.7 (6.2, 10.3)	
Hallmark		1.2 (0.5–2.6)		1.0 (0.5–2.2)
≤ -0.05	14.9 (12.7, 18.3)		7.3 (6.4, 8.7)	
> -0.05	14.3 (11.6, 17.8)		6.7 (6.1, 8.9)	

*Adjusted for the stratification factors and treatment arm (for PFS).

4563 **Poster Session**

Phase Ib study of anti-PD-L1 monoclonal antibody socazolimab in combination with nab-paclitaxel as first-line therapy for advanced urothelial carcinoma. *First Author: Rong Duan, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China*

Background: PD-1/PD-L1 immune checkpoint inhibitors (ICIs)Ohave demonstrated activity in the postplatinum and platinum-ineligible settings for advanced urothelial carcinoma (aUC). As only around 30% of patients with aUC can tolerate platinum standard treatment, first-line ICIs combined with non-platinum drugs have certain research value. Therefore we assessed the safety and efficacy of anti-PD-L1 monoclonal antibody Socazolimab in combination with nab-paclitaxel as first line therapy in aUC (NCT04603846). **Methods:** This is a multi-center,single-arm, phase Ib study which enrolled aUC patients with treatment-naive or first recurrence more than 6 months after the end of adjuvant chemotherapy in China. Eligible patients received Socazolimab (5mg/kg) and nab-paclitaxel (260mg/m^2) every 3 weeks. Primary endpoint was to investigate the safety and tolerability of nab-paclitaxel in combination with Socazolimab. Second endpoints were the objective response rate (ORR) and progression-free survival (PFS). **Results:** 20 patients were enrolled, including 5 renal pelvis urothelial carcinoma, 8 bladder urothelial carcinoma, and 7 ureteral carcinoma. The median age was 69 years. As of January 14, 2022, the median follow-up time was 5.49 months. Median number of treatment cycles was 6.5 cycles. No patients had dose limiting toxicity. Among the 17 patients who had received at least one tumor assessment, 8 patients achieved partial responses. ORR was 52.94% (95% CI, 27.81-77.02). DCR was 88.24% (95% CI, 63.56-98.54). Median PFS was 8.18 months (95% CI, 5.32-13.60). Adverse reactions related to the study drug were mainly Grade 1-2. Common adverse reactions included rash (6/20,30%), increased alanine aminotransferase (6/20, 30%), increased γ-glutamyltransferase (4/20, 20%),sinus bradycardia (4/20, 20%), increased aspartate aminotransferase (4/20, 20%),pruritus (3/20, 15%). Grade 3 or higher treatment-related adverse events occurred in 4 (20%) patients, mainly Grade 3 increases in alanine aminotransferase (2/20, 10%). No confirmed treatment-related deaths occurred, and no treatment-related deaths occurred, and no new safety signals were observed. **Conclusions:** Socazolimab combined with nab-paclitaxel as first-line treatment was effective and well-tolerated in Chinese patients with advanced urothelial carcinoma, warranting phase II trials. Clinical trial information: NCT04603846. Research Sponsor: Funded by Lee's Pharmaceutical Holdings Limited, Hong Kong SAR.

4564 **Poster Session**

Prognostic impact of bone metastasis in patients with metastatic urothelial carcinoma (mUC) treated with durvalumab (D) with or without tremelimumab (T) in the DANUBE study. *First Author: Carlos Stecca, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: In mUC, bone metastases (BM) are associated with significant morbidity and mortality, but their independent impact on outcomes is not well established, especially in the current era of immune checkpoint inhibitors (ICIs). This post-hoc analysis assessed the impact of BM, as well as PD-L1 status (within the same BM category) on outcomes of patients with mUC treated with ICIs. Data was derived from the Phase 3 DANUBE study, which compared D, D+T, and standard chemotherapy (SoC). **Methods:** Patient characteristics, disease characteristics, treatments, and outcomes were collected. Patients were categorized as having BM or no BM. Outcomes included median overall survival (OS) and median progression-free survival (PFS) (in months [mo]), estimated by the Kaplan-Meier method. PD-L1 expression was assessed using the VENTANA PD-L1 (SP263) Assay. **Results:** Overall, 1032 patients were included; 266 had BM (D, 80; D+T, 97; SoC, 89), and 766 had no BM (D, 262; D+T, 249; SoC, 255). Among all patients, those with BM had a lower OS than those with no BM (HR, 1.67; 95% CI, 1.43-1.92; nominal P< 0.0001) when controlling for cisplatin eligibility, PD-L1 expression, presence of visceral metastases, and treatment. Similarly, patients with BM had lower PFS compared to those without BM (HR, 1.52; 95% CI, 1.30-1.75; nominal P< 0.0001) Within each treatment arm, median OS was lower for patients with BM compared to patients with no BM for all patients, regardless of PD-L1 status (Table). Patients with BM and PD-L1–high expression, treated with either D or D+T, had numerically higher median OS compared to those with PD-L1 low; this difference was also seen in patients with no BM. In contrast, there was no difference in median OS, for BM or no BM, based on PD-L1 expression for patients treated with SoC (Table). **Conclusions:** In this post-hoc analysis, presence of BM was significantly and consistently associated with worse outcomes in patients with mUC across all treatment arms of the DANUBE study. PD-L1–high expression was associated with higher median OS in patients treated with D or D+T, regardless of presence of BM. These data reinforce the negative prognostic impact of BM in mUC and the role for PD-L1 expression in predicting benefit for patients treated with ICIs. Funding: AstraZeneca. Clinical trial information: NCT02516241. Research Sponsor: AstraZeneca.

	D (N = 342)	D+T (N = 346)	SoC (N = 344)
Median OS (months)			
Overall Population			
No BM (N = 766)	15.8	17.8	13.8
With BM (N = 266)	6.8	10.4	9.5
By PD-L1 Expression			
No BM, PD-L1 high, n = 470 (61%)	17.9	20.2	13.6
No BM, PD-L1 low, n = 296 (39%)	13.8	14.2	13.9
With BM, PD-L1 high, n = 151 (57%)	7.9	12.5	9.6
With BM, PD-L1 low, n = 115 (43%)	4.7	6.9	9.4

4565 **Poster Session**

Real-world treatment patterns and clinical outcomes with first-line therapy in cisplatin-eligible and ineligible patients with advanced urothelial carcinoma. *First Author: Guru P. Sonpavde, Dana Farber Cancer Institute, Boston, MA*

Background: Advanced urothelial carcinoma (aUC) has a poor long-term prognosis. Despite new clinical trial data for novel therapies including PD-1/L1 inhibitors, data on real-world (RW) treatment patterns and overall survival (OS) in aUC patients (pts) treated with first line (1L) therapy are limited. **Methods:** This retrospective observational study describes the contemporary RW 1L treatment patterns and OS in aUC pts stratified by cisplatin (cis)-eligibility (based on accepted criteria) and treatment. Data were from the nationwide Flatiron Health longitudinal electronic health record-derived database, comprising de-identified patient-level structured and unstructured data. Eligible pts were adults diagnosed with aUC from May 2016-Oct 2020 and followed until death or end of data availability in July 2021. OS was estimated using Kaplan-Meier methods and compared via multivariable Cox proportional-hazard models adjusted for clinical covariates. **Results:** Of 4,300 aUC diagnosed pts, 3,311 (77.0%) received 1L treatment; 1836 (55.5%) cis-ineligible, 1475 (44.5%) cis-eligible. Differences between cis-ineligible and cis-eligible pts were observed, with cis-ineligible more likely to be older (mean age, 75.0 vs 69.0 yrs), have lower CrCl (median, 45.3 vs 80.7 mL/min), and worse ECOG-PS (2+, 29.2 vs 0%). Only 44.4% received 2L therapy: 38.3% cis-ineligible vs 52.0% cis-eligible. Median OS in all 1L treated pts was 11.0 (95% CI, 10.3 – 11.5) mo and was shorter in cis-ineligible than cis-eligible pts (8.6 [95% CI, 8.1 – 9.2] vs 14.4 [95% CI, 13.4 – 16.4]; hazard ratio [HR], 0.8 [0.7 – 1.0]). A number of cis-ineligible pts received cis, and many cis-eligible pts did not (Table), suggesting physicians consider clinical factors beyond conventional criteria to determine cis-eligibility. Cis + gemcitabine (gem) or MVAC was associated with longer OS vs other treatments regardless of cis-eligibility (Table). **Conclusions:** Clinical outcomes in 1L aUC pts were poor, particularly for cis-ineligible pts, which may be partly driven by the specific regimen administered. Many aUC pts did not receive 1L treatment and among those who did, less than half received 2L therapy. These data highlight the need for more effective and tolerable 1L therapy for all aUC pts. Research Sponsor: Seagen Inc. and Astellas, Inc.

	1L-treatment	N	Median OS (95% CI), mo	HR (95% CI)
Cis-ineligible	Overall	1836	8.6 (8.1–9.2)	-
	PD-1/L1	912	6.4 (5.6–7.6)	1.2 (1.0–1.3)
	Cis + gem or MVAC	229	13.5 (10.9–18.6)	0.8 (0.6–0.9)
	Carboplatin + gem	406	9.8 (8.6–11.3)	Reference
	Other	289	8.4 (6.3–10.1)	1.1 (0.9–1.3)
Cis-eligible	Overall	1475	14.4 (13.4–16.4)	-
	PD-1/L1	367	11.7 (10–15.6)	1.4 (1.2–1.7)
	Cis + gem or MVAC	596	20.6 (17.3–24.8)	Reference
	Carboplatin + gem	297	13.0 (10.9–15.9)	1.3 (1.0–1.5)
	Other	215	12.8 (10.2–15.5)	1.3 (1.0–1.6)

HR adjusted for cis-eligibility, primary cancer site, age, sex, ECOG-PS, smoking status, PD-L1 status, and CrCl.

4566 **Poster Session**

Toripalimab (anti-PD-1) monotherapy as a second-line treatment for patients with metastatic urothelial carcinoma (POLARIS-03): Two-year survival update and biomarker analysis. *First Author: Haige Chen, Department of Urology, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China*

Background: Patients with advanced metastatic urothelial carcinoma (mUC) who experience disease progression after standard therapy have limited treatment options. Toripalimab was approved for the 2nd line treatment of mUC based on a phase II clinical study (POLARIS-03) in Chinese patients with mUC (NCT03113266). Here we report the two-year efficacy update and biomarker analysis of the study. **Methods:** Metastatic UC Patients received toripalimab 3 mg/kg Q2W until disease progression, unacceptable toxicity or voluntary withdrawal. Clinical response was assessed every 8 weeks by independent review committee (IRC) per RECIST v1.1. Tumor PD-L1 expression, tumor mutational burden (TMB), and other biomarkers were evaluated for correlation with clinical response. **Results:** From May 2017 to September 2019, 151 patients were enrolled from 15 participating centers. By cutoff date of September 8, 2021, no emergent of new safety signal was identified compared with the previous one-year report. By the cutoff date, 3 CR, 37 PR and 28 SD were observed among the ITT population for an ORR of 26.5% and a DCR of 45.0% as assessed by the IRC. The response was durable as the median duration of response was 25.8 months. The median OS was 14.6 months. Whole exome sequencing (WES) was performed on tumor biopsies and paired PBMCs and the results were available from 135 patients. The median TMB value was 4.1 mutations per million base pairs (Mb) in the cohort. Using 10 mutations/Mb as the cut off, TMB-high patients (n = 27) had better ORR than TMB low patients(n = 108) (48% versus 22%, p = 0.014). The TMB-high group also showed better PFS (12.9 versus 1.8 months, HR = 0.48 [95% CI:0.31-0.74], p < 0.001) and OS (not reached versus 10.0 months, HR = 0.53 [95% CI:0.32-0.88], p = 0.013) than the TMB low group. Patients with mutations in chromatin remodelers SMARCA4/PBRM1 or tumor suppressor RB1 were associated with better responses to toripalimab than patients with wild-type genes. The ORR was 30% (6/20) in patients with FGFR2/FGFR3 mutations or FGFR2/FGFR3 gene fusions, and 42% (5/12) in patients with NECTIN4 genomic alternations. The mutational signature characterized by exposure to aristolochic acid (A:T to T:A transversion) is present in both upper tract urothelial carcinoma (UTUC) and lower tract urothelial carcinoma (LTUC), but enriched in UTUC (p = 0.003). Similar clinical responses were observed in UTUC and LTUC. **Conclusions:** Toripalimab has demonstrated a manageable safety profile and encouraging clinical activity in metastatic UC patients refractory to 1st line chemotherapy. WES analysis identified divergent mutations in the study. We report the utility of TMB to predict not only the response rate but also the PFS and OS benefits in patients with mUC in response to an ICI monotherapy. Clinical trial information: NCT03113266. Research Sponsor: Shanghai Junshi Biosciences.

4567 **Poster Session**

A prospective exploratory clinical study of penpulimab plus anlotinib as first-line treatment for locally advanced or metastatic urothelial carcinoma. *First Author: Bo Yang, Department of Oncology, The First Medical Center of Chinese PLA General Hospital, Beijing, China*

Background: A high unmet need remains for first-line cisplatin-ineligible patients with locally advanced or metastatic urothelial carcinoma (la/mUC).Immune checkpoint inhibitors have been implemented in the management of cisplatin-ineligible la/mUC. Penpulimab is a programmed death 1 (PD-1) inhibitor which had approved by the Chinese National Medical Products Administration (NMPA) on August 2021. Anlotinib is a novel oral multi-target tyrosine kinase inhibitor and primary targeted to VEGFR, FGFR, PDGFR and c-Kit. The current prospective single-arm phase II clinical trial (ChiCTR1900028022) aimed to assess the efficacy and safety of penpulimab plus anlotinib as first-line therapy for la/mUC. **Methods:** Patients (pts) who had no prior systemic therapy and at least one measurable lesion according to RECIST v1.1 with histologically or cytologically confirmed locally advanced unresectable or metastatic urothelial carcinoma (including unresectable or metastatic urothelial carcinoma of the bladder, urethra, ureter, or renal pelvis), 18-75 years, ECOG 0-2, were considered eligible for enrollment. Patients received 200 mg penpulimab intravenously on day 1 plus anlotinib, 8 mg oral daily for days 1-14 of a 21-day cycle until confirmed disease progression, intolerable toxicity, physician/patient decision to withdraw, or completion of 24 months of treatment. The primary endpoint was objective response rate (ORR), and the secondary endpoints included disease control rate (DCR), progression-free survival (PFS) and safety. **Results:** As of Dec. 2021, 10 pts were enrolled, 9 pts had the best overall response assessments which inferred the ORR of 66.7% (95% CI, 29.9-92.5) and the DCR of 88.9% (PR in 6 pts and SD in 2 pts; 95% CI, 51.8-99.7). The median PFS was 8.2 months ((95% CI, 8.0-8.4). Any grades of adverse events (AEs) were observed in 90% (9/10) of pts, containing hyperthyroidism (33%), Creatinine increased (33%),haematuria (22%), anaemia (22%), hypertension (11%), fatigue (11%). High grade AEs of grade IV liver dysfunction were observed in one patient (11%). **Conclusions:** An effective treatment strategy for cisplatin-ineligible patients and for patients unable to receive chemotherapy is an important unmet clinical need. Penpulimab in combination with anlotinib in pts with la/mUC showed encouraging efficacy and satisfactory safety. Clinical trial information: ChiCTR1900028022. Research Sponsor: Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

4568 **Poster Session**

Landscape of fibroblast growth factor receptor (*FGFR*) genomic alterations (GA) in urothelial bladder cancer (UBC). *First Author: Maroun Bou Zerdan, Cleveland Clinic Florida, Weston, FL*

Background: Urothelial bladder carcinomas (UBC) with genomic alterations (GA) in the Fibroblast Growth Factor Receptor (*FGFR*) genes have been postulated to be less responsive to immune checkpoint inhibitors (ICI). Immune microenvironment of these tumors could be altered due to suppression of interferon signaling pathways. Here, we present comprehensive genomic profiling (CGP) of *FGFR* altered UBC to study the underlying immunogenomic mechanisms of response and resistance. **Methods:** 4,035 UBC underwent hybrid capture based CGP. Tumor mutational burden (TMB) was determined on up to 1.1 Mbp of sequenced DNA and microsatellite instability (MSI) was determined using 114 loci. Programmed death ligand (PD-L1) expression in tumor cells was assessed by IHC (Dako 22C3). **Results:** 894 (22%) of UBC featured *FGFR* GA (*FGFR1* 3.7%; *FGFR2* 1.1%; *FGFR3* 17.4%). Gender and age distribution was similar in all groups. *FGFR3* cases had lower GA/tumor and 14.7% GA were fusions. *ERBB2* amplification was significantly higher in *FGFR1/2* altered UBC compared with *FGFR3* altered UBC. MTOR pathway GA were highest in *FGFR3* altered UBC. *FGFR3* altered UBC featured significantly higher frequencies of biomarkers predicting resistance to ICI including lower TMB, lower PD-L1 expression and higher frequencies of GA in *MDM2. FGFR3* driven UBC also features significantly higher frequencies of *CDKN2A/B* loss and *MTAP* loss which have also recently been linked to IO drug resistance. **Conclusions:** UBC harboring *FGFR* GA have increased frequency of alterations that have been linked to ICI resistance. Further evaluation of FGFR-based biomarkers in UBC clinical trials focused on the assessment of the patient response to ICI appears warranted. Research Sponsor: Foundation Medicine Inc.

	UCB All Cases	UBC FGFR1	UBC FGFR2	UBC FGFR3
Number of Cases	4035	148 (3.7%)	43 (1.1%)	703 (17.4%)
MSI High Frequency*	0.80% (n = 3987)	0.00% (n = 143)	7.00% (n = 43)	1.60% (n = 690)
***CD274* (*PD-L1*) Amp**	1.00%	1.40%	2.30%	0.40%
***STK11* Inactivating GA**	1.20%	1.40%	0.00%	0.40%
***MDM2* Amp**	8.80%	10.10%	11.60%	10.00%
Mean TMB	10.2	7.6	14.6	8.5
Median TMB	6.3	6.3	10	6.3
TMB > 10 mut/Mb	36.40%	26.30%	46.51%	27.88%
TMB > 20 mut/Mb	12.40%	6.10%	16.28%	7.68%
PD-L1 Low Positive*	18.32% (n = 131)	40.00% (n = 5)	100.00% (n = 1)	7.70% (n = 26)
PD-L1 High positive*	21.37% (n = 131)	20.00% (n = 5)	0.00% (n = 1)	3.84% (n = 26)

* value in parentheses indicate number of cases evaluable for the biomarker

4569 **Poster Session**

Germline variants across self-reported racial populations with urothelial carcinoma (UC). *First Author: Amin Nassar, Brigham and Women's Hospital, Boston, MA*

Background: Prior studies of the UC germline landscape centered around White patients with minimal representation of other racial populations. Herein, we examine the frequency of germline pathogenic and likely pathogenic (P/LP) variants in 2,582 patients with UC from various racial populations. **Methods:** 2,582 patients with UC underwent germline testing of 1 to 126 genes using massively parallel sequencing with customized capture bait-sets to analyze exonic regions, flanking intronic regions, and copy number alterations (CNAs). P/LP variants including single nucleotide variants, indels and CNAs were reported. Fisher's Exact test and multivariable logistic regression were used after accounting for the number of genes tested, age at diagnosis, site of disease (upper versus lower tract), gender, family history of UC, and personal history of any cancer. **Results:** Among the 2,582 patients with UC, median age at diagnosis was 63 years (range, 4-90) and 1158 (44.8%) were female. There were 58 Asians (2.2%), 110 Blacks (4.3%), and 2,414 Whites (93.5%). Overall, 1,639/2,582 (63.5%) patients had a personal history of another cancer and 284/2,393 (11.9%) had history of UC in a family member. 465 P/LP variants were identified in 18% of patients, among whom 286 (11.1%) harbored ≥1 clinically actionable variants. P/LP in cancer-associated genes were most frequently reported in *MSH2* (72/2,512, 2.9%), monoallelic *MUTYH* (45/2,136, 2.1%), *BRCA2* (44/2,299, 1.9%) and *MSH6* (47/2,511, 1.9%). Patients with upper tract UC had significantly more P/LP (72/247, 29.1%) compared to lower tract UC (332/2,076, 16%, $p = 1.3x10^{-5}$). Age at diagnosis, gender, personal history of other primary cancers, or family history of UC were not significantly associated with the prevalence of P/LP variants. There were no significant differences (p= 0.33) in P/LP variants across Asians (11/58, 19.0%), Blacks (14/110, 12.7%), and Whites (440/2,414, 18.2%) although a trend towards lower P/LP in Blacks is notable. Compared to Whites, Blacks and Asians harbored significantly more variants of unknown significance (VUS, Whites vs Blacks: 241/2414 vs 25/110, p= 0.0015; Whites vs Asians: 241/2414 vs 17/58, p= 4e-7). Asians with UC harbored significantly more P/LP variants in *ATM* (2/50, 4%) compared to Whites (30/2122, 1.4%, OR = 1.1 [95% CI, 1.0-1.2]) and Asian controls from the gnomAD Database. There were no significant differences across racial populations for other highly altered genes (*BRCA1/2, CHEK2, FH, MSH2/6, MUTYH*) or for actionable variants. **Conclusions:** Germline P/LP variants were identified in 18% of patients with UC and were enriched in upper tract tumors. Although no significant differences in P/LP prevalence were noted among patients of different racial populations, a trend towards lower P/LP in Blacks and a higher rate of VUS in Asians and Blacks suggest that ongoing analysis by genetic ancestry may provide richer admixture data and insights. Research Sponsor: InVitae.

4570 **Poster Session**

MRG002-006: A multicenter phase II clinical trial of MRG002-ADC for unresectable locally advanced or metastatic urothelial cancer. *First Author: Wang Qu, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: Overexpression of HER-2 is associated with poor prognosis of urothelial cancer, and anti-HER-2 antibody-drug conjugate (ADC) has shown a promising efficacy among the UC patients (pts) in recently studies. MRG002 is a novel HER2-targeted ADC being investigated in the MRG002-006 trial to evaluate the efficacy and safety in HER2 positive UC pts. **Methods:** This is a single-arm, multicenter phase II study. Eligibility criteria included: histologically HER2-positive (IHC 2+ or 3+) UC pts confirmed by a central-laboratory, ECOG PS 0-1, prior received ≥1 standard treatment. Approximately 40 pts will be enrolled. In the initial dose finding stage, pts were assigned to receive MRG002 at a dose of 2.6 mg/kg or 2.2 mg/kg administered by intravenous infusion every 3 weeks. The dose expanding stage was subsequentially performed based on preliminary results. The primary endpoint was ORR per RECIST 1.1, secondary endpoints are safety, DOR, PFS and, OS. **Results:** As of December 31, 2021, a total of 39 pts were enrolled. Enrollment is estimated be completed in February 28, 2022, and results are expected to be updated before publication. Nine pts were dosed at 2.6 mg/kg and 26 pts were dosed at 2.2 mg/kg. Based on safety analysis, 2.2 mg/kg was adopted as the recommended dosage. At baseline, 80% pts (28/35) had visceral metastasis. Most pts (28/35) received ≥ 2 lines of treatment and 29 (83%) pts had prior immune checkpoint inhibitor (ICI) therapy. By the cut-off date, 23 pts were evaluable and the ORR was 65% (15/23, 95% CI: 44.9%–81.2%), with 9% CR, and the DCR was 91% (21/23, 95% CI: 73.2%–97.6%). The estimated median PFS for the 23 pts was 5.5 months (95% CI: 2.7–NR). Among the evaluable pts, 1 CR responder achieved a response duration of more than 9.5 months. Subgroup analysis indicated that the ORR was 65% among the 17 pts post ≥ 2 lines of treatment, and 78% among the 18 pts failed platinum-containing chemotherapy and ICI treatment. Most common treatment-related AEs determined by investigators were anemia (34%), alopecia (34%), AST increased (31%), neutrophil count decreased (26%), neuropathy peripheral (23%), constipation (17%), decreased appetite (17%); most were grade 1 or 2 per CTCAE 5.0. The incidence of SAE was 17% (6/35). At the dose of 2.6mg/kg, 1 pts discontinued the treatment due to hypotension and 1 pts experienced ileus, which was considered caused by neurotoxicity of MRG002. There were no similar events described above happened among the pts at the dose of 2.2mg/kg. **Conclusions:** Preliminary results of MRG002 demonstrated a clinically meaningful response in pretreated HER-2 positive unresectable locally advanced or metastatic UC patients, especially in those progressed after platinum-containing chemotherapy and ICI therapy. MRG002 at 2.2mg/kg showed a manageable safety profile in these pts. Further evaluation is ongoing. Clinical trial information: NCT04839510. Research Sponsor: Shanghai Miracogen Inc.

4571 **Poster Session**

Genomic and immunologic profiles of concurrent RB1 and CDKN1A/p21(WAF1) truncating mutations (RW+) in bladder cancer. *First Author: Wafik S. El-Deiry, Cancer Center at Brown University, Providence, RI*

Background: p53 target and cell cycle inhibitor CDKN1A/p21(WAF1) was initially not found to be mutated in cancer. TCGA analysis identified CDKN1A mutations are present but rare with frequencies of < 1%, but enrich in bladder cancer (~8%). Truncating WAF1 mutations are associated with sensitivity to cisplatin and are associated with truncating Rb mutations in bladder cancer (RW+). We hypothesized RW+ bladder cancers may represent a unique subgroup with sensitivity to therapeutics. **Methods:** A total of 1104 urothelial tumors underwent molecular profiling at Caris Life Sciences (Phoenix, AZ) utilizing NGS of DNA (592 Gene Panel, NextSeq, or WES, NovaSeq) and RNA (NovaSeq, WTS). Wilcoxon, Fisher's exact were used for statistical significance (p value without and q value with multi comparison correction). Immune cell fraction (QuanTIseq) and pathway analysis (ssGSEA) were assessed by mRNA analysis. Immune epitope prediction was performed using the NetMHCpan v4.0 method in the Immune Epitope Database. **Results:** Concurrent truncating mutation (frameshift, nonsense) for RB1 and WAF1 were detected in 47 tumors (RW+, 4.25%) and tumors with wild-type status for both RB1 and WAF1 genes were classified as RW- group (54.08%). Tumors harboring only one RB1 or WAF1 mutation were excluded for further analysis. When compared to RW- group, RW+ tumors showed lower mutation rate of TP53 (54.5% vs 80.9%, q < 0.05), ARID1A (23.5% vs 38.3%, p < 0.05), and PIK3CA (18.4% vs 31.9%, p < 0.05). Interestingly, RW+ was mutually exclusive with FGFR3 mutation (18.0% vs 0%, p < 0.05). We further evaluated RNA expression of DNA repair and checkpoint arrest pathways. Notably, E2F pathway (Normalized Enrichment Scores, NES: 0.89 vs 0.86, q < 0.01) and DNA G2M checkpoint (NES: 0.89 vs 0.86, q < 0.01) were found to be the most enriched in RW+ with respect to RW- group. In addition, mRNA levels of FANCC/A, CHEK1, WEE1, CDC25A/C, PALB2 and BRCA1/2 were found to be overexpressed in RW+ group (q < 0.05). RW+ tumors also displayed a distinct immunological profile: They were associated with higher PD-L1 status (63.8% vs 37.3%, q < 0.01), higher median TMB (11 mut/Mb vs 8 mut/Mb, q < 0.01) and with less frequent loss of heterozygosity for HLA-DPA1 (51.1% vs 66.7%, p < 0.05), with more high-binding-affinity neoantigen load (4.78 vs 3.89, p < 0.05) to MHC proteins, consistent with the significantly more myeloid dendritic cells in in RW+ group (0.3 vs 0.04, q < 0.001). **Conclusions**: Concurrent truncating mutation in RB1 and WAF1 (RW+) bladder carcinomas have fewer p53, ARID1A, and PIK3CA mutations but are enriched for E2F targets, G2/M checkpoint genes, FANCC/A, CHEK1, WEE1, CDC25A/C, PALB2 and BRCA1/2 and have a distinct immunological profile. The findings suggest therapeutic strategies for RW+ bladder cancers including Chk1/Wee1, PARP inhibitors, -/+ immunotherapy that may impact on clinical outcomes. Research Sponsor: None.

4572 **Poster Session**

Assessment of a HER-2 scoring system and its correlation of HER2-targeting antibody-drug conjugate therapy in urothelial carcinoma. *First Author: Lei Lei, Department of Pathology, National Cancer Center/National Clinical Research Center for Cancer /Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: Human epidermal growth factor receptor 2 (HER2) overexpression is related to many tumor treatments. RC48-ADC, a novel humanized anti-HER2 antibody conjugated with monomethyl auristatin E, has shown a promising efficacy in patients with HER2-positive locally advanced or metastatic urothelial carcinoma (mUC). The characteristic expression and scoring systems of HER2 have existed in breast cancer, gastric cancer for many years, but not in UC. We aimed to explore the expression pattern of HER2 in UC and develop a validated HER2 scoring system. **Methods:** A total of 137 patients and 43 patients in two studies of cohort 1 and cohort 2 were enrolled, respectively. The patients of the cohort 2 were enrolled in the open-label, multicenter, phase II study of RC48-ADC. Formalin-fixed paraffin-embedded urothelial cancer samples were tested for HER2 status using the fluorescence in situ hybridization (FISH) PathVysion HER2 DNA probe kit (PathVysion, Abbott Molecular, USA). Immunohistochemistry (IHC) was performed using the Ventana Benchmark XT (Ventana Medical Systems, USA). The 2018 ASCO/CAP HER2 scoring system of breast cancer was adopted and modified to score HER2 expression level in UC. **Results:** The expression rate of HER2 (IHC 2+/3+) was 24.1% (33/137). In HER2 IHC status 3+ or 2+ patients, the *HER2* amplified rate was 31% (13/42). The objective response rates in RC48-ADC treatment patients with IHC 3+, IHC 2+ and FISH +, IHC 2+ and FISH - were 58.8%, 66.7% and 40%, respectively. Heterogeneity of HER2 protein expression was 55.5% (15/27) and the objective response rate had no significant difference between patients with tumor heterogeneity and homogeneity. **Conclusions:** The modified HER2 testing scoring system could be applied to UC to determine which patient might benefit from anti-HER2-ADC treatment. There was a trend towards a better benefit for patients with *HER2* amplification and the tumor heterogeneity did not influence the drug efficacy. Research Sponsor: None.

4573 **Poster Session**

Outcomes of patients with advanced urothelial cancer who develop infection while on treatment with pembrolizumab.

First Author: Ryan Blair Kieser, Houston Methodist Cancer Center, Houston, TX

Background: Over the past decade, studies have shown the benefit of immune checkpoint inhibitors (IO) in patients with advanced urothelial cancer. These agents work by reconditioning the adaptive anti-cancer immune response within the tumor microenvironment. Immune-related adverse events have been well documented, but there is limited data evaluating infections in patients treated with IO. We performed a retrospective analysis to assess the incidence of infection and its effect on morbidity and mortality in patients treated with pembrolizumab for advanced urothelial cancer. **Methods:** Data was collected from a network of 7 hospitals for patients who received pembrolizumab for advanced urothelial cancer from 1/1/2017-8/1/2021. Date of last follow up was 12/1/2021. Covariates compared among infected and non-infected cohorts included age, gender, race, comorbidities, ECOG, anti-infective therapy at IO initiation, and line of therapy (1L, 2L, > 2L). Univariable analysis with reported odds ratio (OR) and 95% confidence interval (CI) was used to assess risk factors for infection. Outcome measures included all-cause emergency department (ED) visits, inpatient and intensive care unit (ICU) admissions, median number of IO cycles, and overall survival (OS). OS was evaluated using the Kaplan-Meier model. All analyses were deemed statistically significant if the p-value was < 0.05. **Results:** A total of 51 patients were identified. Of these, 34 (66.7%) had at least one documented infection and 17 (33.3%) had no reported infections. Baseline characteristics were similar across cohorts. Compared to non-infected patients, infected patients received fewer cycles of IO (median 4 vs 8, p = 0.016). At last follow-up, 20 (58.8%) patients in the infected cohort and 4 (23.5%) in the non-infected cohort died (p = 0.017). Median OS was 7.4 months (95% CI: 3.4-24.9) among patients with infection while not reached in those without infection (p = 0.014). ED visits (p = 1.00), inpatient admissions (p = 0.21), and ICU admissions (p = 0.17) did not significantly differ between cohorts. Univariable analysis did not identify significant risks among covariates. **Conclusions:** The incidence of infection in patients treated with pembrolizumab for advanced urothelial cancer is high and associated with fewer cycles of IO therapy and shorter OS. Further study of infectious process prevention is of value to maximize immunotherapy benefit. Research Sponsor: None.

4574 **Poster Session**

Preliminary results from phase Ib/II neoadjuvant CG0070 and nivolumab (N) for cisplatin (C)-ineligible muscle invasive bladder cancer (MIBC).

First Author: Roger Li, Department of Genitourinary Oncology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL

Background: CG0070 is a replication-competent oncolytic adenovirus engineered to target RB deficient tumor cells and to express GM-CSF. CG0070 has previously demonstrated safety and efficacy against BCG-exposed high risk non-muscle invasive bladder cancer through tumor lysis and anti-tumor immune activation. We tested the safety and efficacy of CG0070 in combination with N as neoadjuvant therapy for MIBC in C-ineligible patients in this study (NCT04610671). **Methods:** C-ineligible pts with MIBC (cT2-4a, N≤1) were enrolled. Pts received 6 weekly intravesical CG0070 ($1x10^{12}$vp) and 2 doses of N at wks 2 and 6, followed by radical cystectomy (RC). The primary objective is safety of CG0070+N as measured by CTCAEv5.0. Secondary objective is to assess pathologic response (PaR) (pTON0). Exploratory objectives include the assessment of correlation between PaR with baseline 1) E2F expression; 2) immune infiltration; 3) PD-L1 expression; and 4) TLS expression. Results from a prespecified interim analysis following accrual of 15 patients is reported herein. **Results:** Between Nov 2020 and Jan 2022, 15 pts were enrolled with median age 75.5yrs, 73% male, 47% > cT2; 1 patient refused RC but was included in the ITT population. No DLTs were encountered. The overall rate of grade 3-4 AEs was 10/15 (75%), and the vast majority were related to RC (90%). Immune related AEs were seen in one pt, who had grade 2 autoimmune thyroiditis. There was no delay in time to RC and no unexpected surgical complications from treatment. PaR was observed in 6/13 (46%) evaluable pts, and an additional pt had negative post-treatment biopsy but refused RC. **Conclusions:** Neoadjuvant CG0070+N is safe and effective in C-ineligible pts with MIBC. This combination was well tolerated without any delays in RC and induced an overall response rate of 54%. Clinical trial information: NCT04610671. Research Sponsor: U.S. National Institutes of Health, CG Oncology.

Baseline characteristics.

Age	
Median	75.5
Range	56-86
Sex (%)	
Male	11 (73)
Female	4 (27)
Histology	
Squamous	5 (33)
Glandular	2 (13)
Sarcomatoid	1 (7)
Plasmacytoid	1 (7)
Clinical Stage age Baseline (%)	
T2	8 (53)
T3	6 (40)
T4	1 (7)
Reasons for cisplatin ineligibility (%)	
Renal insufficiency	8 (53)
Hearing impairment	5 (33)
Neuropathy	1 (7)
Declined chemotherapy	1 (7)

4575 **Poster Session**

Benchmarking maintenance therapy survival in first-line advanced urothelial carcinoma using disease modeling.

First Author: Matt D. Galsky, The Tisch Cancer Institute, Mount Sinai, New York, NY

Background: First-line (1L) maintenance avelumab (maintA) in patients with advanced urothelial carcinoma (aUC) prolonged overall survival (OS) in the JAVELIN Bladder 100 trial. JAVELIN measured OS from the initiation of maintA among a subgroup of the overall aUC 1L treated population, including only patients who did not progress with 1L platinum-based therapy (PBT) and remained progression free during a 4-10 week treatment-free interval following completion of 1L PBT. As such, patients who progressed on or immediately following PBT were not included in the trial. To address this, we used disease modeling to estimate maintA OS measured from initiation of 1L PBT to align maintA OS with the common initiation point to benchmark with other 1L clinical trials. **Methods:** We developed a simulated cohort to estimate OS from initiation of 1L PBT in all aUC patients including those who received maintA. Eligibility for maintA (PBT progressed vs not progressed) was assessed at 5.6 months post-initiation of 1L PBT, accounting for 6 PBT cycles and a nominal 6-week treatment-free interval. Median OS of 14.3 months from the 1L PBT arm of a recent 1L trial, KEYNOTE-361, was used to represent the OS of the simulated cohort of 1L aUC patients. The simulated cohort was stratified by eligibility for maintA. Among the 1L treated population, 57% were projected to be progression-free and eligible for maintA based on progression-free survival (PFS) from KEYNOTE-361. Among those eligible, 85% were assumed to receive maintA based on expert clinical input. OS of maintA eligible patients was 21.4 months from JAVELIN. Our disease model estimated OS among a maintA ineligible simulated cohort, which was combined with the maintA eligible cohort to yield an estimated OS in the overall aUC population measured from initiation of 1L PBT. **Results:** Approximately 50% of the 1L modeled population receive maintA (i.e., 57% eligible x 85% treated). Our approach estimated a median OS of 9.9 months for the maintA ineligible cohort and 27.0 months for the maintA eligible cohort. Combined, the estimated median OS with maintA, measured from initiation of 1L PBT, in all 1L-treated aUC patients was 15.8 months (vs 14.3 months with PBT only in 1L). **Conclusions:** MaintA improves OS for eligible patients, however our simulation model suggests a significant proportion of patients will not receive MaintA. The estimated OS of 15.8 months for the population-level impact of maintA, accounting for patients ineligible for 1L maintA, demonstrates remaining unmet need in the overall 1L aUC population. Research Sponsor: Seagen Inc. and Astellas, Inc.

4576 **Poster Session**

Digital score of lymphocytic infiltration in tumor-associated stroma in relation to overall survival in bladder cancer.

First Author: Robert Jewsbury, University of Warwick, Coventry, United Kingdom

Background: Bladder Urothelial Carcinoma (BLCA) is the most common type of bladder cancer and the sixth most frequent cancer in the US. High numbers of lymphocytes colocated with tumour-associated stromal (TAS) tissue has demonstrated prognostic significance for overall survival in multiple cancers. Our goal in this study was to explore the prognostic significance of an automated score to quantify the colocalisation of lymphocytes and TAS for overall survival (OS) in BLCA patients from Haematoxylin & Eosin (H&E) stained Whole Slide Images (WSIs). **Methods:** Two cohorts of BLCA patients were included in this study. From the UK, a cohort of 67 BLCA patients constituted cohort A. We also evaluated our method on The Cancer Genome Atlas (TCGA) bladder cancer cohort of 453 cases, which we refer to as cohort B. We developed a two-stage method for digital quantification of lymphocytic infiltrates in TAS. First, we employed an AI algorithm to recognise and classify different regions as areas of high concentration of tumour, lymphocytes and stroma for each WSI creating a segmentation map of the different tissue types. For patients with multiple WSIs, we used the slide with the highest percentage of tumour to predict survival. This algorithm had been pre-trained on a cohort of Oral cancer and was fine-tuned using annotations from 4 BLCA WSIs, 3 from cohort A and 1 from cohort B. These WSIs were excluded from the final survival analysis. Using the segmentation maps, a statistical measure for the colocalisation of TAS and lymphocytes termed the tumour-associated stroma infiltrating lymphocytes or (TASIL) score was computed. Finally, for each cohort, data was right-censored at 10 years and the digital BLCA-TASIL (BT) score's prognostic significance for OS was investigated by fitting a Kaplan-Meier estimator and Cox proportional hazard (PH) analysis, stratifying patients into two groups based on the BT score. In each cohort, two thirds of the data was used as the discovery set to determine the best cut-off for the TASIL Score and the remaining third was used as the validation set. **Results:** Our classification algorithm achieved high average F1-score of 0.88 on a held-out set of unseen data for the classification of tumour, lymphocytic and stromal regions. In cohort A, higher BT score was strongly associated with better OS (P= 0.00906) on the unseen validation data. This significant association was also found in the validation data of cohort B (P< 0.001). Using the BT score as the only covariate, a Cox PH model for the validation data resulted in a C-index of 0.73 for cohort A and 0.57 for cohort B, respectively. **Conclusions:** The digital BT score showed significant prognostic value for overall survival in both BLCA cohorts, reinforcing the findings of prior work. We intend to further validate these findings on another cohort. To the best of our knowledge, this is the first attempt to predict survival solely from H&E slides in BLCA. Research Sponsor: University of Warwick.

4577 **Poster Session**

Defining "platinum-ineligible" patients with metastatic urothelial cancer (mUC). *First Author: Shilpa Gupta, Taussig Cancer Institute, Cleveland Clinic Foundation, Cleveland, OH*

Background: Treatment (tx) landscape has evolved significantly for cisplatin-ineligible mUC patients (pts). Carboplatin and gemcitabine followed by avelumab (Av) maintenance is the current preferred standard. Although pembrolizumab (P) and atezolizumab (At) were approved as 1L therapy for these pts in 2017, the FDA has now restricted the use of 1L P to "platinum ineligible" mUC pts. We previously suggested a consensus definition for "platinum-ineligible" pts with mUC (Gupta et al. ASCO GU 2019). We now updated the consensus definition for standard therapy and clinical trial eligibility in the current tx era. **Methods:** We surveyed 60 genitourinary medical oncologists in the US (similar cohort to 2019) using an online tool consisting of several clinical parameters used in our initial survey with additional questions related to current available tx options. Different age and creatinine thresholds in combination with ECOG PS along with other clinically relevant established criteria were analyzed. We compiled the responses to generate a consensus definition. **Results:** All 60 respondents provided 100% responses. Respondents (94%) reported using a carboplatin-based regimen followed by Av and 6% reported using carboplatin-based regimen followed by P for cisplatin-ineligible mUC pts. 17/60 (28.3%) and 29/60 (48.3%) checked PD-L1 status prior to using P or At respectively. Survey results for the most common responses are presented in the Table. **Conclusions:** Based on the survey, any mUC pt meeting one the following 5 parameters should be considered "platinum-ineligible": ECOG PS > / = 3; Cr Cl < 30 ml/min; peripheral neuropathy > / =Grade 2; NYHA Heart Failure Class > 3; ECOG PS 2 AND Cr Cl < 30 ml/min. These criteria are proposed to guide treatment recommendations and standardization of eligibility criteria. Research Sponsor: None.

What threshold ECOG PS should be used to define "platinum-ineligibility"?	ECOG PS > / = 3	# Responses 41/60 (68.3%)
What threshold Cr Cl should be used for "platinum-ineligibility"?	< 30 ml/min	# Responses 41/60 (68.3%)
What grade of peripheral neuropathy would you consider for "platinum-ineligibility"?	> / = Grade 2	# Responses 32/60 (53.3%)
What class of Heart Failure do you consider to define "platinum-ineligibility"?	NYHA Class III	# Responses 48/60 (80%)
In a patient with ECOG PS 2, what Cr Cl cut-off would you use to define "platinum-ineligibility" differently of what is used for "cisplatin-ineligibility"?	< 30 ml/min	# Responses 29/60 (48.3%)

4578 **Poster Session**

Association of antibiotic therapy and treatment efficacy in urothelial cell carcinoma patients receiving immune checkpoint inhibitors. *First Author: Avery Braun, Einstein Healthcare Network, Philadelphia, PA*

Background: The content of gut microbiome has been linked to the effectiveness of immune checkpoint inhibitory (ICI) therapy in various cancer types. Antibiotic therapy (ABT) induces significant alterations in gut microbiota; however, only a limited number of single-institutional studies have examined the impact of ABT on ICI treatment. Utilizing a national database, we sought to provide 'real world outcomes' by investigating the association between ABT and ICI on overall survival (OS) and real-world progression free survival (rwPFS) in advanced urothelial carcinoma (aUC). **Methods:** We used the electronic health record (EHR)-derived de-identified FlatIron Health (FIH) database after Institutional Review Board approval was obtained, and included a waiver of informed consent to select 1491 subjects with aUC who received ICI therapy. Patient characteristics were described and compared between those with known ABT use and without known ABT use (in the 3 months pre/post ICI initiation), using ANOVA and Chi-square tests. rwPFS and OS were calculated from date of initiation of ICI to date of real-world progression/date of death. 3-month landmark Kaplan Meier methods and log-rank tests were used to estimate and compare rwPFS and OS between patients with-ABT and without-ABT, as well as patients with ABT use pre-ICI initiation, post-ICI initiation, and no known ABT use. Cox proportional models were used to investigate the association between rwPFS, OS, and antibiotic use, adjusting for patient characteristics. **Results:** In patients who received ICI, we included 407 patients who received ABT and 1084 who did not. Those who received ABT were younger ($p < 0.001$), more likely Caucasian ($p = 0.046$) and insured by Medicare ($p < 0.001$). rwPFS (median: 9.0 vs 10.0 months; $p = 0.41$) and OS (median: 14.0 vs 16.0 months; $p = 0.073$) were not significantly different between the with or without ABT subgroups. We included 101, 182, and 715 patients who received ABT prior to ICI, after ICI initiation, or did not receive ABT. When assessing timing of ABT, there was a significant difference in OS amongst pre-ICI initiation ABT, post-ICI initiation ABT and no known ABT groups (median: 17.0 vs 10.9 vs 16.0; $p = 0.005$). However, rwPFS (median: 10.1 vs 7.5 vs 10.0 months; $p = 0.22$) was not statistically different. Multivariable analysis identified no antibiotic use as a significant predictor of improved OS (HR 0.733, CI 0.598-0.898; $p = 0.003$). Other factors associated with OS were male gender (HR 1.158, CI 1.005-1.335; $p = 0.043$) and receipt of extirpative surgery (HR 0.785, CI 0.684-0.900; $p < 0.001$). **Conclusions:** This study identifies a potential negative association of ABT and OS, particularly after starting ICI. These results support the relevance of the gut microbiome on the efficacy of ICI treatment, may guide future efforts to improve the efficacy of ICI, and emphasize the importance of antibiotic stewardship. Research Sponsor: None.

4579 **Poster Session**

Phase Ib study of avelumab and novel AXL inhibitor avb-S6-500 in patients with metastatic urothelial carcinoma (mUC). *First Author: Abhishek Tripathi, Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK*

Background: AXL is a member of the mammalian Tyro3/AXL/Mer (TAM) receptor tyrosine kinase family, which upon binding to its ligand Gas6 promotes immunosuppression in the tumor microenvironment. AVB-S6-500 (AVB) is a novel AXL pathway inhibitor which binds to circulating Gas6 and inhibits ligand-dependent AXL signaling. In this phase Ib investigator-initiated trial (NCT04004442), we evaluated the safety, tolerability, pharmacodynamics, and preliminary antitumor efficacy of AVB with the anti-PD-L1 antibody avelumab in mUC. **Methods:** Patients with PD-1/L1 inhibitor naïve locally advanced unresectable or mUC with measurable disease were eligible if they were either in-eligible for, refractory to, or declined platinum-based chemotherapy. Employing a 3+3 dose escalation design, patients were treated with AVB 5mg/kg weekly (dose level; DL1), or 10 (DL2), 15 (DL3), or 20 (DL4) mg/kg every two weeks along with avelumab 800 mg every 2 weeks administered intravenously. The safety and tolerability of the combination as measured by the incidence of dose limiting toxicities (DLTs) was the primary endpoint while objective response rate (ORR) per RECIST 1.1 was key secondary endpoint. Pharmacodynamic studies evaluated baseline and on therapy (C2D1) Gas6 levels. **Results:** To date, a total of 15 patients have been enrolled (DL1: n = 3, DL2: n = 7, DL3: n = 3 and DL4: n = 2). Among the 13 evaluable patients, DLT was observed in 1 patient (grade 3 fatigue; DL2). Grade ≥3 adverse events irrespective of attribution were seen in 6 patients which included UTI (n = 3), hyponatremia (n = 1), elevated creatinine (n = 1), and anemia, thrombocytopenia, hematuria, anorexia and sepsis (n = 1 each; all in same patient). No treatment related deaths were noted. While enrollment on DL4 is ongoing, the maximum tolerated dose for AVB has not been reached. Treatment with AVB effectively suppressed circulating Gas6 levels from baseline (median: 28.4 ng/mL; range: 20.4-54.0 ng/mL) to below threshold of detection in 85% (n = 11/13) of patients. Median follow up was 10 months (95% CI: 3.9, 18.55). Confirmed ORR was 38% (n = 5/13) while 1 patient had stable disease as best response. Durable responses lasting > 6 months were seen in 3 patients (7, 19 and 21 mos) who continue to be on treatment without disease progression. Additional correlative studies investigating AXL, Gas6, PD-L1 expression and gene expression signatures are currently underway. **Conclusions:** Concurrent avelumab and AVB was safe and AVB effectively neutralized circulating Gas6 across DLs. Albeit small sample size, the efficacy of the combination was encouraging and ORR compares favorably to that previously reported with PD-1/L1 inhibitor monotherapy. Updated safety, efficacy and biomarker data will be presented. Clinical trial information: NCT04004442. Research Sponsor: This research was financially supported by EMD Serono CrossRef Funder ID: 10.13039/100004755), as part of an alliance between the healthcare business of Merck KGaA, Darmstadt, Germany and Pfizer. Aravive Inc. also provided drug and funding support.

4580 **Poster Session**

Interim results from a multicenter clinical study of tislelizumab combined with gemcitabine and cisplatin as neoadjuvant therapy for patients with cT2-T4aN0M0 MIBC. *First Author: Tianxin Lin, Department of Urology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China*

Background: To evaluate the efficacy and safety of tislelizumab combined with gemcitabine and cisplatin as neoadjuvant therapy for patients (pts) with clinical T2-T4aN0M0 (cT2-T4aN0M0) muscle-invasive bladder urothelial cancer (MIBC). **Methods:** This multicenter, open-label, single arm phase II study enrolled pts tolerated with the cisplatin therapy. Eligible pts received tislelizumab 200 mg in day 1 (D1), cisplatin 70 mg/m^2 D2, and gemcitabine 1000 mg/m^2 D1 and D8 every 21 days for four cycles. Radical cystectomy (RC) was performed within 6 weeks after last dose treatment. The primary end point was pathologic complete response (pCR, pT0N0M0). Secondary end points were pathologic downstaging (≤pT1N0M0), EFS, OS and safety. Simon two-stage design was used. If > 5 pts achieved pCR in the first stage (n = 22), study would proceed to the second stage and enroll 33 additional pts. If > 18 of 55 pts achieved pCR, we would deem the study to have met the primary endpoint. **Results:** We reported the results in the first stage. By Oct 2021, 23 eligible pts were enrolled. Eighteen pts have completed neoadjuvant therapy, with median age of 62 (48-72) years and 8 (44.4%) pts of PD-L1 positive, among whom 17 pts underwent RC and one declined RC. At the data cut off time of 14th Jan 2022, among 17 evaluable pts (12 cT2, 3 cT3, and 2 cT4a), 10 (58.8% [95% CI, 32.9-81.6]) pts achieved pCR and 13 (76.5% [95% CI, 50.1-93.2]) achieved pathologic downstaging. No significant differences were found in pCR (62.5% vs. 55.6%) and downstaging (75.0% vs. 77.8%) rates between pts with PD-L1 positive versus PD-L1 negative. Eighteen pts completed 71/72 cycles of tislelizumab, 68/72 cycles of cisplatin and 135/144 cycles of gemcitabine therapy. The rate of dose reduction (all due to AEs) of cisplatin and gemcitabine therapy was 25.0% (17/68 cycles) and 23.7% (32/135 cycles), respectively. The relative dose intensity of tislelizumab, cisplatin and gemcitabine were 93.6%, 84.5% and 85.9%, respectively. Most common neoadjuvant therapy related AEs of any grade were hematologic toxicities (94.4%), nausea (72.2%), vomiting (61.1%), decreased appetite (55.6%), fatigue (27.8%), pruritus (22.2%) and ALT/AST increased (22.2%). Grade ≥3 neoadjuvant therapy related AEs were neutropenia (n = 6), thrombocytopenia (n = 4), anemia (n = 2) and lymphocyte count decreased (n = 1). Eight pts experienced grade 1-2 immune related AEs, including pruritus (n = 4), rash (n = 2), ALT/AST increased (n = 4), GGT increased (n = 2), CPK increased (n = 1), hyperthyroidism (n = 1), hypothyroidism (n = 1). **Conclusions:** Neoadjuvant tislelizumab combined with gemcitabine and cisplatin showed promising anti-tumor activity with high pCR and well tolerance in MIBC pts. The target of first stage has been achieved, and enrollment is ongoing. At the data cut off 14th Jan 2022, 34 pts have been enrolled. Clinical trial information: ChiCTR2000037670. Research Sponsor: BeiGene (Beijing) Co., Ltd.

4581 **Poster Session**

S1314 correlative analysis of ATM, RB1, ERCC2, and FANCC mutations and pathologic complete response (pT0) at cystectomy after neoadjuvant chemotherapy (NAC) in patients with muscle invasive bladder cancer (MIBC): Implications for bladder preservation. *First Author: Elizabeth R. Plimack, Fox Chase Cancer Center, Philadelphia, PA*

Background: SWOG S1314 (NCT02177695) was designed to validate the CoXEN classifier as a predictive biomarker in pts undergoing cystectomy after NAC. We repurposed banked DNA samples and prospective trial data from S1314 to further validate the predictive ability of the Philadelphia 4 gene signature (P4GS: any mutation in ATM, RB1, FANCC, ERCC2) to predict pT0 as previously reported (PMID: 26238431) and used in the RETAIN trial (NCT02710734). The RETAIN trial prospectively enrolled pts to receive NAC (DDMVAC) followed by allocation to bladder observation vs. intervention (cystectomy or RT) based on clinical evaluation and presence vs absence of P4GS. The primary objective of this correlative investigation was to determine whether presence of P4GS is predictive of pT0 at surgery. **Methods**: Eligibility for S1314 included cT2-T4a N0 M0 MIBC, cisplatin eligible, with plan for cystectomy; 237 pts were randomized between ddMVAC and gem/cis (GC) using standard dose/schedule. Of 167 pts who were evaluable for the original COXEN analysis (received 3+ cycles of chemo and evaluable for path response) adequate banked DNA was available for 105. Next-generation sequencing using the CARIS 592 Gene Panel (Caris Life Sciences, Phoenix, AZ) was performed. Pathogenic mutation or VUS of ATM, RB1, FANCC or ERCC2 was noted as present or absent for each pt and correlated with pT0 using logistic regression, adjusting for clinical stage. **Results**: Among the 105 pts, 51% ddMVAC, 49% GC. 15% female, 95% white, 15% clinical stage T3/T4a Prevalence of mutations: ATM (24%), ERCC2 (17%), FANCC (4%), RB1 (24%) and any variant 53%. Presence of any mutation correlated with pT0 (p = 0.0006), sensitivity 79%, specificity 59%. This association did not vary by treatment arm (MVAC vs. GC). The table below shows the contributions of each of the 4 genes with the greatest contribution from ATM and ERCC2. FANCC was non-contributory due to low prevalence. **Conclusions**: Patients with a mutation in ATM, RB1, FANCC or ERCC2 (P4GS) have a statistically significantly higher odds of a pT0 with GC or MVAC compared to those who do not have any variant. This signature was used to prospectively allocate patients to bladder observation as part of the RETAIN trial previously reported (ASCO GU 2021). RETAIN completed enrollment, final analysis of the primary endpoint – 2-year metastasis free survival – is expected later in 2022. Clinical trial information: NCT02177695. Research Sponsor: The Family of George A. Zazanis, MD, Other Government Agency, Pharmaceutical/Biotech Company, U.S. National Institutes of Health.

4582 **Poster Session**

Study EV-103 Cohort H: Antitumor activity of neoadjuvant treatment with enfortumab vedotin monotherapy in patients with muscle-invasive bladder cancer who are cisplatin-ineligible. *First Author: Daniel P. Petrylak, Yale Cancer Center, New Haven, CT*

Background: Up to 25% of all patients (pts) diagnosed with urothelial cancer present with muscle-invasive disease for whom the risk of progression or metastasis is substantial. Neoadjuvant chemotherapy prior to radical cystectomy and pelvic lymph node dissection (RC+PLND) has been shown to prolong overall survival for patients who are cisplatin (cis) eligible. The standard of care for cis-ineligible pts undergoing surgery does not include neoadjuvant therapy. Therefore, safe and effective neoadjuvant therapies are an unmet need for cis-ineligible pts with muscle invasive bladder cancer (MIBC). Enfortumab vedotin (EV) is an antibody-drug conjugate directed to Nectin-4, which is highly expressed in urothelial cancer, and has been shown to benefit previously treated locally advanced or metastatic urothelial cancer pts in phase 2 and 3 trials, including cis-ineligible pts. **Methods:** Cohort H of the EV-103 phase 1b/2 trial (NCT03288545) enrolled pts with cis-ineligible cT2-T4aN0M0 MIBC who were eligible for RC+PLND and had an ECOG of 0-2. Pts received 3 cycles of neoadjuvant EV (1.25 mg/kg) on Days 1 and 8 of every 3-week cycle prior to RC+PLND. The primary endpoint of the study was pathological complete response rate (pCRR; ypT0N0) by central review. Key secondary endpoints included pathological downstaging (pDS) rate (ypT0,Tis,Ta,T1,N0) and safety. Results from a preliminary analysis are presented. **Results:** 22 pts were treated. Pts had cT2 (68.2%), cT3 (27.3%), and cT4 (4.5%) tumors. 68.2% pts had predominant urothelial cancer; 31.8% had a mixed histology. 19 pts completed all 3 cycles of EV. 21 underwent RC+PLND, and 1 had a partial cystectomy. 36.4% pts had a pCR. pDS was seen in 50.0% pts. The most common EV treatment-related adverse events (TRAEs) were fatigue (45.5%), alopecia (36.4%), and dysgeusia (36.4%). 18.2% pts had Grade ≥3 EV TRAEs. No surgeries were delayed due to EV administration. 3 pts had Grade 5 AEs while on study that were unrelated to EV; in 2 pts these AEs occurred > 30 days after RC+PLND. **Conclusions:** Observed pCRR after neoadjuvant EV showed promising activity in cis-ineligible pts with MIBC who have a high unmet need. Adverse events were consistent with the known safety profile of EV. This first disclosure of data supports the ongoing phase 2 and 3 programs evaluating EV in MIBC. Clinical trial information: NCT03288545. Research Sponsor: Seagen Inc. and Astellas Pharma Inc.

4583 **Poster Session**

Clinical utility of urine DNA for noninvasive detection and minimal residual disease monitoring in urothelial carcinoma. *First Author: Zhisong He, Department of Urology, Peking University First Hospital, Institute of Urology, Peking University, Beijing, China*

Background: Current methods for the early detection and minimal residual disease (MRD) of urothelial carcinoma (UC) are often invasive and/or possess sub-optimal sensitivity, especially in upper tract urothelial carcinoma (UTUC). **Methods:** We developed an efficient workflow named the urine tumor DNA multidimensional bioinformatic predictor, utLIFE, by using low-coverage whole-genome sequencing and targeted deep sequencing. We identified the UC specific mutations and large CNV in the discovery cohort. The utLIFE-UC model was trained in a bladder cancer retrospective cohort (n = 150) and validated in an bladder cohort(n = 674) and UTUC cohort(n = 22). 31 patients established diagnosis of BC who are on neoadjuvant were also enrolled, including a MRD training cohort (n = 16) with serial urine samples at baseline, during treatment and before surgery; a independent MRD validation cohort (n = 15) with urine samples before surgery. **Results:** The utLIFE-UC model could discriminate UC with high accuracy (94.3%), sensitivity (92.8%), and specificity (96.0%). Furthermore, compared to cytology, the assay achieved a great improvement in sensitivity in the detection of non–muscle-invasive bladder cancer (NMIBC, 94.7% vs. 31.6%,p = 0.0002), and muscle-invasive bladder cancer(-MIBC, 82.6% vs. 69.6%, p = 0.4894). The utLIFE-UC model was also validated in independent BC cohort (sensitivity 94.3%, specificity 92.6%) and UTUC cohort (sensitivity 90.9%, specificity 90.9%). utLIFE-UC score also showed outstanding potential on dynamic surveillance of residual disease in UC as the score showed dramatically decreased in pCR patients. As expected, utLIFE-UC score could classify pCR and non-pCR(PR, SD, PD) with NPV 100% in MRD training and validation cohorts, which showed superior sensitivity over that of urine cytology (100% vs.37.5%, p = 0.0070) and FISH (100 vs. 42.9%, p = 0.0125). **Conclusions:** utLIFE-UC diagnostic model for early diagnosis, residual disease detection in UC is a cost-effective, rapid, high-throughput, noninvasive, and promising approach, which may reduce the burden of cystoscopy and blind surgery. Research Sponsor: None.

4584 **Poster Session**

Biomarkers of response to neoadjuvant atezolizumab with gemcitabine and cisplatin in muscle-invasive bladder cancer. *First Author: Michael Lattanzi, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: We previously reported the clinical outcomes of a positive multi-center phase II trial of neoadjuvant gemcitabine (G) and cisplatin (C) plus atezolizumab (A) in patients with muscle-invasive bladder cancer (Funt, et al. JCO 2022). In this and another trial of neoadjuvant GC with pembrolizumab (Rose et al, JCO 2021), PD-L1 positivity by immunohistochemistry was not predictive of non–muscle-invasive downstaging (< pT2N0). Therefore, we investigated other pre-treatment tissue-based genomic and gene expression biomarkers of response and resistance. **Methods:** 36 pts had pre-treatment tissue available for genomic analysis. We performed targeted hybridization capture DNA sequencing using the CLIA-certified MSK-IMPACT platform and whole transcriptome RNA sequencing. We examined genomic and gene expression biomarkers which have been previously investigated in the context of neoadjuvant cisplatin-based chemotherapy or anti-PD-1/L1 immunotherapy for MIBC, including tumor mutation burden (TMB), a DNA damage response (DDR) 9-gene panel (NCT03609216) associated with response to neoadjuvant chemotherapy, and an 8-gene cytotoxic T cell transcriptional signature associated with response to neoadjuvant A (tGE8; Powles et al, Nature Medicine 2019). We also evaluated TGF-β pathway activation, which was associated with resistance to A in pts with metastatic BC (Mariathasan et al, Nature 2018). Putative biomarkers were assessed for correlation with < pT2N0, the trial's primary endpoint. **Results:** DNA was available from all 36 pts, and RNA met quality control metrics for 29 pts. TMB was significantly higher in pts with < pT2N0 (median 16 mut/Mb, IQR 12-25) versus ≥ pT2N0 (median 10 mut/ Mb, IQR 8-10; p < 0.01). A single patient had a TMB > 200 Mut/Mb with a *POLE* hotspot mutation and achieved pT0N0; TMB was still significantly higher in responders after omission of this patient (p < 0.01). Nine of 25 pts (36%) with < pT2N0 had a deleterious DDR mutation versus 1 of 10 pts (10%) with ≥ pT2N0 (p = 0.13). While tGE8 was significantly increased in patients with < pT2N0 compared to those without (p = 0.01), TGF-β pathway activation was not increased in pts with ≥ pT2N0 (p = 0.99). **Conclusions:** TMB and the tGE8 cytotoxic T cell transcriptional signature were associated with response to combination GC+A in muscle-invasive bladder cancer. More detailed molecular analyses will be reported. Clinical trial information: NCT02989584. Research Sponsor: Genentech, Inc., U.S. National Institutes of Health.

4585 **Poster Session**

Results for patients with muscle-invasive bladder cancer (MIBC) in the CheckMate 274 trial. *First Author: Alfred Alfred Witjes, Radboud University, Nijmegen, Netherlands*

Background: In the CheckMate 274 trial, disease-free survival (DFS) was significantly improved with nivolumab (NIVO) vs placebo (PBO) both in intent-to-treat (ITT) patients (pts) (hazard ratio [HR], 0.70; 98.22% confidence interval [CI], 0.55–0.90; $P < 0.001$) and in pts with tumor programmed death ligand 1 (PD-L1) expression ≥ 1% (HR, 0.55; 98.72% CI, 0.35–0.85; $P < 0.001$). We report results for the subgroup of pts with bladder cancer, the most predominant type of urothelial carcinoma. **Methods:** CheckMate 274 is a phase 3, randomized, double-blind trial of adjuvant NIVO vs PBO in high-risk muscle-invasive urothelial carcinoma (bladder, ureter, renal pelvis) after radical resection. Pts were randomized 1:1 to NIVO 240 mg intravenously every 2 weeks or PBO for ≤ 1 year of adjuvant treatment and stratified by nodal status, prior neoadjuvant cisplatin, and tumor PD-L1 expression. Pts had radical resection ± neoadjuvant chemotherapy and were at high risk of recurrence on final pathologic staging. Primary endpoints were DFS in ITT pts and in pts with PD-L1 ≥ 1%. Non–urothelial tract recurrence-free survival (NUTRFS) was a secondary endpoint, and distant metastasis-free survival (DMFS) was an exploratory endpoint. This exploratory analysis focused on the subgroup of pts with muscle-invasive bladder cancer (MIBC) after radical resection. **Results:** Of 709 randomized pts in the trial, 560 had MIBC (NIVO, n = 279; PBO, n = 281). With a minimum follow-up of 11.0 months, a DFS benefit was observed with NIVO vs PBO in these pts, regardless of tumor PD-L1 expression (Table). DFS probability at 12 months in all MIBC pts was 66% with NIVO and 45% with PBO. DFS was improved with NIVO vs PBO across subgroups according to age, sex, ECOG performance status, nodal status, and PD-L1 expression status. Improvement in NUTRFS and DMFS with NIVO vs PBO was also observed (Table). Grade 3–4 treatment-related adverse events occurred in 17% and 6% of pts in the NIVO and PBO arms, respectively. **Conclusions:** Improvement in DFS was observed with NIVO over PBO in pts with MIBC after radical resection regardless of tumor PD-L1 expression. The DFS benefit was observed in all prespecified subgroups. These results further support adjuvant NIVO as a standard-of-care treatment for pts with high-risk MIBC after radical resection ± neoadjuvant cisplatin-based chemotherapy. Clinical trial information: NCT02632409. Research Sponsor: Bristol Myers Squibb.

		NIVO		PBO		
		No. of events/ no. of patients	Median (95% CI), months	No. of events/ no. of patients	Median (95% CI), months	HR (95% CI)
DFS	All MIBC	133/279	25.8 (18.9–48.2)	173/281	9.4 (7.4–13.7)	0.61 (0.49–0.77)
	MIBC, PD-L1 ≥ 1%	42/113	NR (25.8–NE)	72/117	8.4 (5.2–15.2)	0.46 (0.31–0.67)
	MIBC, PD-L1 < 1%	87/161	17.7 (14.0–27.6)	99/159	9.7 (7.4–13.8)	0.70 (0.53–0.94)
NUTRFS	All MIBC	132/279	25.8 (18.9-NE)	169/281	9.7 (7.7–13.7)	0.62 (0.50–0.79)
DMFS	All MIBC	109/279	37.2 (24.6–NE)	130/281	19.4 (11.4–NE)	0.69 (0.53–0.89)

NE, not estimable; NR, not reached.

4586 **Poster Session**

Chemotherapy with significant mortality benefit in patients with bladder cancer with variant and non-urothelial histologies (NUVH). *First Author: Stuthi Perimbeti, Roswell Park Comprehensive Cancer Center, Buffalo, NY*

Background: Non urothelial cancers and urothelial cancers with variant histologies(NUVH) have a more aggressive natural history and are at a higher risk of progression to muscle invasive disease(MIBC) when compared to their urothelial counterparts. Although surgical resection is the treatment of choice in localized disease, radiation(RT) is commonly used in patients who are not surgical candidates. The use of chemotherapy has shown modest benefit in some retrospective studies. Considering the low incidence of NUVH, there are no large-scale studies examining the benefits of chemoradiation(CRT) in MIBC with NUVH. **Methods:** The National Cancer Database was queried to identify MIBC patients with NUVH from the years 2004-2018.Inclusion criteria for the study are age > 18 years, Non urothelial or variant histologies and receipt of RT. Patients who underwent cystectomy or had metastatic disease were excluded. The population was divided into two cohorts if they received chemoradiation. Chi-Square test and Mann Whitney U tests were used to compare frequency distributions. Cox proportional Hazard regression was employed to control for confounding factors associated with overall survival. Covariates for confounding included age, race, sex, income, insurance status, charlson-deyo comorbidity index, education. **Results:** Among 1773 observations in the final analysis, 63.05%(n = 1118) received CRT. Small cell, large cell and neuroendocrine cancers composed of the majority of NUVH. 38.01% (n = 641). Other histologies composed of squamous cell cancer 30.34%(n = 538), spindle cell/sarcomatoid cancers10.15%(180), adenocarcinoma 11.44%(203). Patients who received CRT were found to be significantly younger (76 vs 82 years P: < 0.0001) with higher male predominance74.73%. 5 year overall mortality was significaantly lower in the CRT vs RT group (66.47% vs 81.55%, p < 0.001). After controlling for confounding factors, CRT was associated with lower risk of mortality Hazard Ratio(HR)of 0.41(0.36-0.47) p < 0.0001. Added, the survival benefit of CRT continued in the non small cell variant cohort HR: 0.43(0.37-0.51) P < 0.0001. **Conclusions:** In this large retrospective study, CRT was associated with reduced overall mortality among patients with non-urothelial MIBC. The findings suggest the importance of systemic therapy in providing a survival advantage to non-urothelial MIBC, including the non-small cell variants. Research Sponsor: None.

Variable	Univariate HR(95%CI)	p-Value	Multivariate HR (95%CI)	p-Value
Chemoradiation vs Radiation alone	0.37(0.33-0.42)	< 0.0001	0.41(0.36-0.47)	0.0001
Female vs Male	1.17((1.04-1.32)	0.0087	1.04(0.93-1.19)	0.41
Comorbidities 3 vs0	1.48(1.13-1.93)	0.004	1.20(0.92-1.58)	0.17
CCM 2vs0	1.46(1.19-1.79)	0.0003	1.31(1.07-1.62)	0.0089
1 vs 0	1.31(1.13-1.15)	0.0002	1.26(1.09-1.45)	0.0012
Black vs white	10.96(0.79-1.16)	0.6987	1.01(0.89-1.13)	0.88

4587 **Poster Session**

Novel use of ctDNA to identify muscle-invasive and non-organ-confined upper tract urothelial carcinoma. *First Author: Heather L Huelster, Department of Genitourinary Oncology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

Background: Upper tract urothelial carcinoma (UTUC) is an aggressive cancer for which use of neoadjuvant chemotherapy (NAC) is limited by suboptimal clinical staging prior to nephroureterectomy. Detection of circulating tumor DNA (ctDNA) is associated with locally advanced and metastatic urothelial carcinoma of the bladder and may help identify UTUC patients who would benefit from NAC. Here we examine the feasibility and utility of plasma ctDNA in the diagnosis of non-organ confined high-risk UTUC. **Methods:** Patients with high-grade cTa-T2 UTUC without radiographic evidence of metastatic disease undergoing up-front radical nephroureterectomy (RNU) were prospectively accrued for pre- and post-operative plasma collection. Blood was collected preoperatively on the day of surgery, and plasma and buffy coat were processed for extraction of cell-free DNA and genomic DNA, respectively. FFPE tumor samples from RNU were used for tissue genomic DNA extraction. Targeted next-generation sequencing (NGS) was used for variant profiling. ctDNA positivity was defined as the presence of plasma cell-free DNA variants concordant with tissue-based variants. **Results:** NGS analyses of matched FFPE and plasma samples were successfully performed for all 19 accrued UTUC patients. Alterations in the TERT promoter (74%), TP53 (58%), FGFR3 (53%), myc amplification (53%), and ATM (42%) were demonstrated in urothelial tumor tissue. Matched plasma ctDNA showed prevalent alterations in the TERT promoter (42%), TP53 (42%), PIK3CA (37%), ATM (32%) and CD274 (26%). Nine patients (47%) had detectable plasma ctDNA mutations concordant with tumor-specific variants using the targeted NGS panel. All patients with detectable preoperative ctDNA had advanced staging (≥pT2 or ≥pN1) and lymphovascular invasion on final pathology, resulting in a 90% sensitivity. The panel was 100% specific with no patients with pTis, pTa, pT1 and pN0 having detectable concordant ctDNA mutations. Concordant plasma ctDNA was detected in four of nine patients postoperatively. Two of three (67%) who developed metastatic disease had detectable ctDNA while neither of the two who developed non-muscle-invasive bladder recurrences did. **Conclusions:** Prospective ctDNA analysis using a targeted NGS panel can be used to predict muscle-invasive and non-organ-confined UTUC preoperatively. Detectable postoperative ctDNA may indicate residual disease and predate clinical recurrence. Research Sponsor: Predicine Inc.

4588 **Poster Session**

Efficacy and safety of atezolizumab concurrent with radiotherapy in patients with muscle-invasive bladder cancer: An interim analysis of the ATEZOBLADDERPRESERVE phase II trial (SOGUG-2017-A-IEC(VEJ)-4). *First Author: Sergio Vazquez-Estevez, Lucus Augusti University Hospital, Lugo, Spain*

Background: Combined-modality treatments are bladder-preserving alternatives for patients (pts) who are not candidates for radical cystectomy by medical reasons, refusal, or patient's choice. Immune therapies seem to potentiate tumor-specific immune response induced by radiotherapy (RT). Combination of RT with anti-PD-1/PD-L1 therapy appears safe and there are signs of promising activity. The aim of this study is to assess the efficacy and safety of atezolizumab (ATZ) concurrent with external beam radiotherapy (EBRT) for the treatment of muscle-invasive bladder cancer (MIBC) with bladder preservation intent. Here we present an interim analysis. **Methods:** This is an open, multicenter, and phase II trial, sponsored by SOGUG, in pts with confirmed diagnosis of MIBC in clinical stages cT2-T4a N0 M0 who are not candidates for radical cystectomy. Treatment consists of 6 doses of ATZ 1200 mg IV every 3 weeks, starting on day 1 of EBRT, and 60 Gy of RT in 30 fractions over 6 weeks at 2 Gy/day. The primary endpoint of the study is pathological complete response (pCR) defined as a response of grade 5 according to Miller and Payne criteria, 1 to 2 months after the last dose of ATZ. A planned interim analysis has been performed (data cut-off date: November 2021) on the primary endpoint to avoid exposure to ineffective treatment according to the minimax two-stages Simon's design (stopping rule: 9 out of the first 13 evaluable pts should achieve pCR). Incidence of adverse events (AE) and serious AE (SAE) has been also secondarily assessed. **Results:** From September 2019 to November 2021, 39 pts were screened, of whom 13 were excluded due to non-compliance with eligibility criteria. Thus, the evaluable population consisted of 26 pts. The safety analysis was performed in 22 pts who had received at least one dose of ATZ. 14 pts were assessed pathologically and, thus, included in interim efficacy analysis (median age: 78.6 years; clinical stage: 71.4% T2a, 14.3% T2b, 7.1% T3a, 7.1% T3b). All 14 pts had achieved pCR at the cut-off date. 20/22 (91%) pts experienced at least one AE, with asthenia (11 pts), diarrhea (9 pts), and urinary tract infection (4 pts) being the most common. 9 SAEs were reported in 7 (32%) pts (bacteriemia, COVID-19 infection, depressed LVEF, unknown origin fever, hepatic toxicity, kidney failure, rectorrhagia, respiratory infection, and urinary sepsis). 6 (27%) pts suffered AEs leading to treatment discontinuation. No AEs leading to death occurred. 17 pts with available data on survival were alive at the cut-off date. **Conclusions:** Interim results suggest that ATZ combined with EBRT is a feasible and effective treatment in terms of pCR, with a manageable safety profile. The final results from this trial will provide information about its effects on clinical outcome, including survival and updated safety findings. Clinical trial information: NCT04186013. Research Sponsor: Roche Farma S.A.

4589 **Poster Session**

Phase II clinical study of tislelizumab combined with nab-paclitaxel (TRUCE-01) for muscle-invasive urothelial bladder carcinoma: Bladder preservation subgroup analysis. *First Author: Yuanjie Niu, Tianjin Medical University Second Hospital, Tianjin, China*

Background: The current strategy for bladder preservation is focused on trimodality treatment, including complete transurethral resection of bladder tumor (cTURBT), with concurrent chemotherapy and radiotherapy. Chemotherapy is usually a cisplatin-based regimen. However, many pts cannot tolerate cisplatin-based chemotherapy and radiation therapy. It fails to meet clinical needs. Meanwhile, the efficacy and safety of checkpoint inhibitors (ICIs) have now been demonstrated. We conduct a study to evaluate ICIs in combination with second-line chemotherapy agents for patients with MIBC. **Methods:** TRUCE-01 is a phase II trial (NCT04730219) of tislelizumab combined with nab-paclitaxel before cTURBT or radical cystectomy. Pts with pure or mixed urothelial bladder cancer (T2-4a Nx M0) received tislelizumab 200mg on days 1 plus paclitaxel 200mg on days 2 every 3 weeks (Q3W) x 3 cycles followed by cTURBT or radical cystectomy. Imaging evaluation is usually done before and after the drug administration using the same tests to assess the efficacy. Pts who choose to preserve bladder usually continue their medication after cTURBT. This abstract focuses on patients with bladder preservation. **Results:** Between July 2020 and November 2021, 47 pts completed at least 2 cycles of treatment, 22 (47%) pts received cTURBT, 16 (34%) pts received radical cystectomy and 9 (19%) pts refuse surgery. As for radiological response, 22 achieved complete response (CR), 16 achieved partial response (PR). In the bladder-preserving subgroup, 13 CR pts and 9 PR pts selected cTURBT, pathology showed 17 pT0, 1 pTa, 3 pT1 and 1 pTis. The median medication cycle is 9 (6-11). There were 3 pts experienced grade 3-4 adverse events (CTCAE), a grade 3 rash, a grade 3 gastric perforation and a grade 4 acute renal failure. In addition, The most common grade 1-2 adverse events include alopecia (86%), fatigue (77%), rash (41%), appetite decreases (41%), hyperglycemia (36%), fever (18%), and creatinine increased (14%). Median follow-up 357 (438-291) days with 3 recurrences and 1 death. The 1-year recurrence-free survival rate was 82%. **Conclusions:** The early efficacy data further support the role of tislelizumab combined with paclitaxel in bladder preservation setting with an acceptable adverse events. Patients with imaging CR or PR after neoadjuvant therapy are preferred for bladder preservation. Enrollment is ongoing. Clinical trial information: NCT04730219. Research Sponsor: The Natural Science Foundation Project of Tianjin (grant no. 18PTLCSY00010), the Tianjin Urological Key Laboratory Foundation (grant no. 2017ZDSYS13) and the Youth Fund of Tianjin Medical University Second Hospital (grant no. 2020ydey09).

4590 **Poster Session**

Artificial intelligence algorithms for the diagnosis of urothelial carcinoma based on urine cytology: A noninvasive and efficient diagnostic approach. *First Author: Chong Shen, The second hospital of Tianjin Medical University, Tianjin, China*

Background: Urine cytology is a noninvasive and relatively inexpensive approach that plays an important role in both screening/initial diagnosis of urothelial carcinoma, and surveillance of tumor recurrence; However, interpretation of urine cytology is labor-intensive and time-consuming. Artificial intelligence (AI) has been widely used in the field of medically assisted diagnosis, but it is almost blank in the field of urothelial carcinoma diagnosis based on urine cytology. In this study, artificial intelligence (AI) algorithms have been developed to efficiently and automatically analyze urinary cytological specimens stained with Acridine orange fluorescence for screening and diagnosis of urothelial carcinoma with a good clinical application prospect. **Methods:** To develop the algorithms, images of urinary cytological specimens with Acridine orange Fluorescence staining were collected from patients who underwent examination, surgery, or both at the Second Hospital of Tianjin Medical University from August 2015 to August 2021. To standardize the urine cytological determination, the images were determined by 3 certified and experienced cytopathologists in this hospital. Images were collected to establish a dataset containing two major categories: Malignant (Defined as images containing malignant cells) and Benign (Defined as images containing malignant cells). From the acquired database, 2794 malignant and 2787 benign eligible images were selected for AI training/validation/testing. Inception V3, a specific type of neural network optimized for image classification called a deep convolutional neural network was trained based on the database. To prevent the model from over-fitting during training, data augmentation methods, such as rotation and flipping were adopted. The diagnosing performance of the binary classification model was analyzed using accuracy, F1 score, operating characteristic (ROC), and the area under the curve (AUC) generated from the sensitivity and specificity to evaluate. **Results:** A total of 21022 slides of urine cytological specimens with Acridine orange Fluorescence staining were collected. The AI algorithms achieved excellent performance, which showed the best prediction with an accuracy of 92.25%, a sensitivity of *98.50*% along with a specificity of 86.00%, the F1score was 0.9271, and the area under the ROC curve was 0.96. **Conclusions:** Our novel artificial intelligence algorithms could accurately classify urine specimens as malignant or benign efficiently and automatically. The use of AI during cytopathology screening provides a new strategy and technical support for the diagnosis and screen of urothelial carcinoma. Research Sponsor: The Natural Science Foundation Project of Tianjin (grant no. 18PTLCSY00010), The Tianjin Urological Key Laboratory Foundation (grant no. 2017ZDSYS13) and the Youth Fund of Tianjin Medical University Second Hospital (grant no. 2020ydey09).

	Predictive malignant	Predictive benign	Total (n)	Accuracy (%)	Sensitivity (%)	Specificity (%)	F1 score
Malignant	197	3	200	0.9225	0.9850	0.8600	0.9271
Benign	28	172	200				

4591 **Poster Session**

A classification system for urothelial carcinoma (UC) defined by genomic drivers and the tumor microenvironment (TME) is predictive of immunotherapy response. *First Author: Konstantin Chernyshov, BostonGene Corporation, Waltham, MA*

Background: UC is associated with high recurrence rates, progression, and resistance to platinum-based therapy. Checkpoint inhibitors (CPIs) are often used for treating UC, but predictive biomarkers that characterize response are lacking in the majority of patients. Defining the TME is essential to understanding patient response to CPIs. Employing a transcriptome-based classification platform, we sought to identify predictive and prognostic subtypes of UC using malignant cell and TME features. **Methods:** We collected a metacohort of 2,418 UC samples from 14 publicly available datasets, one of which had atezolizumab response data (IMvigor210). Using the methodology described in Bagaev et al. 2021, we selected 28 signatures composed of specific gene sets reflecting distinct cellular processes. Analysis of signature expression and unsupervised clustering was performed. **Results:** We identified 7 recurring novel UC subtypes (Table 1) with unique genomic and molecular characteristics. The subtypes and key findings include: an immune desert (D) subtype characterized by genomic instability high HER2 expression; an immune desert, *FGFR*-altered (D-FGFR) subtype with *FGFR* alterations; an immune enriched (IE) subtype with an enriched TME and high CPI response; a fibrotic (F) subtype with a mesenchymal TME, and strong TGFβ signaling; an immune enriched, fibrotic (IE-F) subtype with a mixed TME and a high CPI response rate; a fibrotic, basal (F-B) subtype with a mesenchymal TME and minimal genomic targets, and a neuroendocrine-like (NE-L) subtype with a high CPI response rate. **Conclusions:** UC can be classified into 7 subtypes with distinct prognoses, CPI response rates, and druggable targets using malignant cell and TME profiling. Patients with IE, IE-F, and NE-L UCs may be good candidates for CPIs. D UCs may benefit from HER2-i and PARP-i, while FGFR-i might be more suitable for D-FGFR UCs. TGFβi and PARPi may be effective for F UCs, but F-B UCs have no targetable findings. These findings warrant additional investigation for clinical translation. Research Sponsor: BostonGene Corporation.

Urothelial cancer subtype characteristics.

UC Subtype	n	TME immune composition	Malignant cell features	Alterations	Cisplatin 5-year OS	Atezolizumab CPI response rate
D	382	Desert	Genomic instability	*TP53, RB1* (del), *MCL* (amp), *HER2*	70%	45% (n=37)
D-FGFR	674	Desert	–	*FGFR3, CDKN2A* (del)	58%	43% (n=79)
IE	360	T, B, NK	–	*ARID1B, MCL* (amp)	77%	58% (n=50)
IE-F	251	Macrophage, MDSC, T, NK	Activated NFκB, JAK-STAT	*RB1, EP300*	60%	52% (n=25)
F	381	Mesenchymal, protumor cytokines, angiogenesis	Activated TGFβ, EMT	*TNFRSF14* (del)	48%	39% (n=56)
F-B	337	Mesenchymal, CAF, ECM	–	–	48%	28% (n=49)
NE-L	33	Desert	Neuroendocrine differentiation	*TP53, RB1*	NA	100% (n=4)

CAF - cancer-associated fibroblasts; ECM - extracellular matrix; " – " no significant events.

4592 **Poster Session**

Efficacy of hyperthermic-intra-vesical chemotherapy in patients with BCG-refractory nonmuscle-invasive bladder cancer. *First Author: Geraldine Pignot, Institut Paoli-Calmettes, Marseille, France*

Background: In Bacillus Calmette-Guérin (BCG) refractory non-muscle-invasive bladder cancer (NMIBC), radical cystectomy is the standard of care. For patients unwilling or unable to undergo cystectomy, alternative intravesical therapies are currently being investigated to minimize the risk of recurrence and progression. Chemohyperthermia by HIVEC (Hyperthermic-Intra-Vesical Chemotherapy) is a therapeutic option in BCG-refractory patients. The objective of our study was to evaluate the 2-year oncological results of HIVEC in BCG-refractory patients. **Methods:** Between June 2016 and September 2021, patients treated with HIVEC (6 weekly instillations) for BCG-refractory NMIBC were prospectively included in our study. These patients had a theoretical indication for cystectomy but were ineligible for surgery or refused it. The primary endpoint was 1-year recurrence-free survival (RFS) rate. Secondary endpoints were 6-month complete response rate for Cis, 1-year overall and cancer-specific survival rates and bladder preservation rate. **Results:** Seventy patients, mean age 70 [42-89] years, were treated consecutively. After a mean follow-up of 20.9 months, 32 patients recurred (mean time of 10.6 months) and 7 patients finally had a cystectomy. The recurrence-free survival rate was 53.1% at 1 year and 20.5% at 2 years. Six patients progressed to a muscle-invasive disease, after a mean delay of 6.7 months. Four of them experienced metastatic progression and died from bladder cancer. Cancer-specific and overall survival rates were 95.1% and 92.9% at 1 year, and 87.5% and 77.8% at 2 years. The bladder preservation rate was 90%. For patients with Cis (34% of the entire series), the 6-month complete response rate was 75%. The presence of Cis was not a predictive factor of response to HIVEC. Tolerance was excellent with 38.2% grade 1-2 adverse events and no grade 3-4 adverse events. **Conclusions:** Chemohyperthermia using the HIVEC device achieved a RFS rate of 53.1% at 1 year and enabled a bladder preservation rate of 90%. While cystectomy remains the standard of care, HIVEC may be discussed cautiously for patients who are not eligible for surgery and well informed of the risk of progression to muscle-invasive disease. Research Sponsor: None.

4593 **Poster Session**

Prognostic factors and clinical outcomes in patients with upper tract urothelial carcinoma undergoing surgery: The Cleveland Clinic experience. *First Author: Ramsha Ahmed, Cleveland Clinic Foundation, Cleveland, OH*

Background: Upper tract urothelial carcinoma (UTUC) is a rare and heterogeneous disease accounting for approximately 5-10% of UC. While tumor grade and stage are known prognostic factors, data on other factors affecting outcomes in UTUC patients (pts) undergoing surgery is scant. We studied effect of various clinical factors and treatment on outcomes in UTUC. **Methods:** This is a single-institution retrospective study of 607 pts with UTUC undergoing surgery (nephroureterectomy (NU) or ureterectomy (U)) between Jan 2000 and Dec 2020. We studied effect of demographics, clinicopathological features, tumor location, preoperative Neutrophil-to-Lymphocyte ratio (NLR) and Albumin-to-Globulin ratio (AGR) and use of neoadjuvant or adjuvant chemotherapy on overall survival (OS) and recurrence free survival (RFS). **Results:** Of the 607 pts 401 (66.06%) were males and 355 (58.48%) were > 70 yrs; 232 pts (38.22%) had UTUC of renal pelvis, 242 (39.87%) of ureter and 133 (21.91%) of both. 542 pts (89.29%) underwent radical NU and 65 (10.71%) segmental U; 328 patients (54.04%) were diagnosed with muscle invasive UC (MIUC) (> / = pT2) and 276 (45.47%) with non-MIUC (< / = pT2). Only 51 (8.4%) pts had lymph node positive (N+) disease. Lymphovascular invasion (LVI) was identified in 163 (26.85%) and carcinoma- in-situ (CIS) in 163 (26.85%) pts. Surgical margins were positive in 92 pts (15.16%). Median NLR cutoff was 3.25 and AGR cutoff was 1.25 (dichotomized based on literature). 44 pts (7.2%) received Neoadjuvant chemotherapy and 49 pts (8%) received adjuvant chemotherapy. Tumor recurrence occurred in 216 pts (35.58%) of which 65% were at urothelial and 35% at non-urothelial sites. With median follow up of 35.2 mos, median OS was 82.69 mos and 5-yr OS rate was 60%; median RFS was 29.47 mos and 5-yr RFS rate was 40%. High grade, age > / = 70 yrs, high NLR, low AGR, presence of LVI, positive margins, CIS, MIUC, N+ disease were associated with worse outcomes. Pts with only renal pelvis involvement had better OS. **Conclusions:** In this large, long term follow-up series of UTUC pts, we identified several prognostic factors besides grade and stage that impact outcomes. These findings warrant further validation for use in clinical practice. Research Sponsor: None.

Prognostic Factors	Median OS (mos)	Median RFS (mos)
Age, > / = 70 vs < 70 yrs	48.3 vs 130.56 (p < 0.0001)	20.5 vs 70.2 (p < 0.0001)
LVI (+ vs -)	29.7 vs 98.63 (p < 0.0001)	12.2 vs 45.5 (p < 0.0001)
Margins (+ vs -)	30.49 vs 90.09 (p < 0.0001)	18.9 vs 32.6 (p = 0.01)
Tumor site (renal pelvis; renal pelvis+ureter; ureter)	108.06; 61.01; 81.51 (p = 0.01)	33.6; 25.1; 27.04 (p = 0.3)
Muscle invasion (+ vs -)	48.8 vs109.6 (p < 0.0001)	17.8 vs 61 (p < 0.0001)
N+ vs N- disease	22.7 vs 84.7 (p < 0.0001)	10 vs 32.6 (p = 0.003)
CIS (+ vs -)	71.8 vs 89.6 (p = 0.02)	24.1 vs 32.13 (p = 0.127)
NLR > / = 3.25 vs < 3.25	69.5 vs112.8 (p = 0.003)	27.2 vs 37 (p = 0.123)
AGR > / = 1.25 vs < 1.25	84.7 vs 51.4 (p = 0.0003)	33.6 vs 17.2 (p = 0.0037)

4594 **Poster Session**

Quantifying the absolute benefit of neoadjuvant chemotherapy followed by definitive therapy in patients with muscle-invasive bladder cancer: A systematic review and meta-analysis. *First Author: Waleed Ikram, Mayo Clinic, Phoenix, AZ*

Background: Cisplatin based neoadjuvant chemotherapy (NAC) followed by definitive therapy improves survival in patients with muscle invasive bladder cancer (MIBC). However, the clinical benefit of NAC might vary with the choice of definitive therapy. Therefore, we assessed the absolute benefit of NAC followed by radical cystectomy or radical radiotherapy separately using the totality of evidence. **Methods:** MEDLINE and EMBASE were systematically searched to identify randomized trials assessing cisplatin based neoadjuvant chemotherapy followed by either radical cystectomy or definitive radiotherapy in patients with MIBC. Outcomes of interest included overall survival (OS) and disease-free survival (DFS). Treatment effects were expressed as hazard ratios (HR) with 95% confidence interval (CI). Incidence rate ratios were calculated to estimate time to event outcomes for trials not reporting HR. A random-effects DerSimonian-Laird meta-analysis was conducted. Absolute effects were then obtained using baseline risks from the control arm of RCTs. **Results:** Of 4887 studies identified, 13 trials with 2529 patients were included in this meta-analysis. Most trials included patients with T2-4 and N0 patients and only 3 trials included patients with node positive disease. Total of 180 (47%) DFS events were observed with NAC+RC compared to 213 (56%) events in RC alone (HR: 0.72; 95% CI: 0.59-0.89) and 346 (58%) OS events were observed with NAC+ RC compared to 385 (52%) events in RC alone (HR: 0.80; 95% CI: 0.69-0.92). Total of 186 (70%) DFS events were observed with NAC + radiotherapy compared to 205 (71%) events in radiotherapy alone (HR: 0.91; 95% CI: 0.74-1.12) and 263 (58%) OS events were observed with NAC+ radiotherapy compared to 294 (61%) events in radiotherapy alone (HR:0.93; 95% CI: 0.79-1.08). **Conclusions:** The choice of definitive therapy after cisplatin-based NAC impacts survival in patients with MIBC. RC after NAC improved DFS (114 fewer events per 1000 events) and OS (76 fewer per 1000 events) whereas radiotherapy after NAC showed no survival benefit. Research Sponsor: None.

Outcome	Studies (Participants)	Relative effect	Anticipated absolute effects	
			Risk with Radical cystectomy	Risk difference with Neoadjuvant Chemotherapy
OS	8 (1511)	HR 0.80 (0.69 to 0.92)	528 per 1,000	76 fewer per 1,000 (from 124 fewer to 28 fewer)
DFS	5 (765)	HR 0.72 (0.59 to 0.87)	563 per 1,000	114 fewer per 1,000 (from 177 fewer to 50 fewer)
			Risk with Radical radiotherapy	Risk difference with Neoadjuvant Chemotherapy
OS	6 (1018)	HR 0.93 (0.79 to 1.08)	632 per 1,000	27 fewer per 1,000 (from 86 fewer to 28 more)
DFS	2 (520)	HR 0.91 (0.74 to 1.12)	734 per 1,000	66 fewer per 1,000 (from 191 fewer to 88 more)

4595 **Poster Session**

Evaluating oncologists' practice patterns and decision-making in locally advanced or metastatic urothelial carcinoma (la/mUC): The U.S. physician PARADIGM study (Part 2). *First Author: Frank Liu, EMD Serono, Rockland, MA*

Background: The treatment (tx) landscape for la/mUC has evolved with the use of immunotherapy (IO) for platinum-refractory la/mUC as well as first-line (1L) maintenance therapy (1LM). This cross-sectional survey explored practice patterns for 1L tx/1LM use and clinical decision-making. **Methods:** Community/academic US oncologists (n = 150) completed an online survey (Sept-Oct 2021) on demographics, 1L tx, 1LM use, attributes in 1L tx selection/1LM use, and factors associated with 1L tx/1LM use. Physicians were dichotomized into 4 pre-specified groups using the median percentage (%) as a cutoff: 1) more frequent 1L prescriber 2) less frequent 1L prescriber (% of pts treated with 1L tx in the past 6 months); 3) more frequent 1LM prescriber 4) less frequent 1LM prescriber (% of pts eligible and received 1LM). Descriptive and bivariate analyses assessing attributes (scored out of 100 points across 16 attributes) in 1L tx selection/1LM use were conducted. Multivariable logistic regression was used to assess factors associated with more/less frequent 1L tx/1LM use. **Results:** Median time in practice was 15 yrs (range, 2-31; 63% community vs 37% academic setting). The median % of la/mUC pts who received 1L tx was 46% (range, 25-89%). 72 physicians were categorized as more frequent 1L prescribers, while 78 were less frequent 1L prescribers. The median % of pts eligible and received 1LM was 71% (range, 0-100%). 71 physicians were categorized as more frequent 1LM prescribers, while 75 were less frequent 1LM prescribers. Attributes used in 1L tx selection differed among more vs less frequent 1L prescribers: mean scores for efficacy/overall survival (OS), disease control rate (DCR), or rate of grade 3/4 adverse events (AEs) were 23 vs 17, 10 vs 8, and 10 vs 5, respectively (all $p < 0.05$). Similarly, for more vs less frequent 1LM prescribers, mean scores for efficacy/OS, rate of grade 3/4 immune-mediated AEs, and inclusion in institutional guidelines/pathways were 23 vs 16, 6 vs 4, and 2 vs 4. Oncologists who stated OS, DCR, or rate of grade 3/4 AEs as important factors impacting tx selection were more likely to prescribe 1L tx (all $p < 0.05$). Regarding 1LM use, oncologists based in the academic setting, those who reported using RECIST 1.1 criteria to assess tx response or agreed 1LM is important to prolong OS were all more likely to prescribe 1LM (all $p < 0.05$). Those who reported that their institutional guidelines/pathways impact tx decisions or cited prior IO use before metastatic diagnosis as reason not to prescribe 1LM were less likely to prescribe 1LM (all $p < 0.05$). **Conclusions:** While several factors were found to be associated with offering 1L tx by US oncologists, including impact on OS and practice setting, variability exists in physicians' attitudes to 1L tx/1LM use. Studies and interventions to explore shared decision-making for optimal 1L tx selection are needed. Research Sponsor: the healthcare business of Merck KGaA, Darmstadt, Germany, Pharmaceutical/Biotech Company.

4596 **Poster Session**

EO2401, a novel microbiome-derived therapeutic vaccine for patients with adrenocortical carcinoma (ACC): Preliminary results of the SPENCER study. *First Author: Eric Baudin, Institut Gustave Roussy, Villejuif, France*

Background: In advanced ACC, no significant progress has been made since introduction of mitotane and cisplatin-based therapy. EO2401 (EO) was designed to activate existing commensal memory T cells cross-reacting with tumor associated antigens (TAAs). EO includes microbial-derived, synthetically produced peptides corresponding to HLA-A2 restricted epitopes with molecular mimicry to three TAAs upregulated in ACC, IL13Rα2, BIRC5 and FOXM1, with the CD4 helper peptide UCP2 and the adjuvant Montanide. Pre-clinically EO generates strong immune responses and cross-reactive CD8 cells recognizing the TAAs. **Methods:** This Phase 1/2 trial (NCT04187404) investigated EO + nivolumab (N) (EO + N = EN) in pts with ACC. Cohort 1 lead-in established safety of EN. Cohort 2 includes pts with metastatic ACC, with (C2a), or without (C2b) prior systemic therapy. EN was given 4 times q2 w, followed by boosters q4 w until PD (iRECIST). **Results:** 33 pts with ACC started study treatment: C2a 26 pts (58% 1; 42% 2 prior lines), C2b 7 pts. Median age 47; 24% men; ECOG 0/52%, 1/42%, 2/6%; 61% ≥2 organs involved by metastases (61% liver, 76% lung). EN was well tolerated. The combination safety profile was consistent with the profile of N monotherapy except for higher local administration site reactions (any erythema/pain/induration in 35% of pts). Overall (n = 33), best RECIST response was PR 12%, SD 24%, PD 45%, NE 18%; median PFS was 1.9 mo (range 0.4-7.6+); median survival not reached, and survival rate at 6-mo 63% (median FU 4.9 mo, range 0.9-12.0). Strong CD8 T cell ELISPOT responses against the vaccine peptides (9/9 pts) and cross-reactivity against targeted TAAs (8/8 evaluable pts) was observed. Tetramer staining of specific CD8 cells for all 3 peptides was detected in 7/8 tested. When investigated, positive staining against BIRC5 was detected as early as 4 w after the first vaccination. In C2a, a group of pts (n = 10) with SD at the first CT (incl. 4 pts with PR) seemed to fare well; all investigated tumor samples in this group showed a low level of TMB, low MSI, and low PDL1 expression. In contrast, 10 pts had PD < 2mo and died < 6mo. There was no correlation between clinical benefit and a large panel of cytokines/chemokines. However, post-hoc analysis identified several clinical factors (prior mitotane, ECOG ≤ 1, ACC 1st diagnosis > 9 mo, max lesion ≤125 mm, ≤3 organs involved, lymphocytes ≤ grade 1) that excluded 90% of pts without benefit to EN. In the post-hoc selected group (n = 14) with median FU 6.9 mo (12 pts censored) the DCR was 64% (4 PR, 5 SD), 6-mo PFS was 42% and 6-mo survival rate 93%. **Conclusions:** EO2401 in combination with nivolumab was well tolerated and induced a specific immune response in all tested pts. In addition, efficacy was seen in a subpopulation of pts with ACC defined by clinical parameters in a post-hoc analysis. A randomized phase 2 study based on the findings of Cohort 2a is being planned. Clinical trial information: NCT04187404. Research Sponsor: Enterome.

4597 **Poster Session**

CORE1: Phase 2, single-arm study of CG0070 combined with pembrolizumab in patients with nonmuscle-invasive bladder cancer (NMIBC) unresponsive to bacillus Calmette-Guerin (BCG). *First Author: Roger Li, Department of Genitourinary Oncology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

Background: CG0070, is an Ad5-based oncolytic vaccine engineered to express GM-CSF and replicate selectively in tumor cells with mutated or deficient RB. The CG0070 mechanism of action includes cell lysis and immunogenic cell death which is enhanced in the presence of GM-CSF. In an open label ph. 2 study, an overall CR rate of 62% and a CR at 12 months (m) of 29% have been observed in patients with high risk NMIBC previously treated with BCG. IV pembrolizumab, was recently approved by the FDA for patients with BCG-unresponsive CIS (with or without papillary tumors) with an overall complete RR of 41% and a 12 m CR rate of ~20%. This ph. 2 study will assess the potential synergy of the two agents in the treatment of BCG-unresponsive NMIBC. **Methods:** 35 pts with BCG-unresponsive CIS with or without concurrent Ta or T1 disease will be treated with intravescical CG0070 ($1x10^{12}$ vp) in combination with pembrolizumab at a dose of 400 mg IV q6 weeks. CG0070 will be administered weekly x 6 as induction followed by weekly x 3 maintenance instillations at months 3, 6, 9, 12, and 18. Pts with persistent CIS or HG Ta at 3 m may receive re-induction with weekly x 6 of CG0070. Pembrolizumab will be administered up to 24 m. Assessment of response will include q 3 m cystoscopy with biopsy of areas suspicious for disease, urine cytology, CTU/MRU, and mandatory bladder mapping biopsies at 12 m. Recurrence of HG disease will be enumerated as disease recurrence. The primary endpoint of the study is CR at 12 m. Secondary endpoints will include CR at any time, progression free survival, duration of response, cystectomy free survival and the safety. Correlate assessments will include changes in the tumor immune microenvironment, systemic immune induction,viral replication and transgene expression. Baseline expression of PD-L1, coxsackie adenovirus receptor, E2F transcription factor as well as anti-Ad5 Ab titer will be correlated with tumor response. **Results:** A CR rate of 87.5% (14/16) at the 3 m assessment timepoint has been observed thus far. All patients in CR at 3 m remain in CR at downstream timepoints including: 9/9 at 6 m, 6/6 at 9 m, and 3/3 at 12 m. Treatment related AE have been generally limited to transient grade 1-2 local-regional genitourinary adverse events with no reports of grade 3, 4 or SAE attributed to treatment with CG0070/Pembroluzimab. **Conclusions:** This initial data on the efficacy and safety of CG0070 plus pembrolizumab for the treatment of BCG unresponsive NMIBC is encouraging. Additional data on efficacy as well as safety and biomarker (CAR, E2F, and PDL1) assessment will be presented for at least 25 of the projected 35 patients at the time of the conference. Clinical trial information: NCT04387461. Research Sponsor: CG Oncology.

TPS4598 **Poster Session**

ALTER-UC-001: Phase II trial of anlotinib plus everolimus as first-line treatment for advanced non–clear cell renal cell carcinoma. *First Author: Hailiang Zhang, Department of Urology Surgery, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: For patients (pts) with recurrent or stage IV non-clear cell renal cancer (nccRCC), the medical treatment guidelines recommend the first choice to participate in clinical trials, or use TKI drugs such as sunitinib, and mTOR inhibitors such as everolimus. Anlotinib is a novel multi-target tyrosine kinase inhibitor (TKI). It's antitumor targets include vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptor (PDGFR) and c-kit. This a single-center, single-arm, phase II trial which will evaluate the efficacy and tolerability of anlotinib hydrochloride plus everolimus as first-line therapy in pts with nccRCC (NCT05124431). **Methods:** Key inclusion criteria are: age ≥18 years; histologically confirmed advanced nccRCC, advanced disease is defined as TNM stage IV, not available for surgery, locally recurrent or metastatic renal cell carcinoma; no prior systemic drug therapy for advanced disease; Eastern Cooperative Oncology Group (ECOG) performance status 0-1. Approximately 30 pts will be assigned to receive anlotinib hydrochloride: 12 mg every 21 days (14 days on treatment from Day 1-14, 7 days off treatment from Day 15-21) by oral, and everolimus 5mg qd, continued for up to 1 year (~17 cycles) or until disease progression, unacceptable toxicity, or withdrawal of consent. The primary endpoint was objective response rate (ORR). Radiographic imaging will be performed every 6 weeks. Secondary endpoints included overall disease control rate (DCR), progression free survival (PFS), and over survival (OS). Adverse events will be monitored throughout the study and graded according to CTCAE V5.0. Recruitment have begun in Jan. 2022. Research Sponsor: Chia Tai Tianqing Pharmaceutical Group Co., Ltd. Clinical trial information: NCT05124431.

TPS4599 **Poster Session**

A phase 1b/2 study of batiraxcept (AVB-S6-500) in combination with cabozantinib, cabozantinib and nivolumab, and as monotherapy in patients with advanced or metastatic clear cell renal cell carcinoma (NCT04300140). *First Author: Katy Beckermann, Vanderbilt-Ingram Cancer Center, Nashville, TN*

Background: In clear cell renal cell carcinoma (ccRCC) the constitutive expression of hypoxia induced factor 1-α leads to increased expression of AXL. AXL overexpression has been associated with the development of resistance to VEGF inhibitors and suppression of the innate immune response through inhibition of macrophage-driven inflammation. Batiraxcept is a recombinant fusion protein dimer containing an extracellular region of human AXL combined with the human immunoglobulin G1 heavy chain (Fc), which demonstrates highly potent, specific AXL inhibition. In preclinical studies using the 786-O, M62, and SN12L1 tumors, batiraxcept monotherapy resulted in a significant reduction of tumor growth compared to control. In healthy volunteer and ovarian cancer clinical studies, batiraxcept was well tolerated with no dose-related adverse events, and a maximum tolerated dose was not reached. Therefore, batiraxcept could be tested as either a monotherapy or in combination with standard of care drugs in patients with metastatic ccRCC. The Phase 1b dose-escalation portion of this study evaluated batiraxcept in combination with standard of care cabozantanib in patients who progressed on or after first line therapy. No DLT was observed at either of two batiraxcept doses evaluated. The recommended Phase 2 dose of batiraxcept has been identified as 15 mg/kg every 2 weeks (q2w) with cabozantinib 60 mg based upon safety, PK/PD, and preliminary efficacy data. **Methods:** This Phase 2, multi-center, open-label study includes three parts: Part A) batiraxcept 15 mg/kg q2w in combination with cabozantinib 60 mg daily for ccRCC subjects who have progressed on or after one line of therapy, n=25. Part B) batiraxcept 15 mg/kg q2w with cabozantinib 40 mg daily and nivolumab at the investigator's choice (240 mg q2w or 480 mg q4w) for first line treatment of advanced or metastatic ccRCC subjects, n=20. If no safety signals are observed in the first 6 subjects enrolled, 10 subjects will be enrolled in the first stage of a Simon 2-stage minmax statistical design. If ≥ 6/10 subjects achieve PR or CR, stage 2 will open to enroll up to 20 total subjects. Part C) batiraxcept 15 mg/kg q2w monotherapy for subjects with advanced/metastatic ccRCC ineligible for curative intent therapies, n=10. The primary objective for each arm is objective response rate by RECIST v1.1. Secondary objectives include safety, duration of response, clinical benefit rate, progression free survival by RECIST v1.1, and overall survival. Exploratory objectives include pharmacokinetic and pharmacodynamic assessments. The Phase 2 portion of this Ph1b/2 study is currently enrolling. Clinical trial information: NCT04300140. Research Sponsor: Aravive, Inc.

TPS4600 **Poster Session**

A phase 1b study (STELLAR-002) of XL092 administered in combination with nivolumab (NIVO) with or without ipilimumab (IPI) or bempegaldesleukin (BEMPEG) in patients (pts) with advanced solid tumors. *First Author: Toni K. Choueiri, Dana-Farber Cancer Institute, Boston, MA*

Background: XL092 is a novel oral inhibitor of receptor tyrosine kinases, including MET, VEGFR2, and TAM kinases (AXL, MER), which are implicated in tumor growth, metastasis, angiogenesis, and immune suppression of the tumor microenvironment. XL092 has a relatively short half-life (~21h) to support convenient daily dosing and help manage tolerability. Preclinical studies of XL092 with an anti–PD-1 immune checkpoint inhibitor (ICI) demonstrated antitumor activity in tumor models, and BEMPEG (IL-2 pathway agonist) showed synergy with anti–PD-L1 and anti–CTLA-4 agents. This phase 1b trial will evaluate the safety and clinical activity of XL092 alone and in combination with NIVO (anti–PD-1 mAb) ±IPI (anti–CTLA-4 mAb) or ±BEMPEG in pts with advanced solid tumors including genitourinary cancers. Presented here is the study design. **Methods:** This multicenter phase 1b, open-label study (NCT05176483) will enroll pts with unresectable advanced or metastatic solid tumors in dose-escalation and expansion stages. In the dose-escalation stage, ~36 pts will be enrolled in three XL092 combination therapy cohorts using a rolling 6 design. Cohort A: XL092 (starting dose [SD] 100 mg PO QD) + NIVO (360 mg IV Q3W); Cohort B: XL092 (SD 80 mg PO QD) + NIVO (3 mg/kg IV Q3W × 4, then 480 mg IV Q4W) + IPI (1 mg/kg Q3W × 4); Cohort C: XL092 (SD 100 mg PO QD) + NIVO (360 mg IV Q3W) + BEMPEG (0.006 mg/kg IV Q3W). The primary objective of the dose-escalation stage is to determine the recommended doses of XL092 with the NIVO regimens to be used in the expansion stage. The expansion stage will include cohorts of advanced genitourinary tumors: Cohort 1, clear-cell renal cell carcinoma (ccRCC), no prior systemic therapy; Cohort 2, ccRCC, 1 prior ICI combination regimen; Cohort 3, metastatic castration-resistant prostate cancer (mCRPC), 1 prior novel-hormonal therapy; Cohort 4, urothelial carcinoma (UC), 1 prior platinum-based regimen, ICI-naïve; Cohort 5, UC, ≤2 prior systemic regimens, ICI-experienced; Cohort 6, non-ccRCC, no prior systemic therapy. In each cohort, pts will be randomized to one of the following treatments (based on tumor cohort): single-agent XL092 (Cohorts 2–6); XL092+NIVO (Cohorts 1–6); NIVO+IPI (Cohort 1); XL092+NIVO+IPI (Cohorts 1, 3, 6); NIVO+BEMPEG (Cohort 1), XL092+NIVO+BEMPEG (Cohort 1, 2, 4–6). Thirty pts will be enrolled in each single-agent XL092 arm and 40 pts in each combination therapy arm. Expansion stage objectives are to assess preliminary efficacy, safety, and pharmacokinetics of XL092 alone or in combination in each tumor-specific cohort. Primary efficacy endpoints include objective response rate by investigator per RECIST v1.1 and progression-free survival by blinded independent radiology committee per Prostate Working Group 3 criteria (mCRPC cohort only). The study is currently enrolling pts. Clinical trial information: NCT05176483. Research Sponsor: Exelixis, Inc.

TPS4601 **Poster Session**

SAMETA: An open-label, three-arm, multicenter, phase III study of savolitinib + durvalumab versus sunitinib and durvalumab monotherapy in patients with MET-driven, unresectable, locally advanced/metastatic papillary renal cell carcinoma (PRCC). *First Author: Toni K. Choueiri, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA*

Background: Papillary renal cell carcinoma (PRCC) is the most common subtype of non-clear cell RCC and accounts for 10–15% of RCCs. Approximately 80% of PRCC cases are MET-driven, characterized by genomic abnormalities resulting in dysregulation of the MET signaling pathway, making these abnormalities a potential therapeutic target for treatment. Savolitinib is an oral, potent and highly selective MET tyrosine-kinase inhibitor (TKI) demonstrating preliminary clinical activity in advanced solid tumors, including in MET-driven PRCC, defined as presence of any of the following molecular alterations, in the absence of co-occurring fumarate hydratase mutations: chromosome 7 gain, MET amplification, MET kinase domain variations, or hepatocyte growth factor amplification. In the Phase III SAVOIR study, in PRCC, savolitinib monotherapy showed encouraging efficacy vs the multi-targeted TKI, sunitinib. In addition, non-clinical studies suggest a possible synergistic anti-tumor effect of MET-inhibitors and programmed cell death-ligand (PD-L1) inhibitors, such as durvalumab; emerging data from the Phase I/II CALYPSO study investigating savolitinib plus durvalumab shows a notable efficacy signal in patients with MET-driven PRCC. Following these findings, the SAMETA study (NCT05043090) is designed to evaluate the efficacy and safety of savolitinib in combination with durvalumab vs sunitinib and durvalumab monotherapy in PRCC. **Methods:** In this open-label, three-arm, multi-center, Phase III study, adult patients with unresectable, MET-driven and locally advanced/metastatic PRCC are eligible. An estimated 200 patients (25 countries, 165 centers) will be randomized in a 2:1:1 ratio into three treatment arms (A–C) with stratification by International metastatic RCC database consortium risk group & PD-L1 expression tumor status. Arm A: oral savolitinib 600 mg once daily (QD) plus intravenous (IV) durvalumab 1500 mg every 4 weeks (Q4W); Arm B: oral sunitinib 50 mg QD for 4 consecutive weeks, followed by a sunitinib-free interval of 2 weeks Q6W; Arm C: IV durvalumab 1500 mg Q4W. Study treatment continues until RECIST 1.1 disease progression or another discontinuation criterion is met. The primary endpoint is progression-free survival (by BICR; RECIST v1.1). Secondary endpoints include overall survival, objective response rate and duration of response. Safety (adverse events, vital signs, ECG, hematology and biochemistry parameters) will also be reported. The first patient was enrolled onto the study on 28 October 2021. Clinical trial information: NCT05043090. Research Sponsor: AstraZeneca.

TPS4602 **Poster Session**

LITESPARK-022: A phase 3 study of pembrolizumab + belzutifan as adjuvant treatment of clear cell renal cell carcinoma (ccRCC). *First Author: Toni K. Choueiri, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA*

Background: Patients with locally advanced renal cell carcinoma (RCC) may experience recurrence after surgery. In the phase 3 KEYNOTE-564 (NCT03142334) trial, adjuvant pembrolizumab demonstrated significant improvement in disease-free survival (DFS) in ccRCC, leading to FDA approval of pembrolizumab (November 17, 2021) for adjuvant treatment of patients with RCC at intermediate-high or high risk for recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions. Despite benefit of pembrolizumab, there is an unmet need for more effective adjuvant treatment for patients at risk for recurrence after definitive surgery. The HIF-2α inhibitor belzutifan (MK-6482) has shown activity and good tolerability in patients with advanced ccRCC and von Hippel-Lindau (VHL) disease–associated RCC. Combining belzutifan with pembrolizumab may be a therapeutic option as adjuvant treatment of ccRCC. This global, multicenter, double-blind, randomized, phase 3 study LITESPARK-022 (NCT05239728) is designed to compare the efficacy and safety of belzutifan + pembrolizumab with that of placebo + pembrolizumab as adjuvant treatment of ccRCC after nephrectomy. **Methods:** Approximately 1600 patients with histologically or cytologically confirmed RCC (intermediate-high [pT2, grade 4 or sarcomatoid, N0, M0 or pT3, any grade, N0, M0], high [pT4, any grade, N0, M0 or pT, any stage/grade, N+, M0] or M1 NED [patients who present with the primary kidney tumor and solid, isolated, soft tissue metastases that can be resected at the time of nephrectomy or ≤2 years from nephrectomy) with a clear cell component and had not previously received systemic therapy will be enrolled. Patients must have undergone nephrectomy and/or metastasectomy ≤12 weeks before randomization and be tumor free, confirmed by CT/MRI. Stratification factors are tumor grade (1 or 2 vs 3 or 4) and risk type (intermediate-high vs high vs M1 NED). Patients will be randomly assigned 1:1 to receive belzutifan 120 mg orally once daily + pembrolizumab 400 mg IV every 6 weeks (Q6W) or oral placebo + pembrolizumab 400 mg IV Q6W. Pembrolizumab treatment will be administered for up to 9 doses (~1 year); belzutifan and placebo may be continued for a maximum of 54 weeks. Disease recurrence will be evaluated radiologically Q12W from randomization through year 2, Q16W in years 3-5, and Q24W in years 6 and beyond. Adverse events (AEs) will be monitored by NCI CTCAE v5.0 through 30 days (90 days for serious AEs) after cessation of study drug. The primary end point is DFS, as assessed by investigator, defined as time from randomization to first documented event of local recurrence, occurrence of distant kidney cancer metastasis, or death from any cause, whichever occurs first. The key secondary end point is overall survival. Other secondary end points are safety, disease recurrence–specific survival and patient-reported outcomes. Clinical trial information: NCT05239728. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

TPS4603 **Poster Session**

STARLITE 2: Phase 2 study of nivolumab plus ^{177}Lutetium-labeled anti-carbonic anhydrase IX (CAIX) monoclonal antibody girentuximab (^{177}Lu-girentuximab) in patients (pts) with advanced clear cell renal cell carcinoma (ccRCC). *First Author: Darren R. Feldman, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: CAIX is a cell surface glycoprotein expressed in > 90% of ccRCC but rarely in normal tissues, providing a target for imaging and therapeutic application. Radiolabeling the anti-CAIX monoclonal antibody girentuximab with ^{89}Zr has shown promise as a novel PET tracer and labeling with ^{177}Lu promise as a therapeutic agent in ccRCC (Muselaers, Eur Urol, 2016). Targeted delivery of radiation to ccRCC cells may prime the immune response by enhancing tumor antigen presentation, providing rationale for combining ^{177}Lu-girentuximab with the anti-PD-1 antibody, nivolumab. This phase 2, open-label, single arm study (NCT05239533) is being conducted to evaluate ^{177}Lu-girentuximab in combination with nivolumab in pts with previously treated ccRCC. **Methods:** Pts with biopsy-proven ccRCC, progressive disease after prior systemic therapy including ≥1 immunotherapy (IO) agent, adequate organ/marrow function, and ≥1 evaluable lesion by RECIST 1.1 that is also avid on ^{89}Zr-girentuximab PET will be enrolled. There is no limit on number of prior lines of systemic therapy, but pts who stopped IO for immune toxicity are excluded. Treatment consists of ^{177}Lu-girentuximab every 12-14 weeks for a maximum of 3 doses plus nivolumab 240mg every 2 weeks until progressive disease (PD) or unacceptable toxicity. Due to expected cumulative myelosuppression, each subsequent ^{177}Lu-girentuximab dose to the same patient is reduced by 25% (dose 2 = 75% of dose 1; dose 3 = 75% of dose 2). Tumor imaging is performed every 12 weeks. Pts will be evaluated in a safety lead-in phase followed by an expansion phase. In the safety lead-in phase, the MTD of ^{177}Lu-girentuximab in combination with nivolumab will be determined with a 3+3 design using a starting dose of 1804 MBq/m^2 (75% of single agent MTD). For cohort 2, dose escalation to 2405 MBq/m^2 (single agent MTD) or de-escalation to 1353 MBq/m^2 will be based on dose-limiting toxicities. In the expansion phase, a Simon 2-stage optimal design is used to evaluate the primary endpoint of response rate by RECIST 1.1 within 24 weeks. With ≥1 response in the first Simon stage (n = 10; includes pts treated at MTD in safety lead-in), a second stage will open (n = 19) for a total of 29 pts with ≥3 responses indicating the regimen worthy of further study. Secondary endpoints include PFS, OS, and toxicity including a continuous safety monitoring rule during expansion. Exploratory imaging with ^{89}Zr-girentuximab PET is performed at baseline and before each ^{177}Lu-girentuximab dose with results correlated with RECIST response on conventional imaging. In addition, whole body planar and SPECT imaging are performed after each ^{177}Lu-girentuximab dose to evaluate distribution, lesion uptake and dosimetry of ^{177}Lu-girentuximab. The trial is currently accruing to the safety lead-in phase. Clinical trial information: NCT05239533. Research Sponsor: Telix Pharmaceuticals.

TPS4604 **Poster Session**

A phase 2 study of bevacizumab, erlotinib, and atezolizumab in subjects with advanced hereditary leiomyomatosis and renal cell cancer (HLRCC) associated or sporadic papillary renal cell cancer (pRCC). *First Author: Gabriela Liliana Bravo Montenegro, Urologic Oncology Branch. National Cancer Institute of the National Institutes of Health, Bethesda, MD*

Background: Papillary RCC accounts for 10-15% of kidney cancers and is the second most common subtype of RCC after clear cell RCC. HLRCC is a familial cancer syndrome characterized by a propensity for developing papillary kidney cancer. HLRCC-associated renal tumors are known to be clinically aggressive, with a paucity of treatment options. The combination of bevacizumab and erlotinib has shown promising activity in patients with HLRCC-associated RCC and sporadic pRCC (Srinivasan et al, ASCO 2020). We hypothesize that the addition of a PDL-1 inhibitor might provide synergistic clinical activity against these tumors. **Methods:** This is an ETCTN-sponsored, open-label, multicenter, phase 2 study evaluating bevacizumab, erlotinib and atezolizumab in adult and pediatric patients with advanced 1) HLRCC-associated RCC or 2) sporadic pRCC. Eligible patients will have cytologically or histologically confirmed advanced HLRCC- associated or sporadic pRCC, age ≥12 years, ECOG PS ≤2, no more than two prior regimens targeting the VEGF pathway, no prior treatment with PD-1 or PD-L1 inhibitors and adequate organ and marrow function. Patients with HLRCC-associated RCC or sporadic pRCC will be enrolled into parallel, independent cohorts. Initially, 12 adult patients with advanced HLRCC-associated RCC or sporadic pRCC will be enrolled into the safety run-in portion of the trial. If ≤ 3 dose-limiting toxicities are observed, enrollment will proceed into both cohorts and pediatric patients will be allowed to enroll. A Simon two-stage phase 2 minimax design will be used to determine accrual to each cohort. In the first stage, 12 evaluable patients will be enrolled into cohort 1) HLRCC-associated RCC or cohort 2) sporadic pRCC. If 0 of 12 patients have a CR, then no further patients will be enrolled in that cohort. If 1 or more of the first 12 evaluable patients enrolled have a clinical response, then accrual will continue until a total of 21 evaluable patients (adult or pediatric) have been enrolled into each cohort for a total of 42 patients. Adult patients will receive a fixed dose of bevacizumab (15 mg/kg IV every 21 days) plus atezolizumab (1,200 mg IV every 21 days) and erlotinib (150 mg PO daily). Pediatric patients will receive bevacizumab (15 mg/kg IV every 21 days) plus atezolizumab 15 mg/kg (max 1,200 mg IV every 21 days) and erlotinib 85 mg/m^2 (max 150 mg PO daily). The primary endpoint is to assess the complete response rate according to RECIST 1.1 in patients with advanced 1) HLRCC-associated RCC and 2) sporadic pRCC. Secondary endpoints include safety and tolerability, objective response rate, disease control rate, progression-free survival and overall survival. Key exploratory endpoints include evaluation of immunologic modulation associated with this regimen. The study has just opened to accrual. Clinical trial information: NCT04981509. Research Sponsor: U.S. National Institutes of Health.

TPS4605 **Poster Session**

TiNivo-2: A phase 3, randomized, controlled, multicenter, open-label study to compare tivozanib in combination with nivolumab to tivozanib monotherapy in subjects with renal cell carcinoma who have progressed following one or two lines of therapy where one line has an immune checkpoint inhibitor. *First Author: Toni K. Choueiri, Dana-Farber Cancer Institute, Boston, MA*

Background: Tivozanib, a highly selective and potent vascular endothelial growth factor receptor tyrosine kinase inhibitor, has demonstrated single-agent efficacy in advanced renal cell carcinoma (aRCC) along with minimal off-target toxicities and a favorable adverse event (AE) profile (Rini et al Lancet Oncol 2020). Tivozanib was approved by the FDA on March 10, 2021, for the treatment of patients with aRCC who had progressed on 2 or more prior systemic therapies. Tivozanib was combined with Nivolumab in the phase 1b/2 TiNivo trial (NCT03136627), showing an objective response rate of 56%, disease control rate of 96%, median PFS of 18.9 months and a tolerable safety profile (Albiges et al Ann Oncol. 2021). **Methods:** TiNivo-2 (NCT04987203) is a phase 3, randomized, controlled, multicenter, open-label study to compare tivozanib in combination with nivolumab to tivozanib monotherapy in subjects with renal cell carcinoma who have progressed following 1-2 lines of therapy including an immune checkpoint inhibitor. Eligibility criteria include age >18 years, clear cell RCC, ECOG PS 0-1, and disease progression during or following at least 6 weeks of treatment with ICI for RCC. Subjects will be stratified by IMDC risk category and whether ICI was received in most recent line of treatment or not. Subjects will receive tivozanib 1.34 mg orally once daily for 21 consecutive days followed by 7 days off, on the monotherapy arm, and tivozanib 0.89 mg at the same schedule in addition to nivolumab 480mg intravenously every 4 weeks on the combination arm. Study assessments include CT scan or MRI of the chest, abdomen, and pelvis every 8 weeks following Cycle 1 Day 1 for 2 years and every 12 weeks thereafter until disease progression is confirmed by independent radiology review (IRR). The primary objective is to compare the progression-free survival (PFS) of tivozanib in combination with nivolumab to tivozanib. A sample size of 326 subjects, with 191 events will provide at least 80% power to detect a 50% improvement in PFS, 12 mos v. 8 mos, as assessed by an IRR. Secondary endpoints include assessment of overall survival (OS), objective response rate (ORR), and duration of response (DoR), as well as safety and tolerability. Exploratory endpoints are to assess the quality of life (FKSI-DRS and EORTC QLQ C-30) and to investigate the pharmacokinetics of tivozanib. TiNivo-2 is actively enrolling and planning to open at 190 sites in the United States, and the European Union. Clinical trial information: NCT04987203. Research Sponsor: Aveo Oncology.

TPS4606 **Poster Session**

A phase I trial to evaluate the biologic effect of CBM588 (*Clostridium butyricum*) in combination with cabozantinib plus nivolumab for patients with metastatic renal cell carcinoma (mRCC). *First Author: Luis A Meza, City of Hope Comprehensive Cancer Center, Duarte, CA*

Background: Combination therapy with the immune checkpoint inhibitor (ICI) nivolumab (nivo) and the tyrosine kinase inhibitor cabozantinib (cabo) is a new standard of care for first line treatment of patients with clear cell mRCC. However, despite the improved clinical benefit obtained with this regimen, a subgroup of patients still presents with progressive disease as best response (Choueiri et al NEJM 2021). There is now evidence supporting the role of the gut microbiome in mediating ICI activity (Routy et al Science 2018) and certain bacterial species, such as *Bifidobacterium spp.* in predisposing clinical response in patients with mRCC receiving ICIs (Salgia et al Eur Urol 2020). Moreover, recent evidence from a phase I clinical trial suggests that the addition of CBM588, a live probiotic comprised primarily of *Clostridium butyricum*, can enhance clinical response in patients with mRCC receiving nivolumab plus ipilimumab without incurring added toxicity (Meza et al ASCO, 2021). Herein we present the study design of an ongoing phase I study evaluating the biological effect of CBM588 in combination with cabozantinib plus nivolumab in patients with mRCC. **Methods:** This is an open label, randomized, single institution phase 1 trial for patients with confirmed mRCC with clear cell, papillary, or sarcomatoid components, who have not received prior systemic therapy for metastatic disease. A total of 30 eligible patient will be randomized 1:2 to receive either cabo/nivo at the standard dose/schedule (40mg PO QD and 480mg IV /4wks, respectively) alone or with CBM588 dosed at 80mg PO bid. The primary objective of the study is to determine the biologic effect of CBM588 with cabo/nivo in the modulation of the gut microbiome. This will be done by assessing the changes in *Bifidobacterium spp.* abundance and Shannon index (a measure of microbiome diversity) in stool specimens. Stool will be collected for bacteriomic profiling at baseline and after 12 weeks of treatment. Metagenomic sequencing will be performed using previously published methods (Dizman et al Cancer Med 2020). Secondary objectives include determining the effect of CBM588 on (1) clinical efficacy, through overall survival, response rate, and progression-free survival; (2) systemic immunomodulation, through assessment of changes in circulating Tregs, circulating cytokines/chemokines, etc; and (3) toxicities. A two-group t-test with a one-sided type I error of 0.05 will be used to assess the study primary endpoint. Clinical trial information: NCT05122546. Research Sponsor: Exelixis is providing funding for this clinical trial.

TPS4607 **Poster Session**

MAIN-CAV: Phase III randomized trial of maintenance cabozantinib and avelumab versus avelumab after first-line platinum-based chemotherapy in patients with metastatic urothelial cancer (mUC) (Alliance A032001). *First Author: Shilpa Gupta, Taussig Cancer Institute, Cleveland Clinic Foundation, Cleveland, OH*

Background: First-line platinum-based chemotherapy followed by maintenance avelumab (Av) is the current preferred standard of care in patients (pts) with mUC who do not progress after platinum-based chemotherapy. There is an unmet need to further improve outcomes by combining Av with an effective, non-cross resistant therapy with non-overlapping toxicity. Cabozantinib (CABO) is an oral inhibitor of MET, VEGFR and TAM family receptors involved in tumor growth, angiogenesis and immune cell regulation and has shown efficacy in UC in combination with PD-1/PD-1L1 inhibitors. We hypothesize that CABO-Av combination will be synergistic in pts with mUC with an acceptable safety profile and will improve upon the benefit seen with Av maintenance in mUC. **Methods:** MAIN-CAV is a phase III randomized, multicenter, international trial for locally advanced/mUC pts (including N3 only disease) who do not progress after 4-6 cycles of any platinum-based chemotherapy (gem-cis, gem-carbo, MVAC or ddMVAC). 654 adult pts will be randomized 1:1 within 3-10 weeks (wk) after last dose of chemotherapy to receive Av 800 mg IV every 2 wk or combination of Av and CABO 40 mg orally daily for up to 2 yrs. Key eligibility criteria include ECOG PS 0-1, no prior use of immunotherapy (exception of BCG), no central nervous system metastases, no major surgery within 4 wk, no uncontrolled hypertension or cardiovascular disorders. Pts will be stratified based on 1) best response to 1L therapy: complete response vs partial response vs stable disease and 2) presence or absence of visceral metastases. The primary endpoint is overall survival (OS) with assumptions of one-sided alpha of 0.025, power of 80%, median OS of 21 months (mo) on Av arm and hazard ratio (HR) of 0.75, thus hypothesizing a median OS of 28 mo on CABO-Av combination arm. Key secondary endpoints include progression-free survival, safety, tolerability, and activity of CABO-Av compared to Av alone based on RECIST 1.1 and iRECIST criteria and PD-L1 status of pts' tumors. Quality of life (QOL) will be assessed using EQ-5D-5L, PROMIS-Fatigue 4a, EORTC QLQ-C30, EORTC QLQ-BLM30 between pts on CABO-avelumab vs avelumab alone. Biomarkers of response and resistance to Av will be assessed using baseline archival tissues, baseline and serial blood, ctDNA, stool and urine. Imaging studies will test correlation of established and new radiomic signatures with OS, adverse events and QOL and incorporate both radiologic and biologic features to predict outcomes. This trial would be the first to systematically address whether adding a multitargeted TKI, CABO to Av leads to improved clinical outcomes compared to Av alone. Support: U10CA180821, U10CA180882, U24CA196171,U10-CA180863 (CCTG); Clinical trial information: NCT05092958. Research Sponsor: U.S. National Institutes of Health.

TPS4608 **Poster Session**

A phase III randomized trial of eribulin (E) with or without gemcitabine versus standard of care (SOC) for metastatic urothelial carcinoma (UC) refractory to or ineligible for PD/PDL1 antibody (Ab): SWOG S1937. *First Author: Sarmad Sadeghi, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: UC is 2nd most common genitourinary cancer. Current SOC offers platinum-based (PB) first line chemotherapy (chemo) with ddMVAC or gemcitabine-cisplatin (GC) regimens. For cisplatin ineligible patients (pts), SOC includes gemcitabine-carboplatin (GCa), and in select pts pembrolizumab. Erdafitinib is approved for pts with FGFR alterations and Enfortumab vedotin (EV) is approved for previously treated pts. A phase I/II CTEP study of eribulin (E) for metastatic UC (mUC) established the activity of E in UC with objective response rate (ORR) of 37.5% and a median progression free survival (PFS) of 4.1 months (mo) and median overall survival (OS) of 9.5 mo (N = 150). A phase II CTEP study of gemcitabine-eribulin (GE) in cisplatin ineligible mUC showed an ORR of 50%, median OS of 11.9 mo and median PFS of 5.3 mo (N = 24). The most common Grade 3-4 toxicities included: neutropenia 63%, anemia and fatigue 29%. Pts with liver metastases benefited from therapy with 5 responders in 7 pts for GE vs 12 out 49 E. **Methods**: This is a phase III, randomized 3 arm study comparing E vs. GE vs. SOC (docetaxel, paclitaxel, or gemcitabine). E is given at 1.4mg/m2 on day (D) 1 and 8 of a 21 D cycle. In the GE arm, gemcitabine is added to E at 1000 mg/m2 dose to D1 and D8. SOC follows standard dosing of the agents. There is no limit to the number/sequence of prior regimens. A simplified summary of eligibility criteria is presented here. All pts must have: received frontline systemic treatment such as PB chemo or a non-platinum regimen. received PD1/PDL1 Ab or be deemed ineligible for PD1/PDL1 Ab. received EV. Assuming a median OS for the SOC arm of 7 mo the study seeks to find at least a 50% increase in median OS to 10.5 mo (Hazard Ratio (HR) = 0.667). One-sided 0.0125 type I error to account for testing of two primary hypotheses (Each arm vs. SOC). 87% power to detect a 3.5 mo improvement in OS. We require 140 eligible (155 total) pts in each arm for a total of 465. The study was activated in Feb 2021 and accrual is ongoing. Clinical trial information: NCT04579224. Research Sponsor: SWOG S1937, National Institutes of Health/National Cancer Institute grants U10CA180888, U10CA180819.

TPS4609 **Poster Session**

^{89}Zirconium-labelled girentuximab (^{89}Zr-TLX250) PET in patients with urothelial cancer (ZiPUP): A phase I trial of a novel staging modality for urothelial carcinoma. *First Author: Dickon Hayne, UWA Medical School, University of Western Australia, Perth, Australia*

Background: Bladder cancer is a lethal disease with a rising incidence. The current standard imaging modalities for staging are either CT of the chest, abdomen and pelvis or FDG PET/CT. However, there are issues with using these modalities for staging. CT is known to have relatively low sensitivity for detecting low volume metastatic disease, while FDG is predominantly renally excreted and therefore has intense activity in the urinary tract, which limits its utility to detect bladder or upper tract lesions, or nodal metastases in close proximity to the urinary tract. Zirconium-89-Girentuximab (89Zr-TLX250) may have utility in the accurate staging of bladder and urothelial cancer, with less renal excretion as compared to FDG, however this has not previously been investigated. ZipUp is an investigator initiated trial. South Metropolitan Health Service WA is the trial sponsor. The study received funding and study drug support from Telix Pharmaceuticals **Methods:** ZiPUP is a single-arm, phase I trial examining the feasibility, safety, and utility of 89Zr-TLX250 PET/CT in patients either undergoing pre-operative staging of urothelial carcinoma or bladder cancer for curative intent, or with known metastatic urothelial carcinoma or bladder cancer. All participants will undergo 89Zr-TLX250 PET/CT and will need to have undergone recent FDG PET/CT for means of comparison. This trial aims to recruit 10 participants undergoing staging and 10 participants with known metastatic disease. The primary endpoint is effectiveness by assessing sensitivity and specificity in detecting lymph node metastases compared to FDG PET/CT; secondary endpoints are safety, tolerability, and feasibility. The first patient was enrolled in this single site study and the study is expected to be completed by December 2022. If 89Zr-TLX250 PET/CT is proven to be feasible, safe, and effective in staging urothelial cancer, it could improve the appropriate selection of treatment for patients with metastatic or primary urothelial carcinoma or bladder cancer. Clinical trial information: NCT05046665. Research Sponsor: Telix Pharmaceutical, South Metropolitan Health Service WA.

TPS4610 **Poster Session**

Trial in progress: A phase II switch maintenance study of live biotherapeutic MRx0518 and avelumab in patients with unresectable locally advanced or metastatic urothelial carcinoma (UC) who did not progress on first-line platinum-containing chemotherapy. *First Author: Amishi Yogesh Shah, MD Anderson Cancer Center, Houston, TX*

Background: Efficacy of avelumab for maintenance treatment of UC was investigated in the JAVELIN Bladder 100 study (NCT02603432), which led to the FDA approval of avelumab for maintenance treatment as the current standard of care for patients with locally advanced or metastatic UC that have not progressed with first-line platinum-based chemotherapy. Outcomes included median overall survival (OS) of 21.4 months (95% CI 0.56-0.86), median progression-free survival (PFS) of 3.7 months (95% CI 3.5-5.5) and objective response rate (ORR) of 9.7% (95% CI 6.8-13). MRx0518 is a novel, human gut microbiome-derived, single-strain, live biotherapeutic. It is a bacterium of the *Enterococcus* genus that was selected for development in solid tumor treatment for its strong *in vitro* and *in vivo* immunostimulatory activity. *In vivo* studies have shown that MRx0518 can inhibit tumor growth in different syngeneic cancer models as both monotherapy and in combination with immune checkpoint inhibitors. MRx0518 has been shown to reduce Treg and increase Th1 and Tc1 lymphocyte differentiation *in vitro* and increase intratumoral CD4+ and CD8+ T cells and NK cells *in vivo*. In clinical studies, preliminary data shows that MRx0518 monotherapy can increase anti-tumor TILs and systemic pro-inflammatory immune signaling molecules. This is a pilot study evaluating whether the addition of MRx0518 to avelumab in the maintenance setting of metastatic platinum-treated UC may improve outcomes. **Methods:** The study will enroll 30 patients with unresectable locally advanced or metastatic UC at multiple US centers. Patients must have measurable disease after a partial response or stable disease on 4-6 cycles of platinum-containing induction chemotherapy. Patients will receive 800 mg avelumab IV infusion every 2 weeks in combination with 1 oral capsule ($10x10^{10}$ – $10x10^{11}$ CFU) MRx0518 twice daily until disease progression, patient withdrawal or unacceptable toxicity. Primary objectives are to assess safety of the combination, and effect on PFS at 6 months. Secondary objectives are to assess other efficacy measures including PFS, ORR, OS, duration of response, time to response, and disease control rate. Collection of paired research biopsies at baseline (after chemotherapy) and on treatment (after 8 weeks of MRx0518 + avelumab), plus longitudinal blood sampling, will allow investigation of immunological changes systemically both in the tumor and as potential predictive markers of response. Stool and urine samples collected before, during and after treatment will allow investigation of changes to the microbiome and metabolome. Recruitment is open, awaiting accrual. Clinical trial information: NCT05107427. Research Sponsor: 4D pharma plc.

TPS4611 **Poster Session**

A phase II clinical trial of neoadjuvant sasanlimab and stereotactic body radiation therapy as an in situ vaccine for cisplatin-ineligible muscle invasive bladder cancer (RAD VACCINE MIBC). *First Author: Raj Satkunasivam, Department of Urology and Center for Outcomes Research, Houston Methodist Hospital, Houston, TX*

Background: The utilization of neoadjuvant immune checkpoint inhibitor (ICI) therapy, including anti-PD1/L1 agents, prior to radical cystectomy (RC), is an emerging paradigm in muscle invasive bladder cancer (MIBC). Pathologic complete responses (pCR) have been observed in 25-40% of patients with neoadjuvant PD1/L1 inhibitor monotherapy for cisplatin-ineligible MIBC. *In situ vaccination* using stereotactic body radiation therapy (SBRT) may augment T-cell responses to tumor-specific antigens through immunogenic cell death. Sasanlimab (PF-06801591) is a humanized IgG monoclonal antibody that targets PD-1 selectively, for which there are both Phase 1 data and ongoing Phase 3 trials in early-stage urothelial carcinoma. There exists a strong rationale to evaluate a novel strategy of combination neoadjuvant ICI therapy with SBRT as an *in situ vaccine* to improve loco-regional control and decrease the risk of distant recurrence in cisplatin-ineligible patients with MIBC. **Methods:** This is a prospective, investigator-initiated, single-arm, single-institution, phase II trial that evaluates neoadjuvant sasanlimab in combination with SBRT as neoadjuvant therapy for patients with MIBC before RC. Eligibility requires patients to be cisplatin-ineligible (one of the following: ECOG-PS=2, creatinine clearance <60 ml/min, or comorbidities such as hearing loss or neuropathy) or those who refuse cisplatin-based chemotherapy. Sasanlimab (300 mg) will be administered subcutaneously on Day 1 of each 28-day cycle for a total of 2 cycles, in combination with SBRT to the primary tumor at a dose of 24Gy given in 3 fractions, starting on Day 1 of Cycle 2 with a 48-hour interval between fractions. The combination treatment will be assessed by using a Simon's 2-Stage design, which the first 10 patients are enrolled as a safety lead-in to evaluate the safety and feasibility. Futility analysis will be performed after a total of 18 patients. The primary endpoint is pCR rate after neoadjuvant sasanlimab/SBRT, followed by RC. If pCR is observed in 4 or fewer patients, further enrollment of patients may be stopped with the conclusion that pT0 cannot be 40% or greater. Otherwise, an additional 15 patients will be accrued in stage II, resulting in a total of 33 patients. Secondary endpoints include adverse events, surgical complication rates, health related quality-of-life, overall survival, and recurrence free survival. Exploratory endpoints include analysis of and association with pCR of the tumor/germline genetic signatures, circulating tumor DNA, tumor PD-L1 expression, blood cytometry time-of-flight analysis to identify immune response. Enrollment opened on February 15, 2022. Clinical trial information: NCT05241340. Research Sponsor: Institutional Funding, Pfizer for Study Drug.

TPS4612 **Poster Session**

A phase II trial evaluating combination pemetrexed and avelumab in patients with MTAP-deficient advanced urothelial cancer. *First Author: Amishi Yogesh Shah, MD Anderson Cancer Center, Houston, TX*

Background: MTAP-deficiency occurs primarily due to homozygous loss in chromosome 9p21 and is seen in approximately 25% of urothelial cancers. MTAP-deficiency portends aggressive biology with poorer outcomes than in MTAP-proficient tumors; for example, in the IMvigor210 data, MTAP-deficient patients had median overall survival of 8.0 months, compared to 11.3 months in MTAP-proficient patients ($p = 0.042$). MTAP-deficient tumors lack salvage nucleotide synthesis pathways and thus are uniquely sensitive to anti-folate agents; however, in prior clinical work with pemetrexed in these tumors, responses are relatively short-lived. In-vivo data has suggested that pemetrexed can increase tumor infiltrating T-cells, macrophages, dendritic cells, and PD-L1 expression in MTAP-deficient tumors and decrease myeloid-derived suppressor cells (MDSCs). As such, it was postulated that sequential treatment with anti-folate chemotherapy (pemetrexed) and immune checkpoint inhibition (avelumab) would improve responses in MTAP-deficient urothelial cancer. **Methods:** A prospective phase II trial of patients with advanced MTAP-deficient urothelial cancer is being conducted under IRB-approved protocol NCT03744793. This study will enroll 25 patients at a single site (The University of TX, MD Anderson Cancer Center). Key eligibility criteria include patients with advanced MTAP-deficient urothelial cancer with measurable disease in second-line or beyond. MTAP-deficiency is confirmed with CLIA-approved IHC or NGS. Patients are stratified as being IO-pretreated versus IO-naïve. All patients receive a lead-in cycle of pemetrexed (500 mg/m2) followed by combination pemetrexed (500 mg/m2) and avelumab (10 mg/kg) IV every three weeks until disease progression, patient withdrawal, or unacceptable toxicity. Three biopsies per patient with tissue collection at trial baseline, on single agent pemetrexed, and on combination pemetrexed-avelumab are performed. The primary objective of this trial is to evaluate response rate with sequential pemetrexed and avelumab in MTAP-deficient urothelial cancer. Imaging response assessment is done via RECIST v1.1. Secondary objectives are to evaluate progression-free survival (PFS) and overall survival (OS), as well as to perform correlative studies evaluating the effect of this therapy on immune cells and tumor microenvironment. This correlative work includes but is not limited to evaluation of peripheral T-cells, tumor-infiltrating T-cells, macrophages, and MDSCs. Interim analyses for futility and safety occur in cohorts of 5 patients and are performed based on Bayesian sequential methods. Fifteen patients have been enrolled thus far. Clinical trial information: NCT03744793. Research Sponsor: EMD Serono.

TPS4613 **Poster Session**

ANTICIPATE: A phase I/II, open-label, multicenter study to evaluate the safety and efficacy of oral APL-1202 in combination with tislelizumab compared to tislelizumab alone as neoadjuvant therapy (NAC) in patients with muscle invasive bladder cancer (MIBC). *First Author: Matt D. Galsky, The Tisch Cancer Institute, Mount Sinai, New York, NY*

Background: Standard treatment for muscle invasive bladder cancer (MIBC) is radical cystectomy (RC) and administration of NAC in patients who are eligible to receive cisplatin. Approximately 50% of patients are ineligible to receive cisplatin as a result of pre-existing contraindications, and some refuse to receive any chemotherapy due to concerns of toxicities. Immune checkpoint inhibitors (ICIs) have been shown to be highly active in metastatic urothelial cancer. APL-1202 (nitroxoline) is a reversible and orally available MetAP2 inhibitor with anti-angiogenic and anti-tumor activities. Synergistic effects of APL-1202 and ICIs have been shown in model systems of bladder cancer. It is hypothesized that APL-1202 in combination with tislelizumab, a humanized IgG4 anti-PD-1 MAb, may be an effective neoadjuvant therapy in MIBC. This trial will evaluate the safety, efficacy, and pharmacodynamic effects of APL-1202 in combination with tislelizumab as neoadjuvant therapy for patients with MIBC who are cisplatin ineligible or refuse cisplatin-based chemotherapy. **Methods:** ANTICIPATE is an open-label, multi-center clinical trial enrolling 79 patients in two phases: Phase I and Phase II. Phase I is a dose escalation study to determine MTD (maximum tolerated dose) and/or RP2D. Phase II is an expanded proof-of-concept study to evaluate the safety and efficacy of APL-1202 in combination with tislelizumab compared to tislelizumab alone as neoadjuvant therapy for MIBC as measured by pathological complete response (pCR). Phase I and Phase II both are divided into 3 periods: screening period of 4 weeks, neoadjuvant therapy comprising 3 cycles (each 21 days) prior to radical cystectomy; and a follow-up period of up to 90 days after surgery. The phase I will determine the RP2D of APL-1202 in combination with tislelizumab as neoadjuvant therapy for MIBC. Eligible patients have newly diagnosed MIBC and are cisplatin ineligible or refuse cisplatin-based NAC and are planned for RC. In phase I, a standard 3+3 dose-escalation design will be used. On day 1 of each cycle, a single dose of 200 mg tislelizumab will be administered intravenously. The daily dose APL-1202 will be escalated in successive cohorts (375 mg à 750 mg à 1,125 mg). The DLT observation window for any dose level will be treatment cycle 1. There will be no intra-patient dose escalation. In phase II patients will be randomly assigned to group 1 (APL-1202 + tislelizumab) or group 2 (tislelizumab only), stratified by PD-L1 expression. The IND has been approved by FDA and NMPA, and the study execution is under preparation both in US and China. Clinical trial information: NCT04813107. Research Sponsor: Asieris.

TPS4614 **Poster Session**

A phase 3 study of the subcutaneous programmed cell death protein 1 inhibitor sasanlimab as single agent for patients with bacillus Calmette-Guérin, unresponsiv,e high-risk, non-muscle invasive bladder cancer: CREST Study Cohort B. *First Author: Neal D. Shore, Carolina Urologic Research Center, Myrtle Beach, SC*

Background: Bacillus Calmette-Guérin (BCG) therapy is the standard of care for high-risk non-muscle invasive bladder cancer (NMIBC) after transurethral resection of bladder tumor. However, disease recurrence or progression is common and patients with BCG-unresponsive disease are unlikely to respond to further BCG therapy. In these patients, the current standard of care is radical cystectomy and bladder-preserving treatment options, limited to intravesical chemotherapy or intravenous pembrolizumab. In a phase 1 study, sasanlimab (PF-06801591), a monoclonal antibody to programmed cell death protein 1 (PD-1), was administered subcutaneously at 300 mg every 4 weeks. Sasanlimab had an acceptable safety profile and showed clinical activity aligned to other anti-PD-1/PD-ligand 1 (PD-L1) agents in patients with advanced urothelial carcinoma and non-small cell lung cancer, while offering the convenience of subcutaneous administration. Therefore, CREST Study Cohort B aims to evaluate sasanlimab administered subcutaneously in patients with BCG-unresponsive NMIBC. **Methods:** CREST Study Cohort B is a non-randomized, multicenter, multinational, open-label, phase 3 study and will enroll ~160 patients with histologically confirmed BCG-unresponsive, high-risk, non-muscle invasive transitional cell carcinoma of the bladder urothelium (high-grade Ta or T1 tumor, or carcinoma in situ [CIS]) in 2 separate Cohorts, B1 and B2 (~110 and ~50 patients, respectively). Cohort B1 will enroll patients with persistent or recurrent CIS with or without concomitant recurrent high-grade Ta/T1 disease, within 12 months of completing adequate BCG therapy. Cohort B2 will enroll patients with recurrent high-grade Ta/T1 disease within 6 months of completing adequate BCG therapy. All patients will receive subcutaneous sasanlimab as a single agent. Efficacy will be assessed at regular intervals by cystoscopy, urine cytology, biopsy, and imaging. The primary endpoint is complete response (CR) and event-free survival (EFS) for Cohort B1 and B2, respectively. Secondary endpoints include duration of CR (Cohort B1 only), EFS (Cohort B1 only), overall survival, time to cystectomy, safety, health-related quality of life, pharmacokinetic parameters, PD-L1 expression, and incidence of anti-drug antibodies. Recruitment of patients in CREST Study Cohort B will be opened in Canada and the United States of America, with other sites in Asia, Australia, and Europe. Clinical trial information: NCT04165317. Research Sponsor: Pfizer.

TPS4615 **Poster Session**

A phase II study of gemcitabine plus cisplatin chemotherapy in patients with muscle-invasive bladder cancer with bladder preservation for those patients whose tumors harbor deleterious DNA damage response (DDR) gene alterations (Alliance A031701). *First Author: Gopa Iyer, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: While a standard approach to muscle-invasive bladder cancer (MIBC) management involves neoadjuvant cisplatin-based chemotherapy (NAC) followed by radical cystectomy (RC), up to 50% of pts recur with metastatic disease. Moreover, removal of the bladder has a significant impact on pts' quality of life. Pathologic downstaging to non-muscle-invasive disease (<pT2) or complete response (pT0) at RC is associated with long-term survival benefit. Somatic DDR gene alterations were shown to be enriched in pts who were pT0 at RC following NAC in multiple retrospective analyses. We hypothesize that MIBC pts with somatic loss-of-function alterations within specific DDR genes and clinical responses to NAC can be uniquely managed with a bladder-sparing approach consisting of close cystoscopic and radiographic surveillance, avoiding the toxicities of definitive local therapy. **Methods:** A031701 is a multicenter phase II trial that will enroll 271 pts with T2-T4aN0/xM0 MIBC diagnosed within 60 days prior to enrollment. Multifocal MIBC, tumors >5 cm by cystoscopic assessment, and Bacillus Calmette-Guérin (BCG)-refractory disease (beyond standard induction and maintenance) are not allowed. Intravesical chemotherapy is allowed. Pts must be eligible for cisplatin chemotherapy. Eligible pts will receive either standard dose or dose dense gemcitabine and cisplatin chemotherapy (investigator's choice) with simultaneous genetic sequencing of pre-treatment transurethral resection specimens. Pts whose tumors contain deleterious alterations in any 1 of 9 pre-selected DDR genes (*ERCC2*, *ERCC5*, *BRCA1*, *BRCA2*, *RECQL4*, *RAD51C*, *ATM*, *ATR*, and *FANCC*) and who exhibit <T1 response on clinical restaging are eligible for organ-sparing management. Pts without deleterious DDR gene alterations or with >T1 disease after NAC will undergo RC or chemoradiation therapy (investigator/patient choice). The primary endpoint is 3-year event-free survival in DDR-altered pts who undergo bladder sparing, defined as the proportion of pts without BCG-unresponsive non-muscle invasive recurrences, any >T2 recurrences, or any metastatic recurrences. Secondary endpoints include clinical response rate (<cT1) in patients with deleterious DDR gene alterations following NAC, bladder-intact survival, overall survival, pT0 rate in DDR-altered pts who elect to undergo RC, pT0 rate in pts without DDR gene alterations, 3-year RC rate in pts with DDR gene alterations, and proportion of pts undergoing intravesical management for in-bladder recurrences. The study opened for enrollment in September 2018. Support: U10CA180821, U10CA180882. Clinical trial information: NCT03609216. Research Sponsor: None.

TPS4616 **Poster Session**

Phase I study of intravesical anti-CD40 agonist antibody 2141-V11 for non-muscle invasive bladder cancer unresponsive to Bacillus Calmette-Guerin (BCG) therapy. *First Author: Jeffrey L. Wong, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: CD40 is an immune-stimulatory receptor centrally involved in activating antigen-presenting cells and downstream anti-tumor immunity. Multiple agonistic anti-CD40 antibodies have been investigated clinically for cancer therapy, but have thus far shown limited efficacy and notable systemic toxicity. Our group has previously demonstrated that the ability of the Fc domain of anti-CD40 agonist antibodies to engage the FcγRIIB receptor, needed for optimal CD40 crosslinking, is critical for CD40 agonist activity. We engineered a fully-human anti-CD40 agonist antibody (2141-V11) with optimized Fc binding to FcγRIIB, which demonstrates significantly enhanced CD40 agonist activity. Non-muscle invasive bladder cancer (NMIBC), which remains an area of significant unmet need, represents an attractive clinical context to pursue CD40 agonist therapy given strong enrichment of CD40 in the bladder tumor microenvironment and routine use of local intravesical delivery as a potential strategy to mitigate systemic toxicity. Our preclinical studies, including in immunocompetent orthotopic murine models of bladder cancer humanized for CD40 and Fcγ receptors, revealed that intravesical delivery of 2141-V11 induced potent and durable anti-tumor immunity in both front-line and BCG-unresponsive settings without associated systemic toxicity (Garris and Wong, et al., *Sci Transl Med*, 2021;13:eabd1346). These data provide rationale to investigate intravesical 2141-V11 for the treatment of BCG-unresponsive NMIBC. **Methods:** This is a phase 1, open-label, dose-escalation study (NCT05126472) to evaluate the safety and tolerability of intravesically-delivered 2141-V11 in patients with BCG-unresponsive NMIBC who are considered ineligible for or have elected not to undergo radical cystectomy. Key inclusion criteria include adults with high-grade NMIBC (Ta, CIS, and/or T1) of urothelial histology that is unresponsive to adequate BCG therapy per consensus 2018 FDA guidelines. The primary objectives are to evaluate the safety and tolerability of 2141-V11 and to define the maximum tolerated dose and/or recommended phase 2 dose. The secondary objectives are to characterize the pharmacokinetics and evaluate the preliminary clinical activity of 2141-V11. Exploratory objectives include assessment of biomarkers of biological activity and disease resistance, their potential associations with clinical outcome measures, and patient-reported outcomes/quality of life measures. The 2141-V11 antibody is administered intravesically once weekly for 3 doses. Depending on disease status at week 13 and week 25 evaluations, patients may be eligible for re-treatment (once weekly for 3 doses) at these time points. Dose exploration utilizes a modified continual reassessment method design. Enrollment began in November 2021 and is ongoing. Clinical trial information: NCT05126472. Research Sponsor: Bochner-Fleisher Scholars Program, Conquer Cancer Foundation of the American Society of Clinical Oncology, Other Foundation, U.S. National Institutes of Health.

TPS4617 **Poster Session**

EA8185: Phase 2 study of bladder-sparing chemoradiation (chemoRT) with durvalumab in clinical stage III, node-positive urothelial carcinoma (INSPIRE), an ECOG-ACRIN/NRG collaboration. *First Author: Monika Joshi, Penn State Cancer Institute, Hershey, PA*

Background: Patients [pts] withlymph node positive (LN+), non-metastatic bladder cancer (BC) have a better prognosis than those with metastatic (M1) disease. However, this population is under-represented in advanced bladder trials and ineligible for bladder-sparing trials. Therefore, there have been no larger prospective trials establishing the standard of care in LN+ BC. Given the promise of immunotherapy in advanced BC and potential synergy between immunotherapy and radiation, INSPIRE was designed to determine the role of concurrent and adjuvant durvalumab (durva) in this patient population when treated with induction chemotherapy (IC) followed by concurrent chemoRT. **Methods:** This is a randomized phase II study that is enrolling BC pts with stage III [N1-3 M0], pure or mixed urothelial cancer. Pts must have received ≥3 cycles of IC [either before or after registration, prior to randomization] without progression. LN+ is defined as radiologically LN ≥1.0 cm in short axis, with or without biopsy prior to IC. As long as pts do not progress on induction chemotherapy, they will be randomized to chemoRT+/- durva using 5 stratification factors (Simon Pocock minimization method) a) IC prior vs. post registration b) cisplatin vs non-cisplatin regimen during RT c) LN size d) response to IC e) extent of TURBT. Pts on the chemoRT+durva arm will get chemotherapy per physician choice + IMRT + 3 x doses of Q3wk durva for 6.5-8 wks, whereas those on the control arm will get chemoRT alone. The primary end point is clinical complete response [CR], defined as no radiologically measurable disease in the LNs and negative cystoscopy and bladder biopsy 8-10 weeks post-chemoRT +/- durva. Pts on the chemoRT + durva arm who have a CR or clinical benefit (> T0 and ≤T2 in bladder per cystoscopy, biopsy + CR/PR/SD in LN by imaging) will get adjuvant Q4wk durva for 9 doses, while those on the chemoRT arm will undergo observation. Secondary end points include OS, PFS, bladder-intact event-free survival, rate of toxicity and salvage cystectomy. This study is designed to detect an improvement of 25% in clinical CR between both arms (37.5% to 62.5%). A total accrual of 114 pts (in order to enroll 92 evaluable pts) will provide 81% power to detect this difference using a Fisher's exact test (assuming 10% drop out + anticipating that 20% chemotherapy-naïve pts will progress post IC). We are banking blood and primary tumor tissue pre- and post-chemoRT in both groups. The study was activated in August 2020 and accrual is ongoing. We expanded eligibility to include N3 in 9/2021. INSPIRE is the first prospective study designed for only LN+ BC and will define both short-term and long-term outcomes for bladder sparing in this patient population and has the potential to define a new treatment strategy for stage III BC. Clinical trial information: NCT04216290. Research Sponsor: U.S. National Institutes of Health, AstraZeneca for sample collection.

TPS4618 **Poster Session**

A phase 2 study of cabozantinib in combination with atezolizumab as neoadjuvant treatment for muscle-invasive bladder cancer (HCRN GU18-343) ABATE study. *First Author: Deepak Kilari, Department of Medicine, Froedtert Cancer Center, Medical College of Wisconsin, Milwaukee, WI*

Background: ABACUS and PURE-01 trials demonstrated the activity of single agent atezolizumab and pembrolizumab respectively as neoadjuvant therapy for muscle invasive bladder carcinoma (MIBC). However, downstaging to non-muscle invasive disease was noted in only 50 percent of patients. Resistance to programmed death (PD)- 1/L1 antibodies is likely to include factors such as impaired dendritic cell maturation/function, infiltration of T-Regs and myeloid derived suppressor cells, impaired T-cell priming and T-cell trafficking in tumors. Cabozantinib is a tyrosine kinase inhibitor which targets MET, AXL, MER, Tyro3 and VEGFR2. Cabozantinib has a unique immunomodulatory profile and has demonstrated clinical activity as monotherapy and in combination with PD-1/L1 antibodies in various solid tumors including urothelial cancer (UC), renal cell, castrate- resistant prostate and non-small cell lung cancer. We hypothesize that the combination of cabozantinib and atezolizumab as neoadjuvant therapy for MIBC would improve rates of pathologic downstaging compared to single-agent checkpoint inhibitors. **Methods:** ABATE is an open-label, single arm, multi-center study to assess the efficacy and safety of cabozantinib with atezolizumab as neoadjuvant therapy for cT2-T4aN0/xM0 MIBC. An estimated 42 patients will be enrolled to obtain 38 evaluable patients, and the study will have over 80% power to declare the investigational combination to be successful using a Bayesian evaluation at 90% posterior probability cutoff, if the response probability is 59%, i.e., 20% higher than the 39% response rate with the single agent atezolizumab. Eligible patients will receive cabozantinib 40 mg PO daily with atezolizumab 1200mg every 3 weeks for a total duration of 9 weeks (3 cycles) followed by radical cystectomy. Adults (≥18 years) with resectable MIBC who are either cisplatin-ineligible or decline cisplatin-based chemotherapy are eligible. Patients are required to have an ECOG PS of 0-2 and provide tumor tissue for PD-L1 expression analysis. UC should be predominant component (≥ 50%). Previous systemic anticancer therapies for MIBC are not permitted. CT/MRI will be performed before investigational therapy and cystectomy. Primary endpoint is pathologic response rate defined as the absence of residual muscle-invasive cancer in the surgical specimen (< pT2). Secondary endpoints are safety and toxicity, pathologic complete response rate and event-free survival. Exploratory end points include patient-reported outcomes and outcome associations with biomarkers. Accrual began May 2020. Clinical trial information: NCT04289779. Research Sponsor: Exelixis and Genentech.

TPS4619 **Poster Session**

CCTG BL13 a randomized phase II trial assessing trimodality therapy with or without adjuvant durvalumab to treat patients with muscle-invasive bladder cancer (NCT03768570). *First Author: Wassim Kassouf, McGill University Health Center, Montréal, QC, Canada*

Background: Immunotherapy improves outcomes in the advanced (Bellmunt 2019; Powles 2020) as well as in the adjuvant setting post cystectomy (Bajorin 2021) for muscle invasive bladder cancer (MIBC) patients. Trimodality treatment (TMT) consisting of transurethral resection of bladder tumor (TURBT) followed by chemoradiotherapy (CRT) may be considered an alternative to radical cystectomy in MIBC. The role of radiotherapy and chemotherapy as immune system stimulants provides a rationale to evaluate the anticancer activity of checkpoint inhibitors in this patient population. Durvalumab, an anti PDL1 inhibitor, administered after CRT leads to improvement in PFS and OS in patients with locally advanced NSCLC, which further supports the rationale for this study (Antonia 2017, 2018). We hypothesized that durvalumab will improve outcomes in patients with MIBC when administered in the adjuvant setting after completion of trimodality therapy. **Methods:** CCTG BL13 is a Canadian Cancer Trials Group, randomized phase II trial in patients with stage T2-T4a N0M0, urothelial carcinoma treated with TURBT followed by radiotherapy with concurrent chemotherapy. Treatment arms consist of durvalumab 1500 mg IV q 4 weeks for 12 months versus surveillance. The primary objective: to compare disease free survival (DFS) between arms (RECIST 1.1, investigator assessed). Secondary endpoints include a non muscle-invasive bladder cancer recurrence rate (< T2); locoregional control rate; overall survival; bladder intact DFS, patterns of disease recurrence; metastasis free survival; safety; quality of life ; economics evaluation. A pilot sub study (BL13F) has been activated and will evaluate the feasibility of electronic real-time patient self-reporting of immunotherapy related symptomatic adverse events using the SYMPTOM-IQ Tool on the uMotif Mobile Health Application (APP). Statistical Design: Randomization 1:1 balanced for stratification factors: ECOG PS; neoadjuvant chemotherapy; radiation field extent; T2 vs T3/T4; centre. Assuming a 2-year DFS rate 65% for patients on the control arm and estimated 12% improvement in the 2-year DFS rate (65% to 77% (HR 0.61)) with 80% power using a 1-sided 10% level test requires a sample size of 190 including 5% drop out rate. Conduct to Date: Study activation Dec 2018. Enrollment as of January 31 2022: 49. The DSMC reviewed and recommended trial continuation in November 2021. Clinical trial information: NCT03768570. Research Sponsor: Canadian Cancer Society, AstraZeneca.

TPS4620 **Poster Session**

Phase 1a/b safety study of intravesical instillation of TARA-002 in adults with high-grade non-muscle invasive bladder cancer (ADVANCED-1). *First Author: Jathin Bandari, Protara Therapeutics, New York, NY*

Background: Bladder cancer is the most common malignancy involving the urinary system, resulting in approximately 18,000 deaths each year in the US. Approximately 70% of new urothelial bladder cancer cases are classified as non-muscle invasive bladder cancer (NMIBC). With the current Bacillus Calmette-Guérin (BCG) shortage and limited effective alternate therapies, there continues to be a significant unmet need for treatment options for patients with NMIBC. TARA-002 is being developed for the treatment of high-grade (HG) NMIBC (consisting of HG Ta, T1, and carcinoma in situ [CIS]). TARA-002 is a lyophilized biological preparation for instillation containing cells of *Streptococcus pyogenes* (Group A, type 3) Su strain treated with benzylpenicillin. TARA-002 is manufactured using the same master cell bank as OK-432 (Picibanil) and is approved in Japan and Taiwan for the treatment of several oncology indications. Nonclinical toxicology studies with TARA-002 and nonclinical and clinical studies with OK-432 (a comparable product to TARA-002) support the starting dose for the planned Phase 1a/b study. **Methods:** ADVANCED-1 is a Phase 1a/b, dose finding, open-label study of intravesical instillation of TARA-002 in adults with HG NMIBC. The study includes a dose escalation phase (Phase 1a) and a dose expansion phase (Phase 1b). The objective of the study is to evaluate the safety and tolerability of TARA-002, to establish the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) in the treatment of subjects with HG Ta or CIS ± Ta NMIBC during Phase 1a, and to further assess the safety and preliminary efficacy of TARA-002 in the treatment of subjects with CIS NMIBC with active disease during Phase 1b. For this first-in-human study, stage T1 is excluded. The study includes eligible male and female subjects ≥ 18 years of age who are unable to obtain BCG or have received at least one dose of intravesical BCG or chemotherapy. Those with current or a history of penicillin allergy or current evidence of any condition, therapy, or laboratory abnormality that might confound the results are excluded. The overall study duration for each subject includes 28 days of screening period, 6-week treatment period, and 6-week follow-up period. During the dose escalation phase (1a), up to 18 subjects with HG Ta or CIS ± Ta NMIBC are enrolled. Up to 3 dose levels are tested sequentially with 6 weekly intravesical doses, starting with the lowest dose using a 3+3 design in a dose escalation manner. At the established RP2D, the dose expansion phase (1b) will enroll approximately 12 new subjects with CIS ± Ta NMIBC with active disease and treat in the same manner to further assess the safety and preliminary efficacy of TARA-002. Phase 1a is currently open for enrollment. Clinical trial information: NCT05085977; NCT05085990. Research Sponsor: Protara Therapeutics.

TPS4621 **Poster Session**

Subcutaneous nivolumab versus intravenous nivolumab in patients with previously treated, advanced, or metastatic clear cell renal cell carcinoma.

First Author: Matias Rodrigo Chacon, Instituto Medico Especializado Alexander Fleming, Buenos Aires, Argentina

Background: Nivolumab (NIVO), a programmed death-1 immune checkpoint inhibitor, has demonstrated clinical efficacy across patients with different tumor types, including clear cell renal cell carcinoma (ccRCC), when administered via IV infusion. As an alternative to IV infusion, subcutaneous (SC) administration alleviates the need for IV ports, thereby lowering the risk of associated complications such as infections and phlebitis. SC formulation also reduces the time for dose preparation and administration, which may decrease overall treatment burden and reduce patient time in the clinic, benefiting patients and healthcare providers and improving overall healthcare resource utilization. SC-administered NIVO consists of NIVO co-formulated with the recombinant human hyaluronidase PH20 enzyme (NIVO + rHuPH20), which aims to increase the dispersion and absorption of NIVO within the SC space. SC NIVO + rHuPH20 was shown to be safe and well tolerated in a phase 1/2 study, warranting further investigation (Lonardi S et al. *J Clin Oncol* 2021;39(suppl 15):2575). **Methods:** CheckMate 67T is a multicenter, randomized, open-label, phase 3 study that will evaluate the noninferiority of SC NIVO + rHuPH20 versus IV NIVO in patients with advanced or metastatic ccRCC who have progressed after receiving ≤ 2 prior systemic treatment regimens. Key inclusion criteria are age ≥ 18 years, histologically confirmed advanced or metastatic ccRCC, measurable disease by RECIST v1.1 within 28 days prior to randomization, and a Karnofsky performance status ≥ 70. Key exclusion criteria are untreated symptomatic metastases to the central nervous system, other malignancy, autoimmune diseases, HIV-positive status with AIDS-defining infection within past year or current CD4 count < 350 cells/μL, other serious or uncontrolled disorders including severe, acute SARS-CoV-2 infection, and prior treatment with immune checkpoint inhibitors, other T-cell–targeting antibody drugs, or live attenuated vaccines within 30 days of first study treatment. At least 454 eligible patients will be randomized to receive SC NIVO + rHuPH20 or IV NIVO. The primary objectives are to demonstrate pharmacokinetic (PK) noninferiority of SC NIVO versus IV NIVO, as measured by time-averaged serum concentration over the first 28 days (Cavgd28) and trough serum concentration at steady state (Cminss) (co-primary endpoints). Secondary endpoints include objective response rate by blinded independent central review, additional PK parameters, safety, efficacy, and immunogenicity of SC NIVO and IV NIVO. This study is currently enrolling patients globally. Clinical trial information: NCT04810078. Research Sponsor: Bristol Myers Squibb.

5000 **Oral Abstract Session**

TheraP: ^{177}Lu-PSMA-617 (LuPSMA) versus cabazitaxel in metastatic castration-resistant prostate cancer (mCRPC) progressing after docetaxel—Overall survival after median follow-up of 3 years (ANZUP 1603).

First Author: Michael S Hofman, Peter MacCallum Cancer Centre and Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, VIC, Australia

Background: We previously reported that in men with mCRPC progressing after docetaxel randomly assigned LuPSMA vs. cabazitaxel (Lancet 2021), those assigned LuPSMA has significant improvements in PSA response rate (66% vs. 37%), RECIST response rate (49% vs. 24%), progression-free survival (HR 0.63), less G3-4 toxicities (33% vs. 53%) and better patient-reported outcomes. We now report the secondary endpoint of overall survival (OS) with mature follow-up, for trial participants, and also those initially excluded because of low PSMA-expression or discordant disease on imaging with PSMA-PET and FDG-PET. **Methods:** Eligibility for the TheraP trial required mCRPC progressing after docetaxel, PET imaging with ^{68}Ga-PSMA-11 that showed high PSMA-expression (at least one site with SUV-max≥20), and ^{18}F-FDG demonstrating no sites of disease of FDG-positive and PSMA-negative (discordant disease). Participants were randomly assigned treatment with LuPSMA (8.5-6GBq every 6 weeks, maximum 6 cycles) vs cabazitaxel (20mg/m^2 every 3 weeks, maximum 10 cycles). OS was analyzed by intention-to-treat and summarized by restricted mean survival time (RMST) to account for non-proportional hazards. **Results:** 291 patients were screened from 6 Feb 2018 to 3 Sep 2019: 200 were eligible and randomly assigned LuPSMA (99) or cabazitaxel (101); 80 of 291 (27%) registered after initial eligibility were excluded after PSMA/FDG-PET(51 SUVmax < 20, 29 discordant), with follow-up available in 61 of the 80 (76%). After a median follow-up time of 36 months (data cut-off 31 Dec 2021), death was reported in 70/101 assigned cabazitaxel, 77/99 assigned LuPSMA, and 55/61 excluded after PSMA/FDG-PET. Subsequent treatments among those assigned cabazitaxel included cabazitaxel in 21, and LuPSMA in 20; and among those assigned LuPSMA included additional LuPSMA in 5, and cabazitaxel in 32. Overall survival was similar in those randomly assigned LuPSMA versus cabazitaxel (RMST to 36 months was 19.1 vs. 19.6 months, difference -0.5, 95% CI -3.7 to + 2.7). No additional safety signals were identified with longer follow-up. Among 61 men excluded by imaging with PSMA/FDG-PET before randomisation, RMST to 36 months was 11.0 months (95% CI 9.0 to 13.1), following treatment that included cabazitaxel in 29 (48%) and LuPSMA in 3 (5%). **Conclusions:** LuPSMA is a suitable option for men with mCRPC progressing after docetaxel, with lower adverse events, higher response rates, improved patient-reported outcomes, and similar OS compared with cabazitaxel. Median survival was considerably shorter for patients excluded on PSMA/FDG-PET due to either low PSMA expression or FDG-discordant disease who would otherwise be eligible for LuPSMA. Clinical trial information: NCT03392428. Research Sponsor: Prostate Cancer Foundation of Australia (PCFA), Other Government Agency, Australian Nuclear Science and Technology Organisation (ANSTO), Endocyte (now part of Advanced Accelerator Applications, now the Radioligand business of Novartis), Its a Bloke Thing, Movember and CAN4CANCER.

5001 **Oral Abstract Session**

[^{177}Lu]Lu-PSMA-617 in PSMA-positive metastatic castration-resistant prostate cancer: Prior and concomitant treatment subgroup analyses of the VISION trial.

First Author: Nitin Vaishampayan, Wayne State University School of Medicine, Detroit, MI

Background: In the phase 3 VISION trial, targeted radioligand therapy with lutetium (^{177}Lu) vipivotide tetraxetan ([^{177}Lu]Lu-PSMA-617; ^{177}Lu-PSMA-617) significantly prolonged radiographic progression-free survival (rPFS) and overall survival (OS) when added to standard of care (SoC) in patients with advanced prostate-specific membrane antigen (PSMA) PET-positive metastatic castration-resistant prostate cancer. Benefits were consistent across most pre-specified subgroups. In this post hoc exploratory analysis, we examined rPFS and OS in the context of prior and concomitant cancer-directed treatments. **Methods:** In VISION, adult patients previously treated with at least 1 androgen receptor pathway inhibitor (ARPI) and 1–2 taxane regimens were randomized 2:1 to ^{177}Lu-PSMA-617 (7.4 GBq Q6W, up to 6 cycles) + SoC or SoC alone. Protocol-permitted SoC excluded cytotoxic chemotherapy, systemic radioisotopes, immunotherapy, or other investigational drugs. Exploratory subgroup analyses of rPFS and OS were performed by: number of prior ARPIs; taxane regimens; non-taxane regimens and immunotherapies; prior treatment with bone-sparing agents; ^{223}Ra and PARP inhibitors; and concomitant treatment with ARPIs, radiation therapy, and bone-sparing agents. **Results:** Prior and concomitant treatments were generally well balanced between study groups (Table). rPFS and OS benefits with ^{177}Lu-PSMA-617 were consistent across all prior treatment subgroups. Notably, there were benefits in patients who had not received a second prior taxane. There were also consistent benefits regardless of concomitant systemic and radiation therapy as part of SoC. **Conclusions:** The clinical efficacy of ^{177}Lu-PSMA-617 was observed regardless of prior treatment or SoC chosen, suggesting that disease biology rather than prior and concomitant treatment context drives outcomes. Small differences in outcomes between subgroups may warrant further study to understand better the predictors of improved clinical benefit. Clinical trial information: NCT03511664. Research Sponsor: Advanced Accelerator Applications, a Novartis Company.

	rPFS			OS		
	% of patients in subgroup			% of patients in subgroup		
	^{177}Lu-PSMA-617 + SoC (N = 385)	SoC alone (N = 196)	HR (95% CI)	^{177}Lu-PSMA-617 + SoC (N = 551)	SoC alone (N = 280)	HR (95% CI)
Prior						
ARPI						
1	54.3	49.5	0.51 (0.35, 0.73)	53.7	46.4	0.74 (0.57, 0.97)
≥ 2	45.7	50.5	0.32 (0.23, 0.45)	46.3	53.6	0.52 (0.41, 0.67)
Taxane						
1	58.2	56.1	0.39 (0.27, 0.54)	62.1	58.9	0.59 (0.46, 0.75)
≥ 2	34.8	39.3	0.44 (0.30, 0.66)	30.9	35.4	0.73 (0.53, 0.99)
^{223}Ra						
Yes	16.4	18.4	0.49 (0.28, 0.87)	17.6	17.1	0.73 (0.47, 1.13)
No	83.6	81.6	0.38 (0.28, 0.50)	82.4	82.9	0.60 (0.49, 0.73)
Concurrent						
ARPI						
Yes	50.1	63.3	0.46 (0.33, 0.65)	52.5	59.3	0.55 (0.43, 0.70)
No	49.9	36.7	0.25 (0.17, 0.38)	47.5	40.7	0.70 (0.53, 0.93)
Bone-sparing agents	45.5	49.0	0.51 (0.36, 0.72)	43.6	44.6	0.59 (0.45, 0.78)
Yes	54.5	51.0	0.29 (0.20, 0.42)	56.4	55.4	0.64 (0.50, 0.82)
No						
All patients			0.40 (0.31, 0.52)			0.62 (0.52, 0.74)

5002 **Oral Abstract Session**

[^{68}Ga]Ga-PSMA-11 PET baseline imaging as a prognostic tool for clinical outcomes to [^{177}Lu]Lu-PSMA-617 in patients with mCRPC: A VISION substudy.

First Author: Phillip Kuo, University of Arizona, Tucson, AZ

Background: In the phase 3 VISION study, gallium (^{68}Ga) gozetotide (^{68}Ga-PSMA-11) PET/CT imaging was used to determine eligibility for lutetium (^{177}Lu) vipivotide tetraxetan (^{177}Lu-PSMA-617). Given that ^{177}Lu-PSMA-617 targets PSMA, we assessed the association between quantitative PSMA imaging parameters and treatment outcomes. **Methods:** In VISION, adults with mCRPC with ≥ 1 PSMA-positive (+) and no PSMA-negative lesions meeting the exclusion criteria were enrolled. In this sub-study, the association between imaging data from pre-enrollment ^{68}Ga-PSMA-11 PET/CT scans of pts in the ^{177}Lu-PSMA-617 group and clinical outcomes was assessed. Imaging data meeting quality requirements were analyzed for 548/551 pts. PSMA expression was quantified by 5 PET parameters: PSMA+ lesions by region, mean standardized uptake value (SUV_{mean}), maximum SUV (SUV_{max}), PSMA+ tumor volume, and tumor load (PSMA+ tumor volume × SUV_{mean}). Parameters were extracted from the whole body and 4 regions. Association between PET parameters and radiographic progression-free survival (rPFS; primary objective), overall survival (OS), objective response rate (ORR), and prostate–specific antigen 50 (PSA50) response was assessed. **Results:** Most pts (92.7%) had PSMA uptake in bone. In both the whole-body and regional analyses, statistically significant associations of PSMA PET parameters to clinical outcomes were observed (whole-body data shown in Table). Higher whole-body SUV_{mean} was associated with improved clinical outcomes; pts in the highest quartile (SUV_{mean}: rPFS, ≥ 10.2; OS, ≥ 9.9) had a median rPFS and OS of 14.1 and 21.4 months, vs 5.8 and 14.5 months for those in the lowest quartile (< 6.0; < 5.7), respectively. Absence of PSMA+ lesions in bone, liver, and lymph node, and lower PSMA+ tumor load, were indicators of good prognosis. **Conclusions:** Higher SUV_{mean} is strongly associated with improved outcomes with ^{177}Lu-PSMA-617; clinical efficacy for different SUV levels vs the SoC arm is being assessed. Data support use of ^{68}Ga-PSMA-11 PET/CT scan to identify pts who will benefit from PSMA-targeted radioligand therapy. Research Sponsor: Advanced Accelerator Applications, a Novartis Company.

Multivariate analysis of whole-body PSMA imaging parameters.[a]

	rPFS[b]	OS[b]	ORR[c]	PSA50[c]
SUV_{mean}	0.86 [0.82, 0.90], < 0.001	0.88 [0.84, 0.91], < 0.001	1.43 [1.24, 1.65], < 0.001	1.34 [1.23, 1.45], < 0.001
SUV_{max}	NS	NS	0.98 [0.96, 0.99], 0.009	NS
PSMA+ tumor volume	NS	NS	NS	NS
Tumor load	1.02 [1.01, 1.04], 0.001	1.04 [1.03, 1.05], < 0.001	NS	NS
Absence of PSMA+ lesions in:				
Bone	0.45 [0.26, 0.78], 0.004	0.38 [0.22, 0.67], < 0.001	3.06 [1.12, 8.38], 0.03	NS
Liver	0.48 [0.34, 0.67], < 0.001	0.49 [0.37, 0.66], < 0.001	2.55 [1.02, 6.34], 0.045	2.42 [1.21, 4.86], 0.013
Lymph node	NS	0.74 [0.58, 0.94], 0.014	0.1 [0.04, 0.25], < 0.001	NS
Soft tissue	NS	NS	NS	NS

[a]Per unit increase for continuous variables. [b]Hazard ratio [95% CI], *p* value; [c]Odds ratio [95% CI], *p* value. NS, not significant.

5005 **Oral Abstract Session**

A phase 3 trial of SHR3680 versus bicalutamide in combination with androgen deprivation therapy (ADT) in patients with high-volume metastatic hormone-sensitive prostate cancer (mHSPC).

First Author: Ding-Wei Ye, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Both TITAN and ARCHES studies have demonstrated significant clinical benefits of second-generation androgen receptor inhibitors (ARIs) plus ADT versus placebo plus ADT in the treatment of mHSPC. However, first-generation ARIs plus ADT is also widely used in clinic and how superior second-generation ARIs is to first-generation ones remains to be determined. Here, we evaluated the efficacy and safety of SHR3680, a novel oral ARI, versus bicalutamide (Bica) in high-volume mHSPC. **Methods:** CHART is a randomized, open-label, phase 3 study (NCT03520478). Patients (pts) with mHSPC were randomized 1:1 to ADT plus either SHR3680 (240 mg/d) or Bica (50 mg/d). All pts had high-volume disease adapted from the CHAARTED study. The primary endpoints were radiographic progression-free survival (rPFS) assessed by independent review committee (IRC) and overall survival (OS). As of May 16, 2021, 209 rPFS events per IRC and 153 deaths occurred and a preplanned interim analysis for rPFS was done. **Results:** 654 pts were randomized to receive SHR3680 (n = 326) or Bica (n = 328). At data cutoff, the median follow-up duration was 22.1 mo in SHR3680 group and 20.4 mo in Bica group. SHR3680 significantly reduced the risk of radiographic progression or death than Bica (HR, 0.44; 95% CI, 0.33-0.58; p < 0.0001; median, not reached vs 25.1 mo). OS data were immature but an improved OS was observed in SHR3680 group compared to Bica group (HR, 0.58; 95% CI, 0.42-0.80; p = 0.0009). All secondary efficacy endpoints favored SHR3680 plus ADT (Table). Frequencies of adverse events of any cause in any grade were similar between groups. Grade ≥3 treatment-related adverse events occurred in 19.2% and 13.9% of pts in SHR3680 and Bica groups, respectively. No seizure occurred in SHR3680 group. **Conclusions:** SHR3680 plus ADT significantly improved rPFS versus Bica plus ADT in pts with high-volume mHSPC, with a desirable safety profile. New drug application has been submitted to seek approval based on the data presented here. Clinical trial information: NCT03520478. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

	SHR3680 (n = 326)	Bica (n = 328)	Treatment Effect*	P value
rPFS by investigator, mo	NR (32.7-NR)	18.5 (14.8-25.1)	0.37 (0.28-0.49)	< 0.0001
Time to PSA progression, mo	NR (NR)	11.0 (9.2-12.9)	0.19 (0.14-0.26)	< 0.0001
Time to next skeletal-related event, mo	NR (NR)	NR (28.5-NR)	0.64 (0.48-0.86)	0.0032
Time to initiation of new anti-prostate cancer therapy, mo	NR (32.7-NR)	15.6 (13.6-19.0)	0.34 (0.26-0.43)	< 0.0001
ORR by IRC	81.0 (74.2-86.6)	68.2 (60.3-75.4)	12.8 (3.40-22.20)	0.0065
PSA undetectable (< 0.2 ng/mL) rate	68.1 (62.7-73.1)	33.2 (28.2-38.6)	34.9 (27.7-42.1)	< 0.0001

Data are median (95% CI) or % (95% CI) unless otherwise indicated. Abbreviations: NR, not reached; ORR, objective response rate; PSA, prostate specific antigen. *HR (95% CI) is shown for time-to-event analysis and rate difference (95% CI) for ORR and PSA undetectable rate.

LBA5004 **Oral Abstract Session**

Updated overall survival outcomes in ENZAMET (ANZUP 1304), an international, cooperative group trial of enzalutamide in metastatic hormone-sensitive prostate cancer (mHSPC). *First Author: Ian D. Davis, Eastern Health Clinical School, Monash University, Box Hill, VIC, Australia*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

5006 **Oral Abstract Session**

Assessing intermediate clinical endpoints (ICE) as potential surrogates for overall survival (OS) in men with metastatic hormone-sensitive prostate cancer (mHSPC). *First Author: Susan Halabi, Duke University Medical Center, Durham, NC*

Background: We hypothesized that radiographic progression free survival (rPFS) and clinical PFS (cPFS) are valid surrogates for OS in men with mHSPC and could potentially be used to expedite phase 3 clinical trials. This hypothesis was investigated by the STOPCAP M1 Collaboration. **Methods:** We obtained individual patient data (IPD) from 13/26 eligible randomized trials comparing treatment regimens (androgen deprivation therapy (ADT) or ADT + docetaxel in the control or research arms) in mHSPC. We evaluated the surrogacy of rPFS and cPFS as potential ICEs. rPFS was defined as time from randomization to radiographic progression (defined per protocol) or death from any cause whichever occurred first; cPFS was defined as time from randomization to date of radiographic progression, symptoms, initiation of new treatment, or death, whichever occurred first. OS was defined as time from randomization to death from any cause, if patients had not died they were censored at the date of last follow-up. We implemented a two-stage meta-analytic validation model where conditions of trial level and patient level surrogacy had to be met. We computed the surrogate threshold effect (STE), which is the minimum ICE treatment effect necessary to estimate a non-zero effect on OS. **Results**: IPD from 8592 patients randomized from 1994-2012 from 13 trials were pooled for a stratified analysis. There were 5377 deaths, of which 3971 (74%) were due to prostate cancer. The median follow-up for surviving patients was 75.6 months. In addition, there were 6227 rPFS and 6314 cPFS events. The median OS, rPFS and cPFS were 49.4, 26.8 and 25.2 months, respectively. The STE was 0.82 for rPFS and 0.84 for cPFS. **Conclusions**: Both rPFS and cPFS appear to be valid surrogate endpoints for OS. A surrogate threshold effect of 0.82 or higher makes it viable for either rPFS or cPFS to be used as the primary endpoint as a surrogate for OS in phase 3 mHSPC trials and would expedite trial conduct. Validation of these ICEs in trials with drugs having other mechanisms of action is planned. Clinical trial information: Several. Research Sponsor: Prostate Cancer Foundation.

Two-stage meta-analytic validation model	Condition 1: ICEs and OS are correlated		Condition 2: Treatment effects on both endpoints are correlated
Endpoint	Correlation at the Patient level, Kendall's Tau (95% CI)	Regression of 5-year OS rate vs 3-year ICE rate by trial and arm weighted by the inverse variances of the ICEs (or OS) * R-square (95% CI)	Regression of log(HR)-OS vs. log (HR)-ICE by trial weighted by the inverse variances of the ICEs (or OS) R-square (95% CI)
rPFS as a surrogate for OS	0.83 (0.82-0.84)	0.76 (0.42- 0.98) **[0.78 (0.43-0.99)]**	0.80 (0.43-0.98) **[0.81 (0.41-0.98)]**
cPFS as surrogate for OS	0.84 (0.83-0.85)	0.76 (0.40- 0.98) **[0.78 (0.42-0.99)]**	0.80 (0.45-0.98) **[0.81 (0.40-0.98)]**

*Excluding 3 studies with median follow up less than 5 years; HR=hazard ratio; CI=confidence interval; bolded numbers weighted by OS estimates.

5007 **Oral Abstract Session**

Defining germline genetics of germ cell tumor: Implications for genetic testing and clinical management. *First Author: Hong Truong, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Epidemiologic studies on germ cell tumors (GCT) in men have shown GCT has a high heritability. Yet, the genetic mechanisms underlying development of GCT in men remain unknown. We sought to determine the prevalence of pathogenic or likely pathogenic (P/LP) germline variants in cancer predisposition genes in men with GCT and identify clinical and pathologic factors associated with the presence of P/LP variants. **Methods:** We retrospectively identified men with testicular (T) or mediastinal (M) GCT who underwent matched tumor–germline sequencing of ≥ 310 genes as part of an institutional genomic profiling initiative from 04/2015 to 12/2020. Presence of germline variants in clinically actionable genes associated with hereditary cancer syndromes were analyzed. Clinicopathologic characteristics, including primary site, histology and family history were assessed by the presence of P/LP variants and compared using Fisher's exact test. **Results:** The study included 480 men, 70 (15%) with M-GCT and 410 (85%) with T-GCT. The median age of diagnosis was 30 years (interquartile range 24 – 39). A total of 81% had non-seminoma; 5% had localized disease; 46%, 14%, and 34% had good, intermediate, and poor risk advanced disease, respectively; 6% had family history of GCT. Among men with T-GCT, 4% had bilateral T-GCT. P/LP variants in clinically actionable genes were identified in 58 (12%) men in the entire cohort. Men with M-GCT had higher frequency of P/LP variants compared to those with T-GCT (15/70 [21%] vs 43/410 [10%], p = 0.02). A total of 7 (10%) men with M-GCT and 20 (5%) with T-GCT had P/LP variants in moderate or high penetrance cancer predisposition genes (p = 0.09). Most P/LP variants in both M-GCT (11/15, 73%) and T-GCT (33/43, 77%) were in genes involved in DNA damage repair pathways. The spectrum of moderate or high penetrance DNA damage repair genes identified is shown in the Table 1. Family history and histology (seminoma vs. non-seminoma) were not associated with the presence of a P/LP variants in the overall cohort (p = 0.8 and 0.7, respectively). Bilateral disease was not associated with the presence of P/LP variants in men with T-GCT (p = 0.4). **Conclusions:** Approximately 1 in 5 men with M-GCT carried a P/LP variant in a clinically actionable cancer susceptibility gene and 10% had a P/LP variant in a high-risk gene such as TP53 and PMS2. As men with GCT tend to develop disease in early adulthood, identification of germline P/LP variant has significant implications for enhanced cancer screening and surveillance, cascade testing for at-risk family members, and potential preconception genetic counseling. Research Sponsor: U.S. National Institutes of Health.

Genes	Mediastinal germ cell tumor N = 70 men, n, (%)	Testicular germ cell tumor N = 410 men, n, (%)
CHEK2	2 (2.9)	4 (1.0)
ATM	1 (1.4)	3 (0.7)
TP53	2 (2.9)	1 (0.2)
PALB2	0	3 (0.7)
BRCA1	0	2 (0.5)
BRIP1	0	2 (0.5)
BRCA2	0	1 (0.2)
NBN	0	1 (0.2)
PMS2	1 (1.4)	0

5008 **Oral Abstract Session**

Late relapses in testicular cancer: Results from a national cohort. *First Author: Torgrim Tandstad, St. Olav's University Hospital, Trondheim, Norway*

Background: Late relapses (LR; relapse occurring after disease-free interval of two years) in testicular cancer are relatively uncommon. The limited data published is hampered by selection bias and incomplete data regarding follow-up. We aimed to investigate the frequency of LR and of very late relapses (VLR; relapse occurring after disease-free interval of five years), and the survival of patients with VLR in a cohort treated after 1995, compared to a cohort before 1995. Finally, we aimed to describe the number of missed relapses beyond a 5-year follow-up scheme. **Methods:** A total of 5712 patients, 2978 seminoma and 2734 nonseminoma, were diagnosed with testicular cancer in Norway, with 2207 patients diagnosed 1980-1995 and 5712 patients diagnosed 1995-2009. Data are complete, due to identification by the Cancer Registry of Norway and Norwegian Cause of Death Registry. Details regarding diagnosis, stage, treatment, and follow-up were obtained from medical records. Relapse rates have been estimated using Kaplan-Meyer. **Results:** A total of 472 patients experienced relapse, 186 seminoma and 286 nonseminoma. Of these 109 were LR (51 seminomas, 58 nonseminomas), 50 VLR (22 seminomas, 28 nonseminomas with 17 relapses (4 seminomas, 13 nonseminomas) beyond ten years. The median time to LR was 4.7 years (range 2.0-21.6). In clinical stage I patients, there were 306 relapses (7.9%); with overall 1.9% LR, 1.0% VLR, and 0.5% relapse beyond ten years. Patients followed with surveillance had a higher rate of LR compared to patients receiving adjuvant therapy (4.0% vs 1.0%). Three patients with LR died of testicular cancer, all three had a VLR and initial nonseminoma. In patients with metastatic disease, 166 patients experienced relapse (10.5%); with overall 3.6% LR 1.6% VLR, and 0,8% relapse beyond ten years. In nonseminoma diagnosed after 1995, the rate of VLR was 0.8% compared to 2.3% in the earlier cohort. Eight patients with VLR died of testicular cancer, all with initial nonseminoma, and seven of these were diagnosed in the earlier cohort. Outside a five-year follow-up scheme, 50 patients would be diagnosed with a VLR. Prolonging follow-up to ten years would potentially identify only 33 of these relapses. **Conclusions:** In this first population-based series investigating late relapses of testicular cancer with complete data regarding treatment and follow-up, we find a low rate of VLR in patients treated according to modern guidelines. We believe centralization of treatment, adherence to guidelines, prospective registration of patients, and subsequent reporting of results are key to these improved results. Patients with CS I followed by surveillance will have higher rate of VLR compared to patients receiving adjuvant treatment, resulting in a higher VLR rate in the modern cohort, without affecting survival. In metastatic disease, the VLR rate was drastically reduced in the modern cohort, with a subsequent improved survival. Research Sponsor: Supported by grants from Helse Nord RHF (grant no. SPF1230-15).

5009 **Poster Discussion Session**

Cohort study of patients with oligorecurrent prostate cancer: Oncological outcomes of patients treated with salvage lymph node dissection via PSMA radioguided surgery. *First Author: Sophie Knipper, Martini-Klinik Prostate Cancer Center, Hamburg, Germany*

Background: Prostate-specific membrane antigen (PSMA) positron-emission tomography (PET) allows detection of small and/or atypically localized metastatic prostate cancer (PCa) lesions. In a subset of patients with recurrent oligometastatic PCa salvage surgery with PSMA-targeted radioguidance (PSMA-RGS) may be of value. We aimed to evaluate the oncological outcomes of salvage PSMA-RGS for oligo-recurrent PCa and determine predictive preoperative factors of improved outcomes. **Methods:** In this cohort study within two tertiary care centers, patients with biochemical recurrence (BCR) after radical prostatectomy (RP) and imaging with PSMA PET receiving salvage PSMA-RGS between 2014 and 2020 were analyzed. Kaplan-Meier and multivariable Cox regression models adjusted for various parameters were used to test for BCR-free survival (BFS) and therapy-free survival (TFS) differences. Postoperative complications were classified according to Clavien-Dindo. **Results:** Overall, 364 patients were assessed. At PSMA-RGS, median (IQR) age and preoperative PSA was 67 (61-71) years and 1.0 (0.5-1.9) ng/ml. Metastatic soft-tissue lesions from PCa metastases could be removed in 343 (94.2%) patients. Within three months from surgery, 24 (6.6%) patients suffered from Clavien-Dindo complications grade III-IV. During follow-up, 225 patients experienced BCR and 121 patients received further therapy. Median follow-up for patients who did not experience BCR and who did not receive further therapy was 10.8 months and 10.3 months, respectively. Median (IQR) BFS and TFS was 7.8 (5.4-10.5) and 35.5 months (25.9-45.9 months). At two years of follow-up, BFS rate was 31.9% and TFS rate was 58.0%. In multivariable analyses, higher preoperative PSA (HR: 1.1), higher number of PSMA-avid lesions on preoperative imaging (HR: 1.2) and multiple (pelvic plus retroperitoneal) localizations (HR: 1.9), as well as retroperitoneal localization (HR: 2.0) of lesions in PSMA PET imaging were independent predictors of BCR after PSMA-RGS. Limitations are the retrospective design and lack of a control group. **Conclusions:** As salvage surgery in oligo-recurrent PCa currently constitutes an experimental treatment approach careful patient selection is mandatory based on life expectancy, low PSA values and low number of PSMA PET avid lesions located in the pelvis. Further studies are needed to confirm our findings and define the oncological value of salvage surgical procedures in oligo-recurrent PCa. Research Sponsor: None.

5011 **Poster Discussion Session**

Prostate-specific membrane antigen PET response associates with radiographic progression-free survival following stereotactic ablative radiation therapy in oligometastatic castration-sensitive prostate cancer. *First Author: Philip Sutera, Johns Hopkins University, Baltimore, MD*

Background: Emerging data suggest metastasis-directed therapy (MDT) improves outcomes in patients with oligometastatic castration-sensitive prostate cancer (omCSPC). Prostate-specific membrane antigen positron emission tomography (PSMA-PET/CT) can detect occult metastatic disease and has been proposed as a biomarker for treatment response. Herein we identify and validate a PSMA-PET biomarker for clinical outcomes following MDT in omCSPC. **Methods:** This was an international multi-institutional retrospective study of two completely independent cohorts of men with omCSPC, defined as ≤3 lesions, treated with metastasis-directed stereotactic ablative radiation therapy (SABR) who underwent PSMA-PET/CT prior to and 3-6 months after treatment. Pre- and post-SABR PSMA-PET/CT standardized uptake value (SUV) was measured for all lesions and PSMA response defined discretely using a cutpoint of ≥ 30% decrease in SUV_{max}. PSMA-PET response was correlated with lesion local control (LLC), radiographic progression-free survival (rPFS) defined using conventional and PET imaging, and metastasis-free survival (MFS) defined by conventional imaging alone. **Results:** A total of 131 patients with 261 treated metastases were included in the analysis, with median follow-up of 29 months (IQR 18.5-41.3). Following SABR, 78.4% of lesions experienced a partial or complete PSMA response. Multivariable analysis demonstrated SUV response significantly associated with improved LLC (HR = 9.97, 95%CI 3.92-25.4; $p < 0.01$). Patients with PSMA response in all lesions experienced significantly better rPFS (HR = 0.49, 95%CI 0.26-0.92; p = 0.03) compared to their counterparts and this maintained significance within both the discovery ($p < 0.01$) and validation (p = 0.01) cohorts. Within the discovery cohort, patients with PSMA response in all lesions also experienced significantly improved MFS (HR = 0.24, 95%CI 0.07-0.85; p = 0.03); analysis of the independent validation cohort is ongoing. **Conclusions:** Following SABR, PSMA-PET response is a robust and externally validated radiographic biomarker for rPFS and appears to be associated with MFS pending validation. This approach holds promise for guiding clinical management of omCSPC. Research Sponsor: Prostate Cancer Fundation, Movember, Distinguished Gentlemens Ride.

5012 **Poster Discussion Session**

Phase II, double-blind, randomized study of salvage radiation therapy (SRT) plus enzalutamide or placebo for high-risk PSA-recurrent prostate cancer after radical prostatectomy: The SALV-ENZA Trial. *First Author: Phuoc T. Tran, University of Maryland School of Medicine, Baltimore, MD*

Background: We sought to investigate whether enzalutamide (ENZA) treatment, without androgen deprivation therapy, increases freedom-from-PSA-progression (FFPP) when combined with salvage radiation therapy (SRT) in men with recurrent prostate cancer post-radical prostatectomy (RP). **Methods:** Men with biochemically recurrent prostate cancer after RP were enrolled into a randomized, double-blind, phase II, placebo-controlled, multicenter study of SRT + placebo vs SRT + ENZA. The randomization (1:1) was stratified by center, surgical margin status (R0 vs R1), PSA prior to salvage treatment (PSA ≥0.5 vs < 0.5 ng/mL), and pathologic Gleason sum (7 vs 8-10) using a minimization algorithm. Following randomization, patients received either placebo or ENZA 160 mg PO once daily for 6 months. Following 2 months of study drug therapy, external beam radiotherapy to 66.6-70.2 Gy was administered to the prostate bed (no pelvic nodes). The primary endpoint was FFPP. The trial design was powered for a HR 0.44 FFPP benefit with intended enrollment of 96 subjects and was closed as planned to enrollment on March 2020 short of that goal. Secondary endpoints were time to local recurrence (LR) within the radiation field, metastasis-free survival (MFS), and safety as determined by frequency and severity of adverse events (AEs). **Results:** A total of 86 patients were randomized with a median follow-up of 34 (range 0-52) months. The median pre-SRT PSA was 0.3 (range 0.06-4.6) ng/mL, 56/86 (65%) had extra-prostatic disease (pT3), 39/86 (45%) had Gleason Grade Group 4 or higher and 43/96 (50%) had positive surgical margins. Trial arms were well balanced. FFPP was significantly improved with ENZA vs placebo, for example 2-year FFPP was 87.1% vs 68.1%, respectively, and overall with a HR 0.40 [95% confidence interval (CI), 0.17-0.92, p-value = 0.026]. Subgroup analyses demonstrate differential benefit (p-value of interaction = 0.031) of ENZA in men with pT3 (HR 0.19, 95%CI 0.05-0.67) vs pT2 disease (HR 1.29, 95%CI 0.34-4.81). There were insufficient secondary endpoint events for analysis. The most common adverse events were grade 1-2 fatigue (13% ENZA vs 9%) and urinary frequency (6 % ENZA vs 8%). **Conclusions:** SRT plus ENZA monotherapy for men with PSA recurrent high-risk prostate cancer following RP is safe and delays PSA progression relative to SRT alone. The impact of ENZA on distant metastasis or survival is unknown at this time. Additional molecular biomarker analyses are being pursued. Clinical trial information: NCT02203695. Research Sponsor: Astellas.

5013 **Poster Discussion Session**

Biomarker-directed therapy in black and white men with metastatic castration-resistant prostate cancer (mCRPC). *First Author: Clara Hwang, Henry Ford Health System, Detroit, MI*

Background: Black men have been underrepresented in large-scale molecular prostate cancer (PC) surveys, despite having higher PC incidence and mortality. Since molecular profiling to guide the use of targeted agents is increasingly important in mCRPC, we compared precision medicine data and utilization in a cohort of black and white men with mCRPC. **Methods:** The PROMISE precision medicine database is an academic collaboration to compile clinical and genomic data from men with PC. All patients have had germline and/or somatic genetic testing performed. Eligibility criteria for this analysis included a diagnosis of mCRPC with available race and biomarker data. The primary outcome was the proportion of non-Hispanic black (NHB) and non-Hispanic white (NHW) men with actionable molecular data, defined as the presence of mismatch repair deficiency (MMRd/MSI-H), homologous recombination repair deficiency (HRRd), tumor mutational burden (TMB) ≥ 10 mut/MB, or AR-V7. Secondary outcomes included the proportion of NHB and NHW men with other alterations, the type and timing of genomic testing performed, and the use of targeted therapy. **Results:** A total of 962 mCRPC patients (21.2% NHB; 78.8% NHW) met inclusion criteria of 1619 in the overall database. Median age (NHB/NHW) was 61/63; 77.5/68.8% had Gleason 8-10; 52.5/56.7% presented with de novo metastatic disease (33.8/29.9% LN, 36.2/32.2% bone and 8.3/6.1% viscera). The median time from diagnosis to first molecular result was 56.3 mo for NHB v 58.7 mo for NHW (p = 0.45). Use of blood-based molecular testing was more common in NHB men (48.7% v 36.4%, $p < 0.001$). Overall, 32.8% of NHB men harbored actionable molecular data compared to 30.3% of NHW men (Table). MMRd/MSI-H was more common in NHB men (9.1 v 4.9%, p = 0.04). Other than PTEN (12.7/23.8% NHB/NHW, p = 0.0001), no significant differences were seen in the 15 most frequently mutated genes, including TP53, AR, CDK12, RB1, and PIK3CA. Tumor suppressor co-mutations (PTEN/TP53/RB1) were found in 13.1% of NHB and 18.0% NHW (p = 0.13). Delivery of targeted therapy was reported in 19.6% of NHB and 23.7% of NHW men (p = 0.25) after a median of 2 CRPC lines. Median OS from development of mCRPC was 41.5 mo (95% CI, 34.7-51.3) and 44.7 mo (95% CI, 41.1-51.5) for NHB and NHW men, respectively (p = 0.14). **Conclusions:** In a real-world mCRPC molecular profiling cohort, we found similar overall rates of actionable molecular alterations in NHB and NHW men, but higher rates of MMRd/MSI-H and lower frequency of *PTEN* alterations in NHB men. We did not find differences in delivery of targeted therapy. Research Sponsor: None.

	NHB, N (%)	NHW, N (%)	p-value
Actionable alteration	65 (32.8)	224 (30.3)	0.55
MMRd/MSI-H	18 (9.1)	36 (4.9)	0.04
HRRd	46 (23.2)	179 (24.2)	0.85
TMB high	8 (4)	21 (2.8)	0.53
AR-V7	2 (1)	12 (1.6)	0.76
Targeted therapies	40 (19.6)	180 (23.7)	0.25
PARP inhibitors	12 (19.4)	55 (18.3)	0.98
Immune checkpoint inhibitors	5 (8.1)	29 (9.6)	0.88
Other	15 (24.2)	75 (24.9)	1.0

5014 **Poster Discussion Session**

Racial concordance and trust in health communications: A randomized trial of videos about prostate cancer. *First Author: Stacy Loeb, NYU Langone Health, New York City, NY*

Background: Black men have a significantly higher risk of prostate cancer and more aggressive disease compared to White men. The Internet is a popular source of health information and is commonly used by Black adults. However, Black adults are underrepresented in online content about prostate cancer. Given that medical mistrust is greater among Black compared to White adults, this study sought to evaluate the association between racial representation in online content about prostate cancer and trust in the content. A secondary objective was to identify additional attributes that influence trust in online content. **Methods:** This was a randomized trial of 2904 U.S. adults age ≥40. Participants were randomly assigned to view one of 8 different online videos. Videos used an equivalent script about either prostate cancer screening or clinical trials presented by one of 4 different presenters: Black physician, Black patient, White physician, or White patient. The primary outcome of the study was trust in the information using a Likert scale. Logistic regression models were applied to compare trust in the videos, based upon the characteristics of the speaker and topic of the video. **Results:** Study participants were 1703 (59%) Black and 1201 (41%) White adults. Black adults were 1.5 times more likely to trust a Black presenter compared to a White presenter (p<0.001). For White adults, no significant difference in trust was identified between Black or White presenters (p=0.21). For both Black and White adults, a physician presenting the information was more trusted than a patient, and videos discussing screening were more likely to be trusted than those discussing clinical trials (Table). **Conclusions:** Racial concordance is significantly associated with trust in prostate cancer information among Black adults. Additionally, health information is considered more trustworthy when delivered by a physician. These results highlight the importance of physicians in disseminating health information to the public, and of increasing racial diversity among healthcare providers. They also suggest an ongoing need for public education about clinical trials to prioritize issues of mistrust and distrust. Research Sponsor: Department of Defense.

Multivariable analysis.

a) Survey of Black Adults		
Outcome: Level of trust in information from the video that participants watched	**P-value**	**Adjusted OR (95% CI)**
Race of presenter in video *(Ref: White)*		
Black	< 0.001	1.49 (1.21, 1.83)
Type of presenter in video *(Ref: Physician)*		
Patient	< 0.001	0.69 (0.56, 0.85)
Video topic *(Ref: Screening)*		
Clinical trial	0.04	0.81 (0.66, 0.99)
b) Survey of White Adults		
Outcome: Level of trust in information from the video that participants watched	**P-value**	**Adjusted OR (95% CI)**
Race of presenter in video *(Ref: White)*		
Black	0.21	1.19 (0.91, 1.54)
Type of presenter in video *(Ref: Physician)*		
Patient	0.008	0.70 (0.54, 0.91)
Video topic *(Ref: Screening)*		
Clinical trial	0.002	0.66 (0.54, 0.91)

5015 **Poster Discussion Session**

Targeting B7-H3 in prostate cancer: Phase 2 trial in localized prostate cancer using the anti-B7-H3 antibody enoblituzumab, with biomarker correlatives. *First Author: Eugene Shenderov, Johns Hopkins University School of Medicine, Baltimore, MD*

Background: B7-H3/CD276, a member of the B7 superfamily, is highly expressed in prostate cancer (PCa) and is associated with rapid biochemical recurrence and early metastases. B7-H3 is the only checkpoint candidate to have a presumptive androgen receptor binding site, suggesting interaction with the androgen axis. Enoblituzumab (MacroGenics) is an investigational humanized Fc-optimized B7-H3–targeting antibody that induces antibody dependent cellular cytotoxicity (ADCC). **Methods:** In this phase 2 single-arm biomarker-rich neoadjuvant trial, men with operable intermediate- and high-risk localized prostate cancer (Grade Groups 3-5) were enrolled to evaluate the safety, anti-tumor efficacy, and immunogenicity of enoblituzumab when given prior to prostatectomy. Patients received enoblituzumab (15 mg/kg IV weekly x 6) prior to surgery. Prostate glands were harvested 2 weeks after the last dose, and were examined for pathologic and immunologic endpoints. The co-primary outcomes were safety and PSA0 at 1 year post-op. Pre-planned secondary outcomes were PSA and Gleason grade group change from biopsy to prostatectomy. **Results:** 32 men were enrolled. Grade 3/4 adverse events occurred in 12% of patients. One patient developed a grade-3 infusion reaction, and one had immune myocarditis that improved with steroids. Pre-prostatectomy PSA declines of >10% were observed in 31% of patients (95% CI: 16-50%). PSA0 at 1 year post-op was seen in 66% of men (95% CI: 47-81%). Median time to PSA recurrence was not reached, with a median follow-up of 30 months. Gleason group upgrade, no change, and downgrade was observed in 13%, 37%, and 50% of patients. Gleason grade group changes were significantly associated with enoblituzumab treatment compared to 1:1 matched historical controls (p=0.023). Tumor microenvironment profiling by NanoString GeoMx spatial proteomics and PanCancer IO 360 mRNA expression analysis revealed post-treatment upregulation of CD8+ T cells, PD-1/PD-L1 expression, and immune activation (granzyme B, IFN signaling, myeloid inflammation). There was a significant association between CD8+ T-cell increases and Gleason grade group declines. First-in-human antigen spread profiling revealed no safety concerns. TCR sequencing showed focused peripheral expansion of tumor associated T-cell clones that correlated with PSA0 at 1 year. Whole exome and RNAseq data, and clinical correlations, will be presented. **Conclusions:** In this neoadjuvant trial, inhibition of B7-H3 with enoblituzumab demonstrated favorable safety and encouraging activity in localized PCa patients. Data suggest robust intratumoral induction (adaptive upregulation) of immune checkpoints, T-cell activation, and myeloid inflammation. Enoblituzumab-induced peripheral expansion of tumor associated T-cell clones may be associated with tumor control. Clinical trial information: NCT02923180. Research Sponsor: Macrogenics, Inc, Conquer Cancer Foundation of the American Society of Clinical Oncology, Other Foundation, Other Government Agency.

5016 **Poster Discussion Session**

A phase 2 randomized study of oral docetaxel plus ritonavir (ModraDoc006/r) in patients with metastatic castration-resistant prostate cancer (mCRPC). *First Author: Ulka N. Vaishampayan, University of Michigan, Ann Arbor, MI*

Background: Intravenous (IV) docetaxel and oral prednisone is a standard of care regimen in patients (pts) with mCRPC. ModraDoc006 is an oral formulation of docetaxel. To enhance bioavailability of ModraDoc006, it is co-administered with ritonavir (/r). The ModraDoc006 and ritonavir combination is active in multiple docetaxel and cabazitaxel-resistant prostate cancer cell-lines The oral combination (ModraDoc006/r) was compared to IV docetaxel in a randomized phase 2b study in pts with mCRPC evaluating two doses of ModraDoc006/r (30-20/200-100 mg and 20-20/200-100 mg). Data on outcomes in the larger cohort, receiving the lower dose, are being presented. **Methods:** Eligible pts had mCRPC, performance status of 0-1 and no prior chemotherapy for mCRPC. Sixty-two pts were enrolled in open label 1:1 randomized study comparing ModraDoc006/r 20-20 mg combined with 200-100 mg ritonavir in a bi-daily weekly schedule ("20-20/200-100 mg"), with IV docetaxel 75 mg/m^2 in 21-day cycles. All pts received 5 mg oral prednisone twice daily. Primary endpoint was radiographic progression free survival (rPFS) per PCWG-3 criteria. Secondary objectives included ORR, PSA-PFS, time to skeletal related events, disease control rate, duration of response, and safety assessments. **Results:** 31 pts were enrolled on IV docetaxel 75 mg/m^2 and 31 on ModraDoc006/r 20-20/200-100 mg. Of these, 57 were included in the analysis for rPFS, and 32 pts with measurable disease were included in the ORR analysis. Median PSA was 46 (range 1 to 1460 ng/ml). Prior therapy with enzalutamide in 8 pts, abiraterone in 10 pts. ModraDoc006/r was better tolerated with 0% all grades neutropenia and anemia, as compared to 26% (19% ≥G3) and 16% respectively on IV docetaxel. Neuropathy was significantly reduced at 9.7% G1 only on ModraDoc006/r vs 9.7% G1 and 19.4% G2 on IV docetaxel, whereas alopecia was reduced to 16.1% G1 and 6.5% G2 on ModraDoc006/r vs. 22.6% G1 and 19.4% G2 on IV docetaxel. GI toxicities were broadly comparable with diarrhea 32% (3% ≥G3) vs 29%, nausea 29% vs 13% and stomatitis 3% (G3) vs 13% (3% ≥G3), respectively. **Conclusions:** ModraDoc006/r demonstrated a favorable safety profile and comparable efficacy to IV docetaxel in pts with mCRPC, thus providing a compelling rationale for conduct of an expanded pivotal program. A key clinical program focus is the comparison of ModraDoc006/r to best available therapy in refractory mCRPC. Studies of ModraDoc006/r in other malignancies are also in active development. Clinical trial information: NCT04028388. Research Sponsor: Modra Pharmaceuticals.

Efficacy results.

Results (all 95% CI)	**IV docetaxel**	**ModraDoc006/r**
Overall Response Rate (ORR)	28.6% (CI 8.4, 58.1)	38.9% (CI 17.3, 64.3)
rPFS at 6 months	0.88 (CI 0.66 - 0.96)	0.75 (CI 0.52 - 0.88)
PSA response (≥50% decline)	50.0% (CI 30.6, 69.4)	48.3% (CI 29.4, 67.5)

5017 **Poster Discussion Session**

PRINCE: Phase I trial of ^{177}Lu-PSMA-617 in combination with pembrolizumab in patients with metastatic castration-resistant prostate cancer (mCRPC). *First Author: Shahneen Sandhu, Peter MacCallum Cancer Centre and Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, VIC, Australia*

Background: The VISION and TheraP trials have established the safety and efficacy of ^{177}Lu-PSMA-617 in mCRPC with a 50% PSA response rate (PSA50-RR) of 46% and 66% and median progression free survival (PFS) of 8.7 and 5.1 months, respectively. More effective treatments are required as disease progression remains universal. Immunotherapy has limited single-agent efficacy in mCRPC. We hypothesise that by potentially inducing immunogenic cell death, ^{177}Lu-PSMA-617 may act synergistically with pembrolizumab, an anti-programmed death 1 inhibitor, to enhance the depth and durability of response. PRINCE is a Phase I trial evaluating the safety and efficacy of this combination. **Methods:** mCRPC patients with high PSMA expression (SUVmax ≥ 20 in an index lesion, SUVmax > 10 for all lesions ≥ 10mm), and no FDG+ve/PSMA-ve lesions on paired baseline PET/CT screening, received up to 6 cycles of ^{177}Lu-PSMA-617 (starting at 8.5 GBq, reducing by 0.5 GBq with each cycle) every 6 weeks in conjunction with 200mg of pembrolizumab every 3 weeks for up to 2 years. Response evaluation was undertaken as per PCWG3 and RECIST criteria. Co-primary endpoints were safety and PSA50-RR. Secondary endpoints included PSA-PFS, radiographic PFS (rPFS), overall survival (OS), and patient reported outcomes (PROs). This analysis was undertaken after the last patient had 12 months follow-up. **Results:** 37 patients (median age 72 years; prior docetaxel 73%; prior androgen receptor targeted agent 100%) received a median of 5 cycles (range: 2 to 6) of ^{177}Lu-PSMA-617 and 12 doses (range: 6 to 19) of pembrolizumab. The median follow up was 16 months. PSA50-RR was 76% (28/37 [95% CI 59-88]) and 7/10 (70%) patients with RECIST-measurable disease had a partial response. Median rPFS, PSA-PFS and OS was 11.2 months (95% CI: 5.1-14.1), 8.2 months (95% CI: 5.1-11.2) and 17.8 months (95% CI:13.4-not estimable). 12-month rPFS and OS was 38% (95% CI: 22-54) and 83% (95% CI: 67-92), respectively. Common (≥10%) treatment-related adverse events (TRAE) were mainly Grade (G) 1-2, including xerostomia (78%), fatigue (43%), pruritus (27%), nausea (27%), rash (24%), diarrhoea (14%), anorexia (16%), thrombocytopenia (16%), elevated ALT (11%), arthralgia (11%) and a flare in bone pain (11%). Haematologic TRAEs included G2-3 anaemia (8%), G1-2 thrombocytopenia (16%), and G1 neutropenia (3%). G3 immune-related AEs occurred in 10 (27%) patients with no dominant manifestation. 5 (14%) patients discontinued pembrolizumab due to toxicity. PROs including BPI-SF and FACT-P were stable throughout the study. **Conclusions:** The combination of ^{177}Lu-PSMA-617 and pembrolizumab had promising activity. Toxicities were generally consistent with those of single-agent ^{177}Lu-PSMA-617 and pembrolizumab and were not clearly augmented by combination use. No new safety concerns were observed. Clinical trial information: NCT03658447. Research Sponsor: Victorian Cancer Agency, Pharmaceutical/Biotech Company.

5018 **Poster Discussion Session**

BRCAAWAY: A randomized phase 2 trial of abiraterone, olaparib, or abiraterone + olaparib in patients with metastatic castration-resistant prostate cancer (mCRPC) with DNA repair defects.

First Author: Maha H. A. Hussain, Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL

Background: The PARP-inhibitor olaparib is approved for mCRPC patients (pts) with deleterious germline or somatic homologous recombination repair gene mutations (HRRm). PARP1 interacts with androgen signaling, and castration-resistant tumor cells exhibit increased PARP1 activity. Preclinically PARP1-inhibition synergizes with androgen receptor (AR) targeted therapy. BRCAAway is a biomarker selected, randomized, open-label, multicenter phase 2 trial evaluating efficacy of targeting AR vs PARP vs combination in first line mCRPC patients with germline and/or somatic HRRm in BRCA1, BRCA2, or ATM. **Methods:** Eligible mCRPC pts underwent tumor next generation sequencing and germline testing. Pts with inactivating BRCA1, BRCA2 and/or ATM alterations were randomized 1:1:1 to Arm 1 abiraterone (1000 mg daily) + prednisone (5mg bid) (Abi/pred), Arm 2 olaparib (300 mg bid) or Arm 3 olaparib + Abi/pred. The primary end point is progression-free survival (PFS) analyzed using Kaplan-Meier estimates and Cox regression. Secondary endpoints include measurable disease response rate (RR) by RECIST, PSA-RR, undetectable PSA (≤ 0.2 ng/ml) and toxicity. Arms 1 and 2 pts were allowed to cross over at progression. Pts with other HRRm were treated with olaparib; Arm 4 (ongoing). **Results:** 161 pts were registered and had NGS testing; 60 pts were randomized to Arms 1-3; to date 59 are evaluable for toxicity and 53 are evaluable for PFS. Baseline median age 67 (range 42-85) years; 54 pts were White, 6 were Black; sites of disease: bone only (n=31), soft tissue only (n=18), bone and soft tissue (n=10); median PSA 14.61 ng/ml (range 0.15-4036.8). Mutational status: BRCA1 only n = 2, BRCA2 only n = 39, ATM only n = 8, and > 1 HRRm n = 11. 34 pts had germline and 26 had somatic mutations. Median (range) follow-up time: 8.3 (0.8, 33.3), 12.2 (2.7, 21.8) and 16.8 (2.9, 41.7) months in Arms 1, 2 and 3. 43 pts had treatment-related adverse events; most common were fatigue (23 pts; 1 Grade (G) 3, 22 G1/2), nausea (17 pts, G1/2), and anemia (9 pts, 2 G3, 7 G1/2). ≥50% PSA decline was 79%, 67%, and 85% of pts in Arms 1, 2, and 3, respectively. Median PSA nadir (ng/mL) (95% CI) Arms 1-3: 2.17 (0.44, 49.27), 3.10 (0.83, 12.01), and 0.50 (0.10, 2.13), respectively. Undetectable PSA, median PFS, and 12-month PFS by Arm are listed in the table. **Conclusions:** In mCRPC pts with inactivating BRCA1, BRCA2 and/or ATM alterations Abi/pred + olaparib was well tolerated and resulted in longer PFS and better PSA response vs either agent alone. Clinical trial information: NCT03012321. Research Sponsor: AstraZeneca.

Arm (evaluable pts)	Undetectable PSA n (%)	Median PFS (95% CI) in Months	12-month PFS rate (95% CI)	Unadjusted hazard ratio (Arm 3 vs Arms 1 and 2)
1: Abi/pred (17)	4 (24%)	11.0 (7.4, NA)	42% (0.22, 0.80)	0.19 (95% CI: 0.06, 0.61)
2: Olaparib (17)	4(24%)	11.3 (8.3, 20.6)	44% (0.25, 0.76)	0.14 (95% CI: 0.04, 0.43)
3: Abi/pred + Olaparib (19)	7 (37%)	NR (23.8, NA)	95% (0.85, 1.0)	-

5019 **Poster Discussion Session**

Tolerability of abiraterone (abi) combined with olaparib (ola) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC): Further results from the phase III PROpel trial.

First Author: Antoine Thiery-Vuillemin, CHRU Besançon Hôpital J.Minjoz, Besançon, France

Background: The Phase III PROpel (NCT03732820) trial demonstrated at interim analysis a statistically significant clinical benefit from combining ola + abi in the first-line (1L) mCRPC setting vs placebo (pbo) + abi. Benefit was seen irrespective of a pt's homologous recombination repair mutation (HRRm) status; median radiographic progression-free survival (rPFS) 24.8 for ola + abi vs 16.6 months for pbo + abi (hazard ratio [HR] 0.66, 95% confidence interval [CI] 0.54–0.81; *P*<0.0001). The safety profile of ola + abi was shown to be consistent with that for the individual drugs. We report additional interim safety analysis from PROpel. **Methods:** Eligible pts were ≥18 years with mCRPC, had received no prior chemotherapy or next-generation hormonal agent treatment at mCRPC stage, and were unselected by HRRm status. Pts were randomized 1:1 to abi (1000 mg qd) plus prednisone/prednisolone with either ola (300 mg bid) or pbo. Primary endpoint was investigator-assessed rPFS. Safety was assessed in all pts receiving ≥1 dose of study treatment by adverse event (AE) reporting (CTCAE v4.03). **Results:** 398 pts received ola + abi and 396 pbo + abi (safety analysis set). At data cut-off (July 30, 2021), median total duration of exposure for ola was 17.5 vs 15.7 months for pbo, and for abi 18.2 months in the ola + abi arm and 15.7 in the pbo + abi arm. Anemia (n=183) was the most common AE in the ola + abi arm, and 34% of these 183 events were managed by dose interruption, 23% by dose reduction, and 8% resulted in treatment discontinuation. Anemia and pulmonary embolism (PE) were the only Grade ≥3 AEs in ≥5% of pts (anemia: ola + abi, 15.1% vs pbo + abi, 3.3%; PE: 6.5% vs 1.8%, respectively). Most PEs were detected incidentally on radiographic imaging (69.2% and 71.4% in the ola + abi and pbo + abi arms, respectively) and no pts discontinued. More pts in the ola + abi arm experienced venous thromboembolism (Table). Arterial thromboembolism and cardiac failure AEs were balanced between the treatment arms. No AE of myelodysplastic syndrome/acute myeloid leukemia was reported in either treatment arm. COVID-19 was reported more frequently with ola + abi (8.3% vs 4.5%). **Conclusions:** PROpel demonstrated a predictable safety profile for ola + abi given in combination to pts with 1L mCRPC unselected by HRRm status. AEs of cardiac failure and arterial thromboembolism were reported at similar frequency in both treatment arms. The majority of PEs were asymptomatic. The safety profile of abiraterone was not adversely impacted by its combination with olaparib. Clinical trial information: NCT03732820. Research Sponsor: This study was supported by AstraZeneca and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, who are codeveloping olaparib.

n (%)	Ola + abi (N=398)	Pbo + abi (N=396)
Cardiac failure*	6 (1.5)	5 (1.3)
Grade ≥3	4 (1.0)	1 (0.3)
Venous thromboembolisms*	29 (7.3)	13 (3.3)
Grade ≥3	27 (6.8)	8 (2.0)
Arterial thromboembolisms*	8 (2.0)	10 (2.5)
Grade ≥3	6 (1.5)	8 (2.0)
Covid 19*	33 (8.3)	18 (4.5)
Grade ≥3	17 (4.3)	8 (2.0)
*Grouped term		

5020 **Poster Discussion Session**

Gene-by-gene analysis in the MAGNITUDE study of niraparib (NIRA) with abiraterone acetate and prednisone (AAP) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) and homologous recombination repair (HRR) gene alterations.

First Author: Shahneen Sandhu, Peter MacCallum Cancer Centre and University of Melbourne, Melbourne, Australia

Background: NIRA + AAP significantly improved outcomes in pts with mCRPC and HRR gene alterations in the Phase 3 MAGNTUDE study. There is a paucity of data supporting use of PARP inhibitors in pts with HRR gene alterations other than *BRCA1/2*. We report on the efficacy of NIRA + AAP in pts with mCRPC and a qualifying single gene HRR alteration other than *BRCA1/2*. **Methods**: A pre-specified analysis was undertaken of the primary endpoint (radiographic progression-free survival [rPFS] by BICR), secondary endpoints (time to cytotoxic chemotherapy [TCC], time to symptomatic progression [TSP], overall survival [OS]), as well as time to PSA progression (TPSA) and overall response rate (ORR) across 186 pts (91 randomized to NIRA + AAP, 95 to PBO + AAP) with an alteration in the *ATM*, *BRIP1*, *CDK12*, *CHEK2*, *FANCA*, *HDAC2*, or *PALB2* gene (excluding cooccurring alterations). This analysis of individual alterations was not powered for formal statistical inference. Given the rarity of some alterations, groups based on functional similarity are also presented. **Results**: (Table). Pts with *PALB2* or *CHEK2* alterations had consistent improvement across all endpoints. In pts with *ATM* alterations benefit was observed in TCC, TSP, TPSA and ORR. There was benefit only in TPSA and ORR for pts with *CDK12* alterations. When combined into functional groups, pts with an alteration in the HRR-Fanconi pathway (*BRIP1*, *FANCA*, and *PALB2*) as well as pts with a HRR associated alteration (*CHEK2* or *HDAC2*) showed improvement in all endpoints. **Conclusions**: These data support the overall conclusions of the MAGNITUDE primary analysis and support benefit of NIRA + AAP in pts with HRR mutations beyond *BRCA1/2*. Clinical trial information: NCT03748641. Research Sponsor: Janssen Research & Development, LLC.

Single gene alteration, HR (95% CI)	PBO+ AAP (N)	Nira+ AAP (N)	rPFS	TCC	TSP	OS	TPSA	ORR (risk ratio)
HRR-Fanconi group	14	17	0.59 (0.23, 1.45)	0.68 (0.17, 2.74)	0.90 (0.24, 3.37)	0.43 (0.12, 1.50)	0.65 (0.27, 1.59)	1.5 (0.38, 6.00)
BRIP1	4	4	0.23 (0.02, 2.26)	NE	1.14 (0.10, 13.27)	NE	0.98 (0.14, 7.00)	0.5 (0.13, 2.00)
FANCA	6	5	1.07 (0.18, 6.44)	0.51 (0.05, 5.16)	1.23 (0.17, 8.74)	NE	0.66 (0.13, 3.47)	NE
PALB2	4	8	0.59 (0.15, 2.22)	0.39 (0.02, 6.19)	0.41 (0.03, 6.62)	0.27 (0.05, 1.66)	0.59 (0.16, 2.20)	2 (0.33, 11.97)
HRR associated group	23	20	0.64 (0.26, 1.58)	0.72 (0.19, 2.69)	0.58 (0.17, 2.00)	0.43 (0.13, 1.38)	0.43 (0.17, 1.10)	6.4 (0.96, 43.25)
CHEK2	20	18	0.66 (0.25, 1.75)	0.36 (0.07, 1.88)	0.54 (0.14, 2.25)	0.44 (0.12, 1.71)	0.37 (0.14, 0.99)	NE
HDAC2	3	2	0.71 (0.06, 8.02)	NE	0.71 (0.04, 11.79)	0.440 (0.04, 5.13)	NE	NE
ATM	42	43	1.11 (0.63, 1.99)	0.26 (0.08, 0.80)	0.75 (0.28, 2.00)	1.07 (0.44, 2.65)	0.73 (0.39, 1.36)	3 (1.12, 8.13)
CDK12	16	11	1.32 (0.43, 3.92)	1.13 (0.27, 5.70)	1.05 (0.28, 3.94)	1.61 (0.49, 5.33)	0.66 (0.24, 1.80)	2.25 (0.64, 7.97)

NE = not estimable due to few or no events.

5021 **Poster Session**

Long-term predictive value of serum PSA values obtained in clinical practice: Results from the Norwegian Prostate Cancer Consortium (NPCC).

First Author: Jan Oldenburg, Department of Oncology, Akershus University Hospital (Ahus), Lørenskog, Norway

Background: A baseline prostate-specific antigen (PSA) level in midlife is strongly associated with risk of lethal prostate cancer several decades later. In most prior studies, PSA was measured in archived blood from men participating in cohort studies unrelated to prostate cancer. In clinical practice, however, men commonly obtain a PSA test because of lower urinary tract symptoms. Here, we study the association between PSA values when a first PSA test was obtained as part of clinical care – and subsequent risks of prostate cancer diagnosis and death. **Methods:** The NPCC database contained laboratory results from 1995-2006 of the first ("baseline") PSA test below 4.0 ng/mL in 157,836 men aged 40-69 years without prior prostate cancer (PCa) diagnosis. PSA strata were pre-defined: < 1, 1-1.99, 2-2.99, 3-3.99 ng/ml and analyses were split in two age groups based on a prior risk: 40-54 ("younger") and 55-69 ("older"). Predictive accuracy was assessed with Harrell's concordance (C) index. The Kaplan-Meier method was used to visualize risk of PCa death as reported on the death certificate by PSA strata for the two age groups. **Results:** Among 157,836 men with a PSA below 4.0 ng/mL, 83% had < 2.0 ng/mL. Risk of prostate cancer and death from prostate cancer were strongly associated with PSA-levels and age: Harrell's C-index 0.75 and 0.72 for diagnosis of younger and older group, respectively and 0.72 for PCa death for both age groups. In the younger age group 196 deaths among 75,446 men (0.26%) were registered, in the older 943 deaths among 82,390 men (1.14%). The risk of PCa death in lowest (< 1) and highest (3-3.99) strata were 0.23% and 3.22%, respectively (189 deaths among 81,982 vs. 274 deaths among 8517 men). **Conclusions:** This population-based NPCC study shows as strong predictive impact of the different strata of the initial PSA measurement in routine clinical care as prior studies based on cryopreserved blood samples. Research Sponsor: Jan Oldenburg.

PSA	Age in years	n PCa deaths	n Men at risk	Proportion	95% CI
0 - 0.99	40-54	52	47301	0.11%	0.08 - 0.14
0 - 0.99	55 -69	137	34681	0.4%	0.33 - 0.46
1.0 - 1.99	40-54	70	21754	0.32%	0.25 - 0.4
1.0 - 1.99	55-69	269	28045	0.96%	0.85 - 1.07
2.0-2.99	40-54	38	4747	0.8%	0.55 - 1.05
2.0-2.99	55-69	299	12791	2.34%	2.08 - 2.6
3.0-3.99	40-54	36	1644	2.19%	1.52 - 2.92
3.0-3.99	55-69	238	6873	3.46%	3.04 - 3.9

5022 **Poster Session**

The association of germline *HSD3B1* genotype with outcomes in metastatic hormone-sensitive prostate cancer (mHSPC) treated with androgen deprivation therapy (ADT) with or without enzalutamide (ENZA) [ARCHES]. *First Author: Nima Sharifi, GU Malignancies Research Center, Cleveland Clinic, Cleveland, OH*

Background: A common missense-encoding germline polymorphism in *HSD3B1*(1245A→C) stabilizes the 3βHSD1 enzyme and increases the rate-limiting step for metabolic flux from adrenal precursors to potent androgens. This adrenal-permissive *HSD3B1*(1245C) allele mechanistically drives more rapid progression after ADT in nonmetastatic and low-volume (LV) mHSPC. It is unknown whether upfront treatment with ENZA could improve these poor outcomes. We sought to determine the association between the *HSD3B1* genotype and outcomes in ARCHES, a randomized, placebo (PBO)-controlled, phase 3 global study of ADT with ENZA or PBO in mHSPC. Overall, 31.3% of men on placebo crossed over to ENZA prior to progression. **Methods:** Germline DNA from 660 men (243 LV and 417 high volume [HV]) in ARCHES was genotyped for *HSD3B1*. Radiographic progression-free survival (rPFS), prostate-specific antigen (PSA) outcomes, and overall survival (OS) were compared between men who inherited 0 (adrenal restrictive) vs. 1–2 copies of the *HSD3B1*(1245C) allele (adrenal permissive) using log-rank tests, Kaplan-Meier estimates, and Cox proportional hazards models for hazard ratios (HRs). **Results:** In ARCHES, 340 and 320 men had the adrenal-restrictive and adrenal-permissive *HSD3B1* genotype, respectively. The adrenal-permissive genotype was not associated with worse rPFS, time to PSA progression (TTPP), or OS. Cox model HRs for death in the adrenal-permissive compared with adrenal-restrictive men in the ENZA + ADT and PBO + ADT arms were 1.21 (95% confidence interval [CI] 0.84, 1.74) and 1.48 (95% CI 0.98, 2.25), respectively. Three-year OS was 82% and 73% in men treated with ENZA + ADT with restrictive vs. permissive genotypes, respectively, and 68% and 70% in men treated with PBO + ADT. ENZA significantly improved rPFS, TTPP, and OS, irrespective of genotype. HRs for ENZA + ADT vs. PBO + ADT in models adjusted for genotype were: rPFS, 0.64 ($p < 0.001$); TTPP, 0.27 ($p < 0.001$), and OS, 0.62 ($p < 0.001$). Of OS events in the *HSD3B1*-genotyped men, 48 (23%) and 163 (77%) deaths occurred in the LV and HV groups, respectively. **Conclusions:** In men with mHSPC, ENZA improved OS, rPFS, and TTPP over PBO + ADT, irrespective of *HSD3B1* genotype. Survival analysis of *HSD3B1*-genotyped men in this study is largely driven by men with HV disease. The analysis of men with LV disease was limited by the small number of events. Clinical trial information: NCT02677896. Research Sponsor: Astellas Pharma, Inc. and Pfizer, Inc.

5023 **Poster Session**

Longitudinal screening for depression and anxiety in prostate cancer (PC) and association with disease and treatment factors. *First Author: Risa Liang Wong, Department of Medicine, Division of Hematology/Oncology, University of Pittsburgh, Pittsburgh, PA*

Background: Untreated depression and anxiety are associated with worse outcomes in patients with cancer. Despite recommendations for longitudinal screening, many patients are only assessed at the start of care. Men with PC often experience many phases of disease or treatment over a span of years, and androgen deprivation therapy (ADT) is associated with mood changes and depression. How depressive or anxiety symptoms fluctuate in men with PC, influenced by disease and treatment factors, is not well-described. **Methods:** Men with ≥1 Urology or Medical Oncology clinic visit for PC in the prior 6 months were emailed the PHQ-9 and GAD-7 depression and anxiety screening tools every 60 days; a score of ≥10 (moderate to severe symptoms) on either was considered a positive screen. Baseline characteristics and disease/treatment changes (PSA, radiographic, or biopsy progression, treatment change or start, or discontinuation of treatment due to lack of efficacy or toxicity) were collected by survey and chart review. We report early findings of factors associated with a positive screen or change in screening status with χ^2 and forward stepwise binary logistic regression (model inputs: receipt of ADT or disease/treatment change during study, and variables previously associated with depression or anxiety: age, race, marital status, education, income, history of psychiatric disorder, use of psychoactive medication, time since diagnosis, and localized, biochemically recurrent, or metastatic disease). **Results:** From 6/2021-12/2021, 201 men enrolled. At baseline, 50.7% had localized, 18.9% biochemically recurrent, and 30.3% metastatic disease; 40.8% were on ADT; 30.8% had a history of psychiatric disorder (22.9% depression, 19.9% anxiety, 9.0% other); and 24.9% were on psychoactive medication (19.9% antidepressant, 8.5% anxiolytic, 2.0% antipsychotic). 184 men completed at least 2 screens with mean follow-up 6.5 months (SD 1.3). 32 men (15.9%) screened positive at least once (15.4% PHQ-9, 4.5% GAD-7), of which half (N = 16) initially screened negative and later positive. Changing from a negative to positive screen was more likely when a disease/treatment change occurred during the study (18.3% vs 4.5%, p = 0.003). A higher proportion of men on ADT screened positive, especially if newly started during the study or in the 60 days preceding (35.7% new ADT vs 24.7% continuing ADT vs 8.0% no ADT, p = 0.002). In fully adjusted multivariable analyses, factors associated with a positive screen were history of psychiatric disorder (OR 6.3, 95% CI 2.6-15.4, p < 0.001), receipt of ADT (OR 3.8, 95% CI 1.5-9.5, p = 0.005), and lower income bracket (OR 1.7, 95% CI 1.3-2.5, p = 0.002). **Conclusions:** Longitudinal screening for depression and anxiety in PC identifies men who initially screen negative. Symptoms are associated with ADT and disease or treatment changes, which may inform optimal screening practices. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology, Other Foundation, U.S. National Institutes of Health.

5024 **Poster Session**

Piflufolastat F 18-PET/CT in patients with prostate cancer: An analysis of OSPREY (cohorts A and B) standardized uptake value (SUV) results stratified by PSA and Gleason score. *First Author: Michael A. Gorin, Johns Hopkins University School of Medicine, Baltimore, MD*

Background: The OSPREY clinical trial was a phase 2/3 prospective study of prostate specific membrane antigen (PSMA) PET/CT using piflufolastat F 18. Piflufolastat F 18 (aka ^{18}F-DCFPyL or PyL) is a novel PSMA-targeting radiopharmaceutical approved for imaging of PCa pts both at initial staging and for disease recurrence. Here we describe SUV results by biopsy status, baseline PSA levels, and Gleason score (GS). **Methods:** Piflufolastat F 18-PET/CT was evaluated in men with NCCN high-risk PCa scheduled to undergo radical prostatectomy with pelvic lymphadenectomy (RP-PLND) (Cohort A) and men with radiologically suspected recurrent/metastatic PCa (Cohort B). A single IV dose of 9 mCi (333 MBq) of piflufolastat F 18 was administered followed by PET/CT acquisition 1-2 hours later. Piflufolastat F 18 uptake in various lesion locations as defined by maximum and peak SUV (SUVmax, SUVpeak) were determined by three blinded, independent central readers for each tissue (e.g., bone, lymph nodes (LN), soft tissue). To measure SUVs, the reader placed a volume of interest (VOI) on each identified lesion. SUVmax was defined as the maximum single-voxel SUV within the VOI. SUVpeak within the VOI was defined as the average SUV within a fixed-sized VOI (1 cm diameter sphere), representing the cluster with the highest average SUV. **Results:** 345 men underwent piflufolastat F 18-PET/CT. Cohort B (n = 93evaluable) SUVmax and SUVpeak were significantly higher for biopsy positive (+)(one biopsy lesion/pt) when compared to biopsy negative (-) lesions from bone and LN. SUVpeak for biopsied bone and LN (Cohort B) appeared to increase with rising baseline PSA. In high-risk PCa pts, SUVpeak for prostate (Cohort A; n = 252 evaluable) increased with baseline PSA and were highest for GS 9-10 (Table). **Conclusions:** Piflufolastat F 18-PET/CT uptake was significantly higher in biopsy + lesions and increased with baseline PSA. Prostate SUVpeak was highest for GS 9-10. Clinical trial information: NCT02981368. Research Sponsor: Progenics Pharmaceuticals, a Lantheus company.

		SUVmax*					SUVpeak*				
		Biopsy +		Biopsy -			Biopsy +		Biopsy -		
	Lesion site	median	n	median	n	P-value	median	n	median	n	P-value
Cohort B	Bone	15.4	38	2.5	15	0.0046	14	38	5	15	0.0031
	LN	28.1	29	2.1	6	0.0012	19.3	29	1.8	6	0.0012
	Soft tissue	30.1	6	2	1	0.2578	23.8	6	1.5	1	0.2578
SUVpeak	Lesion site	PSA (ng/mL)									
		0 to <0.2		0.2 to <4		4 to <20		20 to <50		≥50	
		median	n	median	n	median	n	median	n	median	n
Cohort B	Bone	1.3	4	5.43	17	11.3	20	9.7	6	9.4	6
	LN	1.7	1	1.8	5	8.7	9	38.3	6	17	14
	Soft tissue	0	0	55.33	2	59.2	1	0	0	10.3	4
Cohorts A&B	Aorta (SUVmean ref.)	1.7	5	1.4	43	1.4	218	1.4	46	1.4	32
Cohort A	Prostate	0	0	5.7	18	6.6	187	10.8	34	27.6	9
SUVpeak	Lesion site	GS									
		≤6		3+4		4+3		8		9-10	
		median	n	median	n	median	n	median	n	median	n
Cohort A	Prostate	5	2	5.5	48	7.8	81	6.1	25	8.2	88
	Bone	0	0	0	0	2.4	10	2.5	3	1.8	10
	LN	0	0	2.2	2	2.7	7	2.9	3	3.4	29
	Soft tissue	0	0	5.6	2	7.1	4	0	0	8.5	11
Cohorts A&B	Aorta (SUVmean ref.)	1.2	2	1.4	48	1.5	83	1.4	26	1.5	88

*Cohorts A&B Aorta SUVmean ref.: 1.45 (n=320) & 1.43 (n=25) for Biopsy + & Biopsy -, respectively.

5025 **Poster Session**

Long-term outcomes and genetic predictors of response to metastasis-directed therapy versus observation in oligometastatic castration-sensitive prostate cancer: A pooled analysis of the STOMP and ORIOLE trials. *First Author: Mathew Pierre Deek, Rutgers Cancer Institute, Baltimore, NJ*

Background: Prospective reports suggest metastasis directed therapy (MDT) in oligometastatic castration sensitive prostate cancer (omCSPC) is associated with improved treatment outcomes. Here we present long term outcomes of the phase II STOMP and ORIOLE trials and assess the ability of a high-risk (HiRi) mutational signature to provide prognostic and predictive information regarding MDT response. **Methods:** Patients with omCSPC (< 3 lesions) enrolled on STOMP (n = 62) and ORIOLE (n = 54) randomized to MDT or observation were pooled. The primary endpoint was progression-free survival (PFS) defined as either PSA or radiographic progression, initiation of androgen deprivation, or death. Secondary endpoint was radiographic PFS (rPFS) defined as radiographic progression or death. Both were calculated using the Kaplan-Meier method and stratified by treatment group. Next generation sequencing (NGS) was performed to identify a HiRi mutational signature defined as pathogenic mutations within *ATM*, *BRCA1/2*, *Rb1*, or *TP53*. Cox proportional hazards regressions were fit to calculate hazard ratios (HR) and assess the prognostic and predictive values of HiRi mutational status. **Results:** Median follow-up was 52.5 months. Median PFS was prolonged with MDT (11.9 months) compared to observation (5.9 months) with a pooled HR of 0.44 (95% CI, 0.29 – 0.66, p-value < 0.001). MDT was associated with PSA decrease in a majority of patients (84%) as compared to the observation group (41%). On NGS, the incidence of a pathogenic mutation in a HiRi gene was 24.3%. HiRi mutation was prognostic for PFS – in those without a HiRi mutation median PFS was 11.9 months compared to 5.9 months in those with a HiRi mutation (HR of 1.74, p = 0.06). HiRi mutation was also prognostic for rPFS – those without a high-risk mutation experienced median rPFS of 22.6 months compared to 10.0 months in those with a high-risk mutation (HR 2.62, p < 0.01). Tumors without a HiRi mutation treated with MDT experienced the longest PFS (13.4 months) while those with a HiRi randomized to observation experienced the shortest PFS (2.8 months). Stratifying by both treatment arms and HiRi status appeared to show a differential benefit to MDT, with those with HiRi mutations experiencing a larger relative magnitude of benefit to treatment: (HiRi mutation: HR of 0.05, p < 0.01; no HiRi mutation: HR of 0.42, p = 0.01; p interaction, 0.12) suggesting a HiRi mutational status can provide information regarding differential response to treatment. **Conclusions:** Long-term outcomes from the only two randomized trials in omCSPC suggest a sustained benefit to MDT over observation. A HiRi mutational signature appears prognostic for outcomes in omCSPC and those with HiRi might have a relatively larger magnitude of response to MDT. Future studies are needed to optimize patient selection. Clinical trial information: NCT02680587. Research Sponsor: Prostate cancer foundation.

5026 **Poster Session**

Chromosomal instability (CIN) in circulating tumor cells (CTC) predicts for taxane sensitivity in metastatic castration-resistant prostate cancer (mCRPC). *First Author: Niamh M. Keegan, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Few clinically validated biomarkers can inform therapy (tx) sequencing in mCRPC. Previously, we credentialed a biomarker of CIN in individual CTCs using phenotypic identification of cells with ≥9 large scale transitions (LSTs) and classification of CIN as high when detected in ≥3 CTC/mL (CIN3+). CIN3+ was associated with shorter radiographic progression survival (rPFS) and overall survival (OS) following taxane (T) or androgen receptor signaling inhibitor (ARSi) tx in mCRPC. Similarly, high CIN defined as ≥1 CTC/mL with ≥9 LSTs (CIN1+) predicts worse rPFS and OS following ARSi. Here, we explored if CIN1+ or CIN3+ predicted differential outcomes in pts on-tx with T or ARSi for mCRPC. **Methods:** We analyzed 208 banked CTC samples from 173 mCRPC pts collected within 30 days prior to starting a new tx with either T (n=88) or ARSi (n=120) in 2012-2017. CTCs were detected using Epic Sciences platform and CIN defined using the phenotypic classifier (PMID 32816908). Retrospective clinical annotation was completed for OS, defined as time from index tx start date to death, and rPFS, defined as index date to date of new or/and increasing lesion size in on-tx radiology report or death. Associations with rPFS and OS were studied according to samples' CIN1+ and CIN3+ status. T vs. ARSi comparisons were adjusted using Cox models that incorporated pre-tx covariates, i.e. prior T or ARSi txs, total CTC count, presence of visceral disease, and prognostic lab values. **Results:** The median (range) follow-up from tx start to date of death or last follow-up was 7 (5-9) years. There were 53/120 (44%) pts starting ARSi that had prior ARSi txs and 41/88 (46%) pts starting taxane that had prior taxane txs. CTCs were detected in 184 (88%) samples, CIN1+ in 73 (35%; 64% pre-T, 36% pre-ARSi), and CIN3+ in 47 (22%; 60% pre-T,40% pre-ARSi). Compared to CIN1+, model results (Table) suggest that CIN3+ predicts a longer rPFS (p<0.01), and possibly OS (p=0.05), with T therapy. Compared to CIN1-, CIN3- also predicts a longer OS with ARSi therapy (p=0.04). **Conclusions:** CIN3+ CTC may be a more discriminating predictive biomarker than CIN1+ to help guide selection of T or ARSi tx in pts with mCRPC. Adequately powered prospective studies are planned. Research Sponsor: U.S. National Institutes of Health.

Endpoint	rPFS				OS			
CIN strata	CIN1+	CIN3+	CIN1-	CIN3-	CIN1+	CIN3+	CIN1-	CIN3-
HR (T vs ARSi)*	0.6 (0.3, 1.1) p = 0.12	0.3 (0.1, 0.6) p < 0.01	1.2 (0.8, 1.9) p = 0.40	1.3 (0.8, 2.0) p = 0.21	0.7 (0.4, 1.4) p = 0.36	0.4 (0.2, 0.8) p < 0.01	1.1 (0.7, 1.6) p = 0.78	1.3 (0.9, 2.0) p = 0.15
Ratio of HRs**	2.1 (1.3, 3.6) p < 0.01		0.9 (0.8, 1.1) p = 0.43		1.7 (1.0, 3.0) p = 0.05		0.8 (0.6, 1.0) p = 0.04	

*Adjusted stratum-specific HR for T vs. ARSIs, with 95% confidence interval and p-values.
**Ratio of HR in CIN1 and CIN3 strata.
195 rPFS + 187 OS events as of Jan 1, 2022.
ARSi: enzalutamide = 72, abiraterone = 48; T: docetaxel = 56, cabazitaxel = 30, paclitaxel = 2.

5027 **Poster Session**

Circulating tumour cells (CTCs) and PSMA PET correlates in the phase I PRINCE trial of ^{177}Lu-PSMA-617 plus pembrolizumab for metastatic castration resistant prostate cancer (mCRPC). *First Author: Anis Hamid, Eastern Health and University of Melbourne, Melbourne, Australia*

Background: The Phase I PRINCE trial (NCT03658447) is evaluating the efficacy of ^{177}Lu-PSMA-617 plus pembrolizumab for mCRPC. The utility of serial monitoring of CTCs and PET as biomarkers of prognosis and clinical benefit of ^{177}Lu-PSMA-617-based therapy remains unknown. **Methods:** 36 of 37 pts with high PSMA expression on PSMA PET underwent serial CTC collections in conjunction with PSMA PET at baseline, every 12 weeks for 48 weeks and every 24 weeks thereafter. CK+, CD45- CTCs were enumerated from 3ml of blood and stained for PSMA (Epic Sciences platform). Associations between PSMA+ CTC counts, PET molecular tumor volume (MTV), total lesional activity (TLA; MTVxSUVmean) were assessed by Spearman correlation. Cox models assessed the association of CTC and PSMA PET parameters with radiographic progression-free survival (rPFS) and PSA PFS. A subset of pre-treatment CTCs underwent single cell low-pass whole genome sequencing to characterize copy number aberrations. **Results:** 32/36 pt (89%) had detectable CTCs (median 7, range 0-514) with 23 (64%) being PSMA+ (median 1, range 0-224) at baseline. At w12, 23/33 (70%) had CTCs detected with 10 (30%) being PSMA+. Baseline PSMA+ CTC count and MTV were moderately correlated (r_s= 0.57, p < 0.001). Of 22 evaluable pts with baseline PSMA+ CTC, 18 (82%) showed decrease by w12 with clearance in 13. This paralleled reductions in MTV (-18% med relative change, IQR: -57 to -1) and TLA (-48% med relative change, IQR: -77 to -28). Total CTC and PSMA+ CTC counts at baseline, and PET parameters were not associated with PSA PFS or rPFS. Clearance of PSMA+ CTC by w12 (13/22 pts) was associated with improved rPFS (med NR vs 3.0 mos, HR 0.23, 95%CI 0.07-0.74, p = 0.007) and PSA PFS (med 11.2 vs 3.5 mos, HR 0.28, 95%CI 0.11-0.73, p = 0.006). Persisting PSMA-neg CTCs at w12 trended to worse rPFS (med 4.1 vs 12.3 mos, p = 0.11) and PSA PFS (med 5.1 vs 12.3 mos, p = 0.07). Of pts not progressing by w12, decrease in PSA (HR 0.83 per 10% decrease, 95%CI 0.74-0.93, p < 0.001), MTV (HR 0.85 per 10% decrease, 95%CI 0.75-0.96, p = 0.008), MTV > 30% decrease (HR 0.30, 95% CI 0.08-1.08, p = 0.05) and TLA (HR 0.88 per 10% decrease, 95%CI 0.78-1.00, p = 0.04) associated with improved rPFS beyond w12. Pre-treatment CTCs (18 pts) exhibited genomic heterogeneity and frequent loss of *PTEN*, *TP53* and *RB1*. Pts with compound *TP53* and *RB1* loss at baseline nonetheless had PSMA+ CTCs in high proportion (med 91.3% of total CTCs). **Conclusions:** PSMA PET-positive mCRPC is associated with high rates of PSMA+ CTCs which decline with ^{177}Lu-PSMA-617 plus pembrolizumab in parallel with PSMA MTV/TLA. Despite imaging suitability for therapy, CTCs had heterogenous PSMA expression and genomic alterations associated with aggressive disease. Early changes in PSMA+ CTCs and MTV/TLA were associated with outcomes and may aid in determining clinical activity of LuPSMA-based therapy. Research Sponsor: None.

5028 **Poster Session**

Impact of PSMA PET/CT on prostate cancer salvage radiotherapy management: Results from the prospective randomized phase 3 trial [PSMA SRT NCT03582774]. *First Author: Wesley R Armstrong, Ahmanson Translational Theranostics Division, University of California, Los Angeles, CA*

Background: The purpose of the randomized PSMA SRT trial is to compare the success rate of salvage radiation therapy (SRT) for recurrence of prostate cancer (PCa) after radical prostatectomy (RP) with (intervention arm) and without (control arm) planning based on PSMA PET/CT. Here we report the secondary endpoint of the trial: impact of PSMA PET/CT on the treatment plan. **Methods:** This is a Randomized, controlled, prospective, open label, phase 3 clinical trial with institutional funding. 193 patients were randomized to proceed with standard SRT with any conventional imaging aside from PSMA PET/CT (control arm) or undergo a 68Ga-PSMA-11 PET/CT scan prior to SRT (investigational arm). The following information was collected on case-report forms before randomization (intended SRT plan) and after treatment: Radiation field region (prostate fossa (PF), pelvic lymph node (PLN)), total dose, dose per fraction, duration, ADT use and duration, PSMA influence on target volume, or other (free-text). Changes between SRT plan before randomization and delivered treatment were classified as Major, Minor or No Change. Major change: change of ADT duration ≥3 months, change of standard RT volumes (PF and PLN), target volume delineation beyond standard RT field, simultaneous-integrated boost (SIB) beyond standard RT fields, and initiation of advanced systemic therapy (novel ADT agents, chemotherapy). Minor change: SIB within standard RT fields. Fisher exact test was used to compare prevalence of events between study arms. **Results:** Enrollment is complete. 193 patients enrolled from 09.06.2018 to 8.17.2020: 90 and 103 randomized to the control group and PSMA group. Median Time from RP to enrollment and median PSA was 20.3 months (IQR 1.4–245) and 0.3 ng/ml (IQR 0.2-10.3), and 28.3 months (IQR 1.2–21) and 0.23 ng/ml (IQR 0.1-29.9), respectively. The control arm had 13 dropouts (17%) while the intervention had one (1%). PSMA was positive in 38/102 (38%): 12/102 (12%) outside of pelvis, and 20/102 (20%) in PLNs . Pre-randomization RT plan and Delivered RT plan were available in 193/193 (100%), (77/90 control (86%) and 102/103 PSMA (99%), (p = 0.0004)respectively. There were 0/77 (0%) and 7/102 (7%) minor changes in the control and PSMA groups (p = 0.02). There were 17/77 (22%) and 45/102 (44%), major changes (p = 0.004); 32/45 (71%) were PSMA-related. Treatment escalation occurred in 7/17 (41%) and 36/52 (69%) (p = 0.048), and de-escalation in 10/17 (59%) and 10/52 (19%) (p = 0.004). Nine/102 patients (9%) received advanced systemic therapy in relation to PSMA findings whereas only 1/77 (1%) patient in the control received advanced therapy (p = 0.044). **Conclusions:** In this prospective randomized phase 3 study, proportion of major changes between the pre-randomization SRT plan and the delivered RT plan was 44% in the PSMA intervention group and 22% in the conventional imaging control group. Clinical trial information: NCT03582774. Research Sponsor: None.

5029 **Poster Session**

Genomic alterations and evolution in patients with prostate cancer with histologic evidence of neuroendocrine differentiation. *First Author: Ethan Barnett, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The incidence of transformation to neuroendocrine prostate cancer (NEPC) has increased in castration resistant prostate cancer (CRPC) in parallel with treatment advances inhibiting androgen receptor signaling. The current understanding is that this occurs in ~10-20% of CRPC cases. Missing is a determination of the timing of molecular events that drive the process. **Methods**: Under an IRB-approved protocol, retrospective annotation of all MSK-reviewed pathology reports was conducted for 1447 prostate cancer patients with MSK-IMPACT sequencing data. For patients with pathologically confirmed NEPC, the date of the first sample with unequivocally reported NEPC (described as "neuroendocrine carcinoma" or as having "neuroendocrine differentiation" or "neuroendocrine features") was recorded. Patients with early signs of histologic transformation not specifically reported as NEPC (double negative prostate cancer or rare/focal staining for NE markers) were analyzed separately. Sequencing results were described by castration-status at collection (CRPC vs castration-sensitive) and, if applicable, the relationship to NEPC diagnosis (i.e. pre- vs post-NEPC). Genomic enrichment analysis was used to identify differentially altered genes between groups. **Results**: In total, 95 (6.6%) patients had pathologically confirmed NEPC during their disease course, from whom 150 samples with sequencing results were available: including 18 patients with matched pre- and post-NEPC samples. CRPC samples from patients with NEPC (n = 70) were significantly enriched for *RB1* alterations (50% vs 12%, $p < 10^{-10}$, $q < 10^{-10}$). *AR* alterations were significantly enriched in CRPC samples from patients without NEPC (n = 380) (63% vs 21%, $p < 10^{-10}$, $q < 1.27*10^{-8}$). Further, alterations in numerous genes including *TP53*, *AMER1*, *ARID5B*, *YAP1*, *SOX2*, and *NKX2*.1 were enriched in NEPC patients at the 95% confidence interval (CI) without correction for repeat testing. Matched pre- and post-NEPC samples demonstrated that *TP53* alterations in post-NEPC samples are detected in the majority of pre-NEPC samples (8 of 10 patients), but *RB1* alterations in post-NEPC samples are detected in a minority of pre-NEPC samples (1 of 8 patients). 54 (3.7%) patients had evidence of early histologic transformation. CRPC samples from these patients (n = 29) were enriched for mutations in *RB1*, *MAP2K2*, *MUTYH,* and *CTNNB1* at the 95% CI without correction. *FOXA1* mutations were enriched in patients without transformation. **Conclusions**: *RB1*, consistent with previous findings, is enriched in NEPC. The inability to detect *RB1* alterations in pre-NEPC samples supports divergent evolution, although technical limits of tissue panel sequencing make it difficult to rule out the presence of sub-clonal alterations. Further study of additional genes which contribute to histologic transformation and the development of NEPC is warranted. Research Sponsor: None.

5030 **Poster Session**

18F-FluorThanatrace (18F-FTT) positron emission tomography (PET/CT) in prostate cancer measures in vivo PARP-1 expression and is associated with adverse clinicopathologic features. *First Author: Neil Taunk, Penn Medicine Abramson Cancer Center, Philadelphia, PA*

Background: We performed the first clinical trial to evaluate expression of PARP-1, the target of PARP-inhibitors (PARPi), in prostate cancer (PC) using 18F-FluorThanatrace (18F-FTT), a novel radiopharmaceutical that selectively measures PARP-1 expression with PET/CT. Approvals for PARPi in metastatic castrate resistant prostate cancer (mCRPC) have improved clinical outcomes in men with homologous recombination deficient (HRD) associated PC. Patient selection using genetic biomarkers such as HRD and PARP-1 IHC are insufficient PARPi biomarkers. We report the first trial of assessment of PARP-1 expression in men with prostate cancer. **Methods:** Men with localized PC with planned prostatectomy were included. Patients were required to have 2+ biopsy cores with > 50% involvement, OR > 1cm dominant prostate lesion on MRI. Men received a single pre-operative [18F]FTT scan. [18F]FTT is. Patients received a single injection of 8-12 mCi [18F]FTT and underwent 60 minutes dynamic scanning and static scan at 90 minutes post-injection. Ex vivo IHC, autoradiography, and germline/somatic genomic testing was performed after surgical removal. The study was approved by the University of Pennsylvania IRB (UPCC #13817, ClinicalTrials.gov, NCT03334500). **Results:** 30 men consented for participation (29 with presurgical MRI) from 6/2019 to 12/2020. Mean PSA was 9.8 ng/mL (range 2.35 – 60). Gleason Grade (GG) groups included: GG 1 (n = 1), GG 2 (n = 10), GG 3 (n = 5), GG 4 (n = 7), and GG 5 (n = 7). Stages included: pT2 (n = 12), pT3a (n = 10), pT3b (n = 8). Two patients had pN1 disease (cN0 by MRI). Mean injected dose was 10.32 mCi (range 7.52 – 11.62). There were no serious adverse events noted for any patient. Of patients with presurgical MRI, a range of uptake on the PET/CT correlated to the dominant lesion on MRI. The mean and median SUVMax of all lesions was 3.52 and 3.46, respectively (range 1.03 – 6.56). Both patients cN0 on MRI, had those nodes identified on the [18F]FTT scan. SUVMax was significantly associated with increasing Gleason Grade group Rs = 0.37298, p (2-tailed) = 0.04. SUVMax was significantly associated with Decipher scores (GenomeDx Biosciences, San Diego, CA) Rs = 0.63077, p (2-tailed) = 0.02. Ex vivo IHC showed PARP1 localization to the dominant region on the MRI. Ex vivo autoradiography using [I125]KX1, a FTT analogue, and correlation to genomic HRD (DDR aberrations and HRD scores) is underway. **Conclusions:** [18F]FTT detects *in vivo* PARP-1 expression in prostate cancer and SUVMax is associated with higher Gleason Grade groups and Decipher scores, This tracer may be used as an imaging biomarker for PARP-1 expression in men with prostate cancer, the target of PARPi. A follow-up study to assess change in [18F]FTT uptake before and after administration of PARPi in men with mCRPC is underway to test [18F]FTT as a biomarker PARPi (UPCC #08821). Clinical trial information: NCT03334500. Research Sponsor: None.

5031 **Poster Session**

Need for organ preservation in postchemotherapy retroperitoneal lymph node dissection (PC-RPLND). *First Author: Tim Nestler, Department of Urology, University Hospital Cologne, Cologne, Germany*

Background: The aim ofPC-RPLND for advanced nonseminomatous germ cell tumors is to resect all remaining metastatic tissue. So far, the resection of adjacent visceral or vascular organs is also commonly performed to achieve complete resection of the residual mass. To determine the possibility of more organ preservation, we aimed to analyze the pathohistology of patients with adjunctive surgery as the frequency of metastatic involvement in those organs with teratoma or vital cancer is currently unknown. **Methods:** We reviewed a cohort of 1204 patients who underwent PC-RPLND between 2008 and 2021 as a 2-center study and identified 242 (20.1%) cases of adjunctive surgery during PC-RPLND. We analysed the pathohistological presence of germ cell tumor elements in the resected organs: viable tumor (V), teratoma (T) or necrosis / fibrosis (N). Surgery associated complications were reported according to the Clavien-Dindo classification. Outcomes of subgroups were compared by using log-rank test. **Results:** V, T and N were present in 54 (22%), 94 (39%) and 94 (39%) of all patients with adjunct resected organs. In 242 patients, 325 adjunct organs were resected with 66 (27.3%) of these patients receiving a resection of multiple organs. The kidney was the most often resected organ (n = 77; V: 29% T: 39% N: 32%), followed by V. Cava (n = 67; V: 25% T: 36%, N: 39%) and partial liver resections (n = 50; V: 16%, T: 30%, N: 54%). Postoperative complications occurred in 30% of which 22% were Clavien grade III-V, showing no significant differences between V, T and N; p = 0.093. 27% of all patients suffered from a relapse during a median follow-up of 22 months [0-180]. Patients with T or V in the resected specimens had a significantly reduced 5-year RFS compared to patients with only N (39%, 81%, p < 0.001). **Conclusions:** This study shows tremendous need for more organ preservation as 40% of all resections of adjunct organs are oncologically unnecessary due to the presence of N only in the pathological specimens. Therefore, in case of doubt, we should increase intraoperative frozen section to avoid oncologically unnecessary adjunctive surgeries, especially nephrectomies and vascular resections. Additionally, serological or image-based means for a more accurate presurgical workup are required to spare patients with N from PC-RPLND in general. Research Sponsor: None.

5032 **Poster Session**

Salvage high-dose chemotherapy (HDCT) for relapsed primary mediastinal nonseminomatous germ-cell tumors (PMNSGCT). *First Author: Fadi Taza, Division of Hematology and Oncology, Indiana University Simon Cancer Center, Indianapolis, IN*

Background: Patients with PMNSGCT have high relapse rates after first-line therapy. Historical outcomes in this subset with standard-dose salvage chemotherapy or HDCT+bone marrow transplant (BMT) have been poor. The use of peripheral-blood stem-cell transplant (PBSCT) has allowed for more rapid engraftment and the ability to start the 2nd course 3-4 weeks after the 1st course of HDCT. We report survival outcomes of salvage HDCT+PBSCT in relapsed PMNSGCT. **Methods:** Between 2004-January 2021, 32 pts with relapsed PMNSGCT were treated with HDCT+PBSCTx2 utilizing our institutional regimen: carboplatin 700 mg/m2 + etoposide 750 mg/m2, for 3 consecutive days, followed by PBSCT. Median time between cycle1 day1 to cycle2 day1 was 3.2 wks (range, 2.6-4.6). Kaplan-Meier methods were used for progression-free (PFS) and overall survival (OS) analysis. **Results:** Median age was 30. At the start of HDCT, median AFP was 192 (range, 4-17130) and hCG 1.5 (range, 0.6-15711). First-line therapy was standard germ cell tumor chemotherapy such as bleomycin-etoposide-cisplatin (BEP) or etoposide-ifosfamide-cisplatin (VIP). HDCT was 2nd line in (26, 81.3%) and 3rd line in (6, 18.8%). Eighteen (56.3%) pts had platinum-refractory disease defined as progression within 4 weeks of 1st line chemo. Twenty-three (72%) patients had extra mediastinal metastases (mets) at the start of HDCT. Metastatic sites included pulmonary (17), lymph nodes (2), liver (3), bone (2), brain (1). Median follow-up time from start of HDCT was 1 yr (range, 0.02-14.1). Twenty-six (81%) pts completed both cycles, while 6 (19%) completed only one cycle due to toxicity or progression. The estimated 2-yr PFS was 30.7 (95% CI, 15.8-46.9) and 2-yr OS was 35.2 (95% CI, 18.9-51.9). At the most recent follow-up, 9 (28%) pts were continuously no evidence of disease (NED), including 2 pts who had surgical resection of teratoma following HDCT. Median follow-up from the start of HDCT for the NED pts was 4.6 yrs (range, 1-14.1). Five of the NED pts had extra mediastinal mets, and 2 had platinum-refractory disease. Among the 9 NED pts, HDCT was 2nd line in 7 (77.8%) and 3rd line in 2 (22.2%). These results compare favorably to historical data with standard-dose chemotherapy or HDCT+BMT in relapsed primary mediastinal GCT with salvage rates < 10% (Hartmann et al., JCO 19:1641-1648, 2001). Grade ≥3 toxicity, as previously described in our study (Adra et al., JCO 35:1096-1102, 2017), occurred in 8 (25%) pts. There were two treatment-related deaths. **Conclusions:** HDCT+PBSCT is a safe and effective salvage therapy in pts with relapsed PMNSGCT with curative potential. In our opinion, these complicated patients are best managed at tertiary centers with expertise in medical oncology, stem cell transplantation, and thoracic surgical oncology. Research Sponsor: None.

5033 **Poster Session**

Epigenetic age acceleration in U.S. testicular cancer survivors (TCS). *First Author: Yinan Zheng, Northwestern University, Chicago, IL*

Background: Given the young age at diagnosis and effective therapies (cisplatin-based chemotherapy and/or surgical approaches), most TCS gain many decades of life. Attention has been drawn to the potential downsides of these treatment successes, including the accelerated development of age-related diseases. Previous studies have suggested that cytotoxic treatment and carcinogenesis are associated with epigenetic changes, leading to premature biological aging processes. **Methods:** We recruited 24 TCS managed with surgical approaches alone and 24 cisplatin-treated TCS (all also treated with surgical removal of the cancerous testis) and who had histologic/serological germ cell tumor diagnosis before 55 years, and were disease-free at routine follow up. We also included 310 cancer-free race- and age-matched (+/- 5 years) males from a normative cohort, i.e., the Coronary Artery Risk Development in Young Adults (CARDIA) Study. We undertook genome-wide interrogation of blood DNA methylation (DNAm) using the Illumina Infinium Methylation EPIC BeadChip (EPIC array). We quantified aging using DNAm GrimAge, a validated, composite biomarker consisting of DNAm surrogate biomarkers of seven plasma proteins associated with various age-related conditions plus a DNAm surrogate of smoking pack-years. The comparison analysis was adjusted for age, race, smoking status, blood cell type proportions estimated using DNA methylation batch effect, and other laboratory-related technical factors. **Results:** The median chronological age of TCS was 28 years (range 19-64) with 25% smokers. Compared to their chronological age, TCS managed with surgical approaches alone had a mean GrimAge of 39.4 years (i.e., 9.2 years older, paired t-test P = 0.001), and cisplatin-treated TCS had a mean GrimAge of 45.2 years (i.e., 14.9 years older, paired t-test P < 0.001). Compared to the matched CARDIA controls, TCS managed with surgical approaches alone were on average 3.0 years epigenetically older (P = 0.093), and cisplatin-treated TCS were on average 11.2 years epigenetically older (P < 0.001), suggesting an increasing trend with treatment burden (P-trend < 0.001). **Conclusions:** Our data showed a faster epigenetic aging process in TCS. Consistent with previous studies, our data is in line with the hypothesis that TC cytotoxic treatment may induce premature aging. Although TCS managed with surgical approaches alone had no exposure to cytotoxic drugs, their epigenetic age may also be accelerated due to TC development and/or risk factors that contributed to it as well as post-therapy factors. Research Sponsor: U.S. National Institutes of Health.

5034 **Poster Session**

Management of residual nonretroperitoneal disease in nonseminomatous germ-cell tumors (NSGCT). *First Author: Jennifer King, Indiana University School of Medicine, Indianapolis, IN*

Background: The management of NSGCT patients (pts) with post-chemotherapy residual non-retroperitoneal disease (RP) remains unsettled. Decisions for surveillance vs surgical resection are commonly steered by pathology from retroperitoneal lymph node dissection (RPLND). Data is limited in pts who do not require RPLND (normal or normalized RP post-chemo). **Methods:** The prospectively maintained Indiana University testicular cancer database was queried for pts with metastatic NSGCT who completed first-line chemotherapy and had residual extra-RP disease without residual RP disease. Pts with post-chemo non-RP surgical resection were included. **Results:** 134 pts met eligibility. Median age at diagnosis was 28.6 (range, 16.2-51.5). Primary tumor predominant histology was embryonal (35.1%), mixed (25.4%), seminoma (2.2%), yolk sac (9.7%), choriocarcinoma (15.7%), teratoma (11.2%). 76 pts (56.7%) had teratoma in the primary tumor. Metastatic sites at diagnosis were RP (15.7%), mediastinal LN (8.2%), lung (28.4%), liver (11.2%), bone (6.7%), brain (21.6%). Those with RP mets at diagnosis had normalization of RP nodes after chemo. IGCCCG risk was good in 57, intermediate in 21, and poor in 56 pts. Median pre-chemo AFP was 66 (0.9-467,000). hCG was 960.5 (0.5-1,300,000). First-line chemo was BEPX4 in 68, BEPx3 in 29, EPX4 in 10, VIPX4 in 9, and other in 18 pts. All pts had surgical resection of non-RP disease. None had RPLND. 84 pts had lung nodule resection, 16 had mediastinal LN, 8 had cervical LN, 5 had liver, 6 had bone, and 20 had brain met resection. Of the 76 pts with teratomatous elements in the orchiectomy, 41 (53.9%) had teratoma and 24 (31.6%) had non-teratoma GCT in post-chemo non-RP surgical specimens. Of the 58 pts without teratoma in the orchiectomy, 9 (15.5%) had teratoma and 34 (58.6%) had non-teratoma GCT in the non-RP surgical resection specimens. Teratoma in the orchiectomy was a predictor of non-RP teratoma (Fisher's exact test P<0.0001). **Conclusions:** The presence of teratoma in orchiectomy predicts teratoma in residual post-chemo non-RP disease in pts who do not undergo RPLND. The absence of teratoma in orchiectomy should not preclude resection of residual non-RP disease given a subset of patients had persistent GCT. Research Sponsor: None.

Surgery	Total N= 134	Teratoma in orch N=76	No teratoma orch N=58
Lung	84	52	32
Teratoma	32 (38%)	25 (48%)	7 (22%)
MT*	5 (6%)	4 (8%)	1 (3%)
GCT	22 (26%)	11 (21%)	11 (34%)
Necrosis	34 (41%)	18 (35%)	16 (50%)
Mediastinal	16	11	5
Teratoma	11 (69%)	9 (82%)	2 (40%)
GCT	4 (25%)	2 (18%)	2 (40%)
Necrosis	4 (13%)	1 (9%)	1 (20%)
Cervical LN	8	5	3
Teratoma	3 (38%)	3 (60%)	0
GCT	4 (50%)	2 (40%)	2 (67%)
Necrosis	1 (13%)	0	1 (33%)
Brain	20	9	11
Teratoma	3 (15%)	2 (22%)	1 (9%)
GCT	17 (85%)	8 (89%)	9 (82%)
Necrosis	3 (15%)	1 (11%)	2 (18%)
Bone	6	5	1
Teratoma	2 (33%)	2 (40%)	0
MT*	2 (33%)	2 (40%)	0
GCT	2 (33%)	1 (20%)	1 (100%)
Necrosis	0	0	0
Liver	5	1	4
Teratoma	0	0	0
GCT	4 (80%)	0	4 (100%)
Necrosis	1 (20%)	1 (100%)	0

*Malignant transformation.

5035 **Poster Session**

Identifying germline genetic alterations or environmental factors associated with bilateral germ cell tumor (GCT). *First Author: Jack Patrick Gleeson, University College Cork, Cork, Ireland*

Background: Germline genomic alterations and/or environmental factors are proposed as critical to GCT development given the significant rates of bilateral and familial cases. A number of low-moderate risk loci for GCT have been identified (Litchfield, Eur Urol 2018 & Pluta, Nat Comm 2021), predominantly by analysing unilateral GCT, with a polygenic heritability model proffered. We postulate bilateral GCT represents an extreme phenotype with higher frequency of loss of function germline genomic alterations and/or pre-disposing environmental exposures. **Methods:** Bilateral GCT pts who consented to a prospective clinically annotated GCT DNA registry were included for analysis. The registry integrates self-reported questionnaires on environmental exposures, relevant medical history and germline whole exome sequencing (WES). Pathogenicity of variants identified by WES were classified using the algorithm Pathogenicity of Mutation Analyzer (PathoMAN) [Ravichandran, Genet Med 2019]. Aggregated WES results were curated to identify disruptive or deleterious variants affecting the same genes as the most significant individual variants in the Litchfield series. A < 1% minor allele frequency threshold was set for candidate variants, likely benign/benign variants were excluded. **Results:** Of 43 bilateral cases with germline WES results, median age at first diagnosis was 32.1 years (range 18-73), 9 tumors were synchronous and 34 metachronous with median interval between diagnosis of 76.4 months for metachronous cases. Tumor histology was seminoma in 52 and nonseminoma in 34. 39 of 43 (91%) pts completed questionnaires with 35 (90%) reporting White race, 2 Hispanic/Latino, 1 Asian, and 1 Peruvian. 13 (33%) reported prior smoking, 21 (54%) prior marijuana use, and 6 (15%) other illicit drug use. 6 (15%) pts reported undescended testis and 1 (3%) hypospadias. 24/43 (45%) patients harbored ≥1 variant within 15 Litchfield genes (60%). 43 distinct variants were identified: 33 (77%) nonsynonymous missense alterations, 7 (16%) intron variants, 1 inframe deletion in *STH3TC1*, and 1 initiator and 1 stop codon variant in *DEFB132*, which plays a role in binding spermatozoa. Multiple bilateral patients harbored variants in *MPDZ* (n = 7), *EHBP1L1* (n = 6), *SKIV2L* (n = 5), *FAM160A2* (n = 3), *ADAMTS18* (n = 3), *JMJD4* (n = 3), *ABCC4* (n = 3), *R3HCC1* (n = 2), *MLXIP* (n = 2) and *VPS16* (n = 2). **Conclusions:** In this bilateral GCT cohort, we identified several alterations in candidate susceptibility genes from the Litchfield series, whereas no convincing causative recurrent environmental exposures were observed. Our results support a polygenic model of GCT pathogenesis and show that analyzing enriched cohorts such as bilateral GCT may aid understanding of GCT pathogenesis. Additional analysis of the specific variants is required to further assess pathogenicity, elucidate their role and association with bilateral GCT. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology, U.S. National Institutes of Health, The Tifford Fund, and The Louise B. Blackman Foundation.

5036 **Poster Session**

Prognostic significance of raised serum tumor markers (STM) after 2 cycles of chemotherapy in men with intermediate- and poor-risk non-seminomatous testicular germ cell tumors (NSGCT) treated at a single-centre in India. *First Author: Ankur Nandan Varshney, All India Institute of Medical Science (AIIMS), New Delhi, India*

Background: Testicular GCT is a rare malignancy, with excellent outcomes. However, approximately one-fourth of intermediate risk and half of the patients with poor risk disease succumb to recurrent GCT. We looked at the prognostic significance of raised serum tumor markers after 2 cycles of chemotherapy in patients with poor risk GCT. **Methods:** This is a chart-review based retrospective analysis of patients with intermediate and poor risk NSGCT diagnosed and treated at a tertiary care centre in New Delhi, India from 2015-2021. Risk categories were defined as per the International Germ Cell Cancer Collaborative Group. Multivariable Cox regression models were constructed to analyse the prognostic impact of normal STM at the end of second cycle of chemotherapy on overall survival (OS) and relapse free survival (RFS), while adjusted for measured confounders. **Results:** A total of 312 patients were identified with testicular NSGCT, of whom 109 were intermediate (n = 48, 44%) and poor risk (n = 61, 56%). The median age at diagnosis was 27 (interquartile range, 21-34) years. ECOG PS of patients was 0-1 in 51% and 2-4 in 49%, and poor risk patients were more likely to have a poor ECOG PS at diagnosis (70% vs 30%, P < 0.001). First-line chemotherapy was BEP in 86% patients and VIP in the remaining 14%, and surgery for residual disease was performed in 22%. Overall, 35% patients had normal STM after 2 cycles of chemotherapy, and patients with intermediate risk were likely to achieve normal STM at this time-point (50% vs 23%). At a median follow-up of 62 months, the 5-year RFS rate was 62% (poor risk 52% and intermediate risk 78%), and OS rate was 68% (58% and 80%, respectively). Men with normal STM after 2 cycles chemotherapy had a better RFS (hazard ratio [HR], 0.70; 95% confidence interval 0.48-0.81; P < 0.001) and OS (HR,0.82; 95% CI 0.61-0.99; P = 0.04). After adjusting for risk category, and ECOG PS in a multivariable Cox regression model, patients with normal STM at the end of 2 cycles of chemo continued to have better outcomes (adjusted HR for RFS, 0.78; 95% CI, 0.77-0.89; P = 0.03, and adjusted HR for OS, 0.92; 95% CI,0.81-0.99; P = 0.05). Intermediate risk NSGCT and good ECOG PS also predicted better RFS and OS. **Conclusions:** Patients with NSGCT whose STMs do not normalize after 2 cycles of chemotherapy have worse RFS and OS compared to those with normal STM at this time-point. Further clinical trials will be needed to study the role of escalation or switch of chemotherapy in this subset of population. Research Sponsor: None.

5037 **Poster Session**

Anti-EGFR antibody plus anti-PD-1 antibody and chemotherapy as a neoadjuvant regimen for patients with locally-advanced penile squamous cell carcinoma: A prospective, single-arm, single-center, phase II clinical trial. *First Author: Xin An, Department of Medical Oncology, Sun Yat-sen University Cancer Center; State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine, Guangzhou, China*

Background: Advanced penile squamous cell carcinoma (PSCC) is a rare disease with a poor prognosis. We performed a monocentric, Simon's two-stage phase II study to evaluate the efficacy and safety of PD-1 blockade plus anti-EGFR target therapy and chemotherapy as neoadjuvant therapy in patients with locally advanced PSCC. We previously reported promising results in the first stage. The enrollment of the second stage had been completed by January 2022, herein we reported the updated results. **Methods:** Patients with chemotherapy-naive, locally-advanced PSCC (cT4 or cTxN3M0) were enrolled. The neoadjuvant regimen consists of anti–PD-1 antibody toripalimab, anti–EGFR antibody nimotuzumab, and chemotherapy (albumin-bound paclitaxel plus cisplatin and ifosfamide). Curative surgery was performed following a maximum of four cycles of treatment. The primary endpoint is the pathological complete response (pCR) rate. Secondary endpoints include overall response rate (ORR), relapse-free survival (RFS), overall survival (OS), and treatment-related adverse events (TRAEs). **Results:** A total of 29 patients were enrolled in two stages, with a median age of 57 (range 31-71) years. Till January 2022, 21 patients had completed the neoadjuvant treatment, 17 (81%) achieved an objective response, (CR 5, PR 12), 2 had SD, and 2 showed PD. Among 18 patients who underwent radical surgery, 11 showed no residual tumor on histopathology, with a pCR rate of 61.1% (11/18). The median follow-up time was 10.6 months. Two patients with PD died from disease, and 2 patients who experienced disease relapsed after radical surgery, in which 1 with SD, and 1 with PR. No relapse was observed among patients with pCR. The survival data are still immature. No unexpected toxicities and treatment-related death were recorded. Five out of 21 (23.8%) patients experienced grade 3 or 4 TRAEs. Grade 3 neutropenia occurred in 3 (14.3%) patients with 10 used G-CSF prophylaxis. No febrile neutropenia occurred. Other grades 3 toxicities included 1 case of peripheral sensory neuropathy and 1 anemia. The most common grade 1/2 TRAEs were alopecia (100%), decreased appetite (85.7%), nausea (71.4%), peripheral sensory neuropathy (66.7%), anemia (66.7%), neutropenia (33.3%), and infusion-related reactions (28.6%). The most common immune-related adverse events (IRAEs) were grade 1/2 hypothyroidism (19.0%), and grade 1 hyperthyroidism (4.8%). No severe IRAEs including pneumonitis, colitis, and myocarditis were observed. **Conclusions:** The triple combination is a provoking safe and efficacious neoadjuvant regimen for patients with advanced PSCC. Clinical trial information: NCT04475016. Research Sponsor: None.

5038 **Poster Session**

Influence of darolutamide on cabazitaxel systemic exposure. *First Author: Stefan A.J. Buck, Erasmus MC Cancer Institute, Rotterdam, Netherlands*

Background: Taxane efficacy in metastatic castration-resistant prostate cancer (mCRPC) patients is limited due to resistance development. In preclinical models it has been shown that addition of the androgen receptor signalling inhibitor (ARSI) enzalutamide improves cabazitaxel efficacy. However, we have previously shown that the clinical utility of this combination is hampered by a strong CYP3A4 drug-drug interaction with enzalutamide, resulting in a 22% reduced cabazitaxel systemic exposure. Darolutamide has much weaker CYP3A4 inducing effects and therefore may affect cabazitaxel systemic exposure to a lesser extent. **Methods:** We investigated the influence of darolutamide on cabazitaxel plasma exposure. mCRPC patients were enrolled on cabazitaxel monotherapy (20 mg/m^2 Q3W) on day 1 and received concomitant darolutamide (600 mg b.i.d.) from day 2 onwards for maximal 12 weeks. During cabazitaxel infusion on day 1, and after 6 and 12 weeks of darolutamide treatment, we measured cabazitaxel systemic exposure via Area Under the Curve from 0 to 24 hours ($AUC_{0\text{-}24h}$). **Results:** Cabazitaxel systemic exposure in 18 patients after 6 weeks of darolutamide was not significantly different compared to prior to darolutamide treatment ($AUC_{0\text{-}24h}$: -4%; 95%CI -19 – +13%; $p = 0.58$). Also, after 12 weeks of darolutamide treatment, cabazitaxel systemic exposure was unaltered ($AUC_{0\text{-}24h}$: +4%; 95%CI -10 – +20%; $p = 0.54$). Darolutamide plasma concentrations were constant throughout the study (Table). **Conclusions:** From a pharmacokinetic perspective cabazitaxel and darolutamide can be safely combined in mCRPC patients. Our findings pave the way for testing the efficacy of this promising combination in an era of combination regimens for prostate cancer. Clinical trial information: NL8611. Research Sponsor: Bayer BV.

Pharmacokinetics of cabazitaxel and darolutamide.

	Area Under the Curve (ng*h/mL)	Cycle 1 (CV%)	Cycle 2 (CV%)	Cycle 3 (CV%)	Relative difference (%) (95% CI)	*p* value
6 weeks (n=18)	Cabazitaxel $AUC_{0\text{-}24h}$	173 (26)	165 (27)		-4 (-19 – +13)	0.58
	Darolutamide $AUC_{0\text{-}12h}$		39,175 (41)			
12 weeks (n=12)	Cabazitaxel $AUC_{0\text{-}24h}$	176 (24)		183 (28)	4 (-10 – +20)	0.54
	Darolutamide $AUC_{0\text{-}12h}$		36,549 (33)	40,517 (28)	11 (-2 – +25)	0.09

5039 **Poster Session**

Candidate surrogate endpoints in advanced prostate cancer: Aggregate meta-analysis of 143 randomized trials. *First Author: Laila A Gharzai, Northwestern University, Chicago, IL*

Background: The Intermediate Clinical Endpoints (ICEs) in Cancer of the Prostate (ICECaP) working group identified metastasis-free survival as a valid surrogate endpoint for overall survival (OS) for patients with localized prostate cancer. No comparably validated surrogate endpoints for OS exist in advanced prostate cancer. **Methods**: In this meta-analysis, PubMed was searched for trials in advanced prostate cancer, defined as node positive (N1M0), metastatic castration-sensitive (mCSPC), non-metastatic (MOCRPC), or metastatic castration-resistant prostate cancer (mCRPC). Eligible randomized trials were required to report OS and ≥1 intermediate clinical endpoint (ICE). ICEs included biochemical-failure (BF), clinical failure (CF), BF-free survival (BFS), progression-free survival (PFS), radiographic PFS (radiographic +/- other study defined endpoints). Candidacy for surrogacy was assessed using the second condition of the meta-analytic approach, correlation of the treatment effect of the ICE and OS, using R^2 weighted by the inverse variance of the log ICE hazard ratio and defined as an $R^2 > 0.70$. **Results:** A total of 143 randomized trials (n = 75,601 patients) were included. No candidate endpoints met criteria for surrogacy; R^2 BF (n = 28,922) 0.42 (95%CI 0.18-0.64), BFS (n = 25,741) 0.57 (95%CI 0.37-0.73), CF (n = 22,616) 0.31 (95%CI 0.0075-0.56), PFS (n = 52,639) 0.50 (95%CI 0.35-0.63), and radiographic PFS (n = 52,548) 0.50 (95%CI 0.35-0.63). Within preplanned subgroups by castration sensitive or resistant disease, or by treatment type, neither BFS nor PFS met criteria for surrogacy. When assessing radiographically-defined progression (exclusive or with clinical progression), PFS for the overall group and by castration status did not meet criteria for surrogacy. Sensitivity analyses demonstrated that candidacy for surrogacy of all endpoints tested did not change over time. **Conclusions:** Our aggregate screening method for surrogate endpoints in advanced prostate cancer demonstrated commonly used clinical endpoints are not valid surrogate endpoints for OS, and further composite endpoint construction is necessary. Research Sponsor: Prostate Cancer Foundation, U.S. National Institutes of Health.

5040 **Poster Session**

Safety and survival outcomes in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) treated with lutetium-177–prostate-specific membrane antigen (^{177}Lu-PSMA) after radium-223 (^{223}Ra): Interim analysis of the RALU study. *First Author: Kambiz Rahbar, Department of Nuclear Medicine, University Hospital Münster, Münster, Germany*

Background: ^{223}Ra and ^{177}Lu-PSMA both prolong overall survival (OS) in different mCRPC settings. Previous data from the observational REASSURE (Sartor O, et al. 2021) and WARMTH (Ahmadzadehfar H, et al. 2021) studies suggested the feasibility of sequencing ^{223}Ra and ^{177}Lu-PSMA therapies. Here we used data from the observational, retrospective RALU study to further examine the safety and clinical outcomes of sequential ^{223}Ra/^{177}Lu-PSMA therapy in pts with mCRPC. **Methods:** This interim analysis investigated the baseline characteristics, safety (primary endpoint) and OS (secondary endpoint) in pts who received ^{177}Lu-PSMA after ^{223}Ra using retrospective data collected in German centers. **Results:** Data from 49 pts were available for this interim analysis. At baseline, before the start of ^{177}Lu-PSMA, 73% of pts were Eastern Cooperative Oncology Group performance status (ECOG PS) 1 and 27% ECOG PS 2. Visceral metastases were present in 31% of pts. Median prostate-specific antigen (PSA) and alkaline phosphatase (ALP) were 287 ng/ml and 142 U/L, respectively (Table). 70% of pts received ≥4 life-prolonging therapies prior to ^{177}Lu-PSMA, with abiraterone acetate (80%), enzalutamide (67%) and docetaxel (92%) being the most frequently used. 74% of pts received ≥5 ^{223}Ra injections. Pts received either PSMA-617 (67%) or PSMA I&T (33%): 65% of pts received 1–4 cycles and 33% received 5–6 cycles. Median duration of ^{177}Lu-PSMA therapy was 4.9 months (m) (0–57.1). Median time from the last ^{223}Ra dose to first ^{177}Lu-PSMA dose was 9.3 m (0.9–41.9). Any grade treatment-emergent adverse events (TEAEs) from the start of ^{177}Lu-PSMA therapy to 30 days of follow-up occurred in 91.8% of pts, and serious TEAEs in 20% of pts. Grade 3-4 hematologic laboratory abnormalities up to 90 days post-^{177}Lu-PSMA occurred in 34.7% of pts for anemia, 12.8% for thrombocytopenia and 2.0% for neutropenia. No grade 5 toxicities occurred. 39% of pts had ≥30% decline in PSA during ^{177}Lu-PSMA treatment. Median OS was 12.6 m (95% CI 8.8–16.1) from the start of ^{177}Lu-PSMA therapy. **Conclusions:** In this real-world retrospective analysis of selected pts with advanced mCRPC, the ^{223}Ra/^{177}Lu-PSMA treatment sequence was clinically feasible and well tolerated. Research Sponsor: Bayer.

Baseline characteristics	Patients (N = 49)
Age, median (range) years	72 (57–83)
ECOG PS	36 (73%)
1	13 (27%)
2	
PSA (ng/mL), median (range)	287 (20–12,229)
ALP (U/L), median (range)	142 (48–730)
Visceral metastatic disease at start of ^{177}Lu-PSMA	15 (31%)
Prior taxane-based chemotherapy	45 (92%)
Docetaxel	9 (18%)
Cabazitaxel	
Outcome	
OS from the start of ^{223}Ra, median (95% CI), m	31.4 (25.7–37.6)
OS from the start of ^{177}Lu-PSMA, median (95% CI), m	12.6 (8.8–16.1)

5041 **Poster Session**

Alkaline phosphatase (ALP) decline and overall survival (OS) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) treated with radium-223 (Ra-223) in the REASSURE study. *First Author: Nicholas D. James, The Institute of Cancer Research, London, United Kingdom*

Background: Ra-223 extends OS in pts with mCRPC. Predictive markers of response to Ra-223 are needed to help select pts who would benefit most from Ra-223 therapy. The ALSYMPCA study suggested a correlation between ALP decline and longer OS. Here, we evaluated whether ALP decline is associated with OS in the global real-world REASSURE study. **Methods:** Pts treated with Ra-223 were grouped by baseline ALP ≤147 U/L vs >147 U/L and any ALP decline vs no decline at week 12 from the first Ra-223 dose. The 147 U/L cut-off was selected based on the highest upper limit of normal for ALP from literature. Pts with a trend of decreasing ALP at closest value to week 12 between weeks 8 and 16 were included in the any decline group. Association of ALP decline with OS was assessed in the ≤147 U/L and >147 U/L groups separately. Median OS is provided with an unadjusted hazard ratio (HR) (95% confidence interval [CI]). Multivariate Cox models provided adjusted HRs (95% CI) for the association of ALP decline with OS. Some baseline covariates were not included in the models due to missing data. **Results:** 785 of 1465 pts had baseline ALP measurements, of whom 779 had week 12 ALP measurements: 443 had ≤147 U/L and 336 >147 U/L. In the ≤147 U/L group, median OS was 23.0 months (m) (95% CI 20.9–25.7) in pts with ALP decline (n=329) and 16.4 m (95% CI 14.1–20.4) in pts with no decline (n=114). In the >147 U/L group, median OS was 12.9 m (95% CI 11.7–14.3) in pts with ALP decline (n=295) and 8.1 m (95% CI 5.6–10.3) in pts with no decline (n=41). Comparison of unadjusted and adjusted HRs is shown in the Table. **Conclusions:** Pts with an ALP decline in first 12 weeks of Ra-223 treatment had longer OS. The effect of other baseline variables, including age, PSA, Hgb and prior treatments, provided adjustment but did not change this outcome. Research Sponsor: Bayer.

*†Covariates	Adjusted HR (95% CI)	Unadjusted HR (95% CI)
ALP ≤147 U/L	**N=395**	**N=443**
ALP decline vs no decline	0.672 (0.507–0.901)	0.647 (0.494–0.855)
Age (5-year increase)	1.152 (1.059–1.254)	
Log PSA (10-fold increase, ng/mL)	1.126 (1.043-1.218)	
‡Prior therapies (≥1 vs 0)	1.660 (1.237–2.248)	
ALP >147 U/L	**N=300**	**N=336**
ALP decline vs no decline#Age 73, log PSA 3.5, Hgb 11.9#Age 73, log PSA 5.8, Hgb 11.9‡Prior therapies (≥1 vs 0)	0.218 (0.133–0.379)0.512 (0.323–0.858)1.630 (1.223–2.194)	0.462 (0.331–0.663)

Hgb, hemoglobin; PSA, prostate-specific antigen.
*Includes covariates at 0.10 level of significance: Eastern Cooperative Oncology Group performance status was excluded.
†Albumin and lactate dehydrogenase were not included due to high percentage of missing values.
‡Life prolonging therapies: abiraterone acetate, enzalutamide, docetaxel, cabazitaxel or sipuleucel-T.
#Age, log PSA and Hgb were included in 2-way interactions with ALP decline. HR for ALP decline displayed for age at the mean, log PSA at 25th and 75th percentiles and Hgb at the mean.

5042 **Poster Session**

Outcome of patients with PSMA PET/CT screen failure by VISION criteria and treated with 177Lu-PSMA therapy: A multicenter retrospective analysis. *First Author: Masatoshi Hotta, University of California Los Angeles, Los Angeles, CA*

Background: The VISION trial showed that 177Lu-PSMA prolongs survival and improves the quality of life of patients with advanced mCRPC. It used PSMA-PET/CT to select patients for inclusion. The screen failure rate was "only" 12.6% (126/1003) and some have argued that the trial could have been positive even in an unselected population. It remains unknown whether the VISION-PET criteria were appropriate to stratify patients into likely responders versus non-responders to177Lu-PSMA. Here, we evaluated the outcome of patients who would have been excluded by the VISION-PET criteria and were nevertheless treated with 177Lu-PSMA. **Methods:** Patients treated with ≥1 cycle of 177Lu-PSMA between 11/2017 and 07/2021 (n = 74) who were registered in our institutional database and those enrolled in a multicenter dataset published previously (n = 230) (Gafita A, Lancet Oncol 2021) were retrospectively studied. One dual certified nuclear medicine and radiology reader reviewed baseline PSMA PET/CT studies and classified the patients as eligible (VISION-PET-E) or screen failure (VISION-PET-SF) based on the VISION-PET criteria: 1) absence of metastatic lesion(s) with uptake > liver background (i.e., low PSMA expression) or 2) presence of ≥ 1 metastatic lesion measurable by CT (≥ 1 cm for bone lesions with soft-tissue component (M1b) and solid/visceral organs lesions (M1c); ≥ 2.5 cm for lymph nodes lesions (N1-M1a)) with uptake ≤ liver background (i.e., PSMA-negative lesions). Outcome measures were PSA response rates (decline of ≥50% (PSA50RR), any decline (anyPSARR)), PSA-progression free-survival (PSA-PFS), and overall survival (OS). **Results:** 3/304 patients (1%) were excluded (lost to follow-up (n = 2), missing CT data (n = 1)). The median follow-up time was 22.5 (range: 2.1-62.3) months. 272/301 (90.4%) were VISION-PET-E, while 29/301 (9.6%) were VISION-PET-SF: 8/301 (2.7%) and 21/301 (7.0%) patients with low PSMA expression and PSMA-negative lesions, respectively. The VISION-PET-SF patients had worse PSA50RR (21% vs 50%; p = 0.005), anyPSARR (41% vs 71%; p = 0.003), median PSA PFS (2.1 months (95%CI: 1.1-3.3) vs. 4.1 (4.0-5.8); p = 0.023)), and tended to have a shorter OS (9.6 months (95%CI: 4.7-14.0) vs. 14.2 (12.6-15.9); p = 0.16) than the VISION-PET-E patients. **Conclusions:** VISION-PET-SF patients had worse outcomes than the VISION-PET-E patients. Our cohort only included patients who were eligible by each local site criteria. It did not include those 10-15% of patients who were excluded by local site assessment. Thus, 20-25% of the patients may be screen failures in unselected populations. Refinements in patient selection for 177Lu-PSMA are needed to optimize outcomes. Not characterizing target expression prior to PSMA-targeted treatment appears now non-ethical as a predictive whole-body imaging biomarker for response to PSMA-targeted therapies is available. Research Sponsor: None.

5043 **Poster Session**

PSMA PET tumor-to-salivary glands ratio (PSG score) to predict response to Lu-177 PSMA radioligand therapy: An international multicenter retrospective study. *First Author: Masatoshi Hotta, University of California Los Angeles, Los Angeles, CA*

Background: PSMA-targeted radioligand therapy can improve the outcome of patients with advanced mCRPC. However, patients do not respond uniformly and a PSA decline of ≥50% (PSA50) was achieved only in 46% of the patients in the VISION trial. We hypothesized that using the parotid glands instead of the liver as the reference organ enables more selective stratification. The aim of this study was to test PSMA PET tumor-to-Salivary Glands ratio (PSG score) to predict outcomes after Lu-177 PSMA. **Methods:** This was an international multicenter retrospective study using the established dataset consisting of 270 men with mCRPC treated with Lu-177 PSMA (Gafita A, Lancet Oncol 2021). First, we assessed baseline PSMA PET quantitatively (qPSG score) to calculate the tumor-to-salivary gland ratio (qPSG = SUVmean whole-body-tumor / SUVmean parotid glands) using a semi-automatic segmentation software (qPSMA). Patients were divided into three groups: high (qPSG > 1.5), intermediate (qPSG = 0.5 - 1.5), and low (qPSG < 0.5). Second, we assessed the reproducibility and the predictive value of the PSG score visually (vPSG score) graded by ten nuclear medicine physicians. Each reader read the baseline PSMA PET 3D maximum intensity projection (MIP) images, and classified the patients into three groups: (high) most of the lesions (> 80%) show higher uptake than parotid glands; (intermediate) neither "low" nor "high"; (low) most of the lesions (> 80%) show lower uptake than parotid glands. In case of disagreement, a majority vote was used. Outcome measures were PSA-progression free-survival (PSA-PFS), overall survival (OS), and PSA50. **Results:** 237 men were analyzed after excluding 33 men whose parotid glands were out of the scan range. The number of the patients in the high, intermediate, and low groups were 56/237 (23.6%), 163 (68.8%), and 18 (7.6%) for qPSG score, and 106/237 (44.7%), 96 (40.5%), and 35 (14.8%) for vPSG score, respectively. The inter- and intra-readers reproducibility of the vPSG score showed substantial (Fleiss' weighted Kappa: 0.68) and almost perfect (Cohen's weighted Kappa (mean): 0.83) agreement, respectively. The median PSA-PFS of high, intermediate, and low groups were 7.2, 4.0, and 1.9 months (p < 0.001) for qPSG score and 6.7, 3.8, and 1.9 months (p < 0.001) for vPSG score, respectively. Higher PSA50 rate was observed in the high group followed by the intermediate and low groups (high vs intermediate vs low: [qPSG] 69.6% vs 38.7% vs 16.7%; [vPSG] 63.2% vs 33.3% vs 16.1%). The median OS was longer in the high group than in the intermediate + low (i.e., non-high) group by qPSG (15.0 vs. 11.7 months (p = 0.013)) and vPSG score (14.3 vs.11.0 months (p = 0.038)). **Conclusions:** The PSG score is a valuable predictive biomarker for response to Lu-177 PSMA. The vPSG score yielded substantial reproducibility and comparable predictive value to the qPSG score. Research Sponsor: None.

5044 **Poster Session**

Progression patterns by types of metastatic spread, prostate-specific antigen (PSA), and clinical symptoms: Post-hoc analyses of ARAMIS. *First Author: Alicia K. Morgans, Dana-Farber Cancer Institute, Boston, MA*

Background: Darolutamide (DARO), a highly potent and structurally distinct androgen receptor inhibitor, prolonged metastasis-free survival by nearly 2 years and reduced the risk of death by 31% vs placebo (PBO) with a favorable tolerability profile in patients (pts) with nonmetastatic castration-resistant prostate cancer (nmCRPC) in ARAMIS. We present *post-hoc* analyses of ARAMIS to evaluate the association between metastatic progression with prostate-specific antigen (PSA) and clinical progression and to describe the distribution of metastatic progression between groups. **Methods:** Pts with nmCRPC were randomized 2:1 to DARO (n=955) or PBO (n=554) while continuing androgen-deprivation therapy. Descriptive analyses were performed using the primary data cutoff (Sept 3, 2018) for the double-blind period. Post-baseline metastases were based on central review of conventional radiographic imaging every 16 weeks. PSA and pain progression were defined per primary analysis (*N Engl J Med.* 2019;380:1235-46). **Results:** Metastatic progression was observed in 13.6% of DARO and 28.5% of PBO pts. Most pts had isolated progression as bone (DARO 46%, PBO 39%) or lymph node (32%; 40%) metastasis (Table). Pts with radiographic progression had shorter median time from initial diagnosis to study treatment (DARO 72.9, PBO 74.4 months) vs the overall ARAMIS population (86.2, 84.2 months). Of all pts with metastatic progression, baseline PSA levels (ng/mL) were similar in DARO (12.6) and PBO pts (15.1); DARO pts had lower median PSA before metastasis (16.7) vs PBO pts (48.0) and median absolute/relative PSA decrease from baseline of -0.7/-3.2% vs an increase for PBO pts of 29.5/181%. PSA progression before metastasis was observed in 55.6% (160/288) of pts, occurring in fewer DARO (45.4%) vs PBO pts (63.9%) (treatment difference 18.5%; nominal 95% CI 6.5%–30.6%). The median time between PSA progression and metastasis was 7.0 months with DARO vs 5.6 months with PBO. Pain progression before metastatic progression was rare and similar between groups (DARO 16.9%, PBO 17.7%). **Conclusions:** DARO significantly reduced risk of metastatic progression and improved overall survival vs PBO without changing the pattern of metastatic progression. Many pts with nmCRPC experienced metastatic progression without PSA progression, and pain progression was rare. These results support the use of imaging with PSA monitoring to properly identify disease progression in pts with nmCRPC. Clinical trial information: TBC. Research Sponsor: Bayer AG and Orion Pharma.

Type of metastatic progression by treatment group.

	Darolutamide n=955	Placebo n=554
Metastatic progression,[a] n (%)	130 (13.6)	158 (28.5)
Bone only	60 (46.2)	62 (39.2)
Distant lymph nodes only	41 (31.5)	63 (39.9)
Metastatic progression at ≥1 site[b]	29 (22.3)	33 (20.9)

[a]Post-baseline.
[b]Lymph nodes ± bone ± visceral and/or soft tissue, including 9 DARO and 4 PBO pts with exclusive visceral and/or soft tissue progression.

5045 **Poster Session**

Molecular correlates of high B7-H3-expressing metastatic castrate-resistant prostate cancers (mCRPC) via exome, transcriptome, and epigenome analyses. *First Author: Xiaolei Shi, University of Minnesota, Minneapolis, MN*

Background: mCRPC is a lethal condition with limited effective treatment options. B7-H3, a transmembrane protein of the B7 checkpoint superfamily is overexpressed in prostate cancer (PC) and is associated with poor prognosis. While several novel approaches target B7-H3 in prostate cancer, lack of knowledge about the molecular features and regulatory mechanisms of B7-H3 expression in mCRPC prevents the optimal design of these interventions. We aimed to characterize B7-H3 in mCRPC with the purpose to reveal the roles of B7-H3 in mCRPC pathogenesis, and stratify the patient population optimal for B7-H3–targeted therapies. **Methods:** We conducted bioinformatic interrogations at genome-scale on whole-exome and whole-transcriptome sequencing (WES, WTS) data from SU2C/PCF (n = 209, mCRPC), SUWC (n = 101, mCRPC) and GTEx (n = 246, benign prostate tissue). We developed and utilized novel machine learning (ML) algorithms to examine the association of B7-H3 with other key PC pathways. We examined the genetic and epigenetic regulation of B7-H3 by CHIP-seq. We also performed single-cell mRNA sequencing (scRNA-seq) analysis on one patient before and after treatment with the AR inhibitor, enzalutamide. We utilized both Gene Set Enrichment Analysis (GSEA) and our ML approaches to identify enriched signaling pathways in high B7-H3–expressing mCRPC. **Results:** Expression of B7-H3 was significantly elevated in mCRPC compared to benign prostate tissues, and was distinctive from other B7 family members. High B7-H3 expression was significantly associated with ERG fusions, AR-V7 variant, and increased FOXA1 and androgen receptor (AR) mRNA expression. At gene-level analysis, our ML algorithm suggested that B7-H3 shared similar gene networks as AR and its co-regulators, HOXB13, and FOXA1. CHIP-seq analysis revealed that the distal enhancers of B7-H3 in mCRPC were hyperactive (based on enhanced H3K27Ac marks) relative to primary tumors. Notably, these B7-H3 enhancers were bound by HOXB13, FOXA1 and AR in mCRPC samples. Our scRNA-seq analysis of one patient resistant to enzalutamide showed increased number of B7-H3-expressing cells. Based on integrated GSEA and ML analyses on WTS data, B7-H3 was positively associated with TGF-beta signaling, an enzalutamide resistance pathway. **Conclusions:** In mCRPC, we found B7-H3 overexpression as compared to other B7 family members. The association of B7-H3-high expression and certain genomic alterations may stratify mCRPC patients for B7-H3–targeted therapy. Further, B7-H3 exhibited regulation by AR, HOXB13 and FOXA1, at the B7-H3 enhancers. The activating epigenetic modification at the distal enhancers represents another potential marker to examine B7-H3 expression in tumors. Altogether, our study indicates that B7-H3 is a critical target in mCRPC patients, including those resistant to enzalutamide. Research Sponsor: U.S. National Institutes of Health.

5046 **Poster Session**

Predictors of overall survival among Black South African men treated with androgen-deprivation therapy for metastatic prostate cancer. *First Author: Yoanna S Pumpalova, Columbia University Irving Medical Center, New York, NY*

Background: Men in sub-Saharan Africa (SSA) are disproportionately affected by prostate cancer (PCa), and many have metastatic disease (mPCA) at presentation. In SSA, androgen deprivation therapy (ADT) is the first-line treatment for mPCa, and often the only available therapy. Treatment failure and death is common. We identified predictors of overall survival (OS) in Black South African (SA) men with mPCa on ADT. **Methods:** We performed a retrospective analysis of prospectively gathered data from men diagnosed with mPCA (3/22/2016 - 10/30/2020) at Chris Hani Baragwanath Hospital in Johannesburg, which was also a study site for the concurrent Men of African Descent and Carcinoma of the Prostate study. We included men with mPCA treated with ADT (received at least 1 dose of luteinizing hormone-releasing hormone agonist and/or had surgical castration), who had ≥1 PSA level drawn ≥12 weeks after ADT start. OS was defined from ADT start to death. PSA progression (PSA-P) definition was adapted from PCWG 3. Cox regression models were used to identify predictors of OS. PSA-P was treated as a time-dependent covariate. **Results:** Of 200 men with mPCa, we excluded 6 who did not receive ADT and 41 without sufficient data for PSA-P analysis. Of 153 men, 26.8% were <65 years old and 12% had a family history of PCa. Median PSA at diagnosis was 71.5 ng/mL (interquartile range (IQR) 20.7-432.6), median alkaline phosphatase level (ALP) 108 IU/L (79-224) and median hemoglobin (Hb) 13 g/dL (IQR 10-15). Median PSA nadir was 2.8 ng/mL (IQR 0.55-17.93). The rate of PSA-P at 1- and 2-years was 12.1% [95%CI 5.9-17.8] and 37.5% [95%CI 26.1-47.2]. The median follow-up was 2.75 years, and the 3-year OS was 61.9% [95%CI 52.7-72.6]. Cox proportional hazard ratio (HR) models of risk factors for OS are shown in Table 1. PSA-P was a strong predictor of OS. Men with PSA nadir >4ng/mL after ADT start had a HR for death of 3.77 [1.86-7.62]. Men with ALP >150 IU/L and those with Hb <13.5g/dL at diagnosis were also at higher risk for death (HR 3.09 [1.64-5.83] and HR 2.00 [1.28-6.56] respectively). **Conclusions:** Among Black men in SA treated with ADT for mPCA, PSA-P strongly predicts OS. In this cohort, high ALP and anemia at diagnosis, and PSA nadir >4ng/mL after ADT start are associated with higher risk for death. These factors can be used identify high risk men with mPCA, for whom early treatment escalation to chemotherapy should be considered. Research Sponsor: U.S. National Institutes of Health, Conquer Cancer Foundation of the American Society of Clinical Oncology, U01-CA184374, P30 CA13696.

Multivariate Cox proportional HR model of risk factors for OS in Black men with mPCa treated with ADT in Johannesburg, SA (2016-2020).

Characteristic	Multivariate HR	95% CI	p-value
Age ≥65 years	**2.40**	1.04-5.53	**0.04**
PSA at diagnosis ≥100 ng/mL	0.87	0.45-1.69	0.7
Tumor Volume ≥ 50%	1.29	0.65-2.54	0.5
Gleason Group	1.21	0.82-1.79	0.3
ALP >150 IU/L	**3.09**	1.64-5.83	**<0.001**
Hb <13.5 g/dL	**2.90**	1.28-6.56	**0.01**
PSA Nadir >4ng/mL	**3.77**	1.86-7.62	**<0.001**
PSA-P	**3.52**	1.85-6.70	**<0.001**

5047 **Poster Session**

Tolerability of [^{177}Lu]Lu-PSMA-617 by treatment exposure in patients with metastatic castration-resistant prostate cancer (mCRPC): A VISION study subgroup analysis. *First Author: Scott T. Tagawa, Weill Cornell Medicine, New York, NY*

Background: In the phase 3 VISION study, lutetium (^{177}Lu) vipivotide tetraxetan ([^{177}Lu]Lu-PSMA-617; ^{177}Lu-PSMA-617) + protocol-permitted standard of care (SoC) improved clinical benefit and was generally well tolerated despite a higher rate of adverse events (AEs) than SoC alone. Here we assess AE incidence by exposure to ^{177}Lu-PSMA-617. **Methods:** VISION was an international, open-label study of ^{177}Lu-PSMA-617 in adults with PSMA-positive mCRPC previously treated with ≥ 1 androgen receptor pathway inhibitor and 1–2 taxane regimens. Patients received ^{177}Lu-PSMA-617 (7.4 GBq every 6 weeks, ≤ 6 cycles) + SoC or SoC alone. rPFS and OS were primary endpoints; safety was a secondary endpoint. AE analysis by exposure to ^{177}Lu-PSMA-617 was carried out in pre-specified subgroups. ^{177}Lu-PSMA-617 cycle duration was generally ~6 weeks and cycle 6 duration was until the earliest date of subsequent treatment, and date of last administration of randomized treatment (including SoC) + 30 days. The cycle of onset in which an AE first occurred in a patient at maximum grade was assessed. **Results:** The median duration of cycle of onset for cycles 1 to 5 was 6 weeks; for cycle 6, it was 26.6 weeks (Table). Of the 529 patients in the ^{177}Lu-PSMA-617 group, 240 (45.4%) received ≤ 4 cycles and 289 (54.6%) received 5–6 cycles of treatment. In patients who received ≤ 4 or 5–6 cycles, 234 (97.5%) and 285 (98.6%) treatment-emergent AEs (TEAEs); 100 (41.7%) and 92 (31.8%) serious TEAEs; 205 (85.4%) and 246 (85.1%) treatment-related AEs; and 13 (5.4%) and 6 (2.1%) fatal TEAEs, respectively, were observed. Number of TEAEs and serious TEAEs by cycle of onset are shown in the Table. **Conclusions:** Over 50% of patients with mCRPC received 5–6 cycles of ^{177}Lu-PSMA-617. For cycles 1–5, TEAEs occurred at every cycle, with similar frequency. More TEAEs were observed in cycle 6, reflecting its longer median duration than other cycles. Clinical trial information: NCT03511664. Research Sponsor: Advanced Accelerator Applications, a Novartis Company.

TEAEs in the ^{177}Lu-PSMA-617 group (N = 529) by cycle of onset.

	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6
Number of pts who started the cycle, n	529	503	447	371	300	257
Cycle of onset duration – median, range (weeks)[a]	6.00, 4.9–24.0	6.00, 1.6–15.1	6.00, 1.4–18.1	6.00, 1.6–17.6	6.00, 2.1–19.7	26.57, 1.9–110.3
Number of pts with ≥ 1 event, n (%)[b]						
TEAEs						
All Grades	438 (82.8)	349 (69.4)	294 (65.8)	240 (64.7)	170 (56.7)	184 (71.6)
Grade 3–5	90 (17.0)	80 (15.9)	70 (15.7)	54 (14.6)	40 (13.3)	72 (28.0)
Serious TEAEs						
All Grades	55 (10.4)	42 (8.3)	32 (7.2)	30 (8.1)	24 (8.0)	52 (20.2)
Grade 3–5	47 (8.9)	36 (7.2)	26 (5.8)	23 (6.2)	21 (7.0)	48 (18.7)

[a]Cycle duration is time from cycle start to next cycle start (or earliest date of subsequent anticancer treatment, and date of last administration of randomized treatment + 30 days). Cycle 6 duration is described in the methods. [b]Onset date on or after current cycle but before start of next cycle. Percentages are based on the number of pts who started the cycle.

5048 **Poster Session**

A phase 1/2 multicenter investigator-initiated trial of DKN-01 as monotherapy or in combination with docetaxel for the treatment of metastatic castration-resistant prostate cancer (mCRPC). *First Author: David R Wise, Laura & Isaac Perlmutter Cancer Center at NYU Langone Health, New York, NY*

Background: Dickkopf-1 (DKK1) is a secreted Wnt signaling modulator that is upregulated in prostate cancers with low androgen receptor (AR) expression and co-occurring mutations in Wnt signaling family genes. DKN-01, a potent humanized monoclonal antibody (IgG4) with neutralizing activity against DKK1, delays prostate cancer growth in pre-clinical DKK1-expressing models in an NK cell dependent manner. These data provided the rationale for a prospective clinical trial testing DKN-01 in patients with mCRPC and elevated DKK1. Here, we report the safety and efficacy results of the phase 1 dose escalation cohorts. **Methods:** This is an investigator-initiated parallel-arm non-randomized phase 1/2 clinical trial testing DKN-01 alone or in combination with docetaxel 75 mg/m^2 for men with mCRPC who progressed on ≥1 AR signaling inhibitor. Eligible patients who had progressed on or were intolerant of docetaxel were assigned to the monotherapy cohort whereas taxane-naïve patients were assigned to the DKN-01 plus docetaxel combination cohort. DKK1 status was determined by RNA in-situ expression. The primary endpoint of the phase 1 dose escalation cohorts was safety, characterized by dose-limiting toxicity (DLT). A secondary endpoint of the study was to correlate anti-tumor activity, DKK1 expression (cutoff H-score ≥ 1), and clinical evidence of aggressive variant prostate cancer (AVPC). **Results:** 13 pts were enrolled in the completed phase 1 portion of this study – 7 patients in the monotherapy cohort and 6 patients in the combination cohort. No DLTs were observed at DKN-01 300mg or 600mg dose levels as monotherapy or in combination with docetaxel. No treatment-related serious adverse events occurred in either cohort. A best overall response of stable disease occurred in 2 out of 7 patients in the monotherapy cohort. In the combination cohort, all 5 evaluable patients had a partial response (PR) – 3 confirmed and 2 unconfirmed. All evaluable combination patients had ≥ 50% reduction in either PSA or CEA. Confirmed PRs in the combination cohort were observed in both DKK1 low (DKK1 H-score < 1) and high expressing tumors (H-score ≥1), including in 2 out of 3 patients with AVPC. **Conclusions:** DKN-01 600mg was well tolerated and selected as the recommended phase 2 dose as monotherapy and in combination with docetaxel. DKN-01 in combination with docetaxel showed promising clinical activity in prostate cancers regardless of DKK1 expression and was particularly promising in patients with AVPC. Further accrual into the phase 2 portion of this study is ongoing alongside preclinical and correlative studies aiming to investigate the mechanism of action of this combination therapeutic strategy. Clinical trial information: NCT03837353. Research Sponsor: Leap Therapeutics, Other Foundation.

5049 **Poster Session**

Final analysis of the phase 1b/2 study of sabizabulin in men with metastatic castration-resistant prostate cancer who progressed on an androgen receptor targeting agent. *First Author: Mark Christopher Markowski, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD*

Background: Sabizabulin is a novel oral cytoskeleton disruptor being developed for use in metastatic castration resistant prostate cancer (mCRPC). A Phase 1b/2 clinical study was conducted to establish the maximum tolerated dose (MTD) and evaluate the preliminary efficacy in men with mCRPC resistant to androgen receptor targeting agents. **Methods:** The Phase 1b portion of the study in 39 men utilized escalating and expanding dose and duration. The Phase 2 portion studied 41 men with mCRPC at the recommended Phase 2 dose of 63 mg daily. Efficacy was assessed by bone/CT scans. A final analysis of the safety and efficacy data including the primary endpoint, the median progression-free survival was conducted. **Results:** Although the MTD was not reached in the Phase 1b, the recommended Phase 2 dose was set at 63 mg/day to maximize GI tolerability. The most common adverse events (> 10% frequency) at the 63 mg oral daily dosing (combined Phase 1b/2 data) were predominantly Grade 1-2. Grade ≥3 events included diarrhea (7.4%), fatigue (5.6%) and ALT/AST elevations (5.6% and 3.7%, respectively). Neurotoxicity and neutropenia were not observed. Preliminary efficacy data in patients treated with ≥1 continuous cycle (21 days) of 63 mg or higher (n = 55) included an objective response rate of 6/29 (20.7%) in patients with measurable disease (1 complete, 5 partial). 14/48 (29.2%) of the patients had PSA declines. The Kaplan-Meier median radiographic progression-free survival was estimated to be 11.4 months (95% C.I. 29.63-65.79) (n = 55). Durable responses lasting > 2.75 years were observed with 14.5% (8/55) demonstrating a response greater than 12 months. **Conclusions:** This clinical trial demonstrated that chronic oral daily dosing of sabizabulin has a favorable safety profile with significant preliminary cytotoxic and cytostatic antitumor activity. These data support the ongoing Phase 3 VERACITY trial of sabizabulin in men with mCRPC who have progressed on an androgen receptor targeting agent. Clinical trial information: NCT03752099. Research Sponsor: Veru Inc.

5050 **Poster Session**

Olaparib plus abiraterone as first-line therapy in men with metastatic castration-resistant prostate cancer: Pharmacokinetics data from the PROpel trial. *First Author: Andrew J. Armstrong, Duke University Medical Center, Durham, NC*

Background: PROpel (NCT03732820) is a double-blind, Phase III trial of abiraterone + olaparib vs abiraterone + placebo as first-line treatment in patients with metastatic castration-resistant prostate cancer (mCRPC). Here we report results from the pharmacokinetics (PK) analysis of patients in PROpel. **Methods:** Patients were randomized 1:1 to receive abiraterone (1000 mg qd) plus prednisone/prednisolone with either olaparib (full monotherapy dose: 300 mg bid) or placebo. Eligible patients were biomarker unselected with confirmed prostate adenocarcinoma and castration-resistant metastatic disease. They had not received prior chemotherapy or next-generation hormonal agents (NHAs) for mCRPC. PK sampling was performed in a subset of patients. Concentrations of olaparib and abiraterone, and its active metabolite Δ4-abiraterone, were measured at steady state predose, at 30 min, 2 h, 3 h, 5 h, and 8 h postdose. The data underwent noncompartmental analysis to evaluate the effect of olaparib on abiraterone PK. The PK of olaparib in the presence of abiraterone was also compared with olaparib PK from other monotherapy studies to evaluate the effect of abiraterone on olaparib PK. **Results:** The PK analysis included 66 patients from the olaparib + abiraterone arm and 58 patients from the placebo + abiraterone arm. Olaparib absorption was rapid, with median $t_{max,ss}$ of 2 h. Absorption of abiraterone was rapid in both treatment groups, with median $t_{max,ss}$ observed between 2.00 and 2.04 h. The steady state exposure of olaparib in the presence of abiraterone, based on AUC_{ss}, $C_{max,ss}$ and $C_{min,ss}$, was similar to observations for patients receiving olaparib 300 mg bid monotherapy in other Phase III studies, with values of 39.3 μg·h/mL, 6.3 μg/mL, and 1.0 μg/mL, respectively. Steady state exposures for abiraterone were similar between the two treatment arms (abiraterone + placebo: $AUC_{(0\text{-}8)}$ = 339.5 ng·h/mL, $C_{max,ss}$ = 105.4 ng/mL, $C_{min,ss}$ = 8.5 ng/mL; abiraterone + olaparib: $AUC_{(0\text{-}8)}$ = 393.7 ng·h/mL, $C_{max,ss}$ = 112.6 ng/mL, $C_{min,ss}$ = 7.7 ng/mL), and PK data for the abiraterone + olaparib arm were similar to those reported in the literature for abiraterone monotherapy. **Conclusions:** Combination treatment of olaparib (full monotherapy dose: 300 mg bid) and abiraterone (1000 mg qd) in patients with mCRPC had no clinically significant effect on the PK profiles of either drug. The steady state exposures for abiraterone were similar between the two treatment arms, indicating that co-administration with olaparib 300 mg bid has no effect on the PK of abiraterone. In line with previous Phase II trial data, results from PROpel confirmed that there were no relevant PK based drugdrug-interactions between olaparib and abiraterone. Clinical trial information: NCT03732820. Research Sponsor: AstraZeneca as part of an alliance between AstraZeneca and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ.

5051 **Poster Session**

On-treatment plasma ctDNA fraction and treatment outcomes in metastatic castration-resistant prostate cancer. *First Author: Sofie H. Tolmeijer, Department of Medical Oncology, Radboud Institute of Molecular Sciences, Radboud University Medical Center, Nijmegen, Netherlands*

Background: Androgen receptor pathway inhibitors (ARPI) are standard of care for treatment-naive metastatic castration-resistant prostate cancer (mCRPC), but primary or rapidly acquired resistance is common. Early identification of resistant disease is critical for improving management strategies. We investigated whether on-treatment changes in plasma ctDNA fraction (ctDNA%; the proportion of cell-free DNA that is tumor-derived) associate with ARPI treatment outcomes. **Methods:** We collected serial plasma cell-free DNA from 81 patients with mCRPC: at baseline and following 4 weeks of treatment during two prospective multi-center observational studies (NCT02426333; NCT02471469). CtDNA% was calculated by integrating deep targeted and shallow whole-genome sequencing. Samples were dichotomized at above and below 1%, and designated as high or low ctDNA%, respectively. Outcome measurements were radiographic and/or clinical progression-free survival (rcPFS) and overall survival (OS). Non-durable responses were defined as rcPFS < 6 months, excluding patients with PSA progression alone (n = 3) or treatment cessation for toxicity (n = 4). **Results:** Median follow-up was 27.4 months (IQR 17.7-34.9). CtDNA% was high in 47/81 (58%) patients at baseline and 29/81 (36%) patients at 4 weeks. The median ctDNA% for patients with high ctDNA was 15.0% (IQR 4.9-43.8%) at baseline and 5.0% (IQR 2.0-20.6%) at 4 weeks. High baseline ctDNA% was prognostic for rcPFS and OS (Table). RcPFS and OS was shortest for patients that retained high ctDNA% at 4 weeks. However, patients converting from high to low ctDNA% at 4 weeks did not experience different outcomes to patients with low ctDNA at both timepoints. ctDNA% associations with rcPFS and OS were independent of established clinical prognostic factors. 23/27 (85%) patients experiencing non-durable responses had high ctDNA% at baseline and 4 weeks. Only 3/47 patients (6%) experiencing durable responses had high ctDNA% at both timepoints. Sensitivity and specificity for predicting non-durable response was 85% and 94%, respectively. **Conclusions:** Early changes in ctDNA% are strongly linked to duration of first-line ARPI treatment benefit in mCRPC and may have utility for informing clinical trials testing early therapy switches in patients unlikely to experience durable disease responses. Clinical trial information: NCT02426333; NCT02471469. Research Sponsor: REFINE project (grant no. 836041013) that is funded by ZonMw, The Netherlands Organisation for Health Research and Development, as part of the Goed Gebruik Geneesmiddelen(GGG) program, Pharmaceutical/Biotech Company.

			rcPFS			OS		
Biomarker	**Subgroup**	**Patients (n)**	**Median (months)**	**Univariate HR (95% CI)**	**P-value**	**Median (months)**	**Univariate HR (95% CI)**	**P-value**
Baseline ctDNA%	Low	34	20.0	Ref		NR	Ref	
	High	47	5.8	2.39 (1.41-4.06)	0.001	22.7	3.40 (1.83-6.33)	<0.001
ctDNA% change at 4 weeks	Low > Low	34	20.0	Ref		NR	Ref	
	High > Low	18	15.6	1.31 (0.66-2.60)	0.44	26.0	2.02 (0.93-4.38)	0.07
	High > High	29	4.8	4.65 (2.56-8.46)	< 0.001	16.0	5.22 (2.67-10.20)	<0.001

5052 **Poster Session**

Phase I/II study of the selective PI3Kβ inhibitor GSK2636771 in combination with pembrolizumab in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) and PTEN loss. *First Author: Ecaterina Elena Dumbrava, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: PTEN loss activates the PI3K/AKT signaling pathway, contributes to an immunosuppressive tumor microenvironment, resistance to androgen deprivation therapy and poor clinical outcome in pts with mCRPC. Treatment with anti-PD1 antibodies improves survival in many cancers, but efforts to harness its benefit in mCRPC have been unsuccessful. In preclinical PTEN loss models, selective PI3Kβ inhibitor enhanced survival and the frequency of intratumoral T cells. We hypothesized that the combination of PI3Kβ inhibitor and anti-PD-1 antibody is safe and promotes antitumor activity. To test this, we conducted a phase I/II study (NCT01458067) of PI3Kβ inh GSK2636771 and pembrolizumab in pts with solid tumors (including melanoma and mCRPC) with PTEN loss. We report the results from a cohort of pts with mCRPC and PTEN loss. **Methods:** The phase I primary objective was to determine the safety, tolerability, and recommended phase II dose (RP2D) of GSK2636771 + pembrolizumab using a 3+3 design. Pembrolizumab was given at 200 mg IV Q3W and dose escalation started at 300mg orally daily of GSK2636771 for 21 days cycle. The phase II primary objective was to evaluate the efficacy of the combination using RECIST 1.1. Secondary objectives were to evaluate PK and PD effects in tumor and blood. Tumoral PTEN loss was defined by loss of protein expression by IHC or by presence of an inactivating mutation identified by next-generation sequencing (NGS). **Results:** A total of 12 pts with mCRPC and PTEN loss were enrolled (2 pts in the dose escalation and 10 pts in the dose expansion cohorts). Median age was 67 years (range 55-80) and pts had a median of 4 lines of prior therapies with 83% of pts receiving prior taxane-based chemotherapy. The RP2D was identified at 200mg PO QD of GSK2636771 + pembrolizumab 200mg IV Q3W. Most treatment-related adverse events were grade (G) 1-2 with the most common being diarrhea (33%) and rash (42%). A total of 4 pts had G3 rash, including 2 pts with G3 immune-related bullous pemphigoid. Dose-limiting toxicities in pts with mCRPC included G3 hypophosphatemia and G3 rash. Treatment was discontinued because of G3 toxicity in 1 pt and 42% of pts required a dose reduction of GSK2636771. Among 11 evaluable pts at 200mg daily of GSK2636771, partial response (PR) was achieved in 2 pts (-56% and -59% as compared to baseline, per RECIST1.1), which was associated with ongoing progression free survival (PFS) > 12 months (24.1 and 13.6 months, respectively) and PSA > 50% reduction as compared to baseline. In addition, a pt with tumor reduction of 18% per RECIST1.1 has remained on treatment for 15.8 months. **Conclusions:** GSK2636771 plus pembrolizumab had an acceptable safety and tolerability profile. The combination showed promising preliminary antitumor activity and durable responses in a heavily pretreated population of pts with mCRPC. Clinical trial information: NCT01458067. Research Sponsor: Merck, GSK, Melanoma SPORE.

5053 **Poster Session**

Characterization and impact of canonical Wnt Signaling Pathway (WSP) alterations on outcomes of metastatic prostate cancer. *First Author: Rana R. McKay, University of California San Diego Health, La Jolla, CA*

Background: Recurrent alterations in the WSP have been identified in patients with advanced prostate cancer. Aberrant Wnt signaling has been implicated in disease progression and hormonal resistance in prostate cancer. We utilized a multi-institutional real-world dataset to characterize molecular alterations in the canonical WSP in men with prostate cancer, and correlate that with overall survival (OS). **Methods:** Prostate cancer patients who underwent tissue-based DNA and RNA sequencing utilizing a commercially available CLIA-certified assay (Caris Life Sciences) were investigated. Next generation sequencing (NGS)/ whole exome (WES) and transcriptome sequencing (WTS) was performed on prostate cancer tissue derived from prostatic and/or metastatic sites. Patients with somatic activating mutations in *CTNNB*, pathogenic fusions in *RSPO2*, or inactivating mutations in *APC* or *RNF43* were characterized as having aberrant canonical Wnt signaling (WSP-MT). A subset analysis was conducted in metastatic prostate cancer (mPCa) samples with microsatellite stable (MSS) tumors excluding RNF43 (G569fs*) mutations. Comparative analyses were done using Fisher-Exact or X^2 tests, and significance was determined by adjusted p value using Benjamini-Hochberg correction (q < 0.05). OS was obtained from insurance claims data and calculated using Kaplan-Meier estimates. Enriched mRNA transcripts were identified as those with an adjusted p value < 0.001, logFC > 1.5, and (-)log10 FDR > 20. **Results:** Overall, 21.8% (n = 715/3283) of samples were classified as WSP-MT, of which 297 (41.5%) were from primary tumor samples and 418 (58.5%) were from metastatic sites. WSP-MT were highest in metastases to CNS (54.5%, n = 12/22), liver (43.8%, n = 91/208) and lung (42.3%, n = 91/208). Compared to WSP wild-type, WSP-MT tumors had a greater frequency of dMMR/MSI-H status (18% vs. 2%, q < 0.001). In the subset of mPCa, MSS tumors (WSP-MT excluding RNF43 (G569fs*) mutations, n = 318; WSP wild-type n = 951), WSP-MT were enriched for mutations in SPOP (14.3% vs. 6.9%, q = 0.004). In these tumors, WSP-MT samples were most enriched for mRNA expression of CST1, NKD1, AXIN2, and ZNRF3 (all known canonical WSP activators). OS was inferior in mPCa WSP-MT patients compared to WSP wild-type (HR 0.49, 95% CI 0.37-0.64, p < 0.0001). Relative to WSP wild-type cases, OS was shorter from time of enzalutamide/abiraterone/apalutamide start (HR 0.25, 95% CI 0.15-0.43, p = 0.0001), and from first-line taxane chemotherapy (HR 0.47, 95% CI 0.21-1.02, p = 0.052) in pts with WSP-MT. **Conclusions:** Canonical WSP alterations are enriched in metastatic tumors, with highest prevalence in visceral (CNS, liver, lung) metastases. Clinical outcomes in WSP-mutant cancers are inferior with both hormonal and chemotherapies, heralding an urgent need to develop novel therapeutic strategies for such patients. Research Sponsor: None.

5055 **Poster Session**

Biallelic loss of TP53, PTEN, and RB1 in association to aggressive clinical features and poor outcomes in metastatic castration-resistant prostate cancer (mCRPC). *First Author: Corinne Maurice-Dror, BC Cancer, Vancouver, BC, Canada*

Background: Deleterious alterations in tumor suppressor genes (TSGs) *TP53, RB1*, and *PTEN* are potential markers of small cell neuroendocrine prostate cancer (SCNP), and androgen receptor pathway inhibitor (ARPI) resistance. We examined the outcomes and clinical features of mCRPC patients (pts) harboring biallelic loss in 0, 1, 2 or all 3 TSGs. **Methods:** We identified 210 consecutive mCRPC pts providing ≥1 plasma cell-free DNA sample with ≥20% circulating tumor DNA fraction (ctDNA%) during their mCRPC disease course. ctDNA% ≥20% enabled sensitive characterization of biallelic TSG loss (including by homozygous deletions and mutation plus somatic loss-of-heterozygosity; LOH). Patient records were reviewed for baseline characteristics, SCNP histology, and presence of liver metastases. We investigated associations between TSG loss and the following clinical outcomes: PSA response (PSA decline ≥50% (PSA50 RR)), progression free survival (PFS) on 1L therapy, and overall survival (OS) from 1L therapy. **Results:** Median follow-up was 16.5 months (range: 0.4-112.4) and OS event rate was 95%. Median age at 1L mCRPC was 71 years (range: 48-98). Most pts were ECOG PS 0-1 (79%) and 13% had liver metastases. 91% received ARPI for 1L mCRPC and 7% received ARPI for castration-sensitive disease. *TP53* was primarily inactivated by somatic mutation plus LOH (90%), whereas *RB1* (71%) and *PTEN* (86%) were more commonly inactivated by homozygous deletions. Compared to pts without evidence of biallelic TSG loss, pts with loss of 3 TSGs were significantly enriched for *de-novo* M1 disease (86 vs. 60%, p=0.05) and liver metastases (28.5 vs. 6.8%, p<0.05). Ten pts (4.7%) had histologically confirmed SCNP and provided ctDNA at time of SCNP diagnosis. Of these, 7 (70%) had biallelic loss of ≥2 TSGs. For all pts receiving 1L therapy, loss of ≥1 TSG(s) was associated with decreased OS (HR: 1.86, 95% CI: 1.40-2.48, p<0.01) and PFS (HR:1.74, 95% CI 1.29-2.34, p<0.01) compared to pts with no biallelic TSG loss. Furthermore, a cumulative increase in the number of TSGs lost was associated with an incremental reduction in OS and PFS (Table). **Conclusions:** In a cohort enriched for poor prognosis (i.e. high ctDNA%), cumulative loss of TSGs is associated with aggressive disease features and poor clinical outcomes. These patients may benefit from alternative treatment intensification strategies. Research Sponsor: BC Cancer Foundation, Prostate Cancer Foundation.

	No TSG loss (n=114)	1 TSG loss (n=53)	2 TSG loss (n=28)	3 TSG loss (n=15)
Median OS (months)	19.5	13.2	9.9	9.7
Univariate HR (95% CI)	REF	1.7 (1.2-2.4) p<0.01	1.9 (1.2-2.9) p<0.01	2.7 (1.5-4.8) p<0.01
Median PFSa (months)	5.5	4.2	3.4	1.8
Univariate HR (95% CI)	REF	1.6 (1.2-2.3) p<0.01	1.7 (1.1-2.6) p=0.01	2.4 (1.3-4.4) p<0.01
PSA50 RR (%)	67	58	63	46
χ2 p-value	REF	0.37	0.65	0.21

[a]Time from 1L therapy initiation to earliest clinical, radiographic or biochemical progression.

5056 **Poster Session**

Activation of the AKT pathway and outcomes in patients (pts) treated with or without ipatasertib (ipat) in metastatic castration-resistant prostate cancer (mCRPC): Next-generation sequencing (NGS) data from the phase III IPATential150 trial. *First Author: Christopher Sweeney, Dana-Farber Cancer Institute, Boston, MA*

Background: Ipat + abiraterone (abi) significantly reduced the risk of radiographic disease progression vs placebo (pbo) + abi in pts with mCRPC and PTEN loss tumors by immunohistochemistry (IHC; HR, 0.77; 95% CI: 0.61, 0.98; P=0.034) but not in ITT pts (HR, 0.84; 95% CI: 0.71, 0.99; P=0.043; Sweeney Lancet 2021). A greater risk reduction was seen in pts with *PTEN* loss by NGS (HR, 0.65; 95% CI: 0.45, 0.95). We describe the efficacy and safety of pbo + abi vs ipat + abi at the second interim analysis (IA) of overall survival (OS) and explore the impact of AKT pathway alterations. **Methods:** Pts with mCRPC were randomized 1:1 to ipat (400 mg/d) + abi (1000 mg/d) + prednisone (5 mg bid) or pbo + abi + prednisone. Coprimary endpoints were investigator-assessed radiographic progression-free survival by Prostate Cancer Working Group 3 (PCWG3) criteria in pts with PTEN loss tumors by IHC (PTEN loss in ≥50% of tumor cells) and in ITT pts. Secondary endpoints in both populations included OS, objective response rate (ORR) per RECIST 1.1 and PCWG3 and time to pain progression (TPP). Ad hoc analyses assessed pts with *PIK3CA*/*AKT1*/*PTEN* alterations by NGS vs wildtype (WT). **Results:** Median follow-up was 31 mo (cutoff: 2021 Sept 30). In PTEN loss by IHC pts, median OS was 35.8 mo (n=261) with pbo + abi and 36.8 mo (n=260) with ipat + abi (HR: 0.95; 95% CI: 0.74, 1.21; P=0.665); in ITT pts, median OS was 36.7 mo (n=554) with pbo + abi and 40.3 mo (n=547) with ipat + abi (HR: 0.90; 95% CI: 0.76, 1.07). With longer follow-up, the safety profile was consistent with that of the primary analysis. In the full NGS evaluable population (n=743), ipat + abi was associated with better outcomes in pts with *PIK3CA*/*AKT1*/*PTEN* alterations (Table). Among pts with *PTEN* loss tumors by NGS (205 of the evaluable 518 pts), median OS was 29.8 mo (n=102) with pbo + abi and 35.8 mo (n=103) with ipat + abi (unstratified HR: 0.82; 95% CI: 0.56, 1.19). **Conclusions:** At the second IA, no significant improvement in OS was observed with ipat + abi in pts with PTEN loss by IHC. Exploratory analyses in pts with *PIK3CA*/*AKT1*/*PTEN* alterations by NGS suggest that these patients have poorer prognosis but may derive greater benefit from ipat + abi. Clinical trial information: NCT03072238. Research Sponsor: F. Hoffmann La-Roche Ltd.

	PIK3CA/AKT1/PTEN altered by NGS n=250		*PIK3CA/AKT1/PTEN* WT by NGS n=493	
	Pbo + Abi	Ipat + Abi	Pbo + Abi	Ipat + Abi
n	122	128	257	236
Median OS (95% CI), mo	29.5 (24.6, 36.1)	37.1 (31.4, NE)	40.2 (34.3, 44.7)	40.3 (36.0, NE)
HR (95% CI)[a]	0.73 (0.52, 1.04)		0.98 (0.75, 1.27)	
Median TPP, (95% CI), mo	14.8 (11.1, 24.0)	23.3 (12.9, 41.5)	38.9 (21.2, NE)	26.0 (18.9, NE)
HR (95% CI)[a]	0.69 (0.46, 1.03)		1.10 (0.81, 1.50)	
Confirmed ORR, n/N (%)[b]	20/50 (40)	32/48 (67)	50/102 (49)	48/83 (58)
Duration of response (95% CI), mo	14.5 (8.2, 21.4)	23.3 (18.2, NE)	16.3 (12.8, 20.2)	15.5 (9.2, 20.4)

NE, not estimable.
[a]Unstratified.[b]Per RECIST 1.1 and PCWG3 in pts with baseline lesions.

5057 **Poster Session**

Impact of activating androgen receptor (AR) mutations on AR sensitivity to alternative ligands and response to ODM-208, a selective, first-in-class CYP11A1 inhibitor, in patients with advanced metastatic castration-resistant prostate cancer (mCRPC). *First Author: Alice Bernard-Tessier, Institut Gustave Roussy, Villejuif, France*

Background: Activating AR mutations ensure a continued AR activation by non-androgen steroid ligands, e.g. progesterone and glucocorticoids. CYP11A1 is the only enzyme that catalyzes the conversion of cholesterol to pregnenolone, from which all steroid hormones (glucocorticoids, mineralocorticoids, and sex steroids) are subsequently derived. ODM-208, an oral, selective inhibitor of CYP11A1, is being evaluated for safety and efficacy as a treatment of mCRPC in the ongoing CYPIDES phase I/II trial in men previously treated with both novel hormonal therapies and taxanes (ClinicalTrials.gov identifier: NCT03436485). Preliminary phase 1 results were previously reported (Fizazi K et al., ASCO GU 2022). Here we confirm that the in-vitro sensitivity of common AR mutations to ODM-208 treatment is mirrored in patient response in CYPIDES phase 1. **Methods:** ODM-208 was administered at daily doses between 6-150 mg (phase 2 dose: 10 mg) with dexamethasone and fludrocortisone, resulting in maximal suppression in all measured steroids at all doses. AR ligand-binding domain (LBD) mutations (L702H, V716M, W742L, W742C, H875Y, F877L, T878A, T878S, M896T, M896V) were assessed using a BEAMing assay (Sysmex Inostics) from plasma circulating cell-free DNA (cfDNA) collected before the first dose of ODM-208. The activation of wild-type (wt) and LBD mutated AR with various ligands was also studied in vitro using a luciferase reporter assay in AR negative PC3 cells. **Results:** 17 of 44 patients had at least one AR activating mutation, the most frequent being L702H (n = 11), T878A (n = 10), and H875Y (n = 6). Eleven out of the 16 evaluable patients (68%) with an AR LBD mutation achieved ≥50% reduction in serum PSA compared with 2 out of the 24 evaluable patients (8%) without an AR LBD mutation (P < .0001). The in vitro sensitivity of each of these common AR mutations to a variety of non-androgenic steroids will be presented, along with detailed PSA responses, duration of responses, and safety in mCRPC patients bearing the same mutations. **Conclusions:** AR activating mutations may permit continued hormone dependence in mCRPC, related to actions of non-androgenic steroid hormones. Treatment with ODM-208 blocked all steroid hormone production and resulted in frequent ≥50% PSA reductions in this group of heavily pretreated mCRPC pts with various AR LBD mutations, some being long-lasting. cfDNA AR mutations are a promising predictive biomarker for ODM-208 efficacy. Dexamethasone did not activate mutated ARs, supporting its selection for glucocorticoid replacement therapy in combination with ODM-208. Clinical trial information: NCT03436485. Research Sponsor: Orion Corporation.

5058 **Poster Session**

Transcriptional profiling of matched biopsies reveals molecular determinants of enzalutamide resistance. *First Author: Thomas Westbrook, University of Michigan, Ann Arbor, MI*

Background: Castration-resistant prostate cancer (CRPC) is the lethal form of the disease. One of the principal therapies in CRPC is the potent androgen receptor (AR) signaling inhibitor enzalutamide (enza). Most patients benefit from enza, but disease progression is nearly universal. A variety of resistance mechanisms have been described by comparing enza-naïve and enza-resistant tumors. However, these results are largely from different groups of patients and do not provide information on the changes induced by enza within a given patient. Lineage plasticity—most commonly-exemplified by loss of AR signaling and switch from a luminal to an alternate differentiation program—is a particularly aggressive resistance mechanism. Importantly, lineage plasticity appears to be increasing in incidence since more widespread use of potent AR signaling inhibitors such as enza. To improve our understanding of resistance mechanisms induced by enza treatment, we analyzed the transcriptomes of matched metastatic CRPC patient biopsies obtained prior to treatment and at the time of disease progression. **Methods:** All biopsies were obtained as part of the Stand Up 2 Cancer/Prostate Cancer Foundation-funded West Coast Dream Team, a prospective, IRB-approved protocol focused on understanding the biology of metastatic CRPC. We identified 21 patients for whom matched tumor biopsies with RNA-seq were available prior to starting treatment with enza and at the time of progression while still taking enza. **Results:** Our RNA-seq analysis demonstrates that the majority of progression tumors cluster with their baseline pair, suggesting that enza does not markedly change the tumor transcriptome in most cases. Three of 21 patients showed evidence of lineage plasticity at progression by gene expression analysis. By analyzing the RNA-seq data, we identified pathways linked to stemness that were more activated in baseline tumors from patients whose progression tumors underwent lineage plasticity. Furthermore, we identified a gene signature enriched in these baseline tumors that was associated with risk of lineage plasticity after enza treatment. We determined that high expression of this signature was strongly associated with poor survival from the time of AR signaling inhibitor treatment in independent patient samples, suggesting this signature is linked to poor patient outcome. **Conclusions:** Enza-resistant tumors are heterogeneous. Most tumors do not undergo significant transcriptional changes at progression vs. baseline. Matching recent reports, approximately 15% of tumors underwent lineage plasticity upon progression. Our work implicates a gene program that may predispose tumors to enza-induced lineage plasticity. Finally, the gene signature we identified may be a marker of lineage plasticity risk and tumor aggressiveness in CRPC prior to the initiation of AR signaling inhibitor therapy. Research Sponsor: Stand Up to Cancer-Prostate Cancer Foundation , U.S. National Institutes of Health, University of Michigan Rogel Cancer Center Innovation Award NCI P30 CA046592; Department of Defense Idea Award (W81XWH-20-1-0405); National Comprehensive Cancer Network (NCCN)/ Astellas Pharma Global Development Award.

5059 **Poster Session**

DynAMo: A dynamic allocation modular sequential trial of approved and promising therapies in men with metastatic CRPC. *First Author: Paul Vincent Viscuse, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Response to androgen signaling inhibitors is highly variable and dictates prognosis in castration resistant prostate cancer (CRPC). The development of effective combinations for CRPC has been hampered by the absence of biomarkers to identify its distinct biological subsets, obligating the homogeneous application of therapies to a heterogeneous disease in clinical trials. We previously defined the *aggressive variant prostate cancers* as a framework for the study of those with poor responses to androgen signaling inhibitors (dubbed 'androgen indifferent') and observed improved outcomes in this subset when carboplatin was added to cabazitaxel (CABCARB). In contrast, results of prospective trials suggested that anti-CTLA-4 therapy may benefit patients with androgen responsive disease. We hypothesized that said combinations applied to subsets defined by early marker declines to androgen ablation would improve overall survival (OS) over historical data in unselected CRPC. **Methods:** In an open-label, phase II trial (NCT02703623), men with mCRPC received abiraterone and apalutamide (ABIpAPA; *Mod 1*). At week 8, patients had either a 'satisfactory' (S) decline in PSA (≥ 50% from baseline) and CTC (≤5/7.5mL) or 'unsatisfactory' (US). S patients (*Mod 2)* were randomized to continue ABIpAPA alone (*2A*) or with up to 4 cycles of ipilimumab (IPI, *2B*). US patients (*Mod 3)* continued ABIpAPA with up to 10 cycles of CABCARB. Thereafter patients continued ABIpAPA until progression. OS was calculated from entry into *Mod 2* or *3*. Based on historical data, the estimated median OS for men in *Mod 2* and *Mod 3* were 36 and 16 months respectively. **Results:** 195 men with CRPC were enrolled between May 2016 and August 2019. 128 (67%) were allocated to S of which 64 each were randomized to receive IPI vs. not. 3 went off study during *Mod 1* without clinical decline. Of 64 patients allocated to US, 59 were treated with CABCARB on study. Men in US were more likely to have had *de novo* metastasis (33% vs 59%, p < 0.001), RECIST measurable disease (23% vs 42%, p = 0.01), and liver metastases (3% vs 13%, p = 0.01). Differences in baseline circulating markers between the groups are shown in Table 1. Serious adverse events were reported for 3 (4.7%), 21 (33%), and 6 (10.2%) patients for M*od 2A, 2B,* and *3* respectively. One death due to neutropenic sepsis occurred in *Mod 3*. At a median follow-up of 48 months, the median (95% CI) OS in *Mod2A* was 44.3 (38.1, 47.7) months, 41.4 (33.3 months, not reached) in *Mod 2B*, and 18.7 (14.3, 36.3) months in *Mod 3*. **Conclusions:** These data substantiate the impact of underlying biology on CRPC patient outcomes and the urgent need for biomarkers that can enable the development of therapies specific to each subset. Correlative studies to identify said biomarkers will be presented. Clinical trial information: NCT02703623. Research Sponsor: Janssen, BMS, Sanofi.

5060 **Poster Session**

Health-related quality of life (HRQoL) and pain in the MAGNITUDE study of niraparib (NIRA) with abiraterone acetate and prednisone (AAP) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) and homologous recombination repair (HRR) gene alterations. *First Author: Dana E. Rathkopf, Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine, New York, NY*

Background: Results from the international, randomized, double-blind, phase 3 MAGNITUDE study demonstrated that NIRA + AAP improved radiographic progression-free survival, time to cytotoxic chemotherapy, and time to symptomatic progression, with manageable toxicity in pts with mCRPC and HRR alterations (9-gene panel). Here, we report HRQoL and pain in MAGNITUDE. **Methods**: Eligible pts with mCRPC and HRR alterations were randomized 1:1 to NIRA + AAP or placebo (PBO) + AAP orally daily in 28-day cycles. Pts had ECOG status ≤1 and a Brief Pain Inventory–Short Form (BPI-SF) worst pain score ≤3 in prescreening. HRQoL assessments on day 1 of specified cycles included Functional Assessment of Cancer Therapy–Prostate (FACT-P) and BPI-SF. Changes from baseline were compared between treatment arms using repeated measures analysis. Proportional hazards regression models were used to compare time to deterioration (TTD) in worst pain intensity between arms. **Results**: Compliance for FACT-P and BPI-SF was > 80%. Most pts maintained low pain levels over time. Repeated measures analyses showed no clinically meaningful differences in pain over time or between arms. Median TTD in pain intensity was not reached in either arm. At the 25th percentile, there was a trend toward longer TTD in pain intensity with NIRA + AAP vs PBO + AAP (11.1 vs 10.1 mo; HR, 0.87; 95% CI, 0.61-1.24). HRQoL was maintained with NIRA + AAP, with no clinically meaningful differences in FACT-P total score over time or between arms. There was a trend toward greater worsening in early cycles on FACT-P physical wellbeing with NIRA + AAP vs PBO + AAP, driven by events within the known safety profile of NIRA + AAP (worsening of side effect bother, lack of energy, and nausea); however, overall, most pts reported minimal side effect burden (Table). **Conclusions**: In MAGNITUDE, most pts maintained low pain levels and positive HRQoL over time, with no clinically meaningful differences between treatment arms, further supporting the use of NIRA + AAP in pts with mCRPC and HRR alterations. Side effect burden was perceived as low in both arms. Although more pts on NIRA+AAP reported worsening side effects, the symptoms were generally perceived as mild. Clinical trial information: NCT03748641. Research Sponsor: Janssen Research & Development, LLC.

	Change from baseline				Response of "not at all" or "a little bit" on respective items across cycles	
	Improved/stable		Worsened			
FACT-P item median (range), %	NIRA + AAP	PBO + AAP	NIRA + AAP	PBO + AAP	NIRA + AAP	PBO + AAP
Side effect bother	68.6 (60.8-74.1)	79.7 (74.0-86.5)	31.5 (25.8-39.2)	20.4 (13.5-26.0)	85.4 (81.5-90.8)	92.2 (89.1-94.1)
Lack of energy	67.4 (56.4-75.0)	75.2 (66.7-82.2)	32.6 (25.0-43.6)	24.8 (17.8-33.3)	65.5 (56.4-71.4)	75.9 (69.2-79.0)
Nausea	80.8 (73.2-90.2)	90.9 (88.0-93.1)	19.3 (9.7-26.9)	9.2 (6.9-12.0)	93.9 (89.1-95.9)	96.8 (94.7-100.0)

5061 **Poster Session**

Comparing pretest video genetic education for prostate cancer patients: Do patients need assistance? *First Author: Samantha Greenberg, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT*

Background: Expanded germline genetic testing recommendations for individuals with prostate cancer (PCa) have resulted in increased demand for pre-test genetic education. As a result, alternative service delivery models in genetic counseling (GC) have been suggested. Previous research has shown no difference in genetic testing uptake when video genetic education (VGE) is used rather than face-to-face counseling. However, data is limited when evaluating how VGE is delivered to patients. This study aimed to evaluate the impact of pre-test VGE on genetic testing uptake when facilitated by a GC assistant or self-completed by the patient. **Methods:** PCa patients referred for GC were contacted for pre-test VGE. Patients were randomized to undergo VGE with a GC assistant via Zoom (assistant-led) or perform VGE on their own via email instructions (patient-led). Assistant-led VGE was scheduled via standard of care, and patient-led VGE involved electronic and phone contact. In both arms, pre-test VGE included administrating family history collection via electronic software and viewing of informational genetics video. VGE completion and genetic testing uptake was the primary outcome measured for all participants. Initial pilot data was presented previously. This analysis represents the entire study period outcome. Data analysis used t-test, Fisher's exact and chi square. **Results:** From 10/1/2020-12/31/2021, 266 PCa patients were referred. In total, 254 were randomized, with 130 in the assistant-led intervention and 124 randomized to the patient-led arm. Technological limitations, loss to follow up, and procedural withdrawals resulted in 41 (31.5%) patients in the assistant-led arm and 65 (52.4%) in the self-led arm. The primary reason for discontinuing the process was lack of patient response to contact to schedule their genetics visit (n = 109, 35 patient-led, 74 assistant-led). There was significantly more loss to follow up in the assistant-led arm versus the self-led arm (p < 0.001). Of those who completed VGE, the median age was 66 years, with no difference between the two arms (p = 0.66). Participants primary identified as white (n = 96, 91%) and non-Hispanic (n = 100, 94%). There was no difference in uptake of genetic testing (p = 0.09) between patient and assistant led VGE. **Conclusions:** A randomized intervention suggests no difference in genetic testing uptake when pre-test VGE occurs with an assistant or is patient-led. Analyses of satisfaction, decision conflict, and knowledge are needed to evaluate if patient-led VGE is a suitable alternative to GC. Loss to follow up given standard of care scheduling approaches for assistant-led VGE suggests pre-test VGE may be better delivered during oncology visits. Additional evaluation of the facilitators and barriers, in addition to larger multi-center studies, are required to consider patient-led pre-test VGE as a primary method of pretesting genetic education. Research Sponsor: Huntsman Cancer Institute GU Cancer Center.

5062 **Poster Session**

Epidemiology and racial differences of prostate cancer clinical states. *First Author: Shannon R. Stock, Department of Surgery, Durham Veterans Affairs Health Care System, Durham, NC*

Background: There is a lack of data on the incidence rates (IRs) and racial differences in advanced prostate cancer (PC) clinical states. This is the first study to evaluate PC IRs among Black and White men in the Veterans Affairs Healthcare System (VAHCS) in the following clinical states: non-metastatic hormone-sensitive PC (nmHSPC); de novo metastatic HSPC (mHSPC); non-metastatic castration-resistant PC (nmCRPC); metastatic CRPC (mCRPC). **Methods:** This retrospective cohort study included adult Black and White men who were active users of the VAHCS, having ≥ two visits at VA centers over any 18-month interval during the study period (2012-2019). PC was identified by ≥ two ICD codes for PC on separate dates. Metastatic status was identified by an algorithm of ICD codes and common treatments for metastatic PC. Castrate resistant status was determined based on rising PSA during periods of continuous androgen deprivation therapy. Annual IRs for each clinical state and rate ratios (RR) for race were standardized using age and race-specific population estimates from the U.S. Census. The joinpoint regression software 4.9.0.0 was used to evaluate trends and identify change points in IRs over time. **Results:** 2019 IRs (per 100K person-years) and 95% confidence intervals among Black and White men respectively by clinical state were 453.0 (441.2, 464.7) and 205.3 (201.5, 209.1) (nmHSPC); 33.7 (30.4, 37.0) and 15.1 (14.1, 16.0) (mHSPC); 23.4 (21.0, 25.9) and 8.5 (7.8, 9.1) (nmCRPC); and 49.1 (45.5, 52.8) and 19.4 (18.4, 20.3) (mCRPC). The RR for all clinical states was significantly higher for Black vs. White men (all p < 0.0001): 2.2 (nmHSPC and mHSPC), 2.8 (nmCRPC), and 2.5 (mCRPC). Although IRs varied over time, these RRs were consistent across time. Trends in IRs over time were also consistent by race. From 2012, the IRs for nmHSPC declined to a nadir in 2016 (annual percent change (APC) -9.1%) and then increased through 2019 (APC = 3.1%). IRs for mHSPC increased throughout the study period (APC = 10.6%). IRs for nmCRPC decreased from 2012 to a nadir in 2014 (APC = -9.3%) and then increased through 2019 (APC = 3.8%). IRs for mCRPC increased from 2012 to 2016 (APC = 7.7%) and then leveled off through 2019 (APC = -0.2%). **Conclusions:** Our findings provide novel and comprehensive data on IRs across prostate cancer clinical states by race and over time within the VAHCS. Despite the VAHCS providing an environment of relatively equal access to care, Black men experience a disproportionate burden of PC with IRs over 2-fold higher for all clinical states relative to White men. This highlights that resolving access to care alone is unlikely to fully eliminate PC racial differences and that there are other multifactorial issues to address. The temporal trends for nmHSPC observed in our study, including the nadir in 2016, are consistent with the timing of the 2012 US Preventive Services Task Force guidelines advising against PSA screening and the subsequent draft reversal in 2017. Research Sponsor: Merck & Co., Inc., Kenilworth, NJ, USA.

5063 **Poster Session**

Association of *RB1* mutational status with overall genomic landscape in neuroendocrine prostate cancer (NEPC). *First Author: Petros Grivas, University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: NEPC is a high-grade aggressive form of prostate cancer. We queried whether *RB1* mutation status would impact the genomic features of NEPC in *RB1* mutated vs non-mutated cases. **Methods:** From a series of 13,496 cases of clinically advanced PC, we identified 415 cases (3.1%) with a diagnosis of small cell PC or NEPC as determined by the submitting physician. They were sequenced using a hybrid capture-based FDA-approved clinical genomic profiling (CGP) assay to detect all classes of genomic alterations (GA). Tumor mutational burden (TMB) was determined on 0.8 Mbp of sequenced DNA and microsatellite instability (MSI) was determined on 95 loci. PD-L1 expression was determined by IHC (Dako 22C3) with low tumor cell positive staining 1-49% and high staining ≥50% expression. **Results:** 253 (61%) of NEPC feature GA in *RB1* (RB1 mut+). This contrasts with a 5.8% frequency of *RB1* GA in the non-NEPC (P < .0001). The *RB1* mut+ NEPC featured a slightly greater number of pathogenic GA/tumor than the *RB1* mut- NEPC (5.1 vs 4.2). Age and *TMPRSS2-ERG* fusion frequency were similar between the groups. *RB1* Mut- NEPC was associated with significantly higher amplifications (amp) and total GA in *AR* compared to *RB1* mut+ NEPC. *RB1* mut+ NEPC featured significantly greater frequency of *PTEN* GA. GA frequencies in targetable kinases and DNA repair GA including *BRCA1/2* and *ATM* linked to PARP inhibitor (PARPi) response were similar in both groups. For potential immune-oncology (IO) biomarkers, *RB1* Mut+ NEPC featured significantly greater frequency of positive PD-L1 expression and lower frequencies of *MDM2* and *CDK12* GA. *CD274* (*PD-L1*) amplification, MSI-high status and cases with TMB ≥10 mut/Mb were uncommon in both groups. gLOH was higher in RB1 mut+ than *RB1* mut- (P = .005). There were more cases of non-European ancestry in the *RB1* mut- group. APC I1307K mut were found in 3/162 (1.9%) *RB1* mut- NEPC only. **Conclusions:** In NEPC, the presence of *RB1* mutation is associated with various GA that may have clinical relevance. Further study of *RB1* status as a guide in trial designs on therapy selection for men with NEPC appears warranted. Research Sponsor: Foundation Medicine Inc.

NEPC	RB1 mut+ (253 cases)	RB1 mut- (162 cases)	P Value
AR	5.1%	14.2%	0.002
TP53	68.0%	58.0%	0.02
PTEN	43.1%	25.9%	0.0004
PIK3CA	5.5%	4.9%	NS
gLOH	10.91%	9.08%	.005
MSI High/TMB≥10mut/Mb	1.6%	1.9%	NS
TMB≥10/20 mut/Mb	8.6%/3.0%	6.0%/2.0%	NS
PD-L1 Low/High Positive	28.6%/4.7% (64 cases)	6%/4.1% (49 cases)	0.003

5064 **Poster Session**

Overall survival (OS) and biomarker results from combat: A phase 2 study of bipolar androgen therapy (BAT) plus nivolumab for patients with metastatic castrate-resistant prostate cancer (mCRPC). *First Author: Mark Christopher Markowski, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD*

Background: During BAT, intramuscular (IM) administration of testosterone (T) results in rapid cycling of serum T from supraphysiologic to near-castrate levels in men with mCRPC. In a retrospective study, clinical responses to immune checkpoint blockade (ICB) in mCRPC patients (pts) previously treated with BAT were observed. Here, we report the OS and biomarker results of a Phase 2 study in mCRPC pts treated with BAT in combination with nivolumab (COMBAT; NCT03554317). **Methods:** This was a multi-center, single arm, open label Phase 2 study in mCRPC pts who received T cypionate 400mg IM (BAT) every 28 days plus nivolumab 480mg IV every 28 days. Pts initially received BAT alone for a 12-week period, prior to the addition of nivolumab. Eligible pts were those with asymptomatic mCRPC who had soft tissue metastases amenable to biopsy, and who progressed on at least one prior novel AR targeted therapy (and up to one prior chemo for mCRPC). The primary endpoint was confirmed PSA_{50} response. OS and radiographic progression free survival (rPFS) were key secondary endpoints. All pts underwent baseline metastatic biopsies, and 24 had a second biopsy after 12 weeks of BAT. Semi-quantitative IHC (for AR, Ki67, MYC, PTEN, TP53, RB1) was performed on 24 paired biopsies, of which 15 pairs were also evaluable for RNA (whole transcriptome) sequencing. **Results:** 45 pts were enrolled. As previously reported, the PSA_{50} response was 40% (18/45, 95% CI: 26-56%, P=0.02 against the 25% null hypothesis), and median rPFS was 5.6 (95% CI: 4.4–6.0) months. After a median follow-up of 17.8 months, the median OS was 27.8 (95%% CI: 17.6–NR) months. In 24 pts with paired biopsies prior to administration of nivolumab, BAT significantly decreased median MYC (P=0.046) and Ki-67 (P=0.030) expression by IHC. 71% (17/24) of pts had any decrease in MYC following BAT, with 29% (7/24) having a >50% decrease. A >50% MYC protein decline was associated with longer rPFS (HR 0.33, 95%CI 0.14–0.78, P=0.005) and a nonsignificant association towards longer OS (HR 0.78, 95%CI 0.24–2.48, P=0.679). MYC protein and mRNA levels were tightly intercorrelated (r=0.65, P<0.001). Both rPFS and OS were numerically longer in pts with >50% declines in MYC mRNA levels (P>0.1 for both). **Conclusions:** BAT combined with nivolumab led to a median overall survival of >2 years in heavily pretreated mCRPC pts. BAT attenuated MYC expression, correlating with better outcomes. Clinical trial information: NCT03554317. Research Sponsor: Bristol Myers Squibb, Other Foundation, Other Government Agency.

5065 **Poster Session**

Reasons for oncologist and urologist treatment choice in metastatic castration-sensitive prostate cancer (mCSPC): A physician survey linked to patient chart reviews in the United States. *First Author: Stephen J. Freedland, Division of Urology, Department of Surgery, Cedars-Sinai Medical Center and Department of Surgery, Durham Veterans Affairs Health Care System, Durham, NC*

Background: Based on level 1 evidence of overall survival, ASCO/NCCN/AUA guidelines uniformly recommend novel hormonal therapy (NHT) or chemotherapy (CHT) added to androgen deprivation therapy (ADT) as standard of care in mCSPC. However, real-world evidence across US healthcare systems suggests most patients receive ADT +/- first generation non-steroidal antiandrogens (NSAA). Reasons behind the lack of treatment intensification (TI) in mCSPC have not been studied. **Methods:** Data from medical charts of patients initiating mCSPC treatment from Jul '18-Nov '21 were retrospectively extracted from multiple US academic/community practices. Oncologists and urologists who treated these patients were surveyed to provide reasons for treatment choices including prostate specific antigen (PSA) goals and explicit reasons for not prescribing NHT. Descriptive statistics (Fishers exact tests) were used to compare outcomes between groups; p-values for odds ratios (OR) were generated via Wald test. **Results:** 65 oncologists and 42 urologists provided data on 621 patients. Median age at initial mCSPC treatment start was 68.0 years, 58% were White, 25% Black, 84% had de novo metastases, 30% had high-volume disease including 22% with visceral metastases, and 83% had ECOG PS score ≤1. In the first-line (1L) setting, most mCSPC patients received ADT±NSAA alone (69%), while TI rates with ADT+NHT (26%) or ADT+CHT (4%) were low. An additional 27% (n = 166/621) received subsequent TI while still castration-sensitive. According to the physician survey, the top 5 reasons why their patients did not receive initial NHT were perceptions about: drug tolerability (38%), lack of clinical trial evidence of overall survival improvement (31%), lack of reimbursement (26%), patient financial constraints (20%), and questions about sequencing NHTs earlier vs later in disease (21%). Regarding treatment goals for PSA response, physicians more frequently reported a relative (%) reduction than an absolute PSA reduction (85% vs 51%). Oncologists considered a median PSA reduction of 50% (IQR 25-75) adequate vs 75% (IQR 50-90) among urologists. Urologists had higher rates of TI at 1L and/or subsequent treatment in patients who were still castration-sensitive (p < 0.01). Physicians who aimed for deeper PSA reduction of 75-100% were more likely (OR = 1.63; p = 0.034) to provide TI in 1L compared with physicians with less aggressive PSA goals (0-49%). **Conclusions:** To our knowledge, this is the first study identifying reasons for underutilization of intensified treatment in mCSPC. While survey results suggest perceptions of tolerability and lack of efficacy and financial considerations affect NHT use, in practice, non-guideline driven PSA reduction goals are associated with low rates of TI. These results demonstrate the need for further medical education. Research Sponsor: Pfizer and Astellas Pharma.

5066 **Poster Session**

Genomic aberrations associated with overall survival (OS) in metastatic castration-sensitive prostate cancer (mCSPC) treated with apalutamide (APA) or placebo (PBO) plus androgen deprivation therapy (ADT) in TITAN. *First Author: Neeraj Agarwal, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT*

Background: TITAN, a phase 3 PBO-controlled study in patients (pts) with mCSPC, showed APA + ADT improved radiographic progression-free survival and OS vs PBO + ADT. In this exploratory analysis, we report the relationships between biomarkers and OS in TITAN. **Methods:** Circulating tumor (ct)DNA and genomic aberrations in 17 PC-related genes, including androgen receptor (AR), were assessed at baseline (BL; 114 pts) and end of study treatment (EOST; 129 pts) using next-generation sequencing. ctDNA was assessed qualitatively; genomic aberrations were assessed within ctDNA-positive samples as inactivation (heterozygous/homozygous deletion or single nucleotide variant [SNV]) or activation (amplification or SNV). Associations of detected ctDNA/aberrations at BL or EOST with OS, and biomarkers at EOST with OS on subsequent therapies, were evaluated using univariate or multivariate analyses and Cox proportional hazards model; results were stratified by treatment arm. **Results:** Among pts from both treatment groups, 36% had detectable ctDNA, of which 27% had any genomic *AR* aberration and 24% had *AR* gene amplification at BL; prevalence of these biomarkers increased significantly from BL to EOST (Table). The most prevalent non-AR aberrations at BL (*TP53*, homologous recombination repair [HRR] pathway, *PTEN, RB1*, and *PIK3CA* genes) increased at EOST but not significantly (Table). Among assessed aberrations, presence of ctDNA or any *AR* genomic aberrations at BL (HR, 1.9 or 6.7; all p < 0.05) and any *AR* genomic aberrations or PI3K pathway activation at EOST (1.7, p < 0.05 or 2.2, p < 0.001) was significantly associated with poor OS in multivariate analyses from both treatment groups. In univariate analyses of pts who received subsequent therapy (chemotherapy: 106; hormonal therapy: 161), worse OS was associated only with *PIK3CA* activation, PI3K pathway activation, or *TP53* inactivation at EOST (3.7, p < 0.05; 2.4, p < 0.05; 3.0, p < 0.01, respectively) in chemo-treated pts. A small sample size in some biomarker subgroups limits interpretation. **Conclusions:** These hypothesis-generating data from TITAN show that presence of ctDNA or select AR and non-AR biomarkers at BL or EOST were associated with poor OS. The predictive value of these biomarkers for survival in mCSPC needs further confirmation. Clinical trial information: NCT02489318. Research Sponsor: Janssen Research & Development.

Aberrations with ≥ 15% prevalence at BL from both treatment groups	BL, n/n (%)	EOST, n/n (%)	Pearson's X^2 p value[d]
ctDNA	41/114 (36)	97/129 (75)	< 0.001
Any genomic *AR* aberration	11/41 (27)	65/97 (67)	< 0.001
AR amplification	10/41 (24)	61/97 (63)	< 0.001
TP53[a]	17/41 (41)	52/97 (54)	0.2
HRR pathway[a,c]	9/41 (22)	26/97 (27)	0.5
RB1[a]	8/41 (20)	32/97 (33)	0.11
PTEN[a]	8/41 (20)	31/97 (32)	0.14
PIK3CA[b]	6/41 (15)	29/97 (30)	0.06

[a]Inactivation.
[b]Activation.
[c]Includes: *BRCA1, BRCA2, FANCA, BRIP1, HDAC2, CDK12, ATM, PALB2,* and *CHEK2.*
[d]EOST vs BL.

5067 **Poster Session**

Feasibility of a novel wrist-worn thermal device for management of vasomotor symptoms in patients with prostate cancer. *First Author: Alicia K. Morgans, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*

Background: Vasomotor symptoms (VMS), or hot flashes, are a common side effect of androgen deprivation therapy (ADT) for prostate cancer (PCa). VMS negatively impact sleep, fatigue, and quality of life (QOL) in PCa survivors. There are few nonpharmacological treatments for VMS. The Embr Wave is a wearable thermal device that applies cooling to thermoreceptors on the inside of the wrist and has been associated with patient reported decreases in hot flash interference in women. We performed a single-arm feasibility study evaluating the Embr Wave for management of VMS in PCa survivors. **Methods:** 57 PCa survivors reporting bothersome hot flashes were enrolled and instructed to use the device as needed for VMS during the 4-week study. The primary outcome was device usage recorded by the device (minutes and sessions). Additional outcomes included the change in patient reported Hot Flash Related Daily Interference Scale (HFRDIS, range 0-10) and Patient Reported Outcomes Measurement Information System Sleep Disturbance 4a (PROMIS SD, range 0-100) and Sleep Related Impairment 8a (PROMIS SRI, range 0-100). Study procedures were conducted remotely using a virtual clinical trial management platform. **Results:** The study was conducted from May to Dec 2021 in the US. 44 men completed the study; 39 had retrievable usage data. Median age was 66 (range 57-78) years and median 3 (1-23) years since PCa diagnosis. The most common hormonal treatments were leuprolide (n=22), abiraterone (n=13), and enzalutamide (n=6). Baseline scores indicated moderate hot flash interference and mild sleep disturbance (Table). Mean±SD (median) usage of the Embr device was 3.2±2.5 (2.3) hours and 7.6±3.6 (7.5) sessions per day. 26 (67%) participants reported using the device 7 days/nights each week. Improvements were observed in HFRDIS, PROMIS SD, and PROMIS SRI scores (Table). There were also improvements in subjective ratings of hot flash frequency, duration, interference with daily life/sleep, bothersomeness and control (all p<0.01). The majority (69%) of participants reported that the device was effective at helping them manage hot flashes. No adverse events were reported. **Conclusions:** Results of this study support the feasibility of use of the thermal device for management of bothersome hot flashes in PCa survivors. Future randomized controlled studies are warranted to evaluate patient reported outcomes related to frequency and severity of VMS, sleep quality, fatigue, and overall QOL, in addition to defining the potential utility of the Embr thermal device in PCa survivors experiencing VMS. Clinical trial information: NCT04892914. Research Sponsor: Embr Labs.

Measure	Baseline	Week 4	Change
HFRDIS, mean [95% CI]	4.3 [3.7, 4.9]	3.2 [2.6, 3.8]	-1.1 [-1.6, -0.6] p<0.001
PROMIS SD T-score, mean [95% CI]	56 [54, 58]	50 [48, 53]	-6.0 [-8.0, -4.0] p<0.001
PROMIS SRI T-score, mean [95% CI]	57 [54, 60]	51 [48, 54]	-5.5 [-8.0, -3.1] p<0.001

5068 **Poster Session**

A pilot trial of neoantigen DNA vaccine in combination with nivolumab/ipilimumab and prostvac in metastatic hormone-sensitive prostate cancer (mHSPC). *First Author: Koral Shah, Washington University School of Medicine, Saint Louis, MO*

Background: Treatment with immune checkpoint blockade (ICB) alone results in suboptimal response rates in prostate cancer. Prostvac-VF Tricom is a therapeutic vaccine that incorporates DNA for the shared self-antigen PSA. Personalized neoantigen vaccines based on specific mutated epitopes may have the ability to overcome immunoresistance seen with self-antigens. Even in low mutational burden tumors like prostate cancer, T cell responses against neoantigens have been correlated with favorable clinical outcomes. Thus, we hypothesized that the combination of shared antigen and neoantigen vaccines with dual ICB will induce robust immune responses and improve clinical outcomes. **Methods:** This Phase I clinical trial (NCT03532217) enrolled patients from 2018-2021. Eligible patients had histologically confirmed high risk mHSPC, must have completed a course of docetaxel and received continuous androgen deprivation therapy. Patients were treated with Prostvac-VF in combination with ipilimumab/nivolumab within 60 days of the last docetaxel dose. Then, patients were continued on monthly nivolumab with their personalized neoantigen vaccine administered via intramuscular electroporation. The primary objectives of this study were to assess the feasibility, safety/tolerability, and immune responses of this combination strategy. Key secondary objectives include failure free survival, milestone overall survival (OS), PSA responses, and radiographic progression free survival. **Results:** Nineteen patients were enrolled and treated on trial, and feasibility was shown with 15 (79%) receiving neoantigen vaccines. Four patients did not receive neoantigen vaccines (2 for progressive disease, 2 for ICB toxicity). Treatment was well-tolerated with only 2 (2.4%) grade 3 treatment related adverse events (TRAEs) of colitis, and no grade 4+ TRAEs. The common grade 1-2 TRAEs were diarrhea (10%), injection site reactions (10%), rash (7.4%), and fatigue (6%). Median follow-up to date is 22.6 (11.3-39.6) months, with median OS not yet reached and 2 year milestone OS of 75%. Six (31.5%) patients had PSA progression per PCWG2 criteria while on treatment, with the median time to PSA progression not yet reached for the total population. Increases in activation/co-stimulatory/co-inhibitory seen after treatment with Prostvac/ICB, suggest immune priming. Sample collection is complete and immune correlative analyses are ongoing. Final safety/tolerability and preliminary correlative and clinical outcomes will be reported. **Conclusions:** This is the first clinical trial evaluating the use of personalized neoantigen vaccines in a combination immunotherapeutic approach in mHSPC patients. Clinical trial information: NCT03532217. Research Sponsor: Prostate Cancer Foundation, Other Foundation.

5069 **Poster Session**

Clinical outcomes and safety of enzalutamide (ENZA) plus androgen-deprivation therapy (ADT) in metastatic hormone-sensitive prostate cancer (mHSPC) in patients aged < 75 and ≥ 75 years: ARCHES post hoc analysis. *First Author: Russell Zelig Szmulewitz, The University of Chicago, Chicago, IL*

Background: Patients with metastatic prostate cancer aged ≥75 years have a poorer prognosis compared with younger patients. In ARCHES (NCT02677896), ENZA + ADT improved radiographic progression-free survival (rPFS), overall survival (OS), and other key secondary endpoints vs. placebo (PBO) + ADT in patients with mHSPC. Final OS results confirmed a long-term survival benefit with ENZA + ADT. This *post hoc* analysis of ARCHES data investigated OS and other clinical outcomes in patients aged <75 and ≥75 years. **Methods**: Patients with mHSPC (n=1150) were randomized 1:1 to ENZA (160 mg/day) + ADT or PBO + ADT, stratified by disease volume and prior docetaxel use. Subgroup analysis was performed in patients aged <75 and ≥75 years. Efficacy and safety outcomes were compared across treatment arms. **Results**: Of the ARCHES population, 339 patients (29.5%) were aged ≥75 years (ENZA + ADT, n=170; PBO + ADT, n=169); PBO patients crossing over to ENZA were aged: <75 years, n=133; ≥75 years, n=47. Some differences in baseline characteristics were observed between age groups, such as higher prior docetaxel use in patients aged <75 years (ENZA + ADT, 21.0%; PBO + ADT, 20.4%) vs. those aged ≥75 years (ENZA + ADT, 10.6%; PBO + ADT, 11.2%). When compared to PBO + ADT, ENZA + ADT improved OS and other secondary efficacy endpoints in both age groups without evidence of statistical heterogeneity (Table); however, 95% confidence intervals for OS and rPFS hazard ratios spanned 1 in the older age group. The safety profile of treatment arms was generally similar in both age groups, with a higher incidence of falls, cognitive impairment, and cardiovascular events among elderly patients receiving ENZA + ADT vs. PBO + ADT. **Conclusions**: This *post hoc* analysis of ARCHES data demonstrated that ENZA + ADT provides clinical benefit and is generally well-tolerated in patients with mHSPC aged ≥75 years, supporting the therapeutic role of ENZA in these patients. Clinical trial information: NCT02677896. Research Sponsor: Astellas Pharma Inc. and Pfizer Inc.

Clinical outcomes in patients aged <75 and ≥75 years.

Median time to event, months (95% CI)	<75 years ENZA + ADT (n=404)	<75 years PBO + ADT (n=407)	<75 years HR (95% CI)[a]	≥75 years ENZA + ADT (n=170)	≥75 years PBO + ADT (n=169)	≥75 years HR (95% CI)
OS	NR (54.2, NR)	NR (50.3, NR)	0.61 (0.47, 0.79)	NR (48.8, NR)	49.7 (43.1, NR)	0.76 (0.54, 1.09)
rPFS	NR (47.3, NR)	38.9 (25.0, NR)	0.60 (0.48, 0.75)	48.6 (38.1, NR)	43.1 (19.4, NR)	0.72 (0.52, 1.02)
First symptomatic skeletal event	NR (51.8, NR)	NR (NR, NR)	0.49 (0.35, 0.69)	NR (50.7, NR)	NR (46.4, NR)	0.48 (0.27, 0.86)
Castration resistance	NR (49.8, NR)	13.8 (11.1, 16.5)	0.36 (0.29, 0.44)	48.6 (36.4, NR)	19.1 (13.8, 46.9)	0.53 (0.38, 0.74)
Prostate-specific antigen progression	NR (NR, NR)	16.6 (13.9, 19.5)	0.27 (0.21, 0.35)	NR (NR, NR)	NR (14.8, NR)	0.34 (0.22, 0.53)

[a]HR <1 favors ENZA + ADT; HR >1 favors PBO + ADT. Results not adjusted for crossover.
CI=confidence interval; HR=hazard ratio; NR=not reached.

5070 **Poster Session**

Defining more precisely the effects of docetaxel plus ADT for men with mHSPC: Meta-analysis of individual participant data from randomized trials. *First Author: Claire Vale, MRC Clinical Trials Unit at UCL, London, United Kingdom*

Background: Adding docetaxel to androgen deprivation therapy(ADT) improves survival in metastatic, hormone-sensitive prostate cancer (mHSPC), but uncertainty remains about who benefits most. To investigate this thoroughly and reliably, the STOPCAP M1 collaborationconducted a meta-analysis of individual participant data (IPD) from relevant trials. **Methods:** Methods were included in a registered protocol (CRD42019140591). Updated IPD from the GETUG-15, CHAARTED and STAMPEDE trials were harmonised and checked. The main outcomes were overall survival (OS), progression-free survival (PFS) and failure-free survival (FFS). Overall pooled effects were estimated using intention-to-treat, 2-stage, fixed-effect meta-analysis, adjusted for age, PSA, Gleason sum score, performance status, and timing of metastatic disease (missing covariate values imputed), with 1-stage and random-effects sensitivity analyses. We assessed subgroup effects using 2-stage, fixed-effect meta-analysis of within-trial interactions, adjusted for the same covariates. We based these on PFS to maximise power, and OS whenever interactions were found. To explore multiple subgroup interactions, and to derive subgroup-specific absolute treatment effects, we used 1-stage, flexible parametric modelling and standardisation. **Results:** We obtained IPD for all 2261 men randomised, with median FU of 6 years (all patients). There were clear relative benefits of docetaxel on OS (HR = 0.79, 95% CI 0.70 to 0.88, p<0.0001), PFS (HR = 0.70, 95% CI 0.63 to 0.77, p<0.0001) and FFS (HR = 0.64, 95% CI 0.58 to 0.71, p<0.0001). With evidence of non-proportional hazards, we also estimated 5-year absolute differences: OS 10% (95% CI 6 to 15%), PFS 9% (95% CI 5 to 13%) and FFS 9% (95% CI 6 to 12%). The relative effect of docetaxel on PFS differed by volume of metastases (interaction p=0.027; *high volume* HR = 0.60, 95% CI 0.52 to 0.68; *low volume* HR = 0.78, 95% CI 0.64 to 0.94), and timing of metastatic disease (interaction p=0.077; *synchronous* HR = 0.67, 95% CI 0.60 to 0.75; *metachronous* HR = 0.89, 95% CI 0.67 to 1.18). OS results were similar. When metastatic disease volume and timing were combined, docetaxel appeared to improve PFS and OS for all men, except those with low volume, metachronous disease (Table). **Conclusions:** This IPD meta-analysis provides the most detailed assessment of the effects of docetaxel for mHSPC, and suggests that men with low volume, metachronous disease should be managed differently to those with other types of metastatic disease. Research Sponsor: Prostate Cancer UK; UK Medical Research Council.

Volume & timing of metastatic disease	Absolute effect (95% CI) at 5 years I Change from baseline			
	PFS		OS	
High volume, synchronous	10% (6 to 14%)	10 → 20%	11% (6 to 16%)	25 → 36%
High volume, metachronous	10% (-2 to 22%)	20 → 30%	8% (-6 to 23%)	35 → 43%
Low volume, synchronous	7% (0 to 14%)	40 → 47%	6% (-1 to 13%)	55 → 61%
Low volume, metachronous	-3% (-14 to 9%)	50 → 47%	-1% (-12 to 10%)	70 → 69%

5071 **Poster Session**

Bone biomarkers and overall survival (OS) in men with advanced hormone-sensitive prostate cancer (HSPC): Results from SWOG S1216, a phase III trial of ADT +/- orteronel.

First Author: Primo "Lucky" N. Lara, University of California, Sacramento, CA

Background: Circulating bone biomarkers (BB) are strongly prognostic for OS in castration-resistant PC (CRPC). We prospectively evaluated BB in men with HSPC in S1216, a trial that established new OS benchmarks. We sought to identify patient (pt) subsets with differential OS outcomes as defined by BB. **Methods:** Markers of bone resorption [CTx;PYD] & formation [CICP;BAP] were assessed. Pts were randomly divided into training (1/3) & validation (2/3) sets. In the training set, recursive partitioning of OS was used to identify the ideal dichotomous cutpoint for each BB & for a combination of biomarker split points to define prognostic groups. In the validation set, Cox PH models were used to assess impact of BB on OS, adjusted for pt & tumor characteristics. Adjusted odds ratios for 3-year OS based on BB & baseline clinical factors were developed using logistic regression to estimate receiver operating characteristic (ROC) curves. **Results:** Of 1,279 men, 949 had baseline BB. Median age–68y; median PSA-28 ng/dL; Gleason>7: 60%; Zubrod PS 0/1-97%. Values of BB at the median & at cutpoints maximized for OS were identified. For 3 of the BB, the cutpoint was at the ~85th %ile; for PYD it was at the median. Recursive partitioning algorithms applied to the training set identified 4 groups with differential OS based on a dichotomous split of CTx in combination with additional CICP splits within each group. Hazard ratios (HR) for OS based on elevated BBs are shown. ROC analysis showed that only BAP & PYD had significantly higher AUC(0.73;0.74) compared to AUC of baseline clinical factors(0.71) w/ p=0.02 and 0.03 respectively. There was no evidence of BB x treatment interaction (all p>=0.2). **Conclusions:** In men initiating ADT for HSPC, elevated BB are strongly prognostic for worse OS. BB levels alone & in combination with pt/tumor characteristics identify unique subsets of men with high probability of being alive at 3 years from ADT initiation. These results validate the clinical value of BB in the HSPC state, extending BB utility beyond CRPC. Clinical trial information: NCT01809691. Research Sponsor: U.S. National Institutes of Health, Other Foundation, Pharmaceutical/Biotech Company.

Bone biomarkers (BB) and OS in validation set (N=633).

	Median OS, years	HR forElevated Markers*(95%CI)	p-value*^	AUC**
BB	Hi: 3.3	1.43 (1.02;2.01)	0.04	0.732
Bone Alkaline Phosphatase (BAP; U/L)	Lo: 6.8			
C-terminal collagen propeptide (CICP; ng/mL)	Hi: 2.4	1.93 (1.40;2.64)	<0.0001	0.723
	Lo: 7.6			
C-Telopeptide (CTx; ng/mL)	Hi: 4.0	1.37 (1.07;1.77)	0.01	0.723
	Lo: 7.7			
Pyridinoline (PYD; nmol/L)	Hi: 3.4	1.78 (1.40;2.27)	<0.0001	0.742
	Lo: 8.2			
BB Combination			0.0013	0.726
CTx <0.6 & CICP <161	8.2	1.00 (reference)		
CTx <0.6 & CICP >=161	5.1	1.55 (1.06;2.28)		
CTx >=0.6 & CICP <286	5.0	1.39 (1.04;1.85)		
CTx >=0.6 & CICP >286	2.1	2.12 (1.43;3.16)		

*Adjusted for treatment arm, disease extent, Zubrod PS, PSA, Gleason Score, age, Afr-Amer (Y/N), and visceral mets status; ^p-values from Wald Chi-Square test for Type 3 analysis of effects; ** from logistic model.

5072 **Poster Session**

Radiographic progression in the absence of prostate-specific antigen (PSA) progression in patients with metastatic hormone-sensitive prostate cancer (mHSPC): Post hoc analysis of ARCHES.

First Author: Andrew J. Armstrong, Duke Cancer Institute Center for Prostate and Urologic Cancers, Duke University School of Medicine, Durham, NC

Background: Enzalutamide (ENZA) + androgen deprivation therapy (ADT) significantly reduced the risk of radiographic progression and increased overall survival in men with mHSPC, regardless of baseline PSA levels (ARCHES; NCT02677896). This *post hoc* analysis investigated concordance between PSA progression and radiographic progression in patients with mHSPC. **Methods:** Patients with mHSPC (n=1150) were randomized 1:1 to ENZA (160 mg/day) + ADT or placebo (PBO) + ADT. The concordance between radiographic progression and PSA progression, as defined by Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria, and between any rise in PSA above nadir was assessed. **Results:** In total, 267/1150 patients in ARCHES had radiographic progression (ENZA + ADT, n=79; PBO + ADT, n=188). At radiographic progression, the median (range) PSA for ENZA + ADT-treated patients was 2.25 ng/mL (0–1062.3 ng/mL) and 17.47 ng/mL (0–1779.5 ng/mL) for PBO + ADT-treated patients. Most patients (67%) treated with ENZA + ADT did not have PCWG2-defined PSA progression at radiographic progression, compared with 57% of those treated with PBO + ADT (Table). The median absolute and percentage rise in PSA from nadir to radiographic progression was 0.77 ng/mL and 200%, respectively, with ENZA + ADT compared with 12.23 ng/mL and 367%, respectively, with PBO + ADT. **Conclusions:** In this *post hoc* analysis of ARCHES, we found frequent discordance between radiographic progression and PSA progression by PCWG2 criteria or any PSA rise over nadir in patients with mHSPC treated with ENZA + ADT. Thus, regular imaging is recommended to detect radiographic progression among patients treated with potent androgen receptor pathway inhibitors, such as ENZA + ADT, as serial PSA monitoring alone may not be sufficient to detect radiographic progression in many patients. Clinical trial information: NCT02677896. Research Sponsor: Astellas Pharma Inc., Pfizer Inc.

Concordance of radiographic progression and increasing PSA.

n (%)	ENZA + ADT (n=79)	PBO + ADT (n=188)
PSA progression[a] at time of radiographic progression[b]		
Yes	26 (32.9)	108 (57.4)
No	53 (67.1)	80 (42.6)
Any rise in PSA from nadir at time of radiographic progression[b]		
Yes	52 (65.8)	160 (85.1)
No	27 (34.2)	28 (14.9)

[a]PSA progression is defined as a ≥25% increase and an absolute increase of ≥2 ng/mL above the nadir, confirmed by a second consecutive value at least 3 weeks later; [b]Radiographic progression was assessed by independent central review or death (defined as death from any cause within 24 weeks from study drug discontinuation), whichever occurred first.

5073 **Poster Session**

Efficacy and safety of relugolix in men with advanced prostate cancer based on baseline body mass index (BMI): A subgroup analysis from the randomized, phase 3 HERO study versus leuprolide (LEU).

First Author: Fred Saad, University of Montréal Health Center, Montréal, QC, Canada

Background: BMI has been correlated with adverse prostate cancer outcomes, such as risk of biochemical failure, mortality and androgen deprivation therapy complications. Relugolix is a FDA-approved, once-daily oral GnRH receptor antagonist that has demonstrated superior continuous suppression of testosterone (T) to castrate levels through Week 48 compared to LEU (96.7% vs 88.8%, respectively; Shore N, NEJM 2020;382:2187) in men with advanced prostate cancer (APC). This HERO subgroup analysis looks at the impact of baseline BMI on efficacy and safety. **Methods:** HERO was a phase 3 randomized, open-label study to evaluate relugolix vs LEU in 930 men with APC. This analysis looked at all men enrolled and treated in the HERO study divided by baseline BMI (BMI subgroups: <25.0 [underweight and healthy weight]; 25.0 – 29.9 [overweight]; and >29.9 [obese]). Assessments included sustained T suppression to castrate levels (<50 ng/dL) from Day 29 through 48 weeks, early T suppression to castrate levels (Day 4 and Day 15), prostate specific antigen (PSA) response (>50% decrease from baseline) at Day 15 with confirmation at Day 29, and profound castration rate (<20 ng/dL) at Day 15. T recovery subset analysis was not included due to low patient numbers. All analyses performed were descriptive. **Results:** Of the 930 men (relugolix:622; LEU:308) treated in HERO, 287 (30.9%) men had BMI <25, 424 (45.6%) were 25 – 29.9, 219 (23.5%) were >29.9. Sustained castration rates through 48 weeks were higher for the relugolix group than the LEU group and results for select key secondary endpoints were generally consistent across BMI categories, although PSA response proportions were lower in obese patients (table). No differences were noted in the incidence or types of adverse events within treatment groups in the subgroups analyzed. **Conclusions:** In this HERO study subgroup analysis, relugolix demonstrated greater continuous T suppression than LEU regardless of baseline BMI. Although higher BMI has been associated with poorer outcomes, we did not observe a similar trend with T responses. A numerically lower PSA response was seen in obese patients. Additional research with longer follow-up is warranted. Clinical trial information: NCT03085095. Research Sponsor: Myovant Sciences GmbH, in collaboration with Pfizer, Inc.

Primary and select key secondary endpoints by BMI subgroup.

	Relugolix			Leuprolide		
	<25 (N = 198)	25 – 29.9 (N = 286)	>29.9 (N = 138)	<25 (N = 89)	25 – 29.9 (N = 138)	>29.9 (N = 81)
Sustained T suppression to <50 ng/dL from D 29 to 48 weeks - %	96.4	97.2	96.3	81.9	94.2	87.3
Cumulative probability of T suppression to <50 ng/dL on D 4 - %	52.8	59.8	52.9	0	0	0
Cumulative probability of T suppression to <50 ng/dL on D 15 - %	98.5	98.6	99.3	9.0	13.1	13.6
Proportion of patients with PSA response at D 15 followed with confirmation at D 29 - %	82.3	80.1	76.8	22.5	23.9	11.1
Cumulative probability of profound T suppression to <20 ng/dL on D 15 - %	75.5	80.4	78.3	0	1.5	1.2

5074 **Poster Session**

Prevalence of DNA damage repair (DDR) alterations in patients with metastatic hormone-sensitive prostate cancer (mHSPC) receiving enzalutamide (ENZA) or placebo (PBO) plus androgen deprivation therapy (ADT): ARCHES post hoc analysis.

First Author: Arun Azad, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

Background: DDR alterations are associated with poorer prognosis, including shorter overall survival (OS), in patients with mHSPC. In ARCHES (NCT02677896), patients with mHSPC treated with ENZA + ADT had a reduced risk of radiographic progression or death and improved OS versus PBO + ADT. This *post hoc* analysis assessed the prevalence of DDR alterations and associated baseline characteristics in patients with mHSPC in ARCHES. **Methods**: Patients with mHSPC (n=1150) were randomized 1:1 to ENZA (160 mg/day) + ADT or PBO + ADT. Germline DDR alteration testing was performed in blood using Ambry Genetics CustomNext-Cancer panel; 16 DDR-related genes were reported in the subset of patients who consented to participate in a pharmacogenomic study (n=664; Table). Descriptive analyses of baseline demographics and disease characteristics by DDR status were performed. **Results**: Of 664 patient samples tested, 652 were evaluable for analysis (ENZA + ADT, n=326; PBO + ADT, n=326). Baseline characteristics of these patients were similar to the ARCHES intent-to-treat population. The prevalence of DDR+ patients was lower than expected (n=34/652, 5.2%; Table). Of DDR+ patients, 13 (38.2%) had low-volume disease, compared with 228 (36.9%) of DDR– patients. High-volume disease was present in 21 (61.8%) DDR+ and 390 (63.1%) DDR– patients. Of DDR+ patients, 6 (17.6%) had localized disease at initial diagnosis (M0), compared with 145 (23.5%) DDR– patients. *De novo* metastatic disease at initial diagnosis (M1) was present in 28 (82.4%) DDR+ patients and 465 (75.2%) DDR– patients. Of DDR+ patients, 29 (85.3%) were from Europe, four (11.8%) were from North America, and one (2.9%) was from the Asia-Pacific region. **Conclusions**: This *post hoc* analysis found a lower prevalence of DDR alterations in patients with mHSPC in ARCHES, compared with the 7–12% previously reported in patients with metastatic castration-resistant prostate cancer (Lozano et al. *Br J Cancer* 2021; Pritchard et al. *N Engl J Med* 2016). We did not identify differences in baseline disease characteristics based on DDR status. Clinical trial information: NCT02677896. Research Sponsor: Astellas Pharma Inc. and Pfizer Inc.

DDR alteration frequencies in ARCHES.

n (%)	ENZA + ADT (n=326)	PBO + ADT (n=326)	Total (N=652)
Negative for all DDR alterations	308 (94.5)	310 (95.1)	618 (94.8)
Positive for ≥1 of the following alterations:			
DDR[a]	18 (5.5)	16 (4.9)	34 (5.2)
CHEK2	8 (2.5)	8 (2.5)	16 (2.5)
BRCA1/BRCA2/PALB2	5 (1.5)	6 (1.8)	11 (1.7)
BRCA2	4 (1.2)	5 (1.5)	9 (1.4)
ATM	4 (1.2)	1 (0.3)	5 (0.8)
NBN	1 (0.3)	1 (0.3)	2 (0.3)
PALB2	1 (0.3)	1 (0.3)	2 (0.3)
BRCA1	0	0	0

[a]DDR: *ATM, BRCA1, BRCA2, CHEK2, MLH1, MRE11A, NBN, PALB2, RAD50, RAD51C, FANCC, MSH2, MSH3, MSH6, POLD1, POLE.* No patient had >1 alteration.

5075 **Poster Session**

A phase 1b adaptive androgen deprivation therapy trial in metastatic castration sensitive prostate cancer. *First Author: Jingsong Zhang, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

Background: Despite early utilization of new hormonal agents (NHA, abiraterone, enzalutamide and apalutamide) in metastatic castration sensitive prostate cancer (mCSPC), increasingly more men are dying from prostate cancer. While continued development of new drugs is needed, we propose improved survival of metastatic prostate cancer can be obtained through tumor evolution informed treatment strategies. Compared to the conventional treat until progression paradigm, our previous study (NCT02415621) in metastatic castration resistant prostate cancer reported that on and off abiraterone therapy adapted to individual's PSA response dynamics can provide better cancer control with less abiraterone usage (Zhang et al, Nat Commun. 2017). Here we present the first interim analysis of our adpative therapy trial in mCSPC with a median follow up of 21 months. **Methods:** Men with asymptomatic mCSPC and no liver metastasis were enrolled after achieved > 75% PSA decline with 12 - 16 weeks of luteinizing hormone-releasing hormone (LHRH) analog, and 8 - 12 weeks of NHA. Both treatments were stopped after enrollment. PSA and testosterone levels were measured every 6 weeks, CT and bone scan were performed every 18 weeks while on study. Treatment will be restarted if subjects develop PSA or radiographic progression per prostate cancer working group 3 criteria. If the testosterone level (T) is > 100 ng/dl, LHRH analog will be restarted. If the T is between 50 and 100 ng/dl, NHA will be restarted. If the T is below 50, combined therapy with LHRH analog and NHA will be restarted. Treatment will be discontinued after achieving 50% or more PSA decline. For patients who restarted therapy for radiographic progression, partial response or stable disease needs to be documented on the post treatment scans along with PSA response prior to stopping therapy. The primary objective is feasibility, which is measured by percentage of patients who remain on study without on treatment disease progression at 12 months from first dose of LHRH analog for mCSPC. **Results:** 16 evaluable patients were enrolled between April 2019 and June 2021. Five of the 16 patients had high risk mCSPC based on the LATITUDE trial criteria. The median follow up was 21 months at the data cut off in January 2022. Only one patient was off study due to imaging progression at 27.6 months from first dose of LHRH analog for mCSPC. Three of the 16 patients developed on treatment PSA progression at month 12.3 and 15.2, and 20.5. Given none of the first 14 enrolled patients developed disease progression at 12 months, the study has already met its primary objective of feasibility. **Conclusions:** It is feasible to use individual's PSA response and testosterone level to guide intermittent therapy with LHRH analog and NHA in mCSPC. The study is ongoing to collect data on secondary endpoints of median time to PSA progression and median time to radiographic progression. Clinical trial information: NCT 03511196. Research Sponsor: Moffitt Cancer Center, Clinical Trial innovation award.

5076 **Poster Session**

Survival analysis of the randomized phase II trial to investigate androgen signaling inhibitors with or without androgen deprivation therapy (ADT) for castration-sensitive prostate cancer: LACOG 0415. *First Author: Fernando Cotait Maluf, Hospital Beneficência Portuguesa de São Paulo, Hospital Israelita Albert Einstein, Latin American Cooperative Oncology Group (LACOG), São Paulo, Brazil*

Background: LACOG 0415 is a phase II, open-label, clinical trial evaluating ADT-free alternatives for advanced castration sensitive prostate cancer (CSPC). **Methods:** Patients with locally advanced, high-risk biochemical recurrence or metastatic CSPC were randomized (1:1:1) to receive ADT with abiraterone acetate plus prednisone (ADT+AAP), apalutamide alone (APA), or apalutamide with AAP (APA+AAP). The primary endpoint of the trial was the proportion of patients who achieved PSA≤0.2 ng/mL level at week 25. Patients without disease-progression and with clinical benefit after week 25 were allowed to maintain treatment at the discretion of physicians. Herein, we presented the outcomes of 2 year-overall survival (2y-OS) and time-to-treatment failure (TTF). The time-to-event endpoint was estimated by Kaplan-Meier method and compared by stratified log-rank test. **Results:** 128 patients were randomized to the ADT+AAP (n = 42), APA (n = 42), and APA+AAP (n = 44) arms. At week 25, PSA≤0.2 ng/mL was observed in 75.6% (95%CI 59.7%-87.6%), 60.0% (95%CI 43.3%-75.1%), and 79.5% (95%CI 63.5%-90.7%) of patients in the ADT+AAP, APA, and APA+AAP arms, respectively. 110 patients continued treatment after week 25. At the 2-year visit, 80 (62.5%) patients remained on the study medication. Median TTF was 24.0 months (95%CI 23.3 - 24.0) with ADT+AAP, 24.0 months (95%CI not estimated) with APA, and 24.0 months (95%CI 13.0-24.0) with APA+AAP. The main reasons for treatment discontinuation were disease progression (n = 8, 6.3%), toxicity (n = 10, 7.8%), death (n = 6, 4.7%), withdrawal (n = 4, 3.1%), and other (n = 19, 14.8%). The estimated proportion of patients who were alive at 2 years (2y-OS rate) was 92.5% (95%CI 84.3-100) with ADT+AAP, 87.9% (95%CI 77.9-97.8) with APA, and 92.7% (95%CI 84.8-100) with APA+AAP (p = 0.5926). 2y-OS was 92.9% (95% CI 85.3 - 96.2) in patients with PSA ≤ 0.2 ng/mL at week 25, while 2y-OS was 85.0% (95% CI 72.9-97.1) in patients with PSA > 0.2 ng/mL at week 25 (p = 0.1250). **Conclusions:** Patients with advanced CSPC treated with ADT+AAP, APA, or APA+AAP had high rates of PSA response and favorable 2y-OS. PSA ≤ 0.2 ng/mL at week 25 seems to be a surrogate prognostic predictor of OS in advanced CSPC. In the overall sample, patients with PSA ≤ 0.2 ng/mL at week 25 had higher 2y-OS rate than those with PSA > 0.2 ng/mL at week 25 (92.9% vs. 85.0%), however without statistical significance. Clinical trial information: NCT02867020. Research Sponsor: Janssen-Cilag.

5077 **Poster Session**

Estrogen receptor β and *TMPRSS2-ERG* expression association with clinical outcomes in metastatic hormone-sensitive prostate cancer. *First Author: Caterina Aversa, Medical Oncology Department, Hospital Clínic, Barcelona, Spain, Barcelona, Spain*

Background: *TMPRSS2-ERG* fusion has been associated with estrogen receptor (ER) signalling in prostate cancer (PC). The isoform beta of ER (ERβ), encoded by ESR2, is considered anti-proliferative and tumor-suppressive. In preclinical studies, ESR2 has shown an inhibitory role towards *TMPRSS2-ERG*, resulting in decreased proliferation and tumor regression. In this clinical series, we sought to investigate the correlation between *TMPRSS2-ERG* and ESR2 expression and its impact on clinical outcomes in a cohort of patients (pts) with metastatic hormone-sensitive PC (mHSPC). **Methods:** This is a multicenter retrospective biomarker study. *TMPRSS2-ERG* and ESR2 were tested in total mRNA from FFPE tumor samples by nCounter platform (Nanostring Technologies). *TMPRSS2-ERG* and ESR2 expression were correlated with castration-resistant PC free survival (CRPC-FS) and overall survival (OS) by Kaplan Meier and multivariate Cox modeling. R (v.3.6.3) software was used for statistical analysis. **Results:** 218 mHSPC pts were included: 125 received androgen deprivation therapy (ADT) with Docetaxel and 93 ADT alone. Median age was 66.4 years (range 46.3-84.6), 75.7% (*N*= 165) presented with *de novo* mHSPC, 15.1% (*N*= 33) had visceral metastasis and 68.3% (*N*= 149) had high volume disease. Median follow-up was 38.8 months (m) (range 6.7-223.5) and 189 pts (86.7%) developed CRPC. Five pts were excluded due to lack of follow-up. Median time to CRPC was 18.8 m (95% CI 15.8-20.5) and median OS was 48.8 m (95% CI 43.2-59.1). Pts were grouped according to *TMPRSS2-ERG* fusion detection in TE positive (TE+) (*N*= 108, 49.5%) and TE negative (TE-) (*N*= 110, 50.5%) and according to ESR2 expression levels segregated into tertiles in ESR2 high (ESR2+) (*N*= 74, 33.9%) or ESR2 low-mid (ESR2-) (*N*= 144, 66.1%). TE+ status was associated to higher ESR2 levels (*P*= 0.03). The TE+/ESR2+ group showed longer CRPC-FS and OS, compared with the other groups, as shown in the table. TE+/ESR2 expression was independently associated with longer CRPC-FS (HR 0.3, 95% CI 0.2-0.5, *P*< 0.001) and OS (HR 0.3, 95% CI 0.2-0.5, *P*< 0.001). Moreover, a significant interaction between treatment (ADT vs ADT+Docetaxel) and TE+/ESR2+ status related to CRPC-FS was found (HR: 0.38, *P*= 0.014), suggesting that TE+/ESR2+ pts may benefit more from ADT than from the combination of ADT+Docetaxel. **Conclusions:** Our study suggests a protective role of ESR2 within a subgroup of mHSPC pts characterized by *TMPRSS2-ERG* fusion, which warrants further investigation of ESR2 as a prognostic factor, for treatment selection and as a potential pathway for targeted treatment in PC. Research Sponsor: Instituto de Salud Carlos III-Subdirección General de Evaluación y Fomento de la Investigación [PI18/714]. European Regional Development Fund (ERDF). Institutional funding from CERCA Programme/Generalitat de Catalunya. Grant from Janssen-Pharmaceuticals.

CRPC-FS	*N*	Median (m)	HR	*P*	95% CI
TE-/ESR2-	83	16.7	1		
TE-/ESR2+	26	15.4	0.8	0.454	0.5-1.3
TE+/ESR2-	58	14.7	1.13	0.499	0.8-1.6
TE+/ESR2+	46	40.3	0.4	< 0.001	0.2-0.6
OS	***N***	**Median (m)**	**HR**	***P***	**95% CI**
TE-/ESR2-	83	40.1	1		
TE-/ESR2+	26	44.1	0.7	0.220	0.4-1.3
TE+/ESR2-	58	41.7	1	0.955	0.7-1.5
TE+/ESR2+	46	102.6	0.3	< 0.001	0.2-0.5

5078 **Poster Session**

Association of prostate-specific antigen (PSA) response and overall survival (OS) in patients with metastatic hormone-sensitive prostate cancer (mHSPC) from the phase 3 ARASENS trial. *First Author: Fred Saad, University of Montréal Health Center, Montréal, QC, Canada*

Background: Reductions in PSA level have been associated with improved OS in patients (pts) with mHSPC. In ARASENS (NCT02799602), darolutamide (DARO) + androgen-deprivation therapy (ADT) in combination with docetaxel significantly reduced the risk of death by 32.5% (hazard ratio [HR] 0.675; 95% confidence interval [CI] 0.568–0.801; *P*< 0.0001) vs ADT + docetaxel in pts with mHSPC. We report the association between PSA response and OS from ARASENS. **Methods:** Pts with mHSPC were randomized 1:1 to DARO 600 mg twice daily or matching PBO + ADT and docetaxel. Serum PSA was measured at screening and every 12 weeks. Exploratory analyses included time to PSA progression (≥25% increase from PSA nadir [lowest or at study entry] and PSA increase ≥2 ng/mL ≥12 weeks from nadir [both confirmed by a second value ≥3 weeks later]) and undetectable PSA (< 0.2 ng/mL for 2 samples ≥3 weeks apart) at 24, 36, and 52 weeks and any time during treatment. Comparisons between treatment groups were performed using the Cochran-Mantel Haenszel test stratified by randomization stratification factors (metastatic spread according to TNM classification and alkaline phosphatase levels at study entry). Post hoc landmark analyses evaluated the association between undetectable PSA at weeks 24 and 36 and OS for the overall population. **Results:** Of 1306 randomized pts, 1305 were included in the full analysis set (DARO 651; PBO 654), both with ADT and docetaxel. Median (range) PSA levels at study entry were 30.3 (0.0–9219.0) and 24.2 (0.0–11,947.0) ng/mL, respectively. DARO significantly prolonged time to PSA progression (HR 0.255; 95% CI 0.208–0.313; *P*< 0.0001). Undetectable PSA was achieved in more pts receiving DARO (48.7%) vs PBO (23.9%) at 24 weeks, and the rate continued to increase at 36 and 52 weeks in the DARO group to 57.1% and 60.2%, respectively, vs minimal change in the PBO group (25.1% and 26.1%). Undetectable PSA levels at any time were achieved in 67.3% in the DARO group and 28.6% in the PBO group. A treatment difference in undetectable PSA based on non-overlapping 95% CIs was observed at all time points. For the overall population, OS was improved for pts who achieved undetectable PSA levels vs those who did not at 24 weeks (HR 0.398; 95% CI 0.321–0.493) and 36 weeks (HR 0.351; 95% CI 0.284–0.434). Additional baseline and safety data by PSA level will be reported. **Conclusions:** The combination of DARO + ADT and docetaxel significantly prolonged the time to PSA progression and more pts receiving DARO vs PBO achieved undetectable PSA levels, reflecting strong PSA response over time. In pts with mHSPC, achievement of undetectable PSA at 24 and 36 weeks was associated with improved OS, with risk of death reduced by 60% and 65%, respectively, vs those who did not achieve undetectable PSA at 24 and 36 weeks. Clinical trial information: NCT02799602. Research Sponsor: Bayer AG and Orion Pharma.

5079 **Poster Session**

Effect of docetaxel (D) use on survival outcomes in patients with metastatic castration-sensitive prostate cancer (mCSPC) treated with novel hormonal therapies (NHTs): A meta-analysis. *First Author: Deniz Can Guven, Hacettepe University Cancer Institute, Department of Medical Oncology, Ankara, Turkey*

Background: ARASENS and PEACE-1 trials have shown that the addition of NHTs to D + androgen deprivation therapy (ADT) improves overall survival (OS) outcomes in mCSPC. However, whether a true synergism is present with using NHT+ADT+D is unknown due to the lack of a trial testing the efficacy of adding D to the NHT+ADT backbone. Our objective was to evaluate the survival outcomes with NHTs according to D use in mCSPC. **Methods:** The literature search was done from PubMed and Embase databases to identify published studies until February 12th, 2022 for meta-analysis. The MeSH search terms were "castration-sensitive prostate cancer" OR "hormone-sensitive prostate cancer" OR "hormone-naïve prostate cancer" AND "abiraterone" OR "apalutamide" OR "enzalutamide" OR "darolutamide". The target outcome measures were progression-free survival (PFS) and OS. Generic inverse-variance method with a fixed-effects model was used, with hazard ratios with 95% two-sided confidence intervals (CI) as the principal summary measure (Review Manager software, version 5.3, The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark). P values below 0.05 were considered statistically significant. **Results:** The literature search retrieved a total of 2565 records. Six phase III studies encompassing 6701 patients evaluating survival outcomes with NHTs in mCSPC (TITAN, ARCHES, ENZAMET, LATITUDE, STAMPEDE Abi- M1, and PEACE-1) were included after filtering of the available records. Results summarized in below table. In the combined analysis, the addition of NHTs to standard of care (SOC) improved PFS and OS. PFS benefit with NHTs was similar in studies (or study subgroups) with or without D use. However the relative OS benefit with a NHT was higher in studies (or study subgroups) without D than studies permitting D (concurrent or sequential). **Conclusions:** In this meta-analysis, the PFS and OS benefit with NHT in mCSPC was observed independent of D use. A randomized phase III study comparing D+NHT+ADT with NHT+ADT is needed to evaluate the contribution of D to survival outcomes in patients with mCSPC receiving treatment with NHT+ADT. Research Sponsor: None.

Summary results of PFS and OS benefit with NHT + ADT regardless of D use and without or with D.

	PFS HR (95% CI, p-value)	OS HR (95% CI, p-value)
NHT+SOC vs SOC (SOC: ADT or ADT+D)	0.49 (0.45-0.53, <0.001)	0.68 (0.63-0.73, <0.001)
NHT+ADT vs ADT	0.49 (0.45-0.53, <0.001)	0.62 (0.57-0.68, <0.001)
NHT+ADT+D vs ADT+D (sequential or concurrent)	0.49 (0.42-0.58, <0.001)	0.81 (0.67-0.96, 0.020)

5080 **Poster Session**

Transcriptomic profiling of patients (pts) with de-novo metastatic castration-sensitive prostate cancer (DN-mCSPC) versus those with mCSPC that have relapsed from prior localized therapy (PLT-mCSPC). *First Author: Nicolas Sayegh, Huntsman Cancer Institute-University of Utah Health Care, Salt Lake City, UT*

Background: Pts with DN-mCSPC have been reported to experience worse prognosis and outcomes compared to those with PLT-mCSPC. We hypothesized that gene expression profiling of pre-treatment primary prostate tumors from PLT-mCSPC pts would be distinct from those with DN-mCSPC. **Methods:** Eligibility criteria: histologically confirmed mCSPC and available RNAseq profiling performed by a CLIA certified lab using primary prostate biopsies collected prior to start of treatment. Pts were categorized into two cohorts: PLT-mCSPC versus DN-mCSPC. The DEseq2 pipeline was used to analyze differentially expressed genes between the groups. The data included the Log2 fold change, Wald-Test p-values, and Benjamini-Hochberg adjusted p-values for each differentially expressed gene. These results were subjected to Gene Set Enrichment software analysis (GSEA) in order to identify pathways enriched in each cohort. All bioinformatic analysis was undertaken using R v4.2. **Results:** Ninety-seven (97) patients met eligibility (52 PLT, 45 *de novo*). Characteristics of the overall eligible pts: median age = 65, median baseline PSA = 12.6, Gleason score ≥8 = 71%, and high volume of disease = ~30%. Differential expression and pathway enrichment between cohorts: upregulation of cell-cycle signaling pathways (G2-M checkpoint, E2F) in pts with DN-mCSPC, and upregulation of androgen signaling and immune pathways (inflammatory response, NFKB-mediated TNF-alfa signaling) in pts with PLT-mCSPC (Table). **Conclusions:** These hypothesis-generating data, upon external validation, may provide the rationale for personalized therapy in men with mCSPC, such as the use of CDK4/6 inhibitors in addition to standard of care intensified ADT in men with DN-mCSPC. Research Sponsor: None.

Gene set enrichment scores contrast PLT versus *de novo* pts.

PATHWAY	NORMALIZED ENRICHMENT SCORE (NES)	P-value	P-adjust	Q-values
E2F TARGETS	-2.19	2.99E-10	1.50E-08	1.13E-08
G2M CHECKPOINT	-1.81	6.06E-06	1.01E-04	7.65E-05
ANDROGEN RESPONSE	1.57	0.006003	0.03335	0.02528
INFLAMMATORY RESPONSE	1.60	4.98E-04	0.004976	0.003771
TNFA SIGNALING VIA NFKB	2.08	8.43E-10	2.11E-08	1.60E-08

NES: positive values favor upregulation of PLT pts, negative values favor upregulation of de novo pts.

5081 **Poster Session**

Eight-year survival rates by baseline prognostic groups in patients with metastatic hormone-sensitive prostate cancer (mHSPC): An analysis from the ECOG-ACRIN 3805 (CHAARTED) trial. *First Author: Abhishek Tripathi, Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK*

Background: To date there is no prospective survival data beyond 5 years for patients treated with ADT with or without docetaxel (D) when analyzed by well-defined baseline prognostic risk groups and treatment arms. In this updated analysis of the CHAARTED trial, we report the 8-year survival rate based on disease volume and metachronous vs. *de novo* metastatic disease status with ADT without or with docetaxel. **Methods:** An updated survival sweep was conducted in February 2022. Patients were prospectively identified by the state of metastatic disease as metachronous (prior local therapy) vs. *de novo* and low volume (LV) vs. high volume (HV; visceral and/or ≥4 bone metastases with one lesion beyond the vertebral bodies or pelvis) disease. Overall survival (OS) was defined as time from randomization to death or date last known alive and calculated using the Kaplan-Meier method. **Results:** Of the 790 patients randomized (last patient enrolled December 2012), 238 patients were still alive with a median follow up of 9.7 years for patients still alive. Median OS in the overall population was 60.4 and 47.2 mos in the ADT+ D and ADT arms respectively (Table; HR: 0.77; 95% CI: 0.65, 0.92; p=0.004). ADT+ D was associated with significantly higher 8-yr OS rate (28.5%) compared to ADT arm (15.4%; HR: 0.67; 95% CI: 0.53, 0.84; p=0.0005) in the *de novo* HV group (n=421). Notably, the 8-yr OS rates were almost doubled for patients with HV disease with early docetaxel (16% vs.30.2%, p<.0001) and this was seen in patients with both *de novo* and metachronous HV mHSPC. **Conclusions:** In this long-term updated analysis, ADT+D continued to demonstrate significantly improved OS in the overall population and this is still most clearly evident in patients with *de novo* HV mHSPC. Our findings highlight the role of baseline prognostic risk groups in predicting longer term survival and benefits from treatment intensification. Clinical trial information: NCT00309985. Research Sponsor: U.S. National Institutes of Health, Supported in part by a grant from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services, and by grants (CA180820, CA180794, CA180795, CA180802, CA180799, CA180790, CA180853, CA189829, CA180801, CA180888, CA31946, and CA180821) from the Public Health Service. Sanofi provided the docetaxel and a grant to ECOG-ACRIN.

OS by risk groups.

	ADT+D		ADT Alone		
	# Death/N	8-year OS rate (95% CI)	# Death/N	8-year OS rate (95% CI)	HR[3] (95% CI; p-value)
Overall	266/397	34.9% (30.0, 39.8)	286/393	28.9% (24.3, 33.5)	0.77 (0.65, 0.92; p=0.004)
De novo[1] High Volume	157/214	28.5% (22.2, 35.1)	174/207	15.4% (10.7, 20.8)	0.67 (0.53, 0.84; p=0.0005)
De novo[1] Low Volume	42/75	44.6% (32.9, 55.6)	52/79	40.9% (29.6, 51.9)	0.77 (0.51, 1.18; p=0.23)
Metach[2] High Volume	32/49	37.1% (23.6, 50.6)	34/42	19.8% (9.3, 33.1)	0.84 (0.49, 1.46; p=0.54)
Metach[2] Low Volume	35/59	43.4% (30.1, 55.9)	25/64	64.2% (50.9, 74.8)	1.65 (0.95, 2.87; p=0.07)
High Volume	189/263	30.2% (24.4, 36.1)	209/250	16.0% (11.7, 21.0)	0.67 (0.55, 0.82; p<.0001)

[1] *De novo*: no prior local therapy.
[2] Metach: with prior local therapy.
[3] Hazard ratio of ADT+D vs. ADT alone using Cox's proportional hazards models, stratified on stratification factors at randomization.

5082 **Poster Session**

A randomized phase Ib/II study of intermittent androgen deprivation therapy plus nivolumab with or without interleukin-8 blockade in men with hormone-sensitive prostate cancer (MAGIC-8). *First Author: Matthew Dallos, Columbia University, New York, NY*

Background: Immunotherapy has limited efficacy in castration-resistant prostate cancer. Androgen deprivation therapy (ADT) has significant immunomodulatory effects and initially induces a complex immune infiltrate before castration-resistance develops. However, ADT also recruits immunosuppressive myeloid cells to the tumor microenvironment by increasing interleukin-8 (IL-8). We conducted a phase Ib/II clinical trial of immunotherapy plus ADT in men with recurrent castration-sensitive prostate cancer (CSPC). We hypothesized that anti-PD-1 (nivolumab) +/- anti-IL-8 (BMS-986253) given at the time of castration could induce anti-tumor immune responses and decrease disease progression. **Methods:** MAGIC-8 was a multicenter, phase Ib/II study evaluating nivolumab +/- BMS-986253 combined with a short course of degarelix acetate in patients with recurrent CSPC and rapid PSA doubling time (≤ 12 mos). In the Phase Ib portion, patients were treated with nivolumab (480mg Q4W) for 8 wks followed by nivolumab plus degarelix for an additional 16 wks. In the phase II portion, patients were randomized 1:2 to nivolumab + degarelix (Arm A) versus nivolumab + BMS-986253 (2400mg Q2W) + degarelix (Arm B). The primary endpoints were PSA recurrence at 10 mos following randomization and safety. Key secondary endpoints included biochemical recurrence-free survival (bPFS), time to recovery of testosterone (> 150ng/dl), and bPFS after recovery of testosterone. **Results:** Between October 16, 2019 and March 9, 2021, 59 patients were enrolled. The first 15 patients were treated on Arm A followed by 1:2 randomization to Arm A (N = 15) versus Arm B (N = 29). Median follow up was 11.6 mos at the data cutoff (1/24/22). Patients treated on Arm A had a significantly lower rate of PSA relapse (17.39%) at 10 mos compared to historical controls (p = < 0.001), including a subgroup of patients (6.67%) with recovery of testosterone and no PSA relapse at > 2 years of follow up. Median time-to-recovery of testosterone was 12.7 mos, median bPFS was 14.0 mos and median bPFS after recovery of testosterone was 5.5 mos. In Arm B, there was no difference in PSA relapse at 10 mos (35%, p = 0.09), median time-to-recovery of testosterone, median bPFS and median bPFS after recovery of testosterone compared to historical controls. Treatment in both arms was well tolerated with a lower rate of grade 3-4 treatment-related adverse events in Arm B compared to Arm A (3.5% vs 12.9%). **Conclusions:** A short course of ADT plus nivolumab may decrease the rate of PSA relapse and lead to durable long-term responses after recovery of testosterone in a subset of patients. These data support further evaluation of combining nivolumab with ADT in CSPC. Although the addition of BMS-986253 did not improve rate of PSA relapse, we observed significantly less toxicity with the addition of IL-8 inhibition. Clinical trial information: NCT03689699. Research Sponsor: Bristol-Myers Squibb, Other Foundation.

5083 **Poster Session**

Indirect comparisons of triplet therapy as compared to novel hormonal therapy doublets in patients with metastatic castration sensitive prostate cancer. *First Author: Syed Arsalan Ahmed Naqvi, Mayo Clinic, Phoenix, AZ*

Background: ARASENS and PEACE-1 trials suggests treatment intensification with novel hormonal therapy (NHT) in addition to androgen deprivation therapy (ADT) and docetaxel (DOC) provides survival benefit as compared to DOC+ADT in patients with metastatic castration sensitive prostate cancer (mCSPC). However, the performance of triplet therapy as compared to NHT+ADT remains unexplored. **Methods:** MEDLINE, EMBASE and recent conference proceedings were searched to include phase III trials evaluating triplet therapy in patients with mCSPC and reporting treatment effects in subgroup of patients with and without docetaxel. Outcomes included overall survival (OS) and radiographic progression free survival (rPFS). Precomputed hazard ratios (HRs) and confidence intervals (CIs) from non-randomized subgroup comparisons were pooled after logarithmic transformation using inverse-variance weighting approach. A DerSimonian-Laird random-effects meta-analysis was then performed to assess subgroup differences. Interaction between subgroups was assessed using P-value of heterogeneity. Mixed treatment comparisons were computed using a fixed-effect model within the frequentist framework using subgroup effect estimates from eligible trials. **Results:** This meta-analysis included five clinical trials (ARASENS, PEACE-1, ENZAMET, ARCHES and TITAN) with a total of 5804 patients (docetaxel: 2836; no docetaxel: 2836). Subgroup analysis showed statistically significant difference between treatment effects in patients who received docetaxel (NHT + DOC + ADT; HR: 0.74; 95% CI: 0.66-0.84; I^2: 0%) and those who did not (NHT + ADT; HR: 0.61; 95% CI: 0.53-0.70; I^2: 0%) for OS (p-value of interaction: 0.04). However, no statistically significant interaction was observed in terms of rPFS (p-value: 0.46). Mixed treatment comparisons showed improved OS with NHT + DOC + ADT (HR: 0.74; 95% CI: 0.66-0.84) as compared to DOC + ADT, but not when compared to NHT + ADT (HR: 0.97; 95% CI: 0.78-1.20). NHT + ADT significantly improved OS compared to DOC + ADT (HR: 0.77; 95% CI: 0.64-0.92). Consistently, significant rPFS improvement was observed with NHT + DOC + ADT when compared DOC + ADT (HR: 0.49; 95% CI: 0.42-0.57) but not when compared to NHT + ADT (HR: 0.82; 0.65-1.04). NHT + ADT was observed to improve rPFS compared to DOC + ADT (HR: 0.60; 95% CI: 0.50-0.72). **Conclusions:** This exploratory and hypothesis generating analysis suggests that addition of docetaxel (triplet therapy) may not delay progression or prolong survival compared to NHT-based doublets. These findings provide direction for future clinical trials in this space and suggest an equipoise to the question of how triplet regimens compare with NHT-doublets. The results should be interpreted with caution as this analysis does not account for potential confounding relationships such as volume of disease. Research Sponsor: None.

5084 **Poster Session**

Patient (pt) population and radiation therapy (RT) type in the long-term phase 3 double-blind, placebo (PBO)-controlled ATLAS study of apalutamide (APA) added to androgen deprivation therapy (ADT) in high-risk localized or locally advanced prostate cancer (HRLPC). *First Author: Howard M. Sandler, Cedars-Sinai Medical Center, Los Angeles, CA*

Background: Current management of HRLPC includes long-term ADT with primary RT. Despite definitive primary treatment, these pts have a high risk of metastasis and death. The phase 3 ATLAS study (NCT02531516) is investigating whether treatment intensification with the addition of APA to neoadjuvant and adjuvant treatment with gonadotropin-releasing hormone agonist (GnRHa) and external beam radiation therapy (EBRT) will improve metastasis-free survival (MFS) in high-risk pts. Here we describe (1) the distribution of baseline characteristics in this high-risk pt population and (2) the application of different RT regimens reflecting recent international guidelines and clinical practice changes for pts with HRLPC. **Methods:** Eligible HRLPC pts (Gleason score [GS] ≥ 8 or 7 and prostate-specific antigen [PSA] ≥ 20 ng/mL and stage ≥ cT2c), with ECOG PS 0/1 and Charlson Comorbidity Index (CCI) ≤ 3 are stratified by GS, pelvic nodal status, use of brachytherapy boost, and region; pts are randomized 1:1 to APA or PBO plus GnRHa for 30 (28-d) treatment cycles. Study treatment is applied neoadjuvant/concurrent to RT with APA 240 mg/d vs bicalutamide 50 mg/d for 4 cycles; another 26 cycles are completed adjuvantly after RT with APA 240 mg/d vs PBO. Primary end point is MFS (time from randomization to first distant metastasis on CT/MRI/bone scan by independent central review blinded to treatment or death from any cause). Imaging is conducted at baseline and q6m from biochemical failure until MFS. The protocol has been amended to include PET imaging (PSMA, fluciclovine, or choline). **Results:** Pts (N = 1503) were randomized at 266 sites in 24 countries in North America, Latin America, Europe, and Asia. The study is fully enrolled, but ongoing. Baseline characteristics for the total population: median age, 67 yrs; ECOG PS 0/1; 89%/11%; tumor classification at study entry: high-risk, 66%/very high–risk, 34%; median PSA, 6.3 ng/mL; cT2, 44%/cT3, 50%; cN1, 13%. In 90% of ATLAS pts, RT used was standard EBRT to prostate/pelvis over 6-8 weeks (cumulative 78-81 Gy); in 10%, recent hypofractionation schedules (per CHHiP or NRG/RTOG 0415) were applied (20x3 Gy/d or 28x2.5 Gy/d). 5.6% of pts had EBRT combined with brachytherapy (per ASCENDE-RT). **Conclusions:** Baseline characteristics of the ATLAS study population are reflective of pts with high- and very high–risk features and pelvic nodal involvement undergoing primary RT in clinical practice. The RT schedules applied reflect recent evidence and guideline changes for the use of hypofractionation in this pt population. ATLAS is an example of how RT can be included in phase 3 trials of HRLPC, in combination with next-generation androgen receptor inhibitors (eg, APA). Clinical trial information: NCT02531516. Research Sponsor: Janssen Research & Development.

5085 **Poster Session**

Randomized phase II trial of neoadjuvant androgen deprivation therapy plus abiraterone and apalutamide for patients with high-risk localized prostate cancer: Pathologic response and PSMA imaging correlates. *First Author: Diogo Assed Bastos, Instituto do Câncer do Estado de São Paulo, São Paulo, Brazil*

Background: Patients (pts) with high-risk localized prostate cancer (HRLPC) have a significant risk of disease recurrence and metastasis after radical prostatectomy (RP). Neoadjuvant therapy remains investigational but there may be a role for the next-generation androgen signaling inhibitors. We sought to evaluate pathologic and imaging response after the intense neoadjuvant approach. **Methods:** This is a phase II investigator-initiated randomized trial of 3-month neoadjuvant therapy with goserelin (androgen deprivation therapy, ADT) + abiraterone acetate and prednisone (AAP arm) or AAP + apalutamide (A-APA arm) before RP for pts with HRLPC (Gleason ≥ 8 and/or cT3N0-1 and/or PSA ≥ 20 ng/mL). The primary endpoint was the rate of pathologic complete response (pCR) or minimal residual disease (MRD, tumor ≤ 0.5 cm). The secondary endpoints were safety, rate of residual cancer burden ≤0.25 cm^3 (RCB = tumor volume x cellularity), Gallium 68 prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/magnetic resonance correlates and rate of biochemical relapse (BR). **Results:** Sixty-two pts were randomized to A-APA (N = 31) or AAP (N = 31). Median age was 65 (range 47-77) years. NCCN risk groups included high-risk disease in 19%, very high-risk in 76% and regional (N1) disease in 5% (79% cT3, 65% Gleason 8-10, 57% PSA ≥ 20 ng/mL). Outcomes after intense neoadjuvant ADT are described in the Table. There was no statistically significant difference between study arms regarding pCR/MRD or RCB ≤ 0.25 cm^3 rates. Patients with complete PSMA-PET response (psmaCR) demonstrated a RCB ≤ 0.25 cm^3 rate of 50% compared to 7.5% in pts without a psmaCR (P= 0.001). The rate of BR was 14% for pts with RCB ≤ 0.25 cm^3 versus 38% in pts with RCB > 0.25 cm^3 (P= 0.118). At current median follow-up of 2.6 years, all patients with both psmaCR and RCB ≤ 0.25cm^3 (N = 11, 18%) are free of BR. There were 2 grade (G) 5 adverse events (AEs) in the AAP arm (pulmonary embolism and sudden death, both after surgery). Nine (14.5%) pts (6 in A-APA; 3 in AAP) experienced G3-4 treatment-related AEs. The most common G3-4 AEs were hypertension (11.3%), AST/ALT elevations (3.2%) and skin rash (1.6%). **Conclusions:** No difference in pCR or MRD was observed between arms. Although pCR or MRD after intense neoadjuvant ADT was infrequent, a significant proportion of pts achieved a favorable pathologic response with RCB ≤ 0.25 cm^3. PSMA-PET response is a potential surrogate for pathologic response. Clinical trial information: NCT02789878. Research Sponsor: Janssen.

Outcomes after intense ADT.

	A-APA (N = 31)	AAP (N = 31)	*P* value
Complete PSMA response	15 (48%)	7 (23%)	0.034
pCR or MRD	1 (3%)	2 (7%)	0.554
ypT2N0	12 (39%)	8 (26%)	0.227
ypT3	19 (61%)	22 (71%)	0.421
ypN1	6 (20%)	7 (23%)	0.755
Positive margins	8 (26%)	12 (39%)	0.277
RCB ≤ 0.25m^3	10 (32%)	4 (13%)	0.068
Testosterone recovery	29 (94%)	26 (84%)	0.425
Biochemical relapse	10 (32%)	10 (32%)	1.0

5086 **Poster Session**

Comparative healthcare research outcomes of novel Surgery in prostate cancer (IP4-CHRONOS): Pilot RCT assessing feasibility of randomization for focal therapy in localized prostate cancer. *First Author: Deepika Reddy, Imperial College London, London, United Kingdom*

Background: Randomised comparative data is lacking for focal therapy in localised prostate cancer. Imperial Prostate 4 CHRONOS (IP4- CHRONOS) is an RCT designed to reflect patient and physician equipoise to maximise acceptance to randomisation. **Methods:** Patients and physicians could opt for CHRONOS-A or CHRONOS-B. CHRONOS-A randomised between focal therapy (HIFU/cryotherapy) and radical therapy (radiation/prostatectomy). Using a multi-arm-multistage design, CHRONOS-B randomised between focal and focal combined with neoadjuvant medication (3 months of either finasteride or bicalutamide). We report the pilot phase outcomes on feasibility of randomisation. IP4-CHRONOS had ethics committee approval and was registered (ISRCTN17796995). **Results:** Due to impact of COVID-19, the target for CHRONOS-A was modified from 60 to 36; 36 patients were randomised over 24 months from 7 sites (Nov/2019-Nov/2021). CHRONOS-B randomised 64 patients over 14 months across 6 sites (Dec/2019-Feb/2021). Median (IQR) age and PSA (ng/ml) for CHRONOS-A were 69 (65-72) years and 6 (5-7) and for 66 (60.5-70) years and 6 (4-7) for CHRONOS-B, respectively. 34/36 (94%) and 60/64 (94%) had ISUP Grade Group > / = 2, respectively. 4/18 (22%) randomised to radical in CHRONOS-A withdrew consent; 1/22 (5%) randomised to focal withdrew. In CHRONOS-B, only 1/21 (5%) randomised to focal alone, and another randomised to focal with neoadjuvant bicalutamide withdrew. A qualitative recruitment intervention partially improved accrual to CHRONOS-A. **Conclusions:** IP4-CHRONOS evaluated patient and physician equipoise regarding focal therapy. Randomising between focal and radical therapy is not feasible due to strong patient preferences. A multi-arm, multi-stage RCT investigating the role of neoadjuvant agents combined with focal therapy is feasible. Clinical trial information: 17796995. Research Sponsor: Prostate Cancer UK.

5087 **Poster Session**

Diagnosed with advanced prostate cancer: A population-based cohort from national oncology practices. *First Author: Simon P. Kim, University of Colorado Cancer Center Anschutz Medical Campus, Denver, CO*

Background: Clinical trials can provide access to novel systemic agents and possible improved survival for men diagnosed with regional and metastatic prostate cancer. Although clinical trials should be accessible to all patient populations, racial disparities to enrollment of clinical trials and its outcomes remain an important unknown outcome. Herein, we sought to elucidate the racial disparities in clinical trial enrollment and survival amongst advanced prostate cancer patients from a large community-based medical oncology consortium. **Methods:** Using CancerLinQ, we identified all patients who were diagnosed with regional (N1+) and/or metastatic (M1) prostate cancer from 2011 – 2021. Enrollment into a clinical trial and overall survival constituted the primary outcomes in this study. Multivariable logistic regression and Cox proportional hazard regression were used to identify covariates associated with each outcome. **Results:** Amongst the 160,888 patients with regional/metastatic prostate cancer, only 1.5% patients were enrolled in a clinical trial (n = 2,368). On multivariable analysis, patients with worse ECOG performance status were associated with lowers odds of clinical trial enrollment ($p < 0.001$). Relative to white patients, African-American men (AAM) also had lower odds of clinical trial enrollment (OR: 0.67; $p < 0.001$). For the entire cohort, clinical trial enrollment correlated with higher survival (HR: 1.19; $p < 001$) and lower survival for AAM men (HR: 0.85; $p < 0.001$) compared to white men after adjusting for other covariates. In the subgroup analysis of patients enrolled in clinical trials, AAM demonstrated similar survival to white patients (HR: 0.96, $p = 0.95$). **Conclusions:** Although African-American men with regional/metastatic prostate cancer face barriers to clinical trial enrollment, racial disparities in survival appear to resolve for patients who enroll in clinical trials. Increased attention is needed to address barriers to communication and access to clinical trials. Research Sponsor: Schramm Foundation.

5088 **Poster Session**

Predictive value of extra-prostatic disease detection by pre-operative PSMA-PET for biochemical recurrence-free survival in patients treated with radical prostatectomy: Follow-up analysis of a multicenter prospective phase 3 imaging trial. *First Author: Loic Djaileb, UCLA Ahmanson Translational Theranostics Division, Los Angeles, CA*

Background: To assess the predictive value of pre-operative PSMA-PET staging for biochemical recurrence (BCR) free-survival (BCR-FS) in patients treated with radical prostatectomy (RP) and pelvic lymph node dissection (PLND) with intermediate-risk (IR) to high-risk (HR) prostate cancer (PCa) included in the prospective trial used for the FDA approval of 68Ga-PSMA-11. **Methods:** This is a post-hoc follow-up study of the efficacy analysis cohort included in the multicenter prospective phase 3 imaging trial (n = 764; NCT03368547, NCT02611882, NCT02919111) which assessed the diagnostic accuracy of ^{68}Ga-PSMA-11 PET for pelvic nodal metastasis detection prior to RP and PLND in patients with IR and HR PCa. Each PSMA-PET scan was read by three blinded independent readers. Readers assessed the presence of PCa (positive vs negative) by region: prostate bed (T), pelvic lymph nodes (N), extra-pelvic lymph nodes (M1a) bone (M1b) and visceral (M1c). A centralized per-region majority rule was used in case of disagreement. The surgical pathology report was used to assess the presence of pelvic lymph node metastasis by histopathology (pN0 vs pN1). The patients were followed up for biochemical progression after RP by the local investigators using electronic medical records. BCR was defined by a prostate-specific antigen (PSA) level > 0.2 ng/ml after RP or an initiation of PCa specific adjuvant/salvage therapy. Pairwise comparisons using Log-Rank test was performed to evaluate BCR-FS between the pre-operative PSMA scan reads (N0M0 vs. N+ and/or M+) and the histopathology status (pN0 vs. pN1). **Results:** From December 2015 to December 2019, a total of 764 patients were enrolled in the trial. 277/764 (36%) underwent RP after PSMA-PET. Clinical follow-up was obtained in 240/277 (87%) patients. The median age was 67 years (interquartile range, 61-71 years). The median follow-up time from RP was 21.4 months (IQR: 8.80 - 31.53). One hundred BCR events (41%) were observed, and 98/240 patients underwent salvage therapy or other treatment (40.6%). The BCR-FS was 24.3 (IQR: 7.8 - 48.8) in the whole cohort. 160/240 (66%), 28/240 (11.6%), 39/240 (16%), 13/240 (5.4%) patients were pN0/PSMA- (N0 and M0), pN+/PSMA+ (N+ and/or M+), pN+/PSMA-, and pN0/PSMA+, respectively. BCR-FS was higher in PSMA- than in PSMA+ patients (33 vs 7.3 months; $p < 0.0001$). BCR-FS was higher in pN0/PSMA- than in patients pN+/PSMA-, pN0/PSMA+ and pN+/PSMA+: 46 months vs 12.3, 11.7, and 3, respectively ($p < 0.001$). BCR-FS did not significantly differ between pN0/PSMA+ and pN+/PSMA- (11.7 vs 12.3; $p = 0.64$). **Conclusions:** PSMA PET staging information is predictive of BCR-FS after RP. Patients with extra-prostatic disease detected by pre-operative PSMA-PET scan have a high risk of biochemical relapse. Clinical trial information: NCT03368547. Research Sponsor: None.

5089 **Poster Session**

Salvage radiotherapy guided by functional imaging for macroscopic local recurrence following radical prostatectomy: A multicentric retrospective study. *First Author: Nicolas Benziane Ouaritini, Institut Bergonié, Bordeaux, France*

Background: For prostate cancer (Pca), salvage radiotherapy (sRT) with or without androgen deprivation therapy (ADT) is currently the only curative treatment option in case of post-radical prostatectomy (RP) biochemical relapse (BR). Functional imaging techniques have shown that macroscopic recurrence (MR) in the prostate bed (PB) are frequent. In this study, we aimed to assess efficacy and safety of sRT in patients with MR inside the PB proven by functional imaging. **Methods:** A multicenter retrospective study was conducted in 16 European centers. Patients were included if they displayed BR after RP for Pca, with MR only in the PB proven by functional imaging. All patients had to be eligible for sRT. The overall population was divided along 4 groups according to the delivered treatment: dose escalation on MR (A), dose escalation on PB (B), double dose escalation MR+PB (C), no dose escalation (D). The primary endpoint was progression-free survival (PFS). Secondary outcomes included the metastasis-free survival (MFS), biochemical PFS (bPFS) and overall survival (OS). Grade ≥2 genito-urinary (GU) and gastro-intestinal (GI) acute and late toxicities were collected. **Results:** Between January 2000 and December 2019, 363 patients with isolated MR after RP for Pca were treated by sRT. The median pre-sRT PSA level was 0.63ng/mL (range, 0.2-23.6). At the time of BR, 266 (73%) patients presented MR in the PB proven by magnetic resonance imaging, and 110 (30%) by positron emission tomography. The median follow-up was 53.6 months (range, 47.52; 58.32). The 5-year PFS and MFS were 70% (95%CI [63.8-75.4]) and 83.7% (95%CI [78.4-87.8]), respectively. Grade ≥2 GU and GI late toxicities were found in 43 (12%) and 11 (3%) patients, respectively. A 5-year PFS benefit was highlighted for groups A, B and C (313 patients) when the MR dose was ≥72Gy: 72,8% (95%CI 64.6-79.4) versus 60.3% (95%CI 48,4-70,3), $p = 0.03$. **Conclusions:** In a modern series integrating functional imaging data, we confirmed that sRT is effective in the event of MR inside the PB, with an acceptable toxicity profile. In addition, with the help of functional imaging, we found that dose escalated ≥ 72 Gy on the MR had a significant impact on PFS. Prospective data should further investigate the correlation between MR-targeted dose escalation and PFS. Research Sponsor: None.

5090 **Poster Session**

Recurrence, metastasis, and survival after radical prostatectomy in the era of advanced treatments. *First Author: Kristian D. Stensland, Dow Division of Health Services Research, Department of Urology, University of Michigan Medical School, Ann Arbor, MI*

Background: Accurate survival estimates after prostatectomy are critical for patient counseling, treatment decisions, and trial design. Prior prostate cancer natural history studies may not reflect contemporary outcomes and often lack key endpoints (e.g. incident metastases). For these reasons, we explored population-based recurrence and survival following radical prostatectomy. **Methods:** We conducted a retrospective study of men with localized prostate cancer treated with radical prostatectomy from 2005-2015 with follow up through 2019 in the Veterans Health Administration. We excluded men with adjuvant radiation or hormonal therapy and defined biochemical recurrence (BCR) as a PSA ≥0.2 ng/mL. We used a validated natural language processing encoded dataset to identify incident metastatic disease. We then estimated actuarial time from surgery to BCR, BCR to metastatic disease, and metastatic disease to death using Kaplan-Meier methods. **Results:** Of 22,033 men post-prostatectomy, 5,963 (27%) developed BCR, with 5- and 10-year BCR estimates of 21% and 29% (Table). Of 5,963 men with BCR, 678 (11%) developed metastasis, with 5- and 10-year metastasis-free survival from time of BCR of 91% and 77%. Of these 678 men with metastases, 235 died (35%), with 5- and 10-year overall survival of 61% and 47%. Median actuarial overall survival from incident metastatic disease was 8.8 years. **Conclusions:** On average, we found a man undergoing radical prostatectomy for localized prostate cancer can expect about a 1 in 4 chance of biochemical recurrence. Of men with BCR, we identified a 1 in 10 chance of developing metastases, surviving nearly 9 years after incident metastasis. Both metastasis-free survival after biochemical recurrence and overall survival after developing metastasis appear to have lengthened consistent with a long natural history after prostate cancer surgery. Novel advanced prostate cancer treatments may help explain these findings, though their optimal use warrants further study especially as advanced imaging techniques to characterize recurrence increase. Research Sponsor: U.S. National Cancer Institute.

National cohort of radical prostatectomy patients (n=22,033).

Characteristics	
Age at diagnosis (mean, (SD))	61.7 (6.2) years
Follow-up time (months, median, IQR)	111.3 (37.6) months
TNM stage	
≤cT1c	15660 (71.1)
cT2	6220 (28.2)
cT3	153 (0.7)
PSA	
≤4 ng/mL	3326 (15.2)
4.1-10 ng/mL	15239 (69.6)
10.1-20 ng/mL	2398 (11.0)
≥20 ng/mL	922 (4.2)
Biopsy Gleason score	
≤6	7258 (33.1)
7	11977 (54.6)
8-10	2691 (12.3)
Pathologic Gleason score	
≤6	1861 (18.3)
7	7259 (71.4)
8-10	1050 (10.3)
Surgical Margins	
Positive	3953 (17.9)
Negative	15735 (71.4)
Unknown	2343 (10.6)
Charlson Score	
0	5331 (67.0)
1	2009 (25.3)
≥2	616 (7.7)
Pathologic T stage	
pTa	2763 (12.5)
pT0	18 (0.1)
pT2	15646 (71.0)
pT3	3575 (16.2)
pT4	31 (0.1)
Pathologic N stage	
Unknown	5572 (25.3)
N0	16336 (74.1)
N1	125 (0.6)
Had biochemical recurrence	5963 (27.1)
Had metastatic disease	820 (3.7)

5091 **Poster Session**

Methylated DNA markers in urine aid in the selective identification of patients with prostate cancer as well as clinically significant pathology. *First Author: Paras Shah, Mayo Clinic, Rochester, MN*

Background: Controversy surrounding prostate-specific antigen (PSA) based screening for prostate cancer (PCa) highlights the need for non-invasive assays that better discriminate patients with and without clinically significant prostate cancer (csPCa). Such distinction avoids overtreatment in patients with absent or indolent disease while capturing pathology that would derive benefit from intervention. We analyzed the presence of specific methylated DNA markers (MDMs) within urine samples of patients with biopsy proven PCa and assessed the ability to discriminate these patients from healthy controls with no clinical suspicion for PCa. **Methods**: 24 healthy volunteers with no clinical suspicion for PCa were age-matched to 24 patients with biopsy-confirmed disease across all Gleason scores. Urine collected from subjects was centrifuged with the cell-free supernatant analyzed in a blinded fashion for methylation signal within specific DNA sequences across 14 genes (*HES5, ZNF655, ITPRIPL1, MAX.chr3.193, SLCO3A1, CHST11, SERPINB9, WNT3A, KCNB2, GAS6, AKR1B1, MAX.chr3.727, GRASP, ST6GALNAC2*) by target enrichment long-probe quantitative-amplified signal assays. A patient was considered to have a positive MDM panel if any individual marker exceeded the corresponding100% specificity cut-off value (overall MDM panel specificity of 100%). MDM panel positivity was used to evaluate the sensitivity for distinguishing patients with PCa (any Gleason score) from controls as well as discriminate csPCa cancers from PCa Gleason 6. **Results:** Median age of healthy controls and PCa patients was 70 years (IQR 67-72) and 65 years (IQR 61-71), respectively. Median PSA was 6.4 (IQR 4.9-9.0) among PCa patients, including median PSA of 5 (IQR 4.0-6.1) for Gleason 6, and 7.8 (IQR 5.1-9.2) for Gleason ≥7 disease. Gleason 6, Gleason 7, and Gleason 8+ cancer was noted in 8, 10, and 6 patients, respectively. Utilizing an overall specificity cut-off of 100% for discriminating normal controls from PCa cases across the MDM panel revealed an overall sensitivity of 83% (95% CI: 63-95%) for detection of PCa (6 of 8 Gleason 6, 9 of 10 Gleason 7, 5 of 6 Gleason 8+) and 88% (95% CI: 62-98%) for csPCa (Gleason ≥ 7). When considering a 100% specificity threshold for controls and Gleason 6 patients, the sensitivity the MDM panel was 69% (95% CI: 41-89%) for csPCa (6 of 10 Gleason 7, 5 of 6 Gleason 8+). **Conclusions:** We describe a panel of 14 MDMs within urine that offer high specificity and sensitivity for detection of prostate cancers as well as selective identification of clinically significant disease states. Prospective comparison between urine MDMs and PSA blood testing is necessary to discern the differential clinical impact of each screening methodology. Research Sponsor: Exact sciences.

5092 **Poster Session**

Is there a role for surgery after chemotherapy in recurrent/metastatic adrenal cortical cancer (ACC)? *First Author: Esmail Mutahar Al-Ezzi, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada*

Background: ACC is a rare endocrine malignancy. Patients with metastatic disease at diagnosis are often treated palliatively with systemic therapy. It is unclear if neoadjuvant cytoreduction with chemotherapy can render metastatic or previously resected but locally recurrent patients become surgical candidates and impact overall survival (OS). **Methods:** A retrospective single institution review (2002-2019) of metastatic ACC patients was performed. Descriptive statistics were used and OS was estimated by Kaplan-Meier method. **Results:** Out of 84 patients with metastatic ACC [30 (20.7%) upfront and 54 (37.2%) after definitive therapy], 51 received systemic therapy with mitotane and etoposide-doxorubicin-cisplatin (EDP) as standard 1st line regimen and varied subsequent lines of therapy. Two patients were excluded as they were lost to follow-up. Among the included 49 patients, 29 were females (59.2%) and 26 patients (53.1%) had functional tumors at baseline. Out of 33 patients who had information available on tumor grade, 26 (78.8%) were high grade. Nine pts (18.4%) underwent surgery after receiving systemic therapy (eight after EDP in first line and one after pembrolizumab in third line). These patients were younger (median age 39 years compared to 52.5 years for those receiving only chemotherapy), had locally recurrent disease (all nine patients) with four having evidence of progressive liver metastasis. Median number of EDP cycles delivered before surgery was 4 (range 3-7). The patient who underwent surgery after pembrolizumab received nine cycles of preoperative pembrolizumab. Five pts (55.5%) had partial response, three (33.3%) had disease progression and one (11.1%) had stable disease prior to surgery. Patients underwent surgery after a mean interval of 3.1 months (m) (1.1-5.1) after systemic therapy. Six patients had no evidence of disease (NED) (five with disease limited to adrenal bed) after surgery. Eight out of nine patients recurred after surgery with a median time of 6.1 m (4.4-7.8). The median OS for the entire cohort was 26 m (95% CI 22.3-35.2). This was not significantly better for patients undergoing surgery [median OS 31.2 m (95% CI 21.4-63.3) vs 24.7 m (95% CI 17.7-35.2) p = 0.48]. Patients rendered NED after surgery had numerically better OS than those with residual disease or those receiving only chemotherapy [median OS 39.6 m (24.8.-NR), vs 23.5 m (21.4-NR) vs 24.7 m (17.7-35.2), p = 0.271]. Higher Ki-67 predicted for inferior OS in the entire cohort with no effect of age, gender, tumor grade or functional status. **Conclusions:** Attempting to downstage patients with metastatic or locally recurrence with systemic therapy does not seem to prolong OS in patients with ACC. Selected patients with limited disease burden, who can be rendered disease free by surgery, may be suitable for this approach. Research Sponsor: None.

TPS5093 **Poster Session**

Camrelizumab combined with TIP (paclitaxel+cisplatin+ifosfamide) as neoadjuvant treatment of locally advanced penile cancer before lymphadenectomy: An exploratory, phase II study. *First Author: Yongsheng Chen, Harbin Medical University Cancer Hospital, Harbin, China*

Background: Penile squamous cell carcinoma (PSCC) is a highly aggressive disease that accounts for 95% of penile cancers and is characterized by a high risk of early locoregional spread and morbidity with subsequent potential for distant dissemination. The lymph node invasion is one of the most important factor that affects the prognosis of PSCC. Penile cancer patients with uninvolved inguinal lymph nodes had a 5-year survival rate of 66% compared with 27% for those with involvement, and penile cancer with the pelvic lymph node involvement have a worse 5-year survival rate that is typically less than 10%. Therefore, this study aims to reduce small lesions to reach the radical lymphadenectomy by camrelizumab combined with TIP in the neoadjuvant treatment of PSCC. **Methods:** In this single-arm, prospective, phase II study, 34 patients with histological or cytological diagnosis of locally advanced PSCC (TX, N2-N3, M0), ECOG performance score of 0-1, planned to be recruited. Enrolled patients with inguinal and/or pelvic lymph node metastasis (positive percutaneous lymph node biopsy) after primary tumor resection of penile cancer were treated with combined therapy including camrelizumab (200 mg, iv, Q3W), paclitaxel (175 mg/m^2, iv, Q3W), cisplatin (25 mg/m^2, iv, Q3W) and ifosfamide (1200 mg/m^2, iv, Q3W) for a total of 4 cycles. The primary endpoint is the rate of pathologic complete response (pCR). Secondary endpoints are event-free survival, overall survival, objective response rate, disease control rate and safety. On the basis of a threshold pCR rate of 13.6%, targeting an expected pCR of 34% and assuming 12 months follow-up, 80% power and a one-sided $\alpha = 0.05$, this design requires 34 evaluable patients to be accrued over 3 years. Clinical trial information: ChiECRCT20210503. Research Sponsor: None.

TPS5094 **Poster Session**

A phase II trial of cemiplimab alone or in combination with standard of care chemotherapy in locally advanced or metastatic penile carcinoma (EPIC Trial). *First Author: Emily Renninson, University Hospitals Bristol and Weston NHS FT, Bristol, United Kingdom*

Background: Penile cancer (PC) is rare but its incidence is increasing, with an increase of 21% over the last decade. The rarity of this cancer means a paucity of large prospective clinical trial data to guide the management of locally advanced/metastatic penile cancer (la/mPC). Cisplatin containing combination chemotherapy regimens are widely regarded as the standard of care (SOC) in this setting. However, with response rates of about 50% there is a need to further improve treatment outcomes. PDL1 is upregulated in 40–60% of PC cases and is correlated with poor prognosis making a case for immunotherapy as a treatment for la/mPC. Currently there are ongoing clinical trials exploring immunotherapy on penile carcinoma, however, none of these trials are looking at the combination of immunotherapy and chemotherapy. The novel immune checkpoint inhibitor cemiplimab has been approved for locally advanced and metastatic cutaneous squamous cell carcinoma (mcSCC). In view of this, we sought to evaluate the benefit and safety of cemiplimab alone, or, in combination with SOC chemotherapy in patients with la/mPC. **Methods:** This is a non-randomised, open label, two arm phase II multicentre trial of single agent cemiplimab versus cemiplimab + SOC chemotherapy in la/mPC, choice of arm decided by the investigator site based on chemotherapy eligibility. Eligibility includes patients with la/mPC who are candidates for immunotherapy +/- SOC chemotherapy (local UK centre choice of cisplatin/5FU or TPF or TIP regimes). 47 patients will be recruited from 10 UK centres: 29 patients into ARM 1 who will receive 4 cycles of cemiplimab 350mg IV q3 weekly + SOC chemotherapy, followed by single agent cemiplimab x 30 cycles (24 months total). 18 patients into ARM 2 who will receive single agent cemiplimab 350mg IV q3 weekly, up to 34 cycles (24 months total). The primary endpoint is clinical benefit rate (CBR) of cemiplimab: objective response rate (ORR) plus stable disease as assessed radiologically (RECIST 1.1) post cycle 4 in patients with la/mPC. Secondary end-points include safety, tolerability, CBR at 1, 2 and 3 years, ORR, progression-free survival, overall survival and assessment of patient health status and quality of life using the patient reported outcome measures EQ-5D-5L and EORTC QLQ-C30. Each arm will be analysed separately as a Fleming A'Hern study $\alpha = 0.05$ + power $(1\text{-}\beta) = 0.8$. Arm 1 assumes 25% meeting the clinical end point is a poor treatment (p0 = 0.25) and 50% is a good treatment (p1 = 0.5). Arm 2 assumes 5% meeting the clinical end point is a poor treatment (p0 = 0.05) and 25% is a good treatment (p1 = 0.25). To date, 4 patients have been recruited from 2 centres with the aim to open all UK centres to recruitment by June 2022. The EPIC trial is NCRN badged. Clinical trial information: 95561634. Research Sponsor: Sanofi.

TPS5095 **Poster Session**

ETCTN 10437: A single-arm phase II study of bone-targeted sn-117m-DTPA in symptomatic castration-resistant prostate cancer with skeletal metastases. *First Author: Zin Myint, University of Kentucky, Lexington, KY*

Background: Most patients with metastatic castration resistant prostate cancer (mCRPC) develop bone metastases with debilitating pain that is itself associated with shorter survival. Several bone-seeking radionuclides have been developed for palliation of metastatic bone pain. To date, radium-223 dichloride is the first and only approved targeted alpha therapy for mCRPC; the major dose limitation is bone marrow toxicity with modest pain relief. Sn-117m-diethylenetriaminepentaacetic acid (DPTA), is a complex of a radioisotope of tin with DTPA. It emits a low-energy conversion electron and also yields a gamma emission. Sn-117m-DPTA localizes selectively in bone, and the limited range (0.2-0.3 mm) of its conversion electrons resulting in deeper tissue penetration with less radiation effects on bone marrow as compared to radium-223 dichloride. Srivastava et al. (1998) reported in a phase I/II study of patients with painful bone metastases from a variety of solid tumors, 45% of patients obtained reduction of pain by at least 50%, and 30% had complete relief of pain for more than two weeks after one injection. Thus, Sn-117m-DTPA has high palliative efficacy with little significant toxicity. Additional evaluation of this agent in mCRPC patients is urgently required. **Methods:** The study is a phase 2 single-arm clinical trial of Sn-117m-DPTA (20 mCi/70Kg or 0.28 mCi/kg) intravenously every 8 weeks for two injections for patients with mCRPC metastatic to at least two bone sites with at least one clinically meaningful pain site at baseline. Re-treatment with additional two cycles is allowed if patients meet re-treatment criteria. Key eligibility criteria include 1) refractory mCRPC patients who progressed on any lines of therapies 2) self-reported bone pain (≥4 on an 11-point pain intensity scale), and 3) must be on either regular pain medication or have undergone palliative radiation for bone pain within 12 weeks prior to starting study treatment. Key exclusion criteria include 1) visceral metastases and 2) malignant lymphadenopathy exceeding 3cm in short-axis diameter. Twenty-five patients will be enrolled with a primary objective to assess the efficacy of Sn-117m-DTPA on sustained pain response; defined as 1) achieving pain index ≤3 index within a 12-week period and 2) maintaining pain index ≤3 over a 16-week period. Secondary endpoints include patient reported outcomes, adverse events, progression-free survival and overall survival. Correlative aims include assessing blood (systemic inflammatory markers) and tissue biomarkers (gene sequencing and polo-like kinase-1) for association with clinical benefit. An interim analysis will be performed to assess efficacy after 10 patients become evaluable. The study began enrolling patients in December 2021 and is ongoing. Clinical trial information: NCT04616547. Research Sponsor: ETCTN UM1 grant.

TPS5096 **Poster Session**

TALAPRO-3: A phase 3, double-blind, randomized study of enzalutamide (ENZA) plus talazoparib (TALA) versus placebo plus ENZA in patients with DDR gene–mutated, metastatic castration-sensitive prostate cancer (mCSPC). *First Author: Neeraj Agarwal, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT*

Background: TALA is a poly(ADP-ribose) polymerase inhibitor (PARPi) approved as monotherapy for germline *BRCA1/2*-mutated HER2-negative advanced breast cancer. Clinical efficacy in metastatic castration-resistant prostate cancers (mCRPC) with alterations in DNA damage response (DDR) genes involved directly or indirectly in homologous recombination repair (HRR) has been demonstrated with some PARPi. Phase 3 study findings (de Bono et al. *N Engl J Med*, 2020;382:2091-2102) resulted in the approval of olaparib for mCRPC. ENZA is an androgen receptor (AR) inhibitor and established therapy for mCSPC. Since PARP activity has been shown to support AR function, PARP inhibition may increase sensitivity to AR-directed therapies. In addition, AR blockade downregulates HRR gene regulation, which has been hypothesized to induce a "*BRCA*ness" phenotype. A Phase 2 study of TALA monotherapy (TALAPRO-1) demonstrated robust antitumor activity in men with heavily pretreated, HRR-mutated mCRPC. The Phase 3, double-blind, randomized trial TALAPRO-3 (NCT04821622) herein presented will compare the combination of TALA plus ENZA vs placebo plus ENZA in men with mCSPC with DDR/HRR alterations. **Methods:** Approximately 550 patients with mCSPC harboring DDR/HRR alterations will be randomized to TALA (0.5 mg once daily) plus ENZA (160 mg once daily) or placebo (once daily) plus ENZA (160 mg once daily). Patients will be stratified according to de novo mCSPC vs relapsed mCSPC, high-volume disease vs low-volume disease, where high-volume disease is defined as the presence of visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis and BRCA vs non-BRCA mutational status. Key eligibility criteria include age ≥18 years; histological diagnosis of prostate cancer; alterations in at least one of 12 DDR/HRR genes known to sensitize patients to PARPi (*ATM*, *ATR*, *BRCA1*, *BRCA2*, *CDK12*, *CHEK2*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, *PALB2*, *RAD51C*); and metastatic disease (no brain metastases). Primary endpoint is rPFS (time to radiographic progression in soft tissue per RECIST 1.1 or in bone per PCWG3 criteria by investigator, or death). Secondary endpoints include overall survival, safety, and patient-reported outcomes. Patient recruitment is planned at approximately 285 sites in 27 countries, including the US and Europe, South America, South Africa, and Asia-Pacific. This study was approved by an Institutional Review Board. Clinical trial information: NCT04821622. Research Sponsor: Pfizer.

TPS5097 **Poster Session**

A phase 2, multicenter, parallel-group, open-label study of vudalimab (XmAb20717), a PD-1 x CTLA-4 bispecific antibody, alone or in combination with chemotherapy or targeted therapy in patients with molecularly defined subtypes of metastatic castration-resistant prostate cancer. *First Author: Mark N. Stein, Division of Hematology and Oncology, Herbert Irving Comprehensive Cancer Center, Columbia University Irving Medical Center, New York, NY*

Background: Although immune checkpoint inhibitor (ICI) monotherapy has shown limited clinical benefit in patients with metastatic castration-resistant prostate cancer (mCRPC), better outcomes have been observed with combination anti-PD-1/CTLA-4 therapy. In addition, whereas response rates are low in unselected mCRPC populations, tumors with selected molecular characteristics, including those associated with aggressive variant disease, CDK12 inactivation, and microsatellite instability high (MSI-H) status, have shown increased sensitivity to ICIs. Finally, altering the tumor microenvironment to promote antitumor immunity by combining ICIs with chemotherapy or targeted agents also has potential to increase clinical benefit. Vudalimab (XmAb20717) is a humanized bispecific monoclonal antibody that simultaneously targets PD-1 and CTLA-4 and binds preferentially to PD-1/CTLA-4 dual-positive cells. In a Phase 1 study, vudalimab monotherapy was generally well-tolerated and associated with complete and partial responses in patients with multiple tumor types, including mCRPC. This Phase 2 study is designed to evaluate the safety and antitumor activity of vudalimab in combination with other anticancer agents or alone in subgroups of mCRPC patients with and without specific tumor molecular subtypes. **Methods:** This multicenter, open-label study is being conducted at approximately 20 sites in the United States. Patients with mCRPC that progressed following treatment with ≥ 2 prior lines of anticancer therapy are enrolled into the following parallel cohorts based on the presence or absence of molecular abnormalities from prior sequencing of metastatic tumor: aggressive variant (Cohort 1), homologous recombination deficient or CDK12 mutation positive PARP inhibitor progressor (Cohort 2) or PARP inhibitor naïve (Cohort 3), MSI-H or mismatch repair deficient (Cohort 4), and no targetable mutation (Cohort 5). All patients will receive vudalimab 10 mg/kg intravenously every 2 weeks. Cohorts 1, 2, and 5 (n = 20 each) also will receive carboplatin AUC 4 + cabazitaxel 20 mg/m^2 (or docetaxel 60 mg/m^2, if not received prior) every 3 weeks; Cohort 3 (n = 20) also will receive olaparib 300 mg 2x/day; and Cohort 4 (n = 5) will receive vudalimab monotherapy. The primary objective is to evaluate the safety/tolerability of treatment based on adverse events. Secondary objectives include evaluating objective response (RECIST 1.1, as modified by PCWG3), radiographic progression-free survival, and PSA response. Exploratory objectives include assessing pharmacodynamic activity in peripheral blood and tumor, and correlations of response with cohort-specific molecular tumor characteristics. Enrollment has been initiated. Clinical trial information: NCT05005728. Research Sponsor: Xencor, Inc.

TPS5098 **Poster Session**

A phase Ia/Ib study of talazoparib in combination with tazemetostat in metastatic castration-resistant prostate cancer (mCRPC). *First Author: Atish Dipankar Choudhury, Dana-Farber Cancer Institute, Boston, MA*

Background: Enhancer of zeste homolog 2 (EZH2) is frequently overexpressed in metastatic castration-resistant prostate cancer (mCRPC), and is linked to lineage plasticity and therapy resistance. In pre-clinical studies, EZH2 directly regulates DNA damage repair (DDR) gene expression, and pharmacologic inhibition of EZH2 sensitizes prostate cancer cells to genotoxic stress as induced by poly-ADP ribose polymerase (PARP) inhibition. The PARP inhibitor talazoparib and EZH2 inhibitor tazemetostat are currently under study in mCRPC, and we are conducting a Phase 1 clinical trial of the combination. **Methods:** Phase 1a of the study will define the recommended phase 2 dose (RP2D) and Phase 1b will better assess safety and preliminary clinical activity of the combination at the RP2D. Eligible patients must have progressive disease after at least one secondary hormonal therapy and taxane-based chemotherapy (or felt not to be more appropriate for taxane), have disease evaluable for response (PSA ≥ 2 ng/ml or measurable disease by RECIST 1.1) and have a metastatic lesion amenable to biopsy adequate for next generation sequencing. In Phase 1a (n = 9-18), the starting doses are talazoparib 0.75 mg daily and tazemetostat 600 mg BID, with dose escalation/de-escalation of both agents by up to 2 dose levels [DLs] based on a 3+3 design. The RP2D is the maximum tolerated dose (MTD) or DL +2 (talazoparib 1 mg daily + tazemetostat 800 mg BID) if the MTD is not reached. After 6 patients are treated at the RP2D, phase 1b will enroll an additional 20 patients to an expansion cohort. The primary endpoint of safety and tolerability is based on incidence of dose-limiting toxicities [DLTs] and incidence and grade of adverse events [AEs] by CTCAE version 5.0. For the secondary endpoint of overall response rate (ORR; defined as PSA reduction by ≥ 50% OR radiographic response by RECIST 1.1), with a sample size of 26 (6 patients from dose escalation and 20 from expansion), we deem talazoparib+tazemetostat effective if ORR is ≥ 5/26 (19%). The probability of concluding that the treatment strategy effective is 0.11 if its true response rate is 10% and at least 0.93 if the true response rate exceeds 30%. Mandatory pre-treatment and on-treatment (8-week) biopsies will undergo targeted genetic sequencing, transcriptomic profiling, ChIP (Chromatin ImmunoPrecipitation)-seq, and immunohistochemistry (IHC) for DDR and differentiation markers; blood specimens will undergo circulating cell-free DNA and circulating tumor cell profiling – these studies will nominate possible predictive biomarkers for therapeutic response and serve as pharmacodynamic markers of combined PARP and EZH2 inhibition. The goal of this study is to expand treatment options in mCRPC through a novel approach to exploit EZH2 as a therapeutic target through co-targeting the DDR response. Enrollment began in July 2021. Clinical trial information: NCT04846478. Research Sponsor: Pfizer, Other Foundation, Pharmaceutical/Biotech Company.

TPS5099 **Poster Session**

Trial in progress: Durvalumab and olaparib for the treatment of prostate cancer in men predicted to have a high neoantigen load. *First Author: Alexandra Sokolova, Oregon Health and Science University Knight Cancer Institute, Portland, OR*

Background: Approximately 30% of patients (pts) treated with definitive surgical and/or radiation therapy for localized prostate adenocarcinoma develop biochemical recurrence (BCR). The optimal time to initiate androgen deprivation therapy (ADT) for such patients is controversial and depends on patient and provider preference, absolute PSA value, and PSA doubling time (PSADT), which has been associated with time to metastasis. Because the time from BCR to metastasis can be long in many cases, strategies allowing pts to avoid ADT while extending metastasis-free survival are desirable. Prior studies have shown that a high tumor neoantigen load correlates with response to anti-PD(L)1. We hypothesized that PARP inhibitor-induced genomic instability may sensitize tumors to anti-PD(L)1 through: i) increasing mutational burden and subsequent tumor neoantigen formation, and/or ii) through activation of other immunogenic pathways (e.g. the STING pathway). This trial investigates an ADT-sparing approach for men predicted to have high neoantigen load and who have BCR prostate cancer. **Methods:** This is a phase 2 clinical trial testing durvalumab (1500 mg IV every 4 weeks) and olaparib (300 mg PO twice a day) (one cycle = 4 weeks) in men with BCR (PSADT≤10 months) whose tumors are predicted to have high neoantigen load based on: biallelic *CDK12* mutations (Cohort A), mismatch repair deficiency (MMRd)/high microsatellite instability (MSI-H) (Cohort B), or loss of function mutations in homologous recombination repair (HRR) genes (Cohort C). Cohorts A and B will receive 3 cycles of durvalumab followed by 3 cycles of the combination of durvalumab and olaparib. Given the proven efficacy of olaparib in prostate cancer patient whose tumors posses an HRR gene mutation, Cohort C will receive 6 full cycles of the combination. Ten patients will be enrolled in each cohort (total n = 30) at two collaborating sites. This study was designed to provide preliminary efficacy data across eligible cohorts, with a primary objective of estimating the proportion of pts with an undetectable PSA at 12 months within each cohort. Secondary objectives include safety, proportion of patients with ≥50% decline in PSA from baseline and quality of life measures. Correlative studies will assess blood and tissue molecular biomarkers for association with outcomes. The study is open with two patients enrolled at the time of abstract submission. Clinical trial information: NCT04336943. Research Sponsor: Astra Zeneca.

TPS5100 **Poster Session**

Phase I/II study of ^{225}Ac-J591 plus ^{177}Lu-PSMA-I&T for progressive metastatic castration-resistant prostate cancer. *First Author: Jones T. Nauseef, New York-Presbyterian Hospital/Weill Cornell Medical Center, New York, NY*

Background: PSMA is overexpressed by most prostate cancers and can be successfully targeted by both antibodies (mAb) and small molecule ligands (SML), each with overlapping and distinct binding sites, kinetics, and biodistributions [Kratochwil Sem Nuc Med 2019]. mAbs are larger, with longer circulating times resulting in greater exposure to bone marrow, but lesser access to PSMA expression on luminal tissue (*e.g.* salivary glands, small bowel, and kidney). In contrast, SMLs are rapidly excreted via kidneys and readily diffuse to all PSMA-expressing sites. Toxicities of 177Lu vary with these differences in biodistribution (*e.g.* more hematologic toxicity with mAb, more xerostomia and nausea with SML, $p < 0.001$)[Niaz AUA 2020]. Alpha emitting isotopes have shorter ranges but high potency compared to beta emitters which have longer ranges, but lower linear energy transfer. In preclinical models, the combination of mAb plus SML has demonstrated additive binding in LNCaP, CWR22Rv1, and PC3/PSMA PC cell lines, and synergistic uptake of 177Lu-mAb plus 177Lu-SML in xenograft models. We developed a phase I/II study to test our hypothesis that concomitant mAb and SML targeting, plus the combination of alpha (225Ac) and beta emitters (177Lu), may offer complementary benefits in a safe and effective manner. **Methods:** Key eligibility criteria include progressive mCRPC (PCWG3), at least 1 prior AR pathway inhibitor and taxane chemotherapy (or ineligible/refused), and adequate organ function and performance status. PSMA PET/CT must have at least 1 lesion with SUVmax > liver SUV. Prior PSMA-based therapy with radioisotopes is not allowed. 177Lu-PSMA-I&T (PNT2002) will be administered as in the phase III SPLASH study (6.8 GBq q8w for up to 2 doses). The phase I includes up to two dose-escalation cohorts of concurrent 225Ac-J591 (30 & 40 KBq/Kg q8w x2) in a modified 3+3 schema. All subjects undergo 177Lu SPECT on Day 8 after each dose. The primary objective of the Phase I study is to determine the dose-limiting toxicity and recommended phase II dose (RP2D) for this combination. Primary objective of the Phase II study is to assess the proportion of patients with > 50% PSA decline after treatment. Secondary objectives include radiographic response rate (PCWG3-modified RECIST 1.1), biochemical and radiographic progression-free survival, overall survival, safety (CTCAE 5.0), CTC count changes and conversions, and patient-reported outcomes (FACT-P, BPI-SF, EQ-5D). Exploratory objectives include pre- and post-treatment PSMA-based imaging changes, effects of PSMA radionuclides on the microbiome, relationship between genomic alterations and response, and relationship between PSMA PET/CT results and outcome. The phase I was activated at Weill Cornell Medicine in May 2021. Following determination of the RP2D, a multicenter phase II is planned at Prostate Cancer Clinical Trials Consortium (PCCTC) in 2022. Clinical trial information: 04886986. Research Sponsor: Weill Cornell Medicine, Pharmaceutical/Biotech Company, U.S. National Institutes of Health.

TPS5101 **Poster Session**

A phase 1 study of AMG 509 in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). *First Author: Daniel Costin Danila, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Six-transmembrane epithelial antigen of prostate 1 (STEAP1) is overexpressed on the surface of prostate cancer cells with low or no expression on normal tissue. AMG 509 is a bispecific XmAb 2+1 T-cell engager that simultaneously binds to STEAP1 on tumor cells and the CD3 complex on T cells resulting in T-cell mediated lysis of STEAP1-expressing cells. AMG 509 demonstrated significant antitumor activity in preclinical prostate cancer models. **Methods:** This 4-part, first-in-human study will evaluate AMG 509 in pts with mCRPC previously treated with novel hormonal therapy (NHT) and will assess the safety, tolerability, pharmacokinetics (PK), and efficacy of AMG 509 to establish the maximum tolerated dose (MTD) and/or the recommended phase 2 dose (RP2D). Part 1 is currently enrolling pts previously treated with NHT and up to 2 prior taxanes. As of 31 January 2022, 60 of up to 110 pts have been enrolled for treatment with intravenous (IV) AMG 509 with initial inpatient dosing followed by outpatient treatment. Part 2 will evaluate subcutaneous dosing of AMG 509 in the same patient population as in Part 1. Part 3 will explore AMG 509 IV dosing in chemotherapy-naïve pts who have been treated previously with one NHT and will provide additional data on the safety, PK, efficacy, pharmacodynamics, and correlative biomarkers at the MTD or RP2D determined in Part 1. Part 4 will evaluate the combination of AMG 509 with abiraterone (Part 4A) or enzalutamide (Part 4B) in pts previously treated with one NHT and up to 1 prior taxane for castration-sensitive disease. Primary outcome measures include dose-limiting toxicities, treatment-emergent and treatment-related adverse events, and change in clinical and laboratory parameters. Key secondary outcome measures include PK, objective response per RECIST 1.1, prostate-specific antigen response, progression-free survival, and overall survival. Key inclusion criteria are men ≥18 years of age with pathologically confirmed mCRPC, refractoriness to NHT, evidence of progressive disease, and ECOG performance status of 0–1. Key exclusion criteria are pure small cell or neuroendocrine carcinoma of the prostate, untreated CNS metastases or leptomeningeal disease, recent anticancer therapy or immunotherapy within 4 weeks of start of first dose not including luteinizing hormone-releasing hormone/gonadotropin-releasing hormone analogue (agonist/antagonist) therapy, radiation therapy, and a history of or current autoimmune disease or any disease requiring chronic immunosuppressive therapy. The trial is being carried out in investigative sites in North America, Australia, Asia, and Europe. The study opened in January 2020 and is recruiting pts for the dose exploration phase of Part 1; parts 2 and 4 are open for enrollment. Part 3 will be initiated once the MTD and/or RP2D have been determined in Part 1. Clinical trial information: NCT04221542. Research Sponsor: Amgen Inc.

TPS5102 **Poster Session**

Phase 3 VERACITY clinical study of sabizabulin in men with metastatic castration-resistant prostate cancer who have progressed on an androgen receptor targeting agent. *First Author: Robert Dreicer, University of Virginia Cancer Center, Charlottesville, VA*

Background: Sabizabulin is a first-in-class, oral agent that inhibits microtubule polymerization disrupting the cytoskeleton and arresting cellular proliferation. A Phase 1b/2 clinical study was conducted to establish the MTD and evaluate the preliminary efficacy in men with metastatic castrate resistant prostate cancer (mCRPC) who progressed on at least one androgen receptor targeting agent (ARTA). The most common AEs reported were mild to moderate diarrhea, fatigue, nausea, and vomiting with no clinically relevant neurotoxicity or neutropenia. In the Phase 1b/2, the median radiographic progression free survival for the 63mg dose (n = 55) was 11.4 months (range 6-36+ months) in the Phase 1b portion including responses > 2.75 years. The Phase 3 reformulation which had improved bioavailability is 32mg PO qd. **Methods:** VERACITY is an ongoing Phase 3 multicenter, randomized, active-control study designed to evaluate sabizabulin in the treatment of mCRPC who have progressed on at least one ARTA. Patients on the study will be chemotherapy naive. Subjects (n = 245) are being randomized in a 2:1 ratio to receive sabizabulin (32 mg/d oral) or active control (alternative ARTA) and will remain on study until radiographic progression-free survival (rPFS). Randomization will be stratified by: measurable disease vs bone-only disease and by prior exposure to ARTA (progressed on one vs more than one prior ARTA). The primary efficacy endpoint of the study is median rPFS. Secondary endpoints include: objective response rate (ORR), duration of objective response, overall survival and time to intravenous (IV) chemotherapy. The Phase 3, VERACITY registration clinical trial is current ongoing in approximately 45 clinical sites with enrollment anticipated to be completed in 2022 and with unblinded results presented in 2023 Based upon the Phase 1b/2 clinical trial, sabizabulin daily chronic oral dosing has a favorable safety profile, is feasible to administer chronically, and has significant and durable antitumor activity. mCRPC that has progressed following ARTAs and prior to taxane chemotherapy, remains an urgent unmet medical need for patients with advanced disease. Sabizabulin is an exciting first-in-class agent that may add to the armamentarium for the treatment of mCRPC following progression on ARTA's. Clinical trial information: NCT04844749. Research Sponsor: Veru Inc.

TPS5103 **Poster Session**

DASL-HiCaP: Darolutamide augments standard therapy for localized very high-risk cancer of the prostate (ANZUP1801)—A randomized phase 3, double-blind, placebo-controlled trial of adding darolutamide to androgen deprivation therapy and definitive or salvage radiation. *First Author: Tamim Niazi, Jewish General Hospital, McGill University, Montréal, QC, Canada*

Background: Radiation therapy (RT), plus androgen deprivation therapy (ADT) with a luteinizing hormone releasing hormone analog (LHRHA), is standard of care for men with very high-risk localized prostate cancer (PC), or with very high-risk features and persistent PSA after radical prostatectomy (RP). Despite this, incurable distant metastases develop within 5 years in 15% of men with very high-risk features. Darolutamide is a structurally distinct oral androgen receptor antagonist with low blood-brain-barrier penetration, a demonstrated favorable safety profile, and low potential for drug-drug interactions. Our aim is to determine the efficacy of adding darolutamide to ADT and RT in the setting of either primary definitive therapy, or salvage therapy for very high-risk PC. **Methods:** This study is a randomized (1:1), phase 3, placebo-controlled, double-blind trial for men planned for RT who have very high-risk localized PC on conventional imaging; or very high-risk features with PSA persistence or rise within one year following RP. The trial is stratified by: RP; use of adjuvant docetaxel; pelvic nodal involvement. 1100 participants will be randomized to darolutamide 600 mg or placebo twice daily for 96 weeks. Participants will receive LHRHA for 96 weeks, plus RT starting week 8-24 from randomization. Participants are allowed nonsteroidal antiandrogen in addition to LHRHA for up to 90 days prior to randomization. Early treatment with up to 6 cycles of docetaxel completed at least 4 weeks prior to RT is permitted. The primary endpoint is metastasis-free survival (ICECaP-validated), with secondary endpoints overall survival, PC-specific survival, PSA-progression free survival, time to subsequent hormonal therapy, time to castration-resistance, frequency and severity of adverse events, health related quality of life, fear of recurrence. Tertiary endpoints include incremental cost-effectiveness, and identification of prognostic and/or predictive biomarkers of treatment response, safety, and resistance to study treatment. Clinical trial information: NCT04136353. Research Sponsor: Bayer, Other Government Agency, ANZUP.

TPS5104 **Poster Session**

Phase 1 study of JNJ-69086420, an actinium-225-labeled antibody targeting human kallikrein-2, for advanced prostate cancer. *First Author: Michael J. Morris, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Radioligand therapy for metastatic castration resistant prostate cancer (mCRPC) has been shown to prolong survival, delay disease progression, and improve quality of life, raising hopes that these gains will be amplified with even more cancer-specific targets and more powerful radioligands. Human kallikrein-related peptidase 2 (hK2) is a tumor-associated member of the kallikrein family that shares significant homology to prostate-specific antigen and is minimally expressed in normal non-prostate tissues. JNJ-69086420 (JNJ-420; ^{225}Ac-DOTA-h11B6 [1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid]), is a first-in-class radioimmunotherapy targeted to hK2 antigen. In a phase 0 study of [^{111}In]-DOTA-h11B6, patients with mCRPC (progressed on standard therapies), treatment with a single dose of [^{111}In]-DOTA-h11B6 (2 mg) with/without 8 mg h11B6, demonstrated safety, good tumor localization, nominal normal-organ uptake, and no difference in pharmacokinetics (PK) between 2 and 10 mg antibody mass (Morris *et al. J Clin Oncol.* 2021 39:6 suppl, 122). We have initiated the first-in-human study to assess the safety, PK, pharmacodynamic (PD), and clinical activity of Ac-225 radiolabeled JNJ-420, to determine its recommended phase 2 dose (RP2D) in adults with advanced PC. **Methods:** This open-label, multicenter, phase 1 study will recruit approximately 50 men (aged ≥18 years) with advanced PC across dose escalation (Part 1) and expansion (Part 2) parts. Key eligibility criteria: mCRPC with histologic confirmation of adenocarcinoma, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, adequate organ function based on hematology and serum chemistry, and 1 or more prior novel androgen receptor-targeted therapies (prior chemotherapy acceptable). Key exclusion criteria: prior treatment with radium/strontium/samarium/radioconjugate therapy, superscan findings as protocol defined, active central nervous system metastases. In Part 1, men will receive intravenous (IV) injection of 50 μCi/ 2 mg JNJ-420 (once every 8 weeks) with one or multiple doses; escalation of dose levels to be based on dose limiting toxicities (DLTs) evaluation, until RP2D identification. In Part 2, JNJ-420 is to be given at one of the RP2D(s) determined in Part 1. Primary endpoint is safety (incidence and severity [grading per NCI-CTCAE V5.0] of AEs including DLTs). Secondary endpoints include prostate specific antigen response rate, overall response rate (PCWG3 modified RECIST 1.1 criteria), PK, PD, immunogenicity, and biomarker analyses. Enrollment began in Dec 2020; as of 10 Feb 2022, 4 sites have been initiated and 23 patients enrolled; currently, dose escalation is ongoing. Clinical trial information: NCT04644770. Research Sponsor: Janssen Research & Development, LLC.

TPS5105 **Poster Session**

A phase 1/2 study of REGN4336, a PSMAxCD3 bispecific antibody, alone and in combination with cemiplimab in patients with metastatic castration-resistant prostate cancer. *First Author: William Kevin Kelly, Thomas Jefferson University, Philadelphia, PA*

Background: Prostate cancer is the leading cause of new cancer diagnoses and the second most common cause of cancer-related death in American men. Prognosis is especially poor for men with metastatic castration resistant prostate cancer (mCRPC). Prostate-specific membrane antigen (PSMA) is highly expressed on malignant prostate tissue but shows limited expression on normal tissue. As such, PSMA is an excellent research target for treatment of mCRPC. REGN4336 is a PSMAxCD3 bispecific antibody designed to facilitate T-cell–mediated killing of PSMA-expressing tumor cells. In preclinical models, REGN4336 demonstrated strong PSMA-dependent antitumor activity that was dose-dependent. Preclinical data also support clinical research into the combination of REGN4336 with cemiplimab (anti–programmed cell death-1) for treating mCRPC. **Methods:** This is an open-label, Phase 1/2, first-in-human, multicenter dose-escalation study with dose expansion evaluating safety, tolerability, pharmacokinetics (PK), and antitumor activity of REGN4336 administered subcutaneously alone and in combination with intravenous cemiplimab in patients with mCRPC (NCT05125016). Patients must have received at least two prior lines of systemic therapy approved for metastatic and/or castration-resistant disease including a second-generation anti-androgen therapy. In this study, REGN4336 as monotherapy is administered weekly but may be extended to once every 3 weeks following identification of the minimal pharmacologically active dose. REGN4336 in combination with cemiplimab (350 mg) will be administered once every 3 weeks after a 4-week REGN4336 monotherapy lead-in cycle. Study therapies are administered until disease progression, intolerable adverse events, withdrawal of consent, or study withdrawal criterion is met. The primary objectives in dose escalation are to evaluate the safety, tolerability, PK, and recommended phase 2 dosing regimen (RP2DR) of REGN4336 alone and in-combination with cemiplimab. Expansion cohort(s) will be enrolled once RP2DRs have been determined. During the expansion phase, the primary objective is to assess clinical activity, as measured by objective response rate with REGN4336 alone or in combination with cemiplimab per modified Prostate Cancer Working Group 3 criteria. At selected sites, PSMA positron emission tomography/computed tomography scans will be performed at predefined timepoints on study. This study is currently open to enrollment. Clinical trial information: NCT03088540. Research Sponsor: Regeneron Pharmaceuticals, Inc.

TPS5106 **Poster Session**

Phase 1b study of bavdegalutamide, an androgen receptor PROTAC degrader, combined with abiraterone in patients with metastatic prostate cancer. *First Author: Neal D. Shore, Carolina Urologic Research Center, Myrtle Beach, SC*

Background: Bavdegalutamide (ARV-110) is a novel, oral PROteolysis TArgeting Chimera (PROTAC) protein degrader that targets wild-type androgen receptor (AR) and clinically relevant mutants. Bavdegalutamide demonstrated tumor growth inhibition in multiple xenograft models (eg, AR gene amplification, AR mutation, enzalutamide resistance, and enzalutamide insensitivity). In a phase 1/2 study (NCT03888612), bavdegalutamide showed clinical activity in patients with metastatic castration-resistant prostate cancer (mCRPC) who had previously received 1–2 prior novel hormonal agents (eg, abiraterone and/or enzalutamide), including heavily pretreated patients. Abiraterone is approved, in combination with a corticosteroid, to treat patients with mCRPC or with high-risk castration-sensitive prostate cancer (CSPC). Up to a third of patients treated with abiraterone develop primary resistance to this drug and nearly all patients experience disease progression. Here we describe a phase 1b study that will evaluate the combination of bavdegalutamide with abiraterone at the initiation of progression on abiraterone (prostate-specific antigen [PSA] progression without radiographic progression) to test if the addition of bavdegalutamide will overcome resistance to abiraterone and re-establish the AR pathway blockade in patients with prostate cancer. **Methods:** Eligible patients are men ≥18 years of age with histologically, pathologically, or cytologically confirmed adenocarcinoma of the prostate and Eastern Cooperative Oncology Group performance status of 0 or 1. Patients must be receiving ongoing treatment with stable doses of abiraterone and a concomitant corticosteroid for mCRPC or CSPC and have PSA progression ≥16 weeks after initiation of abiraterone, ≥2 rising PSA values measured ≥1 week apart, and no radiographic evidence of disease progression while receiving abiraterone. Ongoing androgen deprivation therapy with a gonadotropin-releasing hormone analogue or inhibitor or orchiectomy is required. Prior treatment with enzalutamide, apalutamide, darolutamide, or experimental AR-directed therapies is not permitted. Bavdegalutamide, abiraterone, and a corticosteroid will be administered daily in 28-day cycles. Primary objectives are to evaluate the safety and tolerability of bavdegalutamide plus abiraterone and determine the recommended phase 2 dose and schedule of this combination (based on the incidence of first-cycle dose-limiting toxicities and the frequency and severity of adverse events and laboratory abnormalities). Clinical trial information: NCT05177042. Research Sponsor: Arvinas Androgen Receptor, Inc.

TPS5107 **Poster Session**

Alliance A031902 (CASPAR): A randomized, phase (ph) 3 trial of enzalutamide with rucaparib/placebo in first-line metastatic castration-resistant prostate cancer (mCRPC). *First Author: Arpit Rao, Dan L. Duncan Comprehensive Cancer Center, Baylor College of Medicine, Houston, TX*

Background: Despite a growing number of treatment options for first line mCRPC, approximately 40% of patients (pts) have radiographic progression within the first year. Androgen receptor (AR) signaling inhibition increases genomic instability with double-strand DNA breaks & co-inhibition of AR & PARP induces synthetic lethality in multiple preclinical models. Homologous recombination repair (HRR) gene aberrations do not appear to be necessary for this synergy as demonstrated in a ph 3 clinical trial of abiraterone & olaparib where this combination improved radiographic progression-free survival (rPFS) in HRR-wild-type pts compared with abiraterone alone. A ph 1b trial has since shown that enzalutamide plus rucaparib has acceptable safety profile & no significant drug-drug interactions (S-DDI). **Methods:** CASPAR/A031902 (NCT04455750) is a ph 3 study in which 984 pts will be randomized 1:1 to enzalutamide plus rucaparib or placebo. HRR gene aberration is not required for enrollment. All pts will undergo next-generation targeted-exome sequencing from archival tumor tissue (new biopsy only required if no archival tissue available). Treatment will be continued until disease progression & crossover is not allowed. Key eligibility criteria are age ≥ 18 years, ECOG PS 0-2, biopsy-proven prostate adenocarcinoma, progressive (PSA or radiographic) disease per Prostate Cancer Working Group 3 guidelines, measurable or nonmeasurable disease per RECIST 1.1, no prior treatment for mCRPC (prior docetaxel, abiraterone, darolutamide, or apalutamide in non-mCRPC setting is allowed), no significant uncontrolled comorbidity, & no medications with S-DDI with enzalutamide/rucaparib. Hierarchical co-primary endpoints are rPFS & overall survival (OS). The OS analysis will be undertaken as a primary endpoint if the rPFS endpoint is met. For a one-sided logrank test with a type 1 error rate equal to 0.025, the study has 90% power to detect a hazard ratio (HR) of 0.71 in rPFS (median rPFS of 15 & 21 months in control & combination arms, respectively) & 80% power to detect an HR of 0.80 in OS (median OS of 32 & 40 months, respectively). Key secondary endpoints are rPFS & OS in pts with *vs* without pathogenic *BRCA1*, *BRCA2*, or *PALB2* alterations; & differences in adverse events & quality of life (QOL) outcomes between the treatment arms. QOL assessments include Functional Assessment of Cancer Therapy–Prostate (FACT-P), Brief Pain Inventory Short Form (BPI-SF) & EQ-5D-5L. A key correlative endpoint is the sensitivity of ctDNA-based testing for alterations in HRR genes. Enrollment to CASPAR began in July 2021 & the study is available for participation to all US-NCTN sites with a projected enrollment of 3 years. Support: U10CA180821, U10CA180882, U24CA196171; U10CA180888. Clinical trial information: NCT04455750. Research Sponsor: U.S. National Institutes of Health, Clovis Oncology.

ABSTRACT WITHDRAWN

TPS5109 **Poster Session**

177Lu-DOTA-TLX591 safety, biodistribution and dosimetry study (ProstACT-SELECT). *First Author: Paola Antonini, Telix Pharmaceuticals, North Melbourne, Australia*

Background: The cell surface glycoprotein prostate-specific membrane antigen (PSMA) has proven to be an ideal therapeutic target in prostate cancer (PC) as it is highly expressed by malignant prostate cells .1,2 177Lu-DOTA-HuJ591-CHO (TLX591) is a radioimmunoconjugate comprised of the humanized IgG1 mAb rosopatamab, linked to the low energy beta-emitting radioisotope lutetium-177 (177Lu) via the bifunctional chelating agent DOTA-NHS ester. Chinese Hamster Ovary (CHO) cell line has been selected for the manufacture of the recombinant mAb. There is a strong rationale for investigation of TLX591 as a potential radioligand therapy for the treatment of PC, supported by previous clinical evidence of the safety of the antibody, as unconjugated and as a DOTA conjugate, and of the specificity of the antibody for PC tumors. 3,4,5,6. This multicenter Phase 1 radiomics study (ClinicalTrials.gov Identifier: NCT04786847) is designed to evaluate the safety, tolerability, biodistribution and dosimetry of TLX591 administered with best SoC to patients with PSMA-expressing, metastatic castration-resistant prostate cancer (mCRPC) progressing despite prior treatment with a novel androgen axis drug (NAAD). At the time of this abstract the study has commenced recruitment in Australia. This trial is sponsored by Telix Pharmaceuticals. **Methods:** The study will consist of 2 cohorts: Cohort 1: Five patients will be recruited for evaluation of biodistribution of TLX591 administered in combination with SoC. These patients will receive a single tracer (27 mCi) intravenous (IV) infusion of TLX591, and SPECT images and pharmacokinetic blood samples acquired at several time points until Day 13. A qualitative comparison of biodistribution of tracer level TLX591, as demonstrated by SPECT, with 68Ga-PSMA-11 on PET imaging will be performed to ensure equivalent (or improved) radiopharmaceutical tumour targeting. Dosimetry analysis will also be performed. If safety is confirmed by independent DSMB review, each individual patient in Cohort 1 will proceed 14 days following the initial tracer dose to a second administration of TLX591. SoC therapy will continue according to standard practice. Cohort 2: All further enrolled patients will receive two administrations of 76 mCi TLX591 for further evaluation of safety, tolerability and biodistribution, and efficacy in combination with SoC. 1. Pan M-H et al. 2009 2. Dorff TB et al., 2019 3. Tagawa, Milowsky et al., 2013 4. Tagawa et al., 2019 5. Tagawa, Whang et al., 2014 6. Niaz et al., 2020. Clinical trial information: NCT04786847. Research Sponsor: Telix Pharmaceuticals.

TPS5110 **Poster Session**

CCTG PR21: A randomized phase II study of [^{177}lu]lu-PSMA-617 verus docetaxel in patients with metastatic castration-resistant prostate cancer and PSMA-positive disease (NCT04663997). *First Author: Kim N. Chi, BC Cancer Agency, University of British Columbia, Vancouver, BC, Canada*

Background: [^{177}Lu]Lu-PSMA-617 improves outcome in men with metastatic, PSMA positive CRPC post androgen pathway inhibitor therapy and taxane chemotherapy compared to standard care (excluding chemotherapy, immunotherapy, radium-223 and investigational drugs; Sartor et al, NEJM 2021). The relative efficacy, adverse event experience and impact on QOL of [^{177}Lu]Lu-PSMA-617 compared to docetaxel chemotherapy in this patient population is unknown. We hypothesize that [^{177}Lu]Lu-PSMA-617 will improve radiographic PFS (rPFS) compared to docetaxel chemotherapy with a favourable safety and tolerability profile. **Methods:** CCTG PR21 is a Canadian Cancer Trials Group randomized phase II trial with a primary objective to compare rPFS between [^{177}Lu]Lu-PSMA-617 7.4 GBq (+/- 10%) IV q 6 weekly (maximum 6 cycles) versus docetaxel 75 mg/m^2 q 3 weekly (maximum 12 cycles). Secondary objectives are to compare the two arms with respect to: 6-month PFS rate (PCWG3 and RECIST 1.1), second rPFS after crossover to the alternate therapy, time to commencement of 3rd line systemic therapy, OS, PSA decline from baseline, clinical benefit rate and adverse events. Tertiary objectives include evaluation of QOL (FACT-P and EQ5D-5L), cost effectiveness, ctDNA and radiographic based prognostic and predictive biomarkers, dosimetry based approach to measurement of [^{177}Lu]Lu-PSMA-617 activity and creation of tissue and image biobanks. Key eligibility criteria include: mCRPC with PSMA positive disease using ^{18}F or ^{68}Ga radionuclide label, progression on ADT + ARPI therapy (using PSA, RECIST 1.1 or PCWG3 criteria) and adequate organ function. Statistical Design: Patients are allocated in 1:1 ratio to [^{177}Lu]Lu-PSMA-617 or docetaxel balanced for stratification factors of ECOG PS, LDH, visceral metastases, previous docetaxel in the castration sensitive setting > 1 year prior to enrollment as well as centre. Assuming a 6-month median rPFS for the control group, the detection of a hazard ratio (HR) of 0.67 with 80% power using a 1-sided 5% level test will require accrual of 200 participants in 24 months with 12-month follow-up to trigger the primary analysis. Conduct to Date: Study activation Dec 17 2020. Enrollment as of January 31 2022: 25. The DSMC last reviewed and recommended continuation of the trial in December 2021. Clinical trial information: NCT04663997. Research Sponsor: Canadian Cancer Society (Prostate Cancer Canada), AAA Novartis.

TPS5111 **Poster Session**

Open-label study of androgen receptor inhibition with darolutamide plus androgen-deprivation therapy (ADT) versus ADT in men with metastatic hormone-sensitive prostate cancer using an external control arm (ARASEC). *First Author: Neal D. Shore, Carolina Urologic Research Center, Myrtle Beach, SC*

Background: Darolutamide is a structurally distinct and highly potent androgen receptor inhibitor (ARI) that significantly improved metastasis-free survival by ~2 years and reduced the risk of death by 31% vs placebo in patients with nonmetastatic castration-resistant prostate cancer (CRPC). Darolutamide has a favorable safety and tolerability profile, with only ≤2% difference vs placebo for most adverse events (AEs) of interest (falls, fractures, hypertension, mental impairment). Fatigue was the only AE with > 10% incidence in the darolutamide arm (13.2%; placebo, 8.3%). Darolutamide has shown lower blood–brain barrier penetration than other ARIs in preclinical models (supported by human neuroimaging studies), which may lead to a lower risk of central nervous system-related AEs and has a low potential for drug–drug interactions. For patients with metastatic hormone-sensitive prostate cancer (mHSPC), the combination of darolutamide and ADT is expected to offer a favorable benefit–risk profile. ARASEC will evaluate the efficacy and safety of darolutamide plus ADT in mHSPC in the US (NCT05059236) and complement the data in the ongoing ARANOTE study (NCT04736199). **Methods:** ARASEC is a US-based, phase 2, open-label, single-arm study with an external control arm. Eligible patients will have confirmed adenocarcinoma of the prostate, radiologic evidence of metastatic disease by conventional imaging, and Eastern Cooperative Oncology Group performance status (ECOG PS) ≤2. Patients with mHSPC will receive darolutamide 600 mg twice daily plus ADT (luteinizing hormone-releasing hormone agonist/antagonist or orchiectomy). The control arm for ARASEC will be derived from the 393 patients with mHSPC treated with ADT alone in the CHAARTED trial. Patients in the active arm will be matched 1:1 to patients in the control arm using important baseline characteristics such as age, ECOG PS, extent of disease defined as low or high volume according to CHAARTED, and presence of bone and visceral metastases. Study duration was defined as the time from the first patient's first visit until either the event count threshold triggering the primary endpoint analysis has been met or all patients have been followed for ≥2 years after enrollment, whichever occurs later. The primary endpoint is progression-free survival (PFS), defined in CHAARTED as the time from enrollment to prostate-specific antigen (PSA) progression, clinical progression (including radiological or symptomatic progression or clinical deterioration), or death, whichever occurs first. Secondary endpoints are overall survival, radiographic PFS, time to CRPC, complete PSA response rate at 6 months, and safety. Patient recruitment is in progress. Clinical trial information: NCT05059236. Research Sponsor: Bayer AG and Orion Pharma.

TPS5112 **Poster Session**

Veterans affairs seamless phase II/III randomized trial of standard systemic therapy with or without PET-directed local therapy for oligorecurrent prostate cancer (VA STARPORT). *First Author: Abhishek A Solanki, Loyola University Chicago, Maywood, IL*

Background: Two diverging paradigms have been studied in recent years to improve the survival of men with recurrent metastatic prostate cancer (PCa). First, multiple recent phase II randomized trials have demonstrated improved long-term progression-free survival (PFS) with metastasis-directed therapy (MDT) in men with oligorecurrent PCa in the absence of systemic therapy. Yet, most patients receiving MDT for oligorecurrent PCa develop progression in new areas, arguing that systemic therapy is needed to treat occult metastases. The second approach that has recently been studied is whether escalating systemic therapy by adding novel androgen receptor axis targeted agents or chemotherapy improves outcomes in men with metastatic PCa. Multiple phase III randomized trials demonstrate that enhancing hormonal therapy with these therapeutic agents improves progression-free survival (PFS) and overall survival. Therefore, these agents have been integrated into today's standard systemic therapy (SST) for metastatic recurrence, and SST is the current NCCN guidelines standard of care for recurrent metastatic PCa. The primary goal of our study is to determine if adding PET-directed local therapy (PDLT) to SST improves disease control compared to SST alone in Veterans with oligorecurrent PCa. **Methods:** VA STARPORT is a phase II/III randomized trial open at 16 VA medical centers comparing SST with or without PDLT in Veterans with oligorecurrent PCa. Key eligibility criteria include prior localized PCa with biochemical recurrence after initial curative-intent local therapy and workup including any FDA-approved PCa PET/CT that reveals oligorecurrence in 1-5 metastatic lesions. The primary endpoint is castration-resistant prostate cancer-free survival (CRPC-free survival). Secondary endpoints include radiographic PFS, clinical PFS, freedom from index lesion progression, toxicity, quality of life, and prostate cancer-specific and overall survival. SST is delivered with an intent for indefinite SST using any NCCN guideline-concordant regimen in both arms. PDLT (Arm 2) consists of surgery or radiation to metastases and any present prostate/prostate bed local recurrence. Metastasis-directed radiation can consist of stereotactic body radiotherapy or elective nodal radiotherapy per clinician discretion from dose/fractionation options defined in the protocol. All participants undergo somatic tumor sequencing using the VA National Precision Oncology Program. Germline sequencing and tumor banking in a separate biorepository study is recommended. Assuming a hazard ratio of 0.60 for SST + PDLT vs SST, two-sided alpha = 0.05 and 90% power, a total of 464 participants will be randomized to generate 166 primary events (CRPC-free survival) by the end of the 48-month active study phase. The study began enrollment in August 2021. Clinical trial information: NCT04787744. Research Sponsor: Merit Review Award Number I01 CX002277 from the United States (U.S.) Department of Veterans Affairs Clinical Sciences R&D (CSRD) Service.

TPS5113 **Poster Session**

Focal radiation with pulsed systemic therapy of abiraterone, androgen deprivation therapy (ADT), olaparib towards castration-sensitive oligometastatic prostate cancer (FAALCON Trial). *First Author: Zachery R Reichert, University of Michigan, Ann Arbor, MI*

Background: Molecular imaging (i.e. PSMA directed agents) identifies metastatic prostate cancer at an earlier disease state than conventional imaging resulting in a new clinical entity within metastatic hormone-sensitive prostate cancer (mHSPC): molecular positive HSPC (mpHSPC). Historically, patients in this category with prior local therapy would have been classified as having a biochemical recurrence only, and observation was routine. Approaches to mpHSPC include observation or the use of focal and/or systemic therapies. Focal radiation for mpHSPC may delay the need for systemic therapy, yet many patients require further focal or systemic treatment. Androgen deprivation therapy (ADT) with abiraterone (abi) benefits men with high-risk localized disease and standard mHSPC. mpHSPC hypothetically resides somewhere between these two disease states. Finally, the inhibition of poly(ADP-ribose) polymerase (PARP) with olaparib plus abi shows promise in metastatic castration resistant prostate, suggesting this approach may be worthy of testing in earlier disease states. **Methods:** FAALCON is a single-site, phase 2 clinical trial testing olaparib with abi, ADT and radiation therapy in oligometastatic mpHSPC. Oligometastatic mpHSPC is defined as up to 5 radiation treatment sites (5 cm maximum size each) and must encompass all visible disease on the molecular scan. Patients must have had their prostate previously treated. The primary endpoint is the percentage of patients without treatment failure 24 months from study start. Treatment failure is defined as one of the following: new or progressive metastases on CT/MRI, new lesions on bone scan without alternate explanation, clinical progression, or a PSA doubling time under 6 months with an absolute final PSA over 1.5 ng/mL. Additional radiation therapy is deemed progression. Select secondary endpoints include time to any subsequent therapy, and percentage of patients with undetectable PSA with a recovered testosterone at multiple timepoints. Correlative work will analyze quality of life and prior prostatic tissue. ADT and abi (1000 mg daily) are given for 6 months, and radiation is completed by day 40. Olaparib (300 mg PO twice daily) is started 2 weeks after radiation completes and continues for the remaining ~5 months. After therapy completion, patients are monitored by PSA q3 months with imaging based on predetermined PSA cutoffs. Molecular imaging (PSMA-PET) may be offered on study. Historical disease control at 24 months is estimated at 40% from prior molecular guided radiation studies and intermittent ADT. With 80% power and a one-sided 5% type-I error, we can detect a hazard ratio of 0.5 (80% control rate) at 24 months with 26 patients. To account for dropout, 29 patients will be accrued. Clinical trial information: NCT04748042. Research Sponsor: AstraZeneca.

TPS5114 **Poster Session**

A phase III double blinded study of early intervention after radical prostatectomy with androgen deprivation therapy with darolutamide versus placebo in men at highest risk of prostate cancer metastasis by genomic stratification (ERADICATE). *First Author: Alicia K. Morgans, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*

Background: Patients with high-risk scores by Decipher molecular testing after prostatectomy have a 5-year metastasis rate of 28% (Decipher 0.6-0.7) and 38% (Decipher > 0.7), likely due to micrometastatic disease. Clinical trials with intensified systemic treatment are warranted to increase cure rates and address this unmet need. Previous studies of adjuvant androgen deprivation therapy (ADT) in clinically identified high-risk disease have not demonstrated substantial benefit other than in men with lymph node positive disease. Darolutamide is a novel androgen receptor antagonist with demonstrated efficacy in improving metastasis-free survival (MFS) and overall survival (OS) in patients with non-metastatic castration-resistant prostate cancer, and OS in patients with metastatic hormone-sensitive prostate cancer (mHSPC). Whether treatment with ADT and darolutamide can increase MFS versus ADT plus placebo in the adjuvant setting for men with molecularly identified high-risk prostate cancer is unknown. **Methods:** Patients with CAPRA-S scores ≥3 and a PSA < 0.2 after radical prostatectomy undergo Decipher testing provided by the trial. Eligible patients with high-risk Decipher scores (> 0.6) will be randomized to treatment with ADT with darolutamide or placebo for 12 months. Patients are stratified by intent to deliver adjuvant radiation and by baseline PSA (undetectable vs detectable but < 0.2 ng/mL). The primary endpoint is MFS defined by novel PET or conventional imaging. With a sample size of 810 patients, the trial has 80% power with one-sided alpha = 0.025 to detect a HR of 0.60 for the experimental arm vs control arm for the primary endpoint. Secondary endpoints include recurrence-free survival, event-free survival, and quality of life (FACT-P, FACT-Cog, and FACIT-Fatigue), overall survival, and other disease-related outcomes. Trial was activated on December 9, 2020, and is currently enrolling patients. Clinical trial information: NCT04484818. Research Sponsor: CTEP - ECOG, Pharmaceutical/Biotech Company.

TPS5115 **Poster Session**

A phase I study of ADXS-504, a cancer type specific immunotherapy, for patients with biochemically recurrent prostate cancer. *First Author: Karie Runcie, Columbia University Medical Center, New York, NY*

Background: Roughly 20%-30% of prostate cancer patients experience biochemical recurrence (BCR), rising prostate-specific antigen (PSA) levels, after definitive therapy with radical prostatectomy (RP) or radiation therapy (RT). The optimal therapy and timing of treatment for BCR is unknown, however, for patients who are not eligible for salvage radiation, androgen deprivation therapy (ADT) is the standard first-line treatment. ADT is an effective therapy but has many acute and long-term toxicities. Novel strategies to reduce ADT exposure and prolong disease control are needed. ADXS-504 is a live attenuated *Listeria monocytogenes (Lm)*-based immunotherapy consisting of a truncated nonhemolytic fragment of listeriolysin O (tLLO) fused to a total of 24 tumor associated antigens (TAA). ADXS-504 was designed so that nearly 20% of patients with BCR cancer will express at least one of the targeted hotspot mutation peptide antigens and that >90% will express at least one of the TAAs targeted by the sequence-optimized TAA peptide antigens. By combining these shared, commonly expressed antigen targets into a single *Lm*-based immunotherapy, ADXS-504 provides the potential for a potent, disease-specific approach to treating patients with prostate cancer. In addition to the generation of antigen-specific T cell responses, treatment with *Lm*-based immunotherapies has been shown to reprogram the tumor microenvironment (TME), by reducing the frequencies and function of immunosuppressive regulatory T cells and myeloid-derived suppressor cells within the TME. A pre-clinical murine model showed that a proto-type Lm-construct could reduce the number of metastases after removal of the primary tumor by eliminating residual tumor cells. We hypothesize that ADXS-504 is safe and promotes anti-tumor immune responses that may delay or prevent the use of ADT in castration sensitive prostate cancer. **Methods:** This is an open-label dose-escalation phase I trial of ADXS-504 in patients with BCR of prostate cancer previously treated with RP or RT. The study will enroll up to 18 subjects with BCR with a PSA $\geq$ 0.3 and a PSADT $\geq$ 4 months without evidence of metastatic disease on traditional CT imaging and bone scans. ADXS-504 will be given by IV every 4 weeks level for 6 study treatments, followed by maintenance therapy given every 12 weeks for 4 doses for overall total of 10 doses of study treatment. DLTs will be evaluated over the first 28 days of treatment. PSA response, PSADT, and adverse events will be summarized. The Kaplan-Meier method will be used to estimate time to PSA progression and rPFS. Immunologic activity will be evaluated by ELISpot analysis, flow cytometry, and multiplex assays and blood samples will be collected for gene sequencing analysis. The study is currently open to enrollment. Clinical trial information: NCT05077098. Research Sponsor: Advaxis, Inc.

TPS5116 **Poster Session**

A randomized trial on pelvic lymph node dissection versus no lymph node dissection at radical prostatectomy: Report of a trial in progress. *First Author: Nicole Benfante, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The therapeutic benefit of pelvic lymph node dissection (PLND) in the surgical treatment of localized prostate cancer remains unproven. In this trial we aim to evaluate whether PLND reduces biochemical recurrence rates in clinically localized prostate cancer patients. We are presenting our experience in accrual during our first year of implementing this trial at Memorial Sloan Kettering Cancer Center. **Methods:** Patients without evidence of positive or suspicious pelvic lymph nodes on pre-operative imaging, and without prior pelvic radiation for prostate cancer are eligible. Following informed consent prior to radical prostatectomy, patients are enrolled onto the trial and surgeons are randomized using a cluster randomization. Surgeons are randomized to perform a PLND vs. no PLND for a 3-month period. Since our trial began accruing in July 2020, we have enrolled 366 patients (51 high risk, 286 intermediate risk, and 29 low risk) out of 996 eligible patients (37%) through January 2022. We have enrolled 168 patients in the PLND arm and 198 patients in the no PLND arm. Table 1 shows the breakdown of patient consent status in each risk group, by randomization assignment. At this stage in the accrual, we do not see evidence of consenting bias among PLND vs. no PLND randomization and risk group. We conclude that a single-center cluster randomized trial can accrue large numbers of patients in a short period of time, allowing for large scale trials to be completed. Currently, our trial is on track to complete accrual within our 5-year goal. Clinical trial information: NCT01407263. Research Sponsor: U.S. National Institutes of Health.

Consent status by risk group for PLND vs. no PLND randomization arms.

		Consented			Declined			Not Approached		
		High (N=51; 5.1%)	Intermediate (N=286; 29%)	Low (N=29; 2.9%)	High (N=29; 2.9%)	Intermediate (N=131; 13%)	Low (N=14; 1.4%)	High (N=113; 11%)	Intermediate (N=307; 31%)	Low (N=36; 3.6%)
No	PLND	25 (49%)	155 (54%)	18 (62%)	19 (66%)	70 (53%)	5 (36%)	58 (51%)	144 (47%)	20 (56%)
PLND		26 (51%)	131 (46%)	11 (38%)	10 (34%)	61 (47%)	9 (64%)	55 (49%)	163 (53%)	16 (44%)

Values are displayed as frequency (percentage).

LBA5500 **Oral Abstract Session**

ATHENA–MONO (GOG-3020/ENGOT-ov45): A randomized, double-blind, phase 3 trial evaluating rucaparib monotherapy versus placebo as maintenance treatment following response to first-line platinum-based chemotherapy in ovarian cancer. *First Author: Bradley J. Monk, GOG Foundation, University of Arizona College of Medicine, Creighton University School of Medicine, Phoenix, AZ*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

5501 **Oral Abstract Session**

A phase I/II study of ruxolitinib with frontline neoadjuvant and post-surgical therapy in patients with advanced epithelial ovarian, Fallopian tube, or primary peritoneal cancer. *First Author: Charles N. Landen, Univ of Texas MD Anderson Cancer Ctr, Houston, TX*

Background: The Interleukin-6/JAK/STAT3 axis, via an increase in cancer stem-like cell (CSC) survival, is a reported driver of chemotherapy resistance. We hypothesized that addition of the JAK1/2 inhibitor ruxolitinib to standard chemotherapy would be tolerable and, by targeting therapy-resistant cells, improve the progression-free survival (PFS) of ovarian/fallopian tube/primary peritoneal carcinoma (OV/FT/PPC) patients treated in the up-front setting. **Methods:** Patients with OV/FT/PPC dispositioned to neoadjuvant chemotherapy were eligible for NRG-GY007 (NCT #02713386). In phase I, treatment was with dose-dense paclitaxel (P) 70 or 80 mg/m2 days 1, 8, and 15; carboplatin (C) AUC 5 or 6 day 1; and ruxolitinib (R) 15mg PO BID, every 21 days. In the absence of tumor progression or an inability to tolerate surgery, interval tumor reductive surgery (TRS) was required after cycle 3. After TRS, 3 additional cycles were administered, followed by maintenance ruxolitinib until progression, unacceptable toxicity, or voluntary withdrawal. In phase II, patients were randomized to dose-dense PC (arm 1) or dose-dense PC plus ruxolitinib (arm 2) at the phase I-defined dose of 15mg PO BID. After 3 cycles, TRS was performed, followed by another 3 cycles of the randomized regimen, without maintenance ruxolitinib. The primary phase II endpoint was progression-free survival (PFS). **Results:** 17 patients were enrolled in phase I. The MTD was P at 70, C at 5, and R at 15, which was chosen as the phase II dose. 130 patients were enrolled in phase II with a median follow-up of 24 months. There were five Grade 5 events in phase II, 2 in arm 1 and 3 in arm 2, with all except one being unrelated to therapy; a G5 febrile neutropenia in arm 2 was considered possibly related. In arm 2 there was potential trend towards higher grade 3-4 anemia (64% v 27% control), grade 3-4 neutropenia (53% v 37%), thromboembolic events (12.6% v 2.4%), and febrile neutropenia (6% v 0%). The HR for PFS was 0.702 (90% 1-sided CI = 0-0.89, log-rank p = 0.059). The median PFS in arm 1 was 11.6 versus 14.6 in arm 2. The overall survival HR = 0.785 (90% CI = 0.44 to 1.39, p = 0.70). There were no differences between rates of total gross resection. **Conclusions:** Ruxolitinib 15mg PO BID was well-tolerated with acceptable toxicity in combination with dose-dense PC. The primary endpoint of prolongation of PFS was achieved in the experimental arm. Further study of this combination can be considered. This trial also demonstrates the feasibility of early-phase randomized studies with novel agents and biospecimen collection in front line neoadjuvant treatment of ovarian cancer. Clinical trial information: 02713386. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

5502 **Oral Abstract Session**

Bevacizumab in first-line chemotherapy to improve the survival outcome for advanced ovarian clear cell carcinoma: A multicenter, retrospective analysis. *First Author: Toshiyuki Seki, Department of Obstetrics and Gynecology, Kashiwa Hospital, The Jikei University School of Medicine, Chiba, Kashiwa, Japan*

Background: Advanced ovarian clear cell carcinoma (ACCC, stage III/IV disease) is a rare tumor characterized by chemoresistance. Bevacizumab (Bev) was approved in November 2013 in Japan and became incorporated in the treatment of advanced ovarian cancer. However, the efficacy of Bev against ACCC remain unknown. We investigated the survival outcomes for ACCC, following first-line chemotherapy with or without Bev. **Methods:** Patients diagnosed with ACCC at seven institutions between 2008 and 2018 were enrolled in this study. Patients underwent cytoreductive surgery and taxane-carboplatin chemotherapy (78: triweekly regimen; 30: weekly regimen; 25: dose-dense regimen; 12: others) with or without concurrent and maintenance Bev (15 mg/kg/3 weeks). We compared the progression-free survival (PFS) and overall survival (OS) before (group A, n = 102) and after (group B, n = 43) Bev approval, using Kaplan–Meier method and Cox regression model. We excluded patients with poor performance status (PS) in group A, and patients who did not receive Bev due to poor PS or thrombosis in group B. **Results:** There was no significant difference between two groups in terms of age (p = 0.135) and initial CA125 level (p = 0.674). Thirteen (13%) and 11 (26%) patients had stage IV disease (p = 0.058) and 2 (3%) and 7 (16%) patients were of poor PS (PS ≥2) (p = 0.004) in group A and B, respectively (p = 0.058). More patients (29/43, 67%) in group B were achieved complete resection than in A group (52/102, 51%) (p = 0.068). The median cycle of Bev in B group was 16 (interquartile range: 6-21). The median follow-up time was 36 months. The median PFS increased from 12.5months in A group to 29.7 months in B group (log-rank test: p = 0.023, Wilcoxon test: p = 0.006). The median OS increased from 34.7 months in A group to 51.4 months in B group (log-rank test: p = 0.085, Wilcoxon test: p = 0.027). Multivariate analysis revealed that Bev use (Hazard ratio (HR): 0.54, p = 0.011; HR: 0.54, p = 0.019), PS <2 (HR: 0.33, p = 0.013; HR: 0.29, p = 0.006) and completeness of resection (HR: 0.38, p < 0.001; HR: 0.37, p <0.001) were independent prognostic factors for PFS and OS. **Conclusions:** Incorporating Bev in first-line chemotherapy may improve PFS in patients with ACCC. Research Sponsor: None.

Multivariable Cox proportional analysis of risk factors for progression-free survival and overall survival for advanced clear cell carcinoma.

		PFS			OS		
Variable		Hazard ratio	[95%CI]	*p* value	Hazard ratio	[95%CI]	*p* value
Performance Status	0-1 / >/=2	0.34	[0.16-0.78]	0.013	0.3	[0.14-0.68]	0.006
Bevacizumab use	Bev + / -	0.55	[0.32-0.87]	0.011	0.54	[0.30-0.91]	0.019
Completeness of resection	Complete / Others	0.38	[0.26-0.56]	<0.001	0.37	[0.24-0.56]	<0.001

LBA5503 **Oral Abstract Session**

Overall survival data from a 3-arm, randomized, open-label, phase 2 study of relacorilant, a selective glucocorticoid receptor modulator, combined with nab-paclitaxel in patients with recurrent platinum-resistant ovarian cancer. *First Author: Nicoletta Colombo, University of Milan-Bicocca, European Institute of Oncology (IEO) IRCCS, Milan, Italy*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

LBA5504 **Oral Abstract Session**

Randomized phase III trial on trabectedin (ET-743) single agent versus clinician's choice chemotherapy in recurrent ovarian, primary peritoneal, or fallopian tube cancers of BRCA-mutated or BRCAness phenotype patients (MITO23). *First Author: Giovanni Scambia, Fondazione Policlinico Universitario A. Gemelli IRCCS Università Cattolica, Rome, Italy*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

5505 **Oral Abstract Session**

Pembrolizumab, maveropepimut-S, and low-dose cyclophosphamide in advanced epithelial ovarian cancer: Results from phase 1 and expansion cohort of PESCO trial. *First Author: Ana Veneziani, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Platinum-resistant ovarian cancer (PROC) continues to have a poor prognosis. Maveropepimut-S (MVP-S, namely DPX-Survivac) leverages the lipid-based DPX delivery platform to educate a specific and persistent T cell-based immune response to 5 HLA-restricted peptides from survivin, a cancer-related protein commonly upregulated in several cancers. MVP-S in combination with Pembrolizumab (Pemb) and low-dose Cyclophosphamide (CPA) is expected to enhance immune response. This trial aims to assess the safety and efficacy of this regimen in patients (pts) with PROC. **Methods:** Phase 1 escalation cohort allowed all PROC subtypes and comprised 2 dose levels (DL) of MVP-S with 1 initial dose 0.25 mL followed by boosters of 0.25 mL (DL1) or 0.5mL (DL2) SC q6w, combined with CPA (50 mg BID every other week) and Pemb (200 mg q3w). Dose escalation was performed using 3+3 design. Dose-limiting toxicities (DLT) were defined as G4 non-hematologic, ≥G3 persistent non-hematologic toxicity, laboratory value or febrile neutropenia; ≥G2 persistent injection site skin ulceration (> 1wk) or allergic/immune reactions by CTCAE v4.03. DL was considered safe if ≤1 DLT occurred in 6 pts until 21 days after initial and first boosting dose. Pts with high-grade serous (HGSOC) or endometrioid ovarian cancer were allowed in the Phase 2 expansion cohort (P2EC) and treated with the Recommended Phase 2 Dose (RP2D). Response was assessed every 6 wks. Activity in P2EC was defined as at least 2/10 partial response (PR) or stable disease (SD) for 12 wks according to RECIST 1.1. Primary endpoint is overall response rate (ORR), and secondary includes safety, PFS, and OS. Biopsies and blood draws were performed prior to and on treatment for genomic analysis, immune profiling and ctDNA. **Results:** Twenty-six pts were enrolled, 24 were evaluable for safety (8 DL1, 6 DL2, and 10 in P2EC). HGSOC represented 62% of phase I and 100% of P2EC. Median age was 61y (49-78). Pts received a median of 4 (1-7) prior lines of therapy. Median cycles of MVP-S were 2 (1-8). Toxicity G4/G3/G2 occurred in 1/3/7 pts of DL1 and 0/3/6 of DL2. G3/G2 immune-related AE (irAE) and injection site reactions (ISR) were observed in 1/1 and 1/3 pts treated at DL1, and in 1/0 and 2/2 pts at DL2, respectively. DL1 was selected as RP2D due to the occurrence of nephritis and ISR G3 at DL2. No AEs were qualified as DLT. On the P2EC, 5 G3 (1 irAE, 0 ISR) and 28 G2 (0 irAE, 3 ISR) toxicities were observed. At Phase 1, one pt with MSI-High clear cell subtype has ongoing CR after 26 mos of follow-up, 2 pts had PR and 6 SD.There were 1 PR and 3 SD on P2EC, of which 1 and 2, respectively, achieved response > 12wks. **Conclusions:** The combination of MVP-S, low-dose CPA, and Pemb was tolerable and met the efficacy endpoint in the expansion cohort in heavily treated PROC. Immuno-genomic correlative analyses are ongoing. Clinical trial information: NCT03029403. Research Sponsor: Merck and Immunovaccine, OICR (Ontario Institute for Cancer Research) and UHN (University Health Networking) sponsored.

OR	DL1	DL2	P2EC
CR	1	-	-
PR	2	-	1
SD (> 12wk)	2 (1)	4(1)	3 (2)
PD	3	2	6

5506 **Oral Abstract Session**

Pembrolizumab + chemotherapy in patients with persistent, recurrent, or metastatic cervical cancer: Subgroup analysis of KEYNOTE-826. *First Author: Krishnansu Sujata Tewari, Obstetrics & Gynecology, University of California, Irvine, Orange, CA*

Background: In KEYNOTE-826 (NCT03635567),pembrolizumab (pembro) + chemotherapy (chemo) ± bevacizumab (bev) provided statistically significant, clinically meaningful PFS and OS improvements in patients with persistent, recurrent, or metastatic cervical cancer. In the present analysis of KEYNOTE-826, we assessed outcomes in several key patient subgroups. **Methods:** Eligible adult patients had persistent, recurrent, or metastatic squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix not previously treated with chemo and not amenable to curative treatment; measurable disease per RECIST v1.1; ECOG PS 0–1; and a tumor sample to determine PD-L1 status. Patients were randomized 1:1 to pembro 200 mg Q3W or placebo (pbo) for up to 35 cycles + chemo (paclitaxel 175 mg/m^2 + cisplatin 50 mg/m^2 or carboplatin AUC 5) ± bev 15 mg/kg. Dual primary endpoints are PFS by investigator assessment per RECIST v1.1 and OS in patients with PD-L1 CPS ≥1, all comers, and CPS ≥10. Treatment effects on PFS and OS were examined in patient subgroups defined by bev use (yes or no), histology (squamous or non-squamous [including adenocarcinoma and adenosquamous]), platinum use (carboplatin or cisplatin), and prior chemoradiation therapy (CRT). Hazard ratios (HR) and 95% CIs were based on a stratified Cox regression model. **Results:** 617 patients were randomized (pembro + chemo ± bev, n=308; pbo + chemo ± bev, n=309). At the May 3, 2021 data cutoff, median follow-up was 22 months. Pembro + chemo prolonged PFS and OS vs pbo + chemo in all subgroups evaluated in the all-comer population (Table). Similar benefits of pembro + chemo on PFS and OS were also seen in the protocol-specified CPS ≥1 and CPS ≥10 populations. **Conclusions:** Pembro + chemo ± bev prolonged PFS and OS vs pbo + chemo ± bev among the subgroups defined by bev use, histology, platinum use, and prior CRT and provided clinically meaningful benefits similar to the broader population of patients with persistent, recurrent, or metastatic cervical cancer. Clinical trial information: NCT03635567. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Subgroup (N)	Median PFS (mo) Pembro	Median PFS (mo) Pbo	PFS, HR (95% CI)	Median OS (mo) Pembro	Median OS (mo) Pbo	OS, HR (95% CI)
With bev (389)	15.2	10.2	0.61 (0.47-0.79)	Not reached	24.7	0.63 (0.47-.87)
Without bev (228)	6.3	6.2	0.74 (0.54-1.01)	16.8	12.6	0.74 (0.53-1.04)
Squamous (447)	10.4	6.9	0.63 (0.50-0.80)	23.5	14.2	0.61 (0.47-0.80)
Non-squamous (169)	11.6	8.4	0.66 (0.43-1.00)	Not reached	21.3	0.76 (0.47-1.23)
Carboplatin (495)	10.2	7.4	0.69 (0.55-0.86)	21.4	15.9	0.69 (0.54-0.89)
Cisplatin (120)	15.2	8.4	0.47 (0.28-0.77)	Not reached	21.3	0.59 (0.32-1.09)
Prior CRT (243)	10.3	6.3	0.62 (0.45-0.86)	21.3	12.6	0.64 (0.45-0.91)

5507 **Oral Abstract Session**

Tisotumab vedotin (TV) + pembrolizumab (pembro) in first-line (1L) recurrent or metastatic cervical cancer (r/mCC): Interim results of ENGOT Cx8/GOG 3024/innovaTV 205. *First Author: Domenica Lorusso, Fondazione Policlinico Gemelli IRCCS, Rome, Italy*

Background: TV monotherapy has received US accelerated approval for previously treated r/mCC with disease progression on or after chemotherapy based on clinically meaningful tumor response rate and duration of response (DOR) reported from the GOG-3023/ENGOT-cx6/innovaTV 204 study (Coleman et al., Lancet Onc. 2021). Recently, the recommended phase 2 dose (RP2D) and feasibility of TV + pembro, TV + carboplatin (carbo), and TV + bevacizumab in r/mCC were reported from the dose-escalation phase (Monk et al, IGCS 2021); interim safety and efficacy data from 2 dose-expansion cohorts, 1L TV + carbo and second-line/third-line (2L/3L) TV + pembro (Vergote et al, ESMO 2021) from the ENGOT-cx8/GOG-3024/innovaTV 205 (NCT03786081) study, were also reported. Here we report interim safety and efficacy results from a third dose-expansion cohort evaluating 1L TV + pembro in patients with r/mCC. **Methods:** Patients with r/mCC who had not received prior systemic therapy (excluding chemoradiation) for r/mCC were treated with the RP2D of TV 2.0 mg/kg + pembro 200 mg intravenously every 3 weeks. The primary endpoint was investigator-assessed confirmed objective response rate (ORR) per RECIST v1.1; secondary endpoints included DOR, progression-free survival (PFS), overall survival (OS), and safety. **Results:** 33 pts were treated with 1L TV + pembro (median 6 cycles). At data cutoff (July 1, 2021), median duration of exposure to TV + pembro was 5.1 mo (range 1-17) and median follow-up was 12.2 mo (range 1-17). Confirmed ORR among 32 evaluable patients was 41% (95% CI 24-59), with 3 (9%) complete responses and 10 (31%) partial responses. Median time to response was 1.4 mo (range 1.2-2.8); median DOR was not reached, with response ongoing in 7/13 patients. Median PFS was 5.3 mo (95% CI 4.0-12.2); median OS was not reached. The most common treatment-emergent AEs (TEAEs) were alopecia (61%), diarrhea (55%), epistaxis (49%), conjunctivitis (46%), and nausea (46%). Grade ≥3 TEAEs occurred in 67% of patients, the most common being anemia (12%); asthenia (9%); hypokalemia (9%); and increased alanine aminotransferase, decreased white blood cell count, dyspnea, and acute kidney injury (6% each). Three grade 5 TEAEs were reported of which one, disseminated intravascular coagulation, was considered treatment-related. Prespecified AEs of interest (grade 1-2/grade ≥3) with TV included ocular (58%/9%), peripheral neuropathy (45%/3%), and bleeding (61%/6%). Updated results with longer follow-up for this cohort and the 1L TV + carbo and 2L/3L TV + pembro cohorts will be provided at the meeting. **Conclusions:** TV + pembro demonstrated encouraging, durable antitumor activity with a manageable and acceptable safety profile as a 1L regimen for patients with r/mCC. This trial is ongoing and final analyses will be reported in the future. Clinical trial information: NCT03786081. Research Sponsor: Genmab A/S and Seagen Inc.

5508 **Oral Abstract Session**

COVID-19 in patients with gynecologic cancer: A preliminary report from the COVID-19 and Cancer Consortium (CCC19). *First Author: Alicia Beeghly-Fadiel, Vanderbilt University Medical Center, Nashville, TN*

Background: Limited information exists regarding the severity of short-term outcomes among patients with gynecologic cancer who are infected with SARS-CoV-2. **Methods:** Patients with gynecologic cancer and laboratory confirmed SARS-CoV-2 infection were identified from the international CCC19 registry. We estimated odds ratios (OR) from ordinal logistic regression for associations with severity of COVID-19 outcomes, defined from least to most severe as hospitalization, intensive care unit (ICU) admittance, mechanical ventilation, and 30-day mortality. **Results:** Of 842 patients identified, 48% had endometrial cancer, 24% had ovarian cancer, 22% had cervical cancer, and 6% had dual primary/other gynecologic cancers. The majority were from the United States (86%), most were non-Hispanic White (46%), and the median age was 62 years (IQR 52-72). The majority were diagnosed with localized disease (68%); only 18 (2%) and 15 (2%) were fully or partially vaccinated, respectively. In the 3 months prior to COVID-19, 36% had any cancer treatment, with chemotherapy the most common (23%). When diagnosed with COVID-19, most patients were in remission (50%), while 37% had active disease, including 22% with metastatic disease. Most patients presented with typical COVID-19 symptoms (76%); few had a poor ECOG performance status (PS ≥2, 14%). Outcomes included hospitalization (50%), ICU admittance (12%), mechanical ventilation (8%), and death within 30 days of testing positive for SARS-CoV-2 (10%). In unadjusted models, increasing age (OR: 1.03 1.02-1.04) and Black race (OR 1.91, 1.31-2.77) were associated with increased severity of COVID-19 outcomes. Compared to patients in remission for ≥5 years, those with progressive disease had increased severity (OR 1.88, 1.25-2.82), while those in remission for < 5 years or with stable disease had decreased severity of COVID-19 outcomes (OR 0.55, 0.39-0.76). In multivariable models that included adjustment for age, race, and cancer status, additional factors associated with increased COVID-19 outcome severity included cardiac (OR 1.57, 1.13-2.19) and renal (OR 2.00, 1.33-3.00) comorbidities, an ECOG PS ≥2 (OR 5.15, 3.21-8.27), having pneumonia or pneumonitis (OR 4.08, 2.94-5.66), venous thromboembolism (OR 4.67, 2.49-8.75), sepsis (OR 14.2, 9.05-22.1), or a co-infection within ±2 weeks of SARS-CoV-2 (OR: 4.40, 2.91-6.65); asymptomatic SARS-CoV-2 infection was associated with decreased severity of outcomes (OR: 0.25, 0.16-0.38). The overall case fatality rate was 15.7%. **Conclusions:** Patients with gynecologic cancer experience significant morbidity and mortality related to infection with SARS-CoV-2. Age, race, cancer status, co-morbidities, and COVID-19 complications were associated with more severe COVID-19 outcomes, along the continuum from least to most, of hospitalization, ICU admittance, mechanical ventilation, and 30-day mortality. Research Sponsor: U.S. National Institutes of Health.

5509 **Clinical Science Symposium**

Dostarlimab in advanced/recurrent (AR) mismatch repair deficient/microsatellite instability–high or proficient/stable (dMMR/MSI-H or MMRp/MSS) endometrial cancer (EC): The GARNET study. *First Author: Ana Oaknin, Vall d'Hebron Institute of Oncology, Hospital Universitari Vall d'Hebron, and Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain*

Background: Dostarlimab is a programmed death 1 (PD-1) inhibitor approved in the U.S. as a monotherapy in patients (pts) with dMMR AR EC that has progressed on or after treatment with a platinum-containing regimen or dMMR solid tumors that have progressed on or after prior treatment, with no satisfactory alternative treatment options; and in the E.U. as a monotherapy in pts with dMMR/MSI-H AR EC that has progressed on or after treatment with a platinum-containing regimen. Here, we report on efficacy and safety in the 2 expansion cohorts of the GARNET trial that enrolled pts with EC. **Methods:** GARNET is a multicenter, open-label, single-arm phase 1 study. Pts were assigned to cohort A1 (dMMR/MSI-H EC) or cohort A2 (MMRp/MSS EC) based on local assessment. Pts received 500 mg of dostarlimab IV Q3W for 4 cycles, then 1,000 mg Q6W until disease progression, discontinuation, or withdrawal. The primary endpoints are ORR and DOR by blinded independent central review using RECIST v1.1. **Results:** For this third interim analysis, 153 dMMR/MSI-H and 161 MMRp/MSS pts were enrolled and dosed. Of these, 143 dMMR/MSI-H and 156 MMRp/MSS pts had measurable disease at baseline and ≥ 6 mo of follow-up and were included in the efficacy-evaluable population. ORRs were 45.5% (dMMR/MSI-H) and 15.4% (MMRp/MSS; Table). Median (m) DORs were not reached (NR; dMMR/MSI-H) and 19.4 mo (MMRp/MSS). Probability of PFS at 6, 9, and 12 mo was 49.5%, 48.0%, and 46.4% in dMMR/MSI-H EC and 35.8%, 31.3%, and 29.4% in MMRp/MSS EC, respectively. mOS was NR (dMMR/MSI-H) and 16.9 mo (MMRp/MSS). Overall, 27 pts (8.6%) discontinued treatment because of a treatment-related adverse event (TRAE; 13 dMMR/MSI-H, 14 MMRp/MSS). The majority of TRAEs were grade 1 or 2. The most common any-grade TRAEs were fatigue (56; 17.8%), diarrhea (46; 14.6%), and nausea (43; 13.7%). No deaths were attributed to dostarlimab in the EC cohorts. Hypothyroidism (12; 8%) was the most common any-grade immune-related TRAE. **Conclusions:** Dostarlimab demonstrated durable antitumor activity in both dMMR/MSI-H and MMRp/MSS AR EC. dMMR/MSI-H was associated with better outcomes: a higher response rate and longer PFS and OS. Safety was consistent with other PD-1 antibodies. Clinical trial information: NCT02715284. Research Sponsor: GlaxoSmithKline.

	dMMR/MSI-H EC N=143	MMRp/MSS EC N=156
Median follow-up time, mo	27.6	33.0
ORR, n (%, 95% CI)		
Complete response, n (%)	65 (45.5, 37.1–54.0)	24 (15.4, 10.1–22.0)
Partial response, n (%)	23 (16.1) 42 (29.4)	4 (2.6) 20 (12.8)
Disease control rate, n (%, 95% CI)	86 (60.1, 51.6–68.2)	53 (34.0, 26.6–42.0)
Response ongoing, n (%)	54 (83.1)	9 (37.5)
mDOR (range), mo	NR (1.18+ to 47.21+)	19.4 (2.8–47.18+)
mPFS (95% CI), mo	6.0 (4.1–18.0)	2.7 (2.6–2.8)
Estimated probability of PFS, % (95% CI)		
6 mo	49.5 (41.0–57.5)	22.9 (16.5–30.0)
9 mo	48.0 (39.4–56.0)	15.5 (10.1–22.0)
12 mo	46.4 (37.8–54.5)	13.3 (8.3–19.5)
mOS (95% CI), mo	NR (25.7–NR)	16.9 (13.0–21.8)

5510 **Clinical Science Symposium**

An open label, nonrandomized, multisite phase II trial combining bevacizumab, atezolizumab, and rucaparib for the treatment of previously treated recurrent and progressive endometrial cancer. *First Author: William Hampton Bradley, Froedtert and the Medical College of Wisconsin, Milwaukee, WI*

Background: Patients with metastatic recurrent endometrial cancer have limited effective therapies. Single agent pembrolizumab is utilized in mismatch repair deficient (MMRd) patients, while the combination of lenvatinib and pembrolizumab is now more commonly used in MMR intact patients who have progressed after chemotherapy combinations. This trial investigated a novel three drug regimen. **Methods:** Patients with recurrent endometrial cancer not amenable to curative intent surgery or radiation after one or two lines of therapy were eligible regardless of histology. This study is a multicenter, open-label, nonrandomized phase II trial. All subjects initially received the three-drug combination of rucaparib, bevacizumab, and atezolizumab. The primary goal of this trial was to estimate the overall response rate in these patients, and secondarily to estimate the progression-free and overall survival of patients treated with this triplet combination. Total enrollment was 30, with the first six subjects participated in a safety lead-in. Treatments until progression, toxicity, or clinician choice. Subjects could continue past progression if, in the estimate of the treating clinician and subject, clinical benefit was being provided. Subjects were eligible for analysis if they received at least one cycle and had one post-dose tumor assessment. The ORR assumption was 27% with a lower bound of 14%. **Results:** 30 subjects were enrolled between 07/2019 and 06/2021. Of these 26 were evaluable. Median follow up at cut off was 14.9 months. 23 subjects had clinical benefit, with 1 (4%) with CR, 9 (39%) with PR, and 13 (57%) with stable disease as best response. Overall median event-free (progression or death) was 5.3 (95% CI 2.7-7.9) months and overall survival 13.3 (95% CI NA) months at cut off. Median duration of therapy was 4.4 months (IQR 1.7-7.3), with 4 subjects remaining on study directed therapy at data cut off. Histology distribution was 50% serous, 20% endometrioid, and 13% carcinosarcoma. 19 pts were White, 8 African American, 2 identified as Asian, 1 unknown. In the MMR deficient patients, event-free probability was 11.9 months. Grade 3 or 4 treatment related adverse events occurred in 50% patients. **Conclusions:** To our knowledge, this trial represents the first use of a non-chemotherapy-based triplet therapy for recurrent endometrial cancer. The combination of rucaparib, bevacizumab, and atezolizumab may safely be used to treat recurrent/persistent endometrial cancer. This combination demonstrates clinically meaningful improvement in response, with acceptable toxicity. Enhanced response to therapy was seen in MMR deficient subjects. Clinical trial information: NCT03694262. Research Sponsor: Genentech and Clovis Oncology.

5511 **Clinical Science Symposium**

Randomized phase III study of maintenance selinexor versus placebo in endometrial cancer (ENGOT-EN5/GOG-3055/SIENDO): Impact of subgroup analysis and molecular classification. *First Author: Vicky Makker, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Endometrial cancers (ECs) are stratified into four molecular categories: wild type *TP53* with non-specific molecular profile typically with microsatellite stability (NSMP, p53wt/MSS), DNA polymerase ε exonuclease domain-mutated (POLEmut), microsatellite instability high (MSI) and *TP53* abnormal (p53abn). These are associated with specific prognoses. Selinexor (SEL) is a specific XPO1 inhibitor that leads to the nuclear retention and activation of tumor suppressor proteins (TSP) including p53. SEL showed improved progression-free survival (PFS) over placebo (PLB) in the stratification adjusted results of the ENGOT-EN5/GOG-3055/SIENDO study (NCT03555422; ESMO 2022). **Methods:** The SIENDO study is a prospective, multicenter, double-blind, placebo-controlled, phase 3 study of SEL (80 mg once weekly) vs. PLB (2:1 randomization) as maintenance therapy in 263 patients (pts) with advanced or recurrent EC after one line of taxane-platinum therapy with partial or complete remission. *TP53* mutations and MSI were assessed by centralized targeted sequencing and local immunohistochemistry. Classification was based on sequencing 648 genes on tumor samples from 172 pts (107 on SEL), assigned first by POLEmut, then MSI, then p53abn or p53wt (NSMP). Preliminary exploratory analyses based on molecular classification were prespecified in the trial. **Results:** The SIENDO study resulted in a median progression-free survival (PFS) of 5.7 months (SEL) vs. 3.8 months (PLB), with a stratification adjusted (eCRF) hazard ratio (HR) of 0.70 (p = .024; and a stratification non-adjusted (IRT) HR of 0.76 (p=0.063). Among the 172 patients who underwent molecular classification, those on SEL (107 pts) were classified as follows: 37 (35%) NSMP, 2 (2%) POLEmut, 18 (17%) MSI, and 50 (46%) p53abn. A similar distribution was seen in those on PLB (65 pts): 20 (31%) NSMP; 4 (6%) POLEmut; 8 (12%) MSI; 33 (51%) p53abn. Subgroup analysis of pts with *TP53*wt showed a PFS of 13.7 mo with SEL vs. 3.7 mo with PLB (HR 0.375; 95% CI, 0.210-0.670; nominal p = .0003) and pts with MSS/pMMR disease had a PFS of 6.9 mo with SEL vs. 5.4 with PLB (HR 0.593; 95% CI, 0.388-0.905, nominal p = .007). An analysis of patients with NSMP (p53wt, MSS) showed a substantial difference in PFS for SEL vs. PLB: medians NR and 3.71 months, respectively (HR 0.163; 95% CI, 0.060-0.444; nominal p < .0001). Analyses of the other 3 molecular categories did not show significant differences in PFS between SEL and PLB. Additional biomarker identification studies assessing tumor genetics and epigenetics are ongoing. **Conclusions:** SEL showed improved PFS over PLB in the SIENDO study based on the stratification adjusted analysis. As an indirect p53 activator, preliminary exploratory subgroup analyses of SEL showed improvement over PLB amongst the patients with TP53wt, MSS, and the NSMP EC comprising approximately 50% of patients with advanced/recurrent EC. Clinical trial information: NCT03555422. Research Sponsor: Karyopharm Therapeutics.

5512 **Poster Discussion Session**

Mirvetuximab soravtansine (MIRV) in patients with platinum-resistant ovarian cancer with high folate receptor alpha (FRα) expression: Characterization of antitumor activity in the SORAYA study. *First Author: Ursula A. Matulonis, Dana-Farber Cancer Institute, Boston, MA*

Background: SORAYA is a global single arm phase 3 study evaluating MIRV in patients (pts) with FRα high platinum-resistant ovarian cancer (PROC). MIRV is an antibody drug conjugate comprising a FRα-binding antibody, cleavable linker, and maytansinoid DM4, a potent tubulin-targeting agent. In this study, MIRV demonstrated activity in a broad population of PROC, regardless of number of prior lines of therapy or prior PARPi (Matulonis, SGO 2022). Here we describe details of response to treatment important for clinical decision making. **Methods:** SORAYA enrolled PROC pts with high FRα expression by immunohistochemistry (Roche FOLR1 Assay ≥ 75% of cells with PS2+ staining intensity) who had received 1-3 prior therapies, including required prior bevacizumab. Pts received intravenous MIRV at 6 mg/kg, adjusted ideal body weight, on Day 1 of a 21-day cycle until disease progression or unacceptable toxicity. The primary endpoint was confirmed objective response rate (ORR) per RECIST v1.1 by investigator (INV) and the key secondary endpoint was duration of response (DOR); additional endpoints included time to response, CA-125 response, safety and tolerability. **Results:** 106 pts were enrolled; 51% had 3 prior lines; 48% had 1-2 prior lines of therapy; 48% received prior PARPi. ORR by INV was 32.4% (95% confidence interval [CI]: 23.6%, 42.2%), including five complete responses. Median time to response was 1.5 mos (range 1.0 to 5.6) and 71% of pts demonstrated tumor reduction. At the time of the protocol specified primary analysis (16 Nov 2021), the median DOR was 5.9 mos (95% CI: 5.6, 7.7). With 15 responders remaining on MIRV, the DOR continues to evolve. In the 86 response-evaluable patients for CA-125 (by Gynecologic Cancer Intergroup criteria), responses were observed in 46.5% (95% CI: 35.7, 57.6). Updated data will be presented including depth and duration of responses and impact of dose modifications. The most common treatment-related adverse events (TRAE; all grade, grade 3+) included blurred vision (41%, 6%), keratopathy (36%, 9%), and nausea (29%, 0%). TRAEs led to dose delays in 32%, dose reductions in 19%, and discontinuations in 7% of pts; one patient discontinued treatment due to an ocular event. The tolerability profile of MIRV consists of low-grade, reversible ocular and GI events, managed with dose modifications and supportive care. **Conclusions:** Treatment options for pts with PROC are limited. MIRV is the first biomarker-directed therapy demonstrating anti-tumor activity in pts with FRα high PROC. These results support the clinically meaningful impact MIRV has for pts with FRα high PROC, irrespective of prior therapies or dose modifications. Clinical trial information: NCT04209855. Research Sponsor: ImmunoGen.

5513 **Poster Discussion Session**

Safety and efficacy of MORAb-202 in patients (pts) with platinum-resistant ovarian cancer (PROC): Results from the expansion part of a phase 1 trial. *First Author: Shin Nishio, Department of Obstetrics and Gynecology, Kurume University School of Medicine, Fukuoka, Japan*

Background: MORAb-202 is an antibody-drug conjugate consisting of farletuzumab (an antibody that binds to folate receptor alpha [FRα]) paired with eribulin mesylate (a microtubule dynamics inhibitor) conjugated via a cathepsin-B–cleavable linker. The dose-escalation part of this phase 1 study confirmed antitumor activity in pts with ovarian cancer (Shimizu 2021, *CCR*); based on efficacy and safety, MORAb-202 0.9 mg/kg and 1.2 mg/kg Q3W were chosen as doses for the expansion part of this study in pts with PROC. **Methods:** The primary objective for the expansion part of this phase 1 study conducted in Japan was to define the safety and tolerability of MORAb-202. Secondary objectives included PK characterization and efficacy assessment (best overall response, objective response rate, progression-free survival, and overall survival). Eligible pts included those who had received ≤2 regimens of chemotherapy after diagnosis of PROC, had measurable disease per RECIST v1.1, and an ECOG PS of ≤1. Pts (except those with high grade serous histology) in the expansion phase were required to be FRα positive. The expansion phase began at the 0.9 mg/kg dose (Cohort 1); Cohort 2 (1.2 mg/kg) was initiated after safety assessment of Cohort 1 was completed. Tumor responses were assessed per RECIST v1.1 by investigator. **Results:** Twenty-four pts were treated in Cohort 1 and 21 pts were treated in Cohort 2. Grade ≥3 TEAEs occurred in 33.3% of pts in Cohort 1 and 28.6% of pts in Cohort 2. The most common TEAE was interstitial lung disease (ILD)/pneumonitis at both dose levels (Cohort 1: 37.5% [n=9; 8 with grade 1, 1 with grade 2]; Cohort 2: 66.7% [n=14; 6 with grade 1, 7 with grade 2, 1 with grade 3]). Other common TEAEs of any grade were nausea (25.0%; 33.3%), pyrexia (33.3%; 42.9%), malaise (16.7%; 28.6%), and headache (12.5%; 47.6%), in Cohorts 1 and 2, respectively. ORR was 25.0% and 52.4% in Cohorts 1 and 2, respectively (Table). Antitumor activity was observed across FRα-expression levels (<50% and ≥50%) and will be presented. **Conclusions:** In the PROC population, antitumor activity was seen with both the MORAb-202 0.9 mg/kg and 1.2 mg/kg doses. While pt numbers were small, efficacy was observed irrespective of FRα-expression levels. ILD/pneumonitis was the most common TEAE and was low grade in most pts. Dose optimization is ongoing to maximize the benefit/risk profile of MORAb-202. Clinical trial information: NCT03386942. Research Sponsor: Eisai Inc., Nutley, NJ, USA.

Parameter	Cohort 1 MORAb-202 0.9 mg/kg (n=24)	Cohort 2 MORAb-202 1.2 mg/kg (n=21)
CR, n (%)	1 (4.2)	0
PR, n (%)	5 (20.8)	11 (52.4)
SD, n (%)	10 (41.7)	9 (42.9)
PD, n (%)	8 (33.3)	1 (4.8)
ORR, n (%), (95% CI)[a]	6 (25.0), (9.8–46.7)	11 (52.4), (29.8–74.3)
DCR, n (%), (95% CI)[a]	16 (66.7), (44.7–84.4)	20 (95.2), (76.2–99.9)
Median PFS, mos (95% CI)[a]	6.7 (1.5–12.0)	8.2 (4.2–10.4)
Median OS, mos (95% CI)[a]	10.5 (6.4–15.1)	NE (12.5–NE)

[a]CI calculations: ORR, DCR—Clopper-Pearson's exact method; PFS, OS—Kaplan-Meier estimate and Greenwood Formula.

5514 **Poster Discussion Session**

A randomized phase II study of bevacizumab and weekly anetumab ravtansine or weekly paclitaxel in platinum-resistant or refractory ovarian cancer NCI trial#10150. *First Author: Stephanie Lheureux, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Mesothelin and its binder, antigen-CA125, are highly expressed in high grade serous and endometrioid ovarian cancers (HGOC) and, can inhibit paclitaxel-induced cell death. Anetumab ravtansine (AR) is a fully-human antibody directed at the mesothelin antigen, conjugated to a tubulin polymerization inhibitor. We assessed the safety and activity of the combination AR/bevacizumab (ARB) versus weekly paclitaxel/bevacizumab (PB) in patients (pts) with platinum resistant HGOC. **Methods:** An initial run-in phase I assessed the safety of ARB. After determination of the recommended phase 2 dose (RP2D), a multicenter 1:1 randomized phase 2 trial was designed to evaluate the progression free survival (PFS) in pts with platinum resistant/refractory HGOC. Pts were stratified by platinum resistant or refractory and prior bevacizumab (bev). Eligibility required measurable disease and mesothelin tested positive centrally on archival tissue by IHC. No limitation on the number of prior lines of therapy. A futility analysis was planned at 35 PFS events. The control arm was weekly intravenous paclitaxel 80mg/m^2 with bev 10mg/kg every 2 weeks. A CT was performed every 8 weeks for RECIST1.1 assessment. The toxicities were reported according to CTCAE version 5.1. NCT03587311. **Results:** 7 pts were enrolled in the run-in phase 1 and the RP2D determined as bev (10mg/kg) biweekly with AR (2.2mg/kg) weekly on a 28 day-cycle. In the phase 2, 57 pts were enrolled, 28 pts in the ARB and 29 pts in the control group. The positivity rate for mesothelin screening was 88%. Pts were heavily pre-treated, median prior lines of 3 (range (1-9) with 24 pts received prior bev (42%) and 13 pts were platinum refractory (7 in ARB and 6 in PB). At the time of 35 PFS events, one CR and 4 PR were observed (ORR = 18%) in the ARB arm, versus no CR and 16 PR in the weekly PB (ORR = 55%). The estimated median PFS was 5.3 (95% CI: 3.7-7.4) months for ARB and 9.6 (95% CI: 7.4-17.4) months for PB (HR = 1.7(95% CI: 0.9-3.4)). The median number of cycles were 4 (1, 29) and 8 (1, 19) respectively. The most common treatment-related AEs in the ARB arm were mostly grade 1/2 increase AST (71%) and ALT (64%), thrombocytopenia (61%), fatigue (57%), and peripheral neuropathy (46%). In the PB arm, the most common treatment-related AE were anemia (66%), neutropenia (59%), epistaxis (48%), fatigue (45%) and peripheral neuropathy (45%). **Conclusions:** At the time of futility analysis, weekly PB had better outcome than weekly ARB leading to the study termination. Molecular and blood analyses are on-going to assess potential biomarkers of response. This study highlights the importance of randomization in assessment of novel therapies and potential for re-challenge with bevacizumab. These data show that weekly PB is an effective regimen and can be considered as the control arm in platinum resistant HGOC. Clinical trial information: NCT03587311. Research Sponsor: U.S. National Institutes of Health.

5515 **Poster Discussion Session**

IGNITE: A phase II signal-seeking trial of adavosertib targeting recurrent high-grade, serous ovarian cancer with cyclin E1 overexpression with and without gene amplification. *First Author: George Au-Yeung, Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia*

Background: Cyclin E1 gene amplification and protein over-expression is a marker of platinum resistance in high grade serous ovarian, fallopian tube or primary peritoneal cancer (HGSC), and may predict response to WEE1 inhibition. Adavosertib, a WEE1 inhibitor, has demonstrated activity in unselected women with recurrent ovarian and serous endometrial cancer. We aimed to evaluate the efficacy of adavosertib in women with recurrent platinum resistant HGSC with cyclin E1 over-expression, with and without gene amplification. **Methods:** IGNITE is a multicentre, phase 2 trial with 2 cohorts of women with recurrent platinum resistant HGSC. Tumors were assessed for cyclin E1 protein expression by IHC and *CCNE1* copy number by FISH. Patients were assigned to Cohort 1 if tumors were cyclin E1 over-expressed (H-score>50) and amplified (≥8 copies), and Cohort 2 if tumors were overexpressed and nonamplified. Patients with evaluable disease by RECIST v1.1 or GCIG CA-125 criteria were included. Adavosertib 300mg PO was given daily on days 1-5 and 8-12 of a 21-day cycle. The primary endpoint was investigator assessed clinical benefit (CB) defined as absence of progression for ≥ 18 weeks. Here we present the 18-week response data for the first 32 patients treated from Cohort 2, with a data cut-off of August 2021. **Results:** Between Jan-2020 and May-2021, 32 patients were accrued to Cohort 2. Median age was 62 years (range 42-77) and 84% had received ≥2 prior lines of chemotherapy. Median cyclin E1 IHC H-score was 120 and 28 patients (88%) had measurable disease by RECIST. Median number of cycles commenced was 8 (range 1-19). Overall response rate (ORR) was 53% and CB rate was 61% for all evaluable patients. Seventeen patients (53%) required a dose reduction, most commonly for neutropenia or fatigue. Seventeen patients experienced ≥Grade 3 treatment related adverse event, and 4 patients (15%) discontinued due to toxicity. **Conclusions:** The efficacy results in a biomarker-selected cohort of patients are promising with a higher response rate than reported in previous studies of adavosertib in unselected women with recurrent HGSC. Duration of response and progression free survival data will be presented as data matures. Clinical trial information: ACTRN12619001185156P. Research Sponsor: AstraZeneca.

Response	Response evaluable patients (n=32)	CA125 evaluable only patients (n=4)	RECIST measurable patients (n=28)
CR	2 (6%)	-	2 (7%)
PR	14 (44%)	-	14 (50%)
CA125 50% Response	1 (3%)	1 (25%)	-
SD	8 (25%)	-	8 (29%)
No CA-125 response and no PD	3 (9%)	3 (75%)	-
PD	4 (12%)	0 (0%)	4 (14%)
OR (CR/PR/CA-125 50% response)	17 (53% [35, 71])	1 (25% [0, 81%])	16 (57% [37, 76])
CB (No PD>18 weeks)[a]	19 (61% [42, 78])	1 (25% [0, 81%])	18 (67% [46, 83])

a - One patient had SD at week 7 and withdrew consent at week 15 when ceased treatment due to toxicity. This patient was considered not evaluable for clinical benefit and CB rate was calculated excluding this patient.

5516 **Poster Discussion Session**

Adavosertib in combination with carboplatin in advanced *TP53*-mutated platinum-resistant ovarian cancer. *First Author: Alaa Embaby, Department of Clinical Pharmacology, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands*

Background: Ovarian cancer is globally the second most common cause of death among women with gynecologic malignancies. Despite high initial response rates, the overall prognosis of this patient population remains poor. The majority of advanced ovarian cancers will become platinum resistant defined by recurrence within six months after completion of platinum therapy. In the first part of the current phase II study, the combination of carboplatin and the Wee1 inhibitor adavosertib (AZD1775), showed to be safe and effective in patients with *TP53* mutated platinum resistant ovarian cancer. The aim of this additional cohort is to gain more information about the safety and efficacy of the combination and to explore predictive biomarkers for resistance and response to adavosertib. **Methods:** In this additional cohort 29 evaluable were treated with carboplatin AUC 5 mg/ ml·min and adavosertib 225 mg BID for 2.5 days in a 21-day cycle. The anti-tumor activity was assessed according to RECIST 1.1. Pre-, on- and post-treatment biopsies were obtained to explore genetic determinants of drug resistance and response to adavosertib. **Results:** A total of 32 patients with a median age of 62 years (39-77 years) were enrolled in this cohort. All patients had carboplatin/paclitaxel as first line therapy. Six patients received a second-line non-platinum containing regimen. Median platinum free interval was 5.8 months (range 1.7 – 11.9). Twenty-nine patients were evaluable for efficacy. Grade 1-2 bone marrow toxicity, nausea, vomiting and fatigue were the most common adverse events. Dose reductions of carboplatin and/or adavosertib were made in 15/29 evaluable patients (52%). Dose delays occurred in the majority of patients (76%), mostly due to neutropenia and thrombocytopenia. Twelve patients showed PR as best response, resulting in an ORR of 38% in the intention-to-treat population (95% CI 21%-56%). The median PFS was 5.6 months (range 1.1-32 months, 95% CI 4.2-7.0) and median duration of response was 5.3 months (95% CI 0.13-10.5). **Conclusions:** Adavosertib 225 mg BID for 2.5 days and carboplatin AUC 5 in a 21-day cycle could be safely combined and shows promising anti-tumor efficacy in patients with platinum resistant ovarian cancer. Bone marrow toxicity remains the most common reason for dose reductions and dose delays. Translational biomarker results (CCNE1 analysis as potential predictive marker for response and resistance and WGS) to better understand the anti-tumor activity of the combination are pending. Clinical trial information: NCT01164995. Research Sponsor: AstraZeneca.

5517 **Poster Discussion Session**

Efficacy and safety of lucitanib + nivolumab in patients with advanced gynecologic malignancies: Phase 2 results from the LIO-1 study (NCT04042116; ENGOT-GYN3/AGO/LIO). *First Author: Manish R. Patel, Drug Development Unit, Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL*

Background: LIO-1 is assessing the oral antiangiogenic, multikinase inhibitor lucitanib in combination with the programmed cell death receptor 1 (PD-1) inhibitor nivolumab. Individualized lucitanib dose titration is being explored to maximize lucitanib exposure and potential clinical benefit of the combination. Here, we present data from stage 1 of a Simon 2-stage design across 4 different types of advanced gynecologic cancers from the phase 2 part of LIO-1. **Methods:** Patients (pts) with advanced, recurrent, or metastatic endometrial cancer (EC, who received ≥1 prior platinum-based chemotherapy); cervical cancer (CC, who received ≥1 prior platinum-based chemotherapy ± bevacizumab); high-grade ovarian cancer (OC, who received ≥2 prior chemotherapies); or EC/OC with clear-cell histology (EOCC, who received ≥1 prior platinum-based chemotherapy + taxane) were enrolled. Prior PD-1 or programmed cell death ligand 1 (PD-L1) inhibitor treatment was excluded, except for up to 10 pts in the EC cohort. Pts received lucitanib at a starting dose of 6 mg once daily (QD), escalating to 8 mg QD and then 10 mg QD if safety-based titration criteria were met, plus intravenous nivolumab 480 mg every 28 days. The data cutoff was Jan 10, 2022. **Results:** Across cohorts, 100 pts were enrolled to stage 1; 27 (27%) remain on treatment. To date, 28 (28%) have escalated to lucitanib 8 mg, and 17 (17%) have escalated to the maximum dose of 10 mg. Confirmed responses per RECIST v1.1 have been reported in 5/22 (22.7%; 5 partial responses [PRs]) EC pts, 7/22 (31.8%; 2 complete responses [CRs], 5 PRs) CC pts, 4/33 (12.1%; 4 PRs) OC pts, and 5/23 (21.7%; 1 CR, 4 PRs) EOCC pts. Response duration ranges from 1.9+ to 13.1+ months. Of 5 pts with EC who received prior PD-1 inhibitor, there were 2 PRs, and 1 pt with ongoing stable disease of 7+ months. Grade ≥3 treatment-emergent adverse events (TEAEs) considered related to study treatment were reported in 43 (43%) pts, with hypertension the most frequent (n = 25 [25%]). Forty-six (46%) pts had a lucitanib-related TEAE that led to lucitanib interruption and 12 (12%) had one that led to lucitanib dose reduction. Eleven (11%) and 8 (8%) pts discontinued lucitanib and nivolumab, respectively, due to a treatment-related TEAE. Safety results were generally consistent across tumor cohorts. **Conclusions:** The combination of lucitanib + nivolumab is active in the treatment of advanced gynecological malignancies and has a manageable safety profile through effective dose titration. Stage 2 enrollment has continued in the CC cohort. Biomarker analysis is ongoing, and more mature efficacy and safety data will be presented at the meeting. Clinical trial information: NCT04042116. Research Sponsor: Clovis Oncology, Inc.

5518 **Poster Discussion Session**

Real-world effectiveness of first-line maintenance olaparib in women with *BRCA*-mutated advanced ovarian cancer: U.S. retrospective cohort study. *First Author: Ramez Nassef Eskander, UC San Diego Moores Cancer Center, San Diego, CA*

Background: Following cytoreductive surgery and first-line (1L) platinum based chemotherapy, 70% of patients (pts) with newly diagnosed advanced ovarian cancer (AOC) experience relapse within 3 years. 1L maintenance treatment (tx) with olaparib monotherapy, a poly (ADP-ribose) polymerase inhibitor, extended progression free survival in pts with BRCA mutated (BRCAm) AOC in the SOLO-1 (NCT01844986) randomized controlled trial (RCT). We aimed to describe real world characteristics, tx patterns, and clinical outcomes of pts with newly diagnosed, BRCAm AOC. **Methods:** Data were collected from 457 pts via electronic case report forms in the US. Pt eligibility criteria were positive BRCAm test result between Jan-June 2019 (6 months post 1L olaparib FDA approval), newly diagnosed AOC (no maintenance tx prior to index), aged ≥18 years, no RCT enrollment, no active neoplasia, no prior tx for metastatic/stage IV cancer. Pt follow up was until July 2021. Kaplan-Meier (KM) estimation was used for time to event analysis using progression proxies: Time to subsequent therapy and discontinuation (or death for both) from initiation of 1L maintenance olaparib monotherapy. **Results:** Pt mean age (±SD) at index was 62 (±10) years, 64% of pts were white and 18% African American; further clinical characteristics are in the table. 95% of pts received ≥1 pharmacological tx. At 1L, 36% of pts (156/433) received maintenance tx after chemotherapy, with 64% of pts (277/433) receiving routine surveillance (no maintenance tx). Olaparib was the most common maintenance tx (67%, 105/156), with 67% of pts (70/105) prescribed olaparib monotherapy. At 24 months, the KM model estimated 91% of pts (95% confidence interval: 82, 96) would not progress to their subsequent therapy, with a median discontinuation of olaparib monotherapy of 25.0 (interquartile range [IQR]: 21.0, not estimable) months, over a median follow-up of 22.0 (IQR: 20.6, 24.0) months. **Conclusions:** This real world study complements SOLO-1 RCT data by demonstrating prolonged benefit of 1L olaparib in newly diagnosed pts with BRCAm AOC in terms of lower likelihood of progression (tx switch/death). To assess real world tx effectiveness globally, data collection across further eight countries is due to be completed in 2022. Research Sponsor: AstraZeneca and Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc, Kenilworth, NJ, USA, who are codeveloping olaparib.

Selected clinical characteristics of pts with newly diagnosed BRCAm AOC.

		Base n=457	Olaparib monotherapy n=70	Any olaparib n=105	Routine surveillance n=277
Stage at AOC diagnosis, n (%)	Stage III	258 (56)	48 (69)	61 (58)	142 (51)
	Stage IV (a and b)	199 (44)	22 (31)	44 (42)	135 (49)
ECOG score at AOC diagnosis, n (%)	0	99 (22)	23 (33)	38 (36)	51 (18)
	1	259 (57)	42 (60)	57 (54)	163 (59)
	2+	99 (22)	5 (7)	10 (10)	63 (23)
Surgery status, n (%)	No surgery	157 (34)	12 (17)	19 (18)	117 (42)
	At least 1 surgery	300 (66)	58 (83)	86 (82)	160 (58)

5519 **Poster Discussion Session**

Maintenance olaparib in patients (pts) with platinum-sensitive relapsed ovarian cancer (PSROC) by somatic (s) or germline (g) BRCA and other homologous recombination repair (HRR) gene mutation status: Overall survival (OS) results from the ORZORA study. *First Author: Sandro Pignata, Istituto Nazionale Tumori 'Fondazione G Pascale', IRCCS, Napoli, Italy*

Background: In the SOLO2 (NCT01874353) trial, maintenance olaparib provided clinically meaningful improvement in OS for PSROC pts with a gBRCA mutation (m) compared with placebo (median 51.7 vs 38.8 months [mo], respectively). The ORZORA trial (NCT02476968) assessed efficacy and safety of maintenance olaparib in PSROC pts with a BRCAm (s or g) or a non-BRCA HRRm. Median progression-free survival (18.0 mo, BRCAm; 16.4, non-BRCA HRRm) was reported at primary data cutoff (DCO). We report final OS analyses. **Methods:** We conducted an open-label, single-arm, multicenter study of PSROC pts in response to platinum-based chemotherapy (PBC) after ≥2 prior lines of PBC. Pts underwent prospective central screening for tumor BRCAm status (myChoice CDx, Myriad Genetic Laboratories, Inc.), then central gBRCAm testing (BRACAnalysis CDx, Myriad Genetic Laboratories, Inc.) to determine s or g status. An exploratory cohort comprised of pts with predefined non-BRCA HRRm (FoundationOne CDx, Foundation Medicine, Inc.). Pts received maintenance olaparib (400 mg bid; capsules) until progression. OS and time to second progression (PFS2) were secondary endpoints. **Results:** 181 pts were enrolled (BRCAm n = 145 [s, n = 55; g, n = 87; s/g status unknown, n = 3]; non-BRCA HRRm, n = 33; unassigned, n = 3). At DCO (June 25, 2021), median OS follow-up in censored pts was 42.6 mo in BRCAm and 39.3 mo in non-BRCA HRRm pts. OS and PFS2 are reported in the Table. PBC was received as a subsequent therapy by 33.1% BRCAm, 32.7% sBRCAm, 33.3% gBRCAm, and 45.5% non-BRCA HRRm pts. 177 pts received ≥1 dose of olaparib and were included in safety analyses; 6.2% of pts discontinued because of adverse events (AEs). 37.9% of pts reported grade ≥3 AEs, the most common being anemia (16.4%). Since primary DCO, one new primary malignancy and four myelodysplastic syndrome events occurred. **Conclusions:** In final OS analyses, maintenance olaparib capsules showed consistent clinical activity in BRCAm and sBRCAm PSROC pts. Exploratory analyses suggest similar activity in non-BRCA HRRm pts. No new safety signals were observed. Findings highlight that PSROC pts, beyond those with a gBRCAm, can benefit from maintenance olaparib. Clinical trial information: NCT02476968. Research Sponsor: This study was sponsored by AstraZeneca and is part of an alliance between AstraZeneca and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

	BRCAm (n = 145)	sBRCAm (n = 55)	gBRCAm (n = 87)	Non-BRCA HRRm (n = 33)
Deaths, n (%)	68 (46.9)	28 (50.9)	40 (46.0)	14 (42.4)
Median OS, mo (95% CI)	46.8 (37.954.4)	43.2 (31.7NC)	47.4 (37.9 NC)	44.9 (28.9NC)
36 mo OS, %* (95% CI)	60.4 (51.668.2)	56.8 (42.468.8)	62.6 (51.072.2)	56.6 (36.872.4)
PFS2 events, n (%)	62 (42.8)	27 (49.1)	34 (39.1)	
Median PFS2, mo (95% CI)	34.0 (29.344.2)	29.3 (23.744.2)	40.0 (30.9NC)	
36 mo PFS2, %* (95% CI)	49.0 (38.858.3)	39.9 (24.754.8)	54.1 (40.665.7)	

*KaplanMeier estimate; PFS2 not prespecified. CI, confidence interval; NC, not calculated.

5520 **Poster Discussion Session**

Role of cytoreductive surgery for the second ovarian cancer relapse in patients previously treated with chemotherapy alone at first relapse: A subanalysis of the DESKTOP III trial. *First Author: Jalid Sehouli, Charité – Medical University of Berlin, Berlin, Germany*

Background: The DESKTOP III trial has demonstrated a significant survival benefit in AGO-score positive patients who underwent complete cytoreduction at 1st relapse compared to those treated with chemotherapy alone. The question whether eligible patients who missed the opportunity of potentially life prolonging surgery at 1st relapse would benefit from surgery at the time of their second relapse, remains open. **Methods:** Patients randomized in the standard, non-surgical arm of the DESKTOP III trial who underwent cytoreductive surgery at a subsequent relapse at investigator's discretion were separately analyzed. **Results:** The median progression-free survival (PFS) counted from randomization of 201 patients in the control arm of DESKTOP III was 14.0 months. 171 (85%) had progressive or relapsing disease and 32 of 171 (19%) underwent cytoreductive surgery. Patients' median age at this subsequent surgery was 63 years (range: 46 – 78). Complete tumor resection was achieved in 19 patients (60%), while 5 (16%) had postoperative residual disease (n = 8 missing data). Sixteen patients (50%) commenced systemic treatment within 90 days from surgery, as documented. Thirty- and 90-day surgical mortality rates were 1 (3%) and 2 (6%), respectively. Within a postoperative median follow-up time of 43.8 months, 12 (38%) deaths were reported. Median overall survival after surgery (OS) was 54.0 months. One- and 2-year OS rates were 91% and 84%, respectively. **Conclusions:** Cytoreductive surgery for subsequent ovarian cancer relapse appears feasible and with low mortality in selected patients who received non-surgical treatment at 1st relapse despite a positive AGO-score. Surgery should be considered as an option in carefully selected patients also later in their journey within a specialized gynecological cancer setting. Clinical trial information: NCT01166737. Research Sponsor: Grants received from GSK and medac.

5521 **Poster Discussion Session**

Basket study of oral progesterone antagonist onapristone extended release (ONA-XR) in progesterone receptor positive (PR+) recurrent granulosa cell (GCT), low-grade serous ovarian (LGSOC), or endometrioid endometrial cancer (EEC). *First Author: Rachel N. Grisham, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY*

Background: ONA-XR is a type I full progesterone antagonist that inhibits progesterone-mediated PR activation and stabilizes PR association with corepressors. GCT (98% of cases PR+), LGSOC (58% of cases PR+) and EEC (67% of cases PR+) are hormonally driven cancers that generally have poor responses to chemotherapy. **Methods:** This is an open-label, single-institution basket study of ONA-XR in patients with PR+ recurrent GCT (cohort 1), LGSOC (cohort 2), or EEC (cohort 3) (NCT03909152). Eligible patients required receipt of >1 prior line of chemotherapy, measurable disease by RECIST 1.1, and tumor tissue collected ≤3 years prior to enrollment with PR ≥ 1% by IHC. Patients received ONA-XR 50 mg PO BID until progression or intolerable toxicity. The study was designed as 3 parallel Simon 2-Stage studies. The primary objective was to evaluate efficacy, determined by RECIST 1.1, with at least 1/14 (cohort 1), 2/16 (cohort 2) or 4/19 (cohort 3) responses needed during stage 1 for advancement to stage 2. Secondary objectives included safety and tolerability, clinical benefit rate (CBR; stable disease lasting ≥ 16 weeks), and progression-free survival (PFS) as estimated by Kaplan Meier method. **Results:** The study enrolled patients to cohorts 1-3 from 5/2019 to 5/2020. Cohort 2 (LGSOC) enrolled 5 patients and cohort 3 (EEC) enrolled 1, both closed early due to slow accrual. Cohort 1 (GCT) enrolled 14 patients and completed Stage 1 accrual. There were no responses by RECIST 1.1 criteria observed in cohorts 1-3. In cohort 2 (LGSOC), 4/5 enrolled patients were evaluable, the median PFS was 4.4 months (1.8-NE) and CBR was 50% (6.8-93.2%). All 14 patients enrolled to cohort 1 (GCT) were evaluable with a median PFS of 3.5 months (1.6-8.8%), 6-month PFS rate of 30.1 % (8.4-56%), and 12-month PFS rate of 20.1% (3.5-46.4%). The CBR was 35.7% (12.8-64.9%). Two patients with GCT remain on active treatment for > 18 months. Grade 3 adverse events occurred in 5 patients: abdominal pain (2), small bowel obstruction (1), syncope (1), thromboembolism (1), urinary tract infection (1), and febrile neutropenia (1). Grade 3 laboratory toxicity occurred in 5 patients: anemia (2), neutropenia (1) and lymphopenia (2). **Conclusions:** ONA-XR was well tolerated and exhibited a 12-month PFS rate of 20.1% and a CBR of 35.7% in patients with GCT. No objective responses were observed. Cohorts 1-3 have closed to accrual, with 2 patients continuing active treatment for >18 months. Cohort 4, which combines ONA-XR with anastrozole, is currently enrolling patients with GCT. Clinical trial information: NCT03909152. Research Sponsor: Context Therapeutics.

Cohort	Evaluable (N)	Median PFS	CBR%	PFS 6M0	PFS 12M0
Cohort 1 (Granulosa Cell)	14	3.5 (1.6-8.8)	35.7% (12.8-64.9%)	30.1% (8.4-56%)	20.1% (3.5-46.4%)
Cohort 2 (LGSOC)	4	4.4 (1.8-NE)	50% (6.8-93.2%)	NR	NR
Cohort 3 (Endometrial Cancer)	1	1.6	0%	NR	NR

NR: Not Reached, (2-sided 95% CI)

5522 **Poster Discussion Session**

A pilot phase II study of neoadjuvant fulvestrant plus abemaciclib in women with advanced low-grade serous carcinoma. *First Author: Lauren P. Cobb, Department of Gynecologic Oncology & Reproductive Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Neoadjuvant chemotherapy has demonstrated limited activity in low-grade serous carcinomas (LGSOC) of the ovary, fallopian tube, and peritoneum, with objective response rate of 11% and complete gross resection (CGR) rate of 38% at the time of interval cytoreductive surgery (ICS). LGSOC has many similarities to hormone receptor positive (HR+) breast cancer, including clinical benefit from endocrine therapies in the recurrent and maintenance settings. Based on the activity of antiestrogen plus CDK4/6 inhibitor combination therapy in HR+ breast cancer, we conducted a phase II pilot study to assess the clinical benefit of neoadjuvant treatment with fulvestrant and abemaciclib for women with advanced LGSOC. **Methods:** Women with unresectable, untreated stage III or IV LGSOC of the ovary, fallopian tube or peritoneum were eligible. Patients received fulvestrant (500 mg IM on day 1 and 15 of the first 28-day cycle, followed by day 1 of subsequent cycles) and abemaciclib 150 mg orally BID. Pre/perimenopausal patients also received goserelin 10.8 mg subcutaneously every 12 weeks for ovarian suppression. Patients continued treatment until deemed resectable by the treating surgeon with imaging re-assessment every 8 weeks using RECIST 1.1. Following ICS, patients receive 4 cycles of adjuvant fulvestrant and abemaciclib and then transition to maintenance letrozole. Patients with progressive disease (PD) were removed from study and received standard of care chemotherapy. Primary endpoint is clinical benefit rate (CBR). **Results:** Fifteen patients were enrolled and evaluable. At data cutoff date (January 20, 2022), 7 of 15 patients (47%) had partial response (PR) (one patient with radiologic PR had a pathologic complete response at ICS), 5 of 15 (33%) had stable disease (SD), and 3 of 15 (20%) had progressive disease (PD), resulting in a CBR of 80%. Of the 7 patients with PR, 3 have had ICS with CGR, 3 have not yet had ICS, and 1 underwent resection of supraclavicular disease with small volume residual disease in the chest. Of the 5 patients with SD, one underwent ICS with CGR, and two have been on treatment for 8 and 16 weeks with reduction in measurable disease but not yet deemed to be candidates for surgery. Four of the 5 patients (80%) who had ICS, had CGR. Median time on study prior to surgery was 24 weeks. Adverse events (grade 3 or 4) possibly related to abemaciclib occurred in 2 patients (13.3%) and included acute kidney injury (6.7%) and neutropenia (6.7%). **Conclusions:** Neoadjuvant treatment with fulvestrant and abemaciclib was tolerable and demonstrated unprecedented response and CGR rates in this pilot study. These results compare favorably to published outcomes of neoadjuvant chemotherapy in LGSOC. Further studies are planned to explore this new treatment option in a larger study population. Clinical trial information: NCT03531645. Research Sponsor: Eli Lilly and AstraZeneca.

5523 **Poster Discussion Session**

Cervical cancer geographical burden analyzer: An interactive, open-access tool for understanding geographical disease burden in patients with recurrent or metastatic cervical cancer. *First Author: Tara Castellano, Louisiana State University, Department of Gynecologic Oncology,, New Orleans, LA*

Background: Examining geographic distributions of high and low proportions of recurrent or metastatic cervical cancer (r/mCC) can identify regions with high need of intervention and advance our understanding of r/mCC community-specific risk factors. Previous studies of epidemiologic or geographic clusters in late-stage cervical cancer were conducted prior to the availability of modern treatments for r/mCC. Due to the rapidly evolving treatment landscape for r/mCC use of commercial claims is an important way to follow dynamic practice changes. Our study objective was to understand recent geographical disparities among r/mCC patients in the US. **Methods:** We developed a web-based tool, Cervical Cancer Geographical Disease Burden Analyzer, that allows users to quantify r/mCC disease burden across metropolitan statistical areas (MSA) over multiple years. The inputs to the web-based tool were extracted through a retrospective analysis of the 2015-2020 MarketScan commercial claims database using a previously validated methodology. We then calculated the r/mCC rate as the ratio of r/mCC cases over cervical cancer (CC) cases for each of the >400 MSA considered. The calculated MSA-specific r/mCC rate was visualized in an interactive US map,. The online interactive tool allowed the users to filter the results by year, age group, and minimum number of diagnoses at the MSA level. **Results:** Our findings showed that there is large variation with respect to r/mCC disease burden across MSA in the US, with a range of 0-45%. The top five MSA with the highest r/mCC rates from 2018-2020 are presented in the table. In particular, r/mCC rates in Sacramento-Roseville-Arden-Arcade (SRAA), CA and Boston-Cambridge-Newton (BCN), MA were on an increasing trajectory (33% in 2018 to 50% in 2020 in SRAA, CA; and from 41% in 2018 to 50% in 2020 in BCN, MA). On the other hand, while disease burden remained high, we observed decreasing r/mCC rates in Grand Rapids, MI (55% in 2018 and 31% in 2020, resulting in an average r/mCC rate of 42%). Finally, in Cape Coral-Fort Myers, FL and Baltimore-Columbia-Towson, MD the r/mCC rates have fluctuated across time but were consistently >30%. **Conclusions:** Our web-based online interactive tool can help with identifying areas with high need of intervention, and inform how access, prevention and new or emerging therapies may potentially change the distribution of r/mCC disease burden. To better understand underlying drivers of geographic disparities observed, further efforts should be targeted towards identifying local-level factors. Research Sponsor: Seagen Inc.

MSA	r/mCC rate 2020	r/mCC rate 2019	r/mCC rate 2018	Average r/mCC rate
Cape Coral-Fort Myers, FL	40%	31%	64%	45%
Sacramento-Roseville-Arden-Arcade, CA	50%	46%	33%	45%
Grand Rapids, MI	31%	36%	55%	42%
Boston-Cambridge-Newton, MA	50%	45%	41%	40%
Baltimore-Columbia-Towson, MD	38%	33%	39%	36%

5524 **Poster Session**

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) versus intravenous chemotherapy in unresectable peritoneal metastases secondary to platinum-resistant ovarian cancer: Interim analysis of Indian randomized control trial. *First Author: S.P. Somashekhar, Manipal Comprehensive Cancer Center, Bangalore, India*

Background: PIPAC has emerged as a novel way to deliver intraperitoneal chemotherapy. PIPAC has shown improved response rate and quality of life in patients with inoperable peritoneal carcinomatosis. **Methods:** The trial is registered with Clinical Trials Registry – India (CTRI) REF/2018/08/021223. Interim analysis is presented here. Primary endpoint was to assess the objective response rate (With RECIST 1.1) between PIPAC and IV chemotherapy arm. Secondary endpoints were to assess quality of life (QLQ C-30) and morbidity (CTCAE 4.0 and Clavien dindo) between the two groups. PIPAC was done with dose of cisplatin 15mg /m2 and doxorubicin at 3mg/m2. The choice of chemotherapy was left at the discretion of treating physician. The response rate (With MRI & Ca-125) & quality of life assessment (QLQ C-30) of both the group was done periodically and recorded. **Results:** 40 patients underwent 105 PIPAC applications with nearly 25 (62.5%) had 3 cycles completed. 40 patients underwent IV chemotherapy same time with nearly 23 (57.5%) having received atleast 5 cycles. Mean age 57.3±8.05, PCI 24.45±6.39, with nearly 45.5% of patients had previous surgery and 72.5% of patients having received atleast 2 lines of prior chemotherapy and nearly 60 % having ascites. The objective response rate is 66.6% versus 22.5%, grade 3-4 events were 10.0% vs. 35.7 % in PIPAC and IV arm respectively. Histological regression was seen in 67.5% of patients with 3 cycles PIPAC. Functional, symptom and global health score at day 120 was significantly better with PIPAC arm when compared to IV arm. **Conclusions:** PIPAC is safe and feasible for patients with unresectable platinum resistant ovarian cancer. PIPAC showed better objective response rates and improved quality of life when compared to chemotherapy arm with acceptable morbidity. Clinical trial information: REF/2018/08/021223. Research Sponsor: None.

5525 **Poster Session**

Cytoreductive surgery plus HIPEC for advanced epithelial ovarian cancer: Analysis from a multicentric national Indian HIPEC registry of 1,470 patients—An ISPSM Collaborative study. *First Author: S.P. Somashekhar, Manipal Comprehensive Cancer Center, Bangalore, India*

Background: Improved long-term results can be achieved in advanced epithelial ovarian cancer (EOC) patients using optimal cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC). **Methods:** Indian society of peritoneal surface malignancy (ISPSM) is a registered body which maintains prospective data of 26 centers across India who perform CRS –HIPEC. From February 2017 until January 2022, 1470 patients with advanced EOC were treated with CRS-HIPEC. He general practice patterns and the oncological outcomes in terms of progression free survival (PFS) and overall survival (OS) & post-operative morbidity and mortality is reported. **Results:** Upfront (n = 156), interval (n = 645) and recurrent (n = 669) cytoreductions were performed based on the timeline at presentation. Mean age 54.5±10.74, PCI 13. 6±5.2, duration of surgery 10.6±1.h hrs. 36.4% had total peritonectomy, 12.7% had multivisceral resection, 41.8%had bowel resections and stoma rate was 7.4% . 60.3% had semi-open HIPEC, 83.1% used cisplatin for HIPEC and 83.1 % had HIPEC for 90 minutes. Overall G3-G5 morbidity was 25.4% with major ones being post-operative intra-abdominal collection (21.8%), electrolyte imbalance (16.4%), pulmonary (16.4%) followed by hematological (12.7%). Surgical morbidity was more in upfront cytoreduction group compared to interval group (20% versus 13.5%) and recurrent group (20% versus 15%), respectively. The 30 day mortality was 3.8%. With a median follow-up of 46 months, median PFS was 33 months in primary (upfront plus interval) group and 16 months in recurrent cytoreduction group. Median OS was not achieved in both primary and recurrent groups (4 year OS rates: 60 and 55%, respectively). **Conclusions:** This prospective database provides a collation and audit of the management of advanced epithelial ovarian cancer with CRS HIPEC in multiple centers registered under ISPSM. In advanced EOC patients, CRS plus HIPEC offers potential benefits in PFS and OS rates, with acceptable rates of morbidity and mortality and can be practiced even in resource constrained setting. Research Sponsor: None.

5526 **Poster Session**

Efficacy and safety of the anti–PD-L1 monoclonal antibody socazolimab for recurrent or metastatic cervical cancer: Results from the phase I dose-escalation and expansion study. *First Author: Jusheng An, Cancer Institute and Hospital, Chinese Academy of Medical Sciences, Beijing, China*

Background: The study (NCT03676959) is an open-label, phase I study investigating the safety and efficacy of the recombinant, fully human anti-programmed death-ligand 1 (PD-L1) monoclonal antibody socazolimab for recurrent or metastatic cervical cancer. **Methods:** Patients received socazolimab every 2 weeks until disease progression. The study was divided into a dose-escalation phase and a dose-expansion phase. Safety and tolerability were primary endpoints of the dose-escalation phase. Primary endpoints of the dose-expansion phase were safety and overall response rate (ORR) of the 5mg/kg dose. Efficacy was assessed by a third-party independent review committee (IRC) using the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) as the evaluation standard. Pharmacokinetics and pharmacodynamics were also studied. **Results:** One hundred four patients were enrolled. Twelve patients were included in the dose-escalation phase, with one complete and two partial responses in the 5mg/kg treatment group. Ninety-two patients (5mg/kg) were enrolled in the dose-expansion phase, with 54 patients (59.3%) expressing baseline PD-L1-positive tumors. ORR was 15.4% (95% CI, 8.7 to 24.5%). Median PFS was 4.44 months (95% CI, 2.37 to 5.75 months), and the median OS was 14.72 months (95% CI, 9.59 to NE months). ORRs for PD-L1-positive and PD-L1-negative patients were 16.7% and 17.9%, respectively. Treatment-related grade 3 to 4 adverse events occurred in 7.7% of patients. No treatment-related deaths had occurred. **Conclusions:** Our study demonstrates that socazolimab has remarkable safety and efficacy for the treatment of recurrent or metastatic cervical cancer and exhibits a safety profile similar to other anti–PD-1/PD-L1 monoclonal antibodies. Clinical trial information: NCT03676959. Research Sponsor: Lee's Pharmaceutical Holdings Limited.

Anti-tumor efficacy assessment by IRC evaluation.

Efficacy	5 mg/kg Dose Expansion (N = 91)	CPS < 1 (N = 28)	CPS ≥ 1 (N = 54)	CPS < 10 (N = 52)	CPS ≥ 10 (N = 30)
ORR	14 (15.4%; 8.7%, 24.5%)	5 (17.9%; 6.1%, 36.9%)	9 (16.7%; 7.9%, 29.3%)	8 (15.4%; 6.9%, 28.1%)	6 (20.0%; 7.7%, 38.6%)
PFS, months (95% CI)	4.44 (2.37, 5.75)	2.79 (1.81, 5.72)	5.29 (2.56, 10.58)	3.58 (2.00, 5.78)	7.56 (2.56, NE)
12-month PFS	28.4% (18.2%, 39.5%)	30.5% (13.8%, 49.2%)	32.5% (18.5%, 47.2%)	22.8% (10.7%, 37.7%)	45.5% (26.2%, 63.0%)
OS, months (95% CI)	14.72 (9.59, NE)	15.84 (7.10, NE)	NE (13.34, NE)	15.84 (8.54, NE)	NE (13.34, NE)
12-month OS	58.2% (45.4%, 69.0%)	59.3% (36.6%, 76.3%)	68.3% (51.4%, 80.4%)	57.2% (39.5%, 71.5%)	77.0% (55.3%, 89.1%)
TOR, months (range)	2.00 (1.64 - 3.65)	2.43 (1.84 - 3.61)	1.87 (1.64 - 3.65)	2.25 (1.74 – 3.65)	1.77 (1.64 – 2.00)

Data noted as No. (%; 95% CI) unless stated. Abbreviation: TOR, Time to Response.

5527 **Poster Session**

SPECT-defined, active bone marrow–sparing, volumetric-modulated arc therapy reduces the incidence of acute hematologic toxicity in patients with locally advanced cervical cancer who receive chemoradiotherapy. *First Author: Shan Bing Wang, Department of Oncology,the Second People Hospital of YiBin City, Yibin, China*

Background: Acute haematologic toxicity is the most common side effect of chemoradiotherapy in patients with locally advanced cervical cancer .We are aim to test the efficacy of defined active bone marrow sparing volumetric-modulated arc therapy reduces grade 3 or higher (grade 3+) acute haematologic toxicity for patients with locally advanced cervical cancer treated with chemoradiotherapy. **Methods:** This was a prospective, single-center, open label, randomized clinical trial that enrolled locally advanced cervical cancer.Patients were randomized to ^{99m}Tc sulfur colloid SPECT-defined active bone marrow sparing volumetric-modulated arc therapy group (ABMS group) or control group.The control group received weekly cisplatin concurrently with volumetric-modulated arc therapy(VMAT),followed by high-dose-rate intracavitary brachytherapy. The active bone marrow sparing volumetric-modulated arc therapy group additionally received ^{99m}Tc sulfur colloid SPECT-defined active bone marrow dose constrain. The primary endpoint was the incidence of grade 3 or higher (grade 3+) acute haematologic toxicity. Secondary objectives included acute gastrointestinal toxicity, planning Target Volume (PTV) coverage and dosimetric parameters of organs at risk(OARs). **Results:** A total of 148 patients with Federation of Gynaecology and Obstetrics(FIGO) stage IB-IIIB from-January 2017 to April 2019 were randomized， and 146 were treated(74 in ABMS group and 74 in control group). The median follow-up was 20.0 months.The incidence of grade 3 or higher (grade 3+) acute haematologic toxicity in the ABMS group was 29.7%,significantly lower than the 48.6% incidence in the control group(p = 0.03).The incidence of grade 3+ neutropenia (ABMS group： 20.3%,control group:36.5%;p = 0.04), Grade 3+ leukopenia (ABMS group： 25.7%,control group:44.6%;p = 0.02) and Grade 3+ lymphopenia (ABMS group： 4.1%,control group:14.9%;p = 0.04) were significantly differences between the two group.The were no differences in Grade 3+ anemia (ABMS group： 1.4%,control group:5.5%;p = 0.37) and Grade 3+ acute gastrointestinal toxicity(ABMS group： 1.4%,control group:1.4%;p = 1.00) between the two group.The number of patients completing five cycles of cisplatin in the ABMS group was 88.5%,,significantly higher than the 75% in the control group(p = 0.02).There were no differences in PTV coverage and dosimetric parameters of OARs between the two group. **Conclusions:** SPECT-defined active bone marrow sparing VMAT significantly reduced grade 3+ acute haematologic toxicity,and improved chemotherapy delivery compared with control group. Clinical trial information: ChiCTR-IOR-16010214. Research Sponsor: the Sichuan Medical Association youth innovation project (NO. Q16082) and the health commission of YIbin City (NO.2019yw029).

5528 **Poster Session**

Phase 1 trial of first-line bintrafusp alfa in combination with other anticancer therapies in patients (pts) with locally advanced or advanced cervical cancer. *First Author: Ana Oaknin, Vall d'Hebron Institute of Oncology, Hospital Universitari Vall d'Hebron, and Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain*

Background: Until the recent FDA approval of pembrolizumab in combination with chemotherapy ± bevacizumab, there have been limited treatment options that address the underlying biology for pts with persistent, recurrent, or metastatic (P/R/M) or locally advanced (LA) cervical cancer. Persistent HPV infection is associated with 99% of cervical cancers and is linked to upregulation of TGF-β. Bintrafusp alfa, a first-in-class bifunctional fusion protein composed of the extracellular domain of TGF-βRII (a TGF-β "trap") fused to a human IgG1 mAb blocking PD-L1, has shown promising clinical activity and manageable safety in pts with recurrent or metastatic cervical cancer. We report data from a phase 1 trial evaluating safety of first-line bintrafusp alfa plus chemotherapy ± bevacizumab for pts with P/R/M cervical cancer or bintrafusp alfa plus chemoradiotherapy for pts with LA cervical cancer (INTR@PID 046; NCT04551950). **Methods:** Pts with P/R/M cervical cancer who had not received prior systemic therapy received bintrafusp alfa 2400 mg Q3W plus cisplatin/carboplatin and paclitaxel with (cohort 1A) or without (cohort 1B) bevacizumab. Pts with LA cervical cancer received bintrafusp alfa 2400 mg Q3W plus concurrent weekly cisplatin and radiotherapy followed by maintenance therapy with bintrafusp alfa (cohort 2). Pts were treated until disease progression, death, unacceptable toxicity, or withdrawal. Primary endpoints were safety and tolerability of bintrafusp alfa in combination with current standard-of-care therapies in pts with P/R/M or LA cervical cancer. **Results:** As of November 25, 2021, 8 pts in cohort 1A, 9 in cohort 1B, and 8 in cohort 2 had received bintrafusp alfa for a median of 11.6, 10.0, and 5.6 cycles, respectively. At the time of this analysis, 11 of 25 pts remained on bintrafusp alfa therapy. Any-grade bintrafusp alfa–related adverse events (AEs) occurred in 75.0%, 100.0%, and 75.0% of pts in cohorts 1A, 1B, and 2, respectively (Table). The most-common grade ≥3 AEs were anemia and hematuria (25.0% each) in cohort 1A and vaginal hemorrhage (22.2%) in cohort 1B. One pt had grade 4 anemia and vaginal hemorrhage in cohort 1B. No treatment-related deaths occurred. AEs led to permanent discontinuation of bintrafusp alfa in 37.5%, 33.3%, and 12.5% of pts in cohorts 1A, 1B, and 2, respectively; the most common any-grade AE was vaginal hemorrhage (22.2%). **Conclusions:** No new safety signals were observed with first-line bintrafusp alfa plus chemotherapy ± bevacizumab or chemoradiotherapy in pts with P/R/M or LA cervical cancer. Clinical trial information: NCT04551950. Research Sponsor: the healthcare business of Merck KGaA, Darmstadt, Germany.

	Cohort 1A, % n = 8	Cohort 1B, %n = 9	Cohort 2, %n = 8
Bintrafusp alfa–related AEs			
Any grade	75.0	100.0	75.0
Grade ≥3	50.0	44.4	25.0
Any-grade AEs of special interest			
Anemia	75.0	77.8	62.5
Bleeding events	75.0	77.8	62.5
Immune-related AEs	37.5	33.3	37.5
Infusion-related reactions	12.5	11.1	12.5
Any-grade TGF-β–mediated skin AEs	0	11.1	0

5529 **Poster Session**

GOTIC-018: Phase I, open-label, multicenter study to assess the safety of pre- and co-administration of ONO-4538 (nivolumab) with concurrent chemoradiation (CCRT) in patients (pts) with locally advanced cervical carcinoma (LACvCa). *First Author: Akira Yabuno, Department of Gynecologic Oncology, Saitama Medical University International Medical Center, Hidaka, Japan*

Background: LACvCa has a poor prognosis. CCRT is the standard treatment for LACvCa, and the 5-year survival rate is estimated at around 60%. Nivolumab (Nivo), an anti-PD1 monoclonal antibody, showed clinical activity in recurrent or persistent CvCa pts. Nivo may enhance antitumor immune responses induced by CCRT. The safety and feasibility of Nivo plus CCRT for LACvCa pts has not yet been reported. We report data from a phase I trial evaluating safety and feasibility of pre- and co-administration of Nivo with CCRT in pts with LACvCa (GOTIC-018; JMA-IIA00425). **Methods:** The treatment plan in cohort A is co-administration of Nivo (240mg/body once every 2 weeks) with CCRT followed by maintenance therapy with Nivo. The treatment plan in cohort B is pre- (two doses of Nivo before CCRT) and then co-administration of Nivo with CCRT followed by Nivo maintenance. The CCRT regimen includes 4 or more cycles of cisplatin (40 mg/m^2 weekly) and external beam radiotherapy (EBRT) followed by brachytherapy. The Nivo maintenance therapy was scheduled for 52 weeks after completion of CCRT. The primary objective is the rate of Grade≧3 adverse events (AEs) during the acute phase, which is defined as 90 days from the start date of EBRT. Secondary objectives include the incidence of dose limiting toxicity (DLT) and progression-free survival. **Results:** A total of 30 patients, 15 patients in each cohort, was enrolled in this study. This report is a safety evaluation in the acute phase of the study. There were 1 stage IVA, 11 stage IIIB, 16 stage II and 2 stage IB tumors based on FIGO 2009. 28 squamous cell and 2 adeno/adenosquamous carcinomas were included. No DLT was observed in the first 6 DLT-evaluable pts in each cohort. All 30 patients completed planned EBRT and brachytherapy. 2 and 0 patients required a break from EBRT in cohort A and B, respectively. The median cycles of cisplatin administration was 5 and 6 in cohort A and B, respectively. 2 and 0 patient required cisplatin dose reduction in cohort A and B, respectively. 1 patient required cisplatin discontinuation in each cohort. The median cycles of Nivo administration were 6 and 9 in cohort A and B, respectively. 1 patient required Nivo discontinuation due to AEs in each cohort. All patients experienced Grade≧3 AEs. Most common Grade≧3 AEs were neutropenia (60.0 and 26.7% in cohort A and B, respectively), anemia (13.3 and 16.7%) and diarrhea (13.3 and 26.7%). In cohort B, no patients required delay in starting CCRT due to the AEs related to pre-administration of Nivo, and no patients had disease progression before starting CCRT. **Conclusions:** No DLT was reported during the acute phase in both cohort A and B, and no new safety signals were observed. Addition of pre-and co- administration of Nivo appears safe and feasible in patients with LACvCa treated with CCRT. Clinical trial information: JMA-IIA00425. Research Sponsor: Ono Pharmaceutical CO., LTD..

5530 **Poster Session**

Cervical cancer prevention program in Nepal: A comprehensive "train the trainer" approach. *First Author: Samantha Batman, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Cervical cancer is the leading cause of cancer and cancer-related deaths among women in Nepal, due in part to a lack of access to screening and limited medical providers trained to diagnose and treat women with preinvasive cervical disease. Cancer Care Nepal has partnered with The University of Texas MD Anderson Cancer Center (MD Anderson) and the American Society of Clinical Oncology (ASCO) to implement a 'train the trainer' (TOT) program to teach visual inspection with acetic acid (VIA), colposcopy, cervical biopsy, cryotherapy, thermal ablation, and loop electrosurgical excision procedure (LEEP). **Methods:** An initial cervical cancer prevention course was held in Kathmandu, Nepal in November 2019, supported by ASCO and with faculty from Civil Service Hospital, Bhaktapur Cancer Hospital, and National Academy of Medical Sciences and MD Anderson. As a continuation of this program, a TOT course was implemented for local specialists from five participating institutions throughout Nepal to learn how to deliver these trainings. Each participating institution then holds their own local course for nurses and doctors in their region. The training is complemented with monthly Project ECHO (Extension for Community Healthcare Outcomes) telementoring videoconferences. **Results:** The program was launched in November 2021. To date, two TOT training courses (2-day duration) have been held for clinicians from the 5 participating regions. Due to COVID-19 pandemic travel restrictions, didactic lectures were held virtually with MD Anderson and ASCO staff and included epidemiology of cervical cancer, screening guidelines, colposcopy, and treatment of cervical dysplasia. This was followed by hands-on training using simulation models to teach VIA, colposcopy, ablation and LEEP, led by the Nepalese faculty who had participated in the 2019 course. There were 41 participants in total (23 in the first course and 18 in the second course), including 21 gynecologists, 4 gynecologic oncologists, 1 medical oncologist, 1 general practitioner, and 14 nurses. 39 participants (73%) completed both the pre- and post-survey results. 86% of respondents from the first course and 100% of respondents from the second course reported that they intended to change their practice as a result of knowledge gained from the course. In addition, Cancer Care Nepal became a new hub for Project ECHO and held its first session in January 2022, with 20 participants representing two regions. The specialists from each of the 5 participating sites will be holding local courses for doctors and nurses in their respective regions throughout 2022. **Conclusions:** Our work shows that the TOT strategy can widen the reach of training in cervical cancer prevention in Nepal. Despite travel restrictions during the COVID-19 pandemic, global health training and mentoring can continue, though they require adaptions and use of virtual platforms. Research Sponsor: Prevent Cancer Foundation.

5531 **Poster Session**

Staging locally advanced cervical cancer with FIGO 2018 versus FIGO 2008: Impact on overall survival and progression-free survival in the OUTBACK trial (ANZGOG 0902, RTOG 1174, NRG 0274). *First Author: Linda R. Mileshkin, Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia*

Background: The International Federation of Obstetrics and Gynecology staging system for cervical cancer (FIGO 2008) was revised in 2018 to incorporate lymph node involvement (FIGO 2018). OUTBACK is an international, randomized phase 3 trial of adjuvant chemotherapy versus observation after standard of care treatment with chemoradiation for women with locally advanced cervical cancer. OUTBACK found no benefit from the addition of adjuvant chemotherapy. We evaluated the effects of classifying participants with these 2 staging systems in the OUTBACK trial population. **Methods:** OUTBACK recruited April 2011 to June 2017 and staged participants according to FIGO 2008. Lymph node status, smoking status, age, race and histological subtype were documented at trial entry as important prognostic factors. We assessed the effects of stage grouping into stage I, II, and III/IVa with FIGO 2008 versus FIGO 2018, on progression-free survival (PFS) and overall survival (OS) at 5 years using Kaplan-Meier estimates, and in univariable proportional-hazards regression analyses, and in multivariable analyses adjusting for important prognostic factors and randomly allocated treatment. **Results:** All 919 study participants had complete data for staging according to the 2 staging systems and most prognostic factors for adjustment. Among all participants, the 5-year outcomes were PFS = 62% and OS = 72%. Classification according to FIGO 2018 rather than FIGO 2008 yielded higher 5-year PFS and OS in each stage group (see table for numbers of participants, PFS and OS for each stage group). Predictors of PFS in multivariable analysis included squamous vs non-squamous histology (HR 0.71 for FIGO 2008 and 0.74 for FIGO 2018), but not nodal involvement when FIGO 2018 was used. Both staging systems were the only independently significant prognostic factors in both univariable and multivariable analyses (all $p < 0.0001$) for both PFS and OS. **Conclusions:** Compared to FIGO 2008, reclassifying pts by FIGO 2018 staging resulted in more pts being classified as stage 3 due to the incorporation of nodal status. Staging locally advanced cervical cancer using FIGO 2018 rather than FIGO 2008 resulted in higher PFS and OS in each stage grouping that reflected stage migration, not a true improvement in outcomes. FIGO stage remains the strongest predictor of overall survival after CRT but survival outcomes by stage in trials using the old vs new staging system are not comparable. Clinical trial information: ACTRN12610000732088. Research Sponsor: NHMRC Project Grant (APP1044349), U.S. National Cancer Institute.

	Number (%)	Number (%)	PFS 5Y %		OS 5Y %	
Stage Group	FIGO 08	FIGO 18	FIGO 08	FIGO 18	FIGO 08	FIGO 18
I	242 (26%)	105 (12%)	71	81	78	89
II	457 (50%)	261 (28%)	65	68	75	78
III/IVa	220 (24%)	553 (60%)	48	56	58	66

5532 **Poster Session**

Factors associated with receipt of second-line recurrent or metastatic cervical cancer treatment in the United States: A retrospective administrative claims analysis. *First Author: Kalyani Sonawane, University of Texas Health Science Center at Houston, Houston, TX*

Background: There is limited real-world data on the proportion of eligible patients who received second-line (2L) treatment following progression on first-line (1L) systemic therapy for recurrent or metastatic cervical cancer (r/mCC). In addition, factors impacting selection of 2L are not well-understood. The objective of this study was to determine the prevalence and predictors of subsequent therapy among patients with 1L-treated r/mCC. **Methods:** We conducted a retrospective analysis of the 2015-2020 MarketScan claims database. Women ≥18 years of age with at least one inpatient claim or two outpatient claims with a diagnosis for malignant neoplasm of the cervix followed by 1L therapy codes were identified. The last recorded date of 1L treatment was assigned as the index date for each woman. Continuous enrollment criteria of minimum 3-month pre-index and 12-month post-index were applied. Women with claims for a new therapy after 60 days but no later than 365 days from the end of 1L treatment were identified as those who continued r/mCC treatment. We used descriptive statistics to examine the baseline characteristics of the final analytical cohort. A multivariable logistic regression model examined the factors associated with treatment discontinuation. All analyses were performed using SAS, Cary, NC. P-value was tested at 0.05. **Results:** A total of 1,080 patients with 1L-treated r/mCC were identified, of whom 384 met the study criteria. Post-1L treatment, 196 (51.0%) patients received a new therapy within a median duration of 122 days. A total 188 (49.0%) patients did not receive subsequent therapy. The geographic location of patient (identified based on census region as Northeast, Midwest, South, or West) and prior bevacizumab exposure were significant predictors of receiving subsequent therapy. Specifically, patients from the Midwest (odds ratio [OR] = 0.43; 95% CI: 0.23-0.84) and Southern (OR = 0.53; 95% CI: 0.29-0.96) regions had lower likelihood of receiving 2L treatment after 1L, compared to those living in the Northeast. Women without prior bevacizumab treatment were also less likely to receive subsequent therapy (OR = 0.65; 95% CI: 0.42-0.99). Age, type of health plan, and comorbidities were not associated with the likelihood of receiving subsequent treatment. **Conclusions:** Overall, nearly half of the 1L-treated r/mCC patients did not continue to 2L therapy, with findings showing treatment drop-off differing significantly by geographic region and prior treatment. Additional research and targeted outreach efforts are needed to understand geography-, population-, or practice-specific barriers impacting access to therapy among r/mCC patients. Research Sponsor: Seagen.

5533 **Poster Session**

Examining differences based on gender and sexual orientation for cervical cancer screening and prevention behaviors. *First Author: Prajakta Adsul, University of New Mexico Comprehensive Cancer Center, Albuquerque, NM*

Background: Population-based studies to examine cervical cancer screening (CCS) and prevention among sexual and gender diverse (SGD) individuals have been limited. We conducted a state-wide survey in New Mexico to examine differences in CCS and HPV vaccination uptake based on gender and sexual orientation. **Methods:** The survey was advertised using mailed flyers, social media, and targeted internet ads across the state. We received a total of 2534 responses, of which 797 respondents were CCS eligible (i.e., between 21-65 years old, had a cervix, and did not have a prior cervical cancer diagnosis) and provided information about CCS and were included in this analysis. Descriptive statistics were conducted using SAS 9.4. **Results:** Of the 797 respondents, 83% were 21 - 40 years old, 44% were white, 34% reported an annual household income below $50,000, 83% were employed, 81% had health insurance, and 73% reported having a primary care provider. Fourteen percent were transgender men or nonbinary, 86% were cisgender women, 34% were bisexual, 48% were lesbian, and 18% were queer. While there were no statistical differences in self-reported CCS based on gender identity, 31% of cisgender women and 25% of transgender men and nonbinary individuals reported never receiving a Pap test. The top reason for never receiving a Pap test among cisgender women was that their healthcare provider told them they did not need it (17%) and for transgender men and nonbinary individuals the top reasons were that they had an HPV vaccine (21%) or that it was too painful, unpleasant, or embarrassing (21%). There were significant statistical differences based on sexual orientation for receiving a Pap test ($p < 0.001$) and for being up to date on screening (Pap test in the past 3 years, a co-test, or primary HPV test in the past 5 years) ($p = 0.03$). Among lesbians, 39% reported never having a Pap test, compared with 17% of bisexuals and 30% of queer individuals. For lesbians, the top reason for not receiving a Pap test was not knowing that Pap tests existed (19%), while the top reason for both bisexual and queer individuals was that their healthcare provider told them they did not need it (17% and 19%, respectively). No significant differences were noted in HPV vaccination uptake among respondents. **Conclusions:** In order to address sexual orientation differences noted in our study, future research is needed to explore mechanisms through which these differences operate using community-based approaches. Additionally, educational interventions inclusive of different gender identities and sexual orientations are needed to improve motivations for screening uptake among SGD individuals. Finally, specific considerations for SGD individuals should be incorporated into screening recommendations and guidelines and clearly communicated to providers, further enabling them to make recommendations for these populations. Research Sponsor: American Cancer Society.

5534 **Poster Session**

Combination of nivolumab with chemoradiotherapy for locally advanced cervical cancer: NiCOL phase I trial. *First Author: Manuel Rodrigues, Medical Oncology, Institut Curie, Paris, France*

Background: Current management of locally-advanced cervical cancers (LACC) relies on chemoradiotherapy (CRT) and brachytherapy. The causal relation between cervical cancer and human papillomavirus infection, which engenders tumor expression of immunoreactive neo-antigens, together with high PD-L1 expression, warrants consideration of immune checkpoint inhibitors (ICI) in the definitive treatment of this disease. We assessed the safety of concurrent and maintenance nivolumab in addition to CRT in patients with LACC. **Methods:** This prospective, multi-center, dose-confirmation, phase I clinical trial (NiCOL trial; NCT03298893) evaluated the tolerance profile of concurrent and maintenance nivolumab in addition to CRT (45 Gy in 25 fractions with cisplatin 40mg/m^2 q1w, followed by a brachytherapy boost to 85 Gy) for stage IB3-IVA cervical cancers. Nivolumab was administered at 240 mg q2w starting on day 1 of CRT and in maintenance after CRT completion for up to 6 months (13 cycles). The primary endpoint was the incidence of dose-limiting toxicities (DLT) within 11 weeks after the initiation of treatment (defining the DLT assessment period), corresponding to the first 6 cycles of nivolumab. DLT were defined as grade ≥3 non-hematological toxicities, grade ≥3 immune-related adverse event (irAE), persistent grade ≥2 irAE for ≥1 week despite optimal supportive care, or ≥1-week radiotherapy delay related to treatment toxicity. Secondary endpoints included overall response rate (ORR), progression-free survival (PFS) and treatment tolerance profile. **Results:** 16 patients (pts) were recruited between 11/2017 and 07/2020. Median age was 46 years [range: 27-77]. Histological types were squamous cell carcinomas (n = 14) and adenocarcinomas (n = 2). Tumors were staged as FIGO IB3 (n = 2), IIB (n = 8), IIIB (n = 1), IIIC1 (n = 4) and IVA (n = 1); 13 tumors were HPV-positive. Three patients experienced DLT, corresponding to grade 3 hypotension (n = 2) and grade 3 acute kidney injury (n = 1). Following the DLT assessment period, while receiving maintenance nivolumab, one patient developed a grade ≥3 irAE corresponding to a grade 3 diarrhea. Two months after brachytherapy completion, ORR was 93.8% [95%CI: 69.8%-99.8%]. With a median follow-up of 16.6 months, three patients experienced disease control failure (at 3,4 and 5 months); site of disease progression was local for two patients, and simultaneously local and distant for one patient. One-year PFS was 81.2% [95% CI: 64.2%-100%]. **Conclusions:** Concomitant nivolumab with definitive CRT, followed by maintenance nivolumab, appears to be a safe and feasible therapeutic option for LACC, associated with encouraging PFS rates. Further trials evaluating ICI combined with CRT for LACC are warranted in light of these promising results and of those from recent studies evaluating ICI in the metastatic setting. Clinical trial information: NCT03298893. Research Sponsor: Bristol-Myers Squibb.

5535 **Poster Session**

Efficacy and safety of QL1706, a novel dual immune checkpoint blockade containing a mixture of anti-PD1 IgG4 and anti-CTLA4 IgG1 antibodies, for advanced cervical cancer: Cohort data from a phase 1b trial. *First Author: Jihong Liu, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Anti-cytotoxic T lymphocyte antigen 4 (CTLA-4) and anti-programmed cell death 1 (PD-1) antibodies have synergistic effect. QL1706 is a novel dual immune checkpoint blockade containing a mixture of anti-PD-1 IgG4 and anti-CTLA4 IgG1 antibodies produced by a single cell line. QL1706 showed promising anti-tumor activity in multiple solid tumors. Here we reported the cervical cancer cohort data from the phase 1b trial of QL1706 (NCT05171790). **Methods:** Eligible patients had a pathologically confirmed diagnosis of squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix, with recurrent or metastatic, immunotherapy-naive disease at the time of enrollment. Patients were required to have ≥one lesion measurable by RECIST v1.1 and disease that had relapsed after a first-line, platinum-based regimen. Patients were included regardless of PD-L1 expression status at baseline. Patients received intravenous QL1706 5.0 mg/kg q3w (i.e., recommended phase 2 dose, defined in a phase 1a trial), for up to 24 months. The primary endpoint was confirmed overall response rate (ORR) per RECIST v1.1 by investigator. The secondary endpoints included disease control rate, duration of response (DoR), progression-free survival (PFS), overall survival (OS), safety, etc. **Results:** As of Dec 31, 2021, totally 53 patients with cervical cancer were enrolled (median age, 52 years [range 33-72]). Median follow-up was 5.6 months. Most patients (45 [85%]) had ECOG performance status of 1. Histological breakdown was squamous cell carcinoma (44 [83%]) and adenocarcinoma (nine [17%]). 33 (62%) patients had received one prior chemotherapy, 20(38%) patients had received ≥two prior chemotherapy. The confirmed ORR was 28% (95% CI 17%-42%; 15 patients), including one (2%) complete response and 14 (26%) partial response, with median duration of response not reached (95% CI 2.8 months-not estimable). Disease control was observed in 29 (55%; 95% CI 40%-68%) patients. Median PFS was 4.2 months (95% CI 1.7-6.9), and 6-month PFS rate was estimated as 37% (95% CI 24%-51%). Treatment-related adverse events (TRAE) were observed in 40 (75%) patients. Nine (17%) experienced grade ≥3 TRAE. The most common TRAE were rash (eight [15%]), hyperthyroidism (eight [15%]), and pyrexia (seven [13%]). Three (6%) patients suffered TRAE leading to dose discontinuation. The immune-related TRAE and serious TRAE were observed in 28 (53%) and eight (15%) patients, respectively. **Conclusions:** QL1706 demonstrated promising and durable clinical activity, with favorable tolerability in patients with recurrent and/or metastatic cervical cancer. Further investigations in this setting are continuing. Clinical trial information: NCT05171790. Research Sponsor: Qilu Pharmaceutical Co,.Ltd.

5536 **Poster Session**

Overall survival results from a phase II trial of anlotinib plus sintilimab in patients with recurrent advanced cervical cancer. *First Author: Qin Xu, Fujian Cancer Hospital, Fuzhou, China*

Background: The anlotinib (a novel multi-target TKI, inhibiting tumor angiogenesis and proliferative signaling) plus sintilimab (an antibody against PD-1) in patients with advanced cervical cancer trial was a multicenter, single-arm, phase II study (ChiCTR1900023015) that showed promising activity. The results of this trial have been previously reported and here we present updated survival data after a median follow-up of 13.0 months. **Methods:** Pts who have received at least once platinum-based chemotherapy, recurrent advanced cervical cancer, PD-L1 for CPS≥1, ECOG 0-1 were considered eligible for enrollment. Anlotinib was taken orally (10mg, qd, d1-14, 21 days per cycle), and sintilimab was administered intravenously (200mg, q3w, d1). The primary endpoint was objective response rate (ORR) and the secondary endpoints included disease control rate (DCR), progression free survival (PFS), overall survival (OS), safety and biomarkers. **Results:** Between December 2019 and December 2020, 42 patients with a median age of 53 years (range 36 to 67 years) were enrolled and received study treatment (ITT population and safety population). The data cutoff date was February 10, 2022. The patients were followed up for median duration of 13.0 months (range 0.03 to 24.8 months). In the ITT population, 2 (4.8%) patients achieved CR and 21 (50%) attained PR, the confirmed ORR was 54.8% (95% CI 38.7% to 70.2%). Fourteen (33.3%) patients had SD and the DCR was 88.1% (95% CI 74.4% to 96.0%). In the efficacy-evaluable patients (n = 39), the ORR was 59% (95% CI 42.1% to 74.4%) and the DCR was 94.9% (95% CI 82.7% to 99.4%). The median PFS was 9.46 months (95% CI 8.2 to 11.9) and the 6-month PFS rate was 73.4% (95% CI 60.6% to 89.0%). OS events occurred in 18 patients (42.9%). The median OS was 17.4 months (95% CI 12.4 to not reached). The 12-month OS rate and 24-month OS were 71.8% (95% CI 59.0% to 87.4%) and 49.1% (95% CI 34.5% to 69.9%), respectively. **Conclusions:** Anlotinib plus sintilimab showed a long-term survival benefit for patients with recurrent advanced cervical cancer. Additional investigations in larger randomized controlled trials are warranted in the future. Clinical trial information: ChiCTR1900023015. Research Sponsor: None.

5537 **Poster Session**

Immunological correlatives of durable responses and survival benefit for patients with cervical cancer in a trial of combined chemotherapy and immune therapy. *First Author: Amanda M Honan, Department of Microbiology and Immunology, University of Miami Miller School of Medicine, Miami, FL*

Background: Recurrent, metastatic, or persistent cervical cancer is largely an incurable disease due to lack of effective therapies. New treatment strategies are needed to provide long-term anti-tumor responses. We sought to gain insight into the immune pathways contributing to treatment response to immunotherapy. **Methods:** Fourteen patients with recurrent, persistent, or metastatic cervical cancer were enrolled in a single-arm phase II clinical trial (NCT03367871) with the combination of chemotherapy, bevacizumab and pembrolizumab regardless of tumor PD-L1 status. We designed a 40-color full spectrum flow cytometry panel to profile the protein markers of immune cells in peripheral blood mononuclear cells (PBMCs) at the single cell level to assess immunological correlates in blood with patients' anti-tumor responses. **Results:** In this trial with a cohort of predominantly Black and Hispanic patients (93%), 50% had durable responses to a combination therapy, and no difference was observed in the combined PD-L1 score (CPS) between responders and non-responders. With 40-color flow cytometry multiplex assays, we detected several differences between the non-responders and responders within the B and T cell populations. Within the B cell population, we observed a significant increase in the HLA^+CD200^{hi} B cells, a potentially suppressive cell subset, within the non-responders while among the responders we observed an increase in the number of HLA^+CD200^{lo} B cells. This HLA^+CD200^{lo} subset was mainly composed of IgD^-CD27^- memory B cells, a population suggested to have effector function. Moreover, the HLA^+CD200^{hi} B cell population contained a higher percentage of PD-L1 expressing cells than the HLA^+CD200^{lo} population, further supporting the suggestion that the HLA^+CD200^{hi} population may be an immunosuppressive subset. Within the T cell compartment, we observed an increase in the number of $CD4^+CD69^+$ T cells, which represent an activated CD4 T cell population, in the responder group compared to the non-responder group. The number of activated $CD4^+$ T cells was observed to correlate ($r = 0.5$) with the HLA^+CD200^{hi} B cell subset. **Conclusions:** This study identified novel immunological correlates in peripheral blood that were associated with durable antitumor responses and survival benefit for cervical cancer patients. These results suggest a role for T-B collaboration in effective antitumor immunity induced by combination of chemotherapy and immune therapy against cervical cancer. Clinical trial information: NCT03367871. Research Sponsor: Sylvester Comprehensive Cancer Center , Pharmaceutical/Biotech Company, U.S. National Institutes of Health.

5538 **Poster Session**

Toripalimab combined with chemoradiotherapy for patients with locally advanced cervical squamous cell carcinoma. *First Author: Dan Ou, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China*

Background: To assess the safety and efficacy of toripalimab combined with chemoradiotherapy for locally advanced cervical squamous cell carcinoma (Chinese Clinical Trial Registry number, ChiCTR2000032879). **Methods:** Twenty-two locally advanced cervical cancer patients, regardless of programmed death ligand-1 status, received toripalimab treatment combined with concurrent chemoradiotherapy. Concurrent chemoradiotherapy(CCRT) includes cisplatin (40 mg/m2, once a week for 5 weeks), radiotherapy (external irradiation 45-50.4Gy/25-28Fx, 5 fractions a week, followed by brachytherapy 24-30Gy/3-5Fx) and toripalimab (240mg on days 1, 22 and 43). The primary end-point was safety and feasibility. Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), overall survival (OS). **Results:** The median age was 55 years old (range, 42 to 72 years old), with 2 patients in FIGO stage II, 15 patients in stage IIIC, and 5 patients in stage IVA. All patients have received CCRT successfully. Grade III and higher adverse events (AEs) were observed in 10 patients (10/22, 45.5%), and no patient had a grade V AE. The most frequent grade III AE was leukopenia (8/22, 36.4%). The most common immunotherapy-related adverse reaction was hypothyroidism (2/22, 9.1%). The 3-month ORR rate was 95.5%. At data cutoff (Jan 31, 2022), the median follow-up was 10 months (range, 3.30 to 16.73 months). One patient developed multiple metastases 3 months after treatment, and 1 patient developed lung metastasis 6 months after treatment. The ORR was 100%, while the PFS rate was 90.1%, and the OS rate was 95.5%. **Conclusions:** Toripalimab combined with concurrent chemoradiotherapy demonstrated a manageable safety profile and promising anti-tumor activity in patients with locally advanced cervical cancer, thus might represent a novel treatment option for this patient population. Longer follow-up results and further phase II/III studies are expected. Clinical trial information: ChiCTR2000032879. Research Sponsor: None.

5539 **Poster Session**

A phase 1 trial of the PARP inhibitor fuzuloparib in combination with the anti-angiogenic apatinib in recurrent ovarian or triple-negative breast cancer. *First Author: Huiping Li, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Breast Oncology, Peking University Cancer Hospital and Institute, Beijing, China*

Background: The combination of an anti-angiogenic agent with a poly (ADP-ribose) polymerase (PARP) inhibitor has demonstrated improved clinical outcomes as treatment/maintenance treatment in gynecological cancers. Here we aimed to characterize the safety profile and recommended phase 2 dose (RP2D) of the combination of fuzuloparib (formerly fluzoparib), a PARP inhibitor, and apatinib, a VEGFR inhibitor in recurrent ovarian cancer (OC) or triple-negative breast cancer (TNBC). **Methods:** This was a dose-escalation and PK-expansion phase 1 trial conducted in China. Patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer or metastatic TNBC were eligible. No prior PARP/VEGFR inhibitors were allowed. The study used a standard 3+3 dose-escalation design, with additional patients (a total of 8-12 patients per dose level) enrolled for PK assessment. Patients received orally a single dose of fluzoparib on D1 and apatinib on D4, followed by continuous dosing of fluzoparib (bid) plus apatinib (qd) starting on D8. Endpoints were RP2D, safety, PK, and anti-tumor activity. **Results:** Between 03/17/2017 and 03/02/2021, 52 patients (30 OC, 22 TNBC) were enrolled to 7 dose levels (up to fuzuloparib 100 mg plus apatinib 500 mg). A total of 2 DLTs occurred: grade 4 decreased white blood cell count (WBC)/febrile neutropenia (fuzuloparib 100 mg plus apatinib 250 mg) and grade 4 thrombocytopenia (fuzuloparib 100 mg plus apatinib 375 mg). No maximum tolerated dose was reached. The most common treatment-related grade ≥3 toxicities included hypertension, anemia/decreased hemoglobin, thrombocytopenia, and decreased WBC. In PK analysis, steady-state plasma concentrations of apatinib was decreased when combined with fuzuloparib, as compared with apatinib alone. Higher dose of apatinib in combination with fuzuloparib 100 mg was associated with higher exposure and improved clinical activity. The ORR was 44% (95% CI, 32-58; OC, 60% [95% CI, 42-75]; TNBC, 23% [95% CI, 10-43]) across all dose levels and 62.5% (95% CI, 31-86) at fuzuloparib 100 mg plus apatinib 500 mg (all OC), which was determined to be the RP2D. **Conclusions:** Fuzuloparib plus apatinib has acceptable safety in patients with recurrent ovarian cancer and triple-negative breast cancer. With the promising clinical activity observed in ovarian cancer, this combination is warranted to be further explored as a potential alternative to chemotherapy. Clinical trial information: NCT03075462. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co. LTD.

5540 **Poster Session**

The effect of advances in epithelial ovarian cancer treatment on population mortality. *First Author: Aifen Wang, Suzhou Municipal Hospital Affiliated to Nanjing Medical University, Suzhou, China*

Background: Epithelial ovarian carcinoma is the most common and progressive subtype of ovarian cancer. Mortality trends based on race remains unclear. **Methods:** SEER was used to assess epithelial ovarian cancer mortality and relevant deaths from epithelial ovarian cancer to incident cases. Population-level mortality trends were evaluated according to specific causes. In addition, epithelial ovarian cancer incidence and survival was assessed according to calendar year and race. We applied Joinpoint software to evaluate trends in incidence or incidence-based mortality. **Results:** Age-adjusted incidence of white patients was the highest, followed by Asians and Black patients. Incidence-based mortality of Asian patients was the lowest among all patients, followed by White and Black patients. Incidence-based mortality of all causes of death of epithelial ovarian cancer increased sharply by 65.09% annually from 2000 through 2002, then rose gradually by 9.45% annually from 2002 through 2005, and then increased more slowly annually from 2005 through 2018. Other causes of death of incidence-based mortality displayed similar trends. However, incidence-based mortality of specific ovarian epithelial cancer deaths displayed an annual decrease of 0.08% from 2005 through 2018, following a sharp annual increase of 65.68% from 2000 through 2002 and 6.55% from 2002 through 2005. White patients with epithelial ovarian cancer showed the highest 2-year relative survival, followed by Asians, Black patients and Native Americans, with all patients showing an improved survival rate. Among White patients with epithelial ovarian cancer, incidence increased annually by 1.98% from 2000 through 2011 and then flattened out to an annual increase of 0.03%. Incidence-based mortality of White patients increased sharply by 56.70% annually from 2000 through 2002, then increased slowly by 7.90% annually from 2002 through 2005, and 2.00% annually from 2005 through 2018. Among Asian patients with epithelial ovarian cancer, incidence increased at an annual rate of 2.39% from 2000 through 2018. Incidence-based mortality of Asian patients increased steeply by 78.70% annually from 2000 through 2002, then slowed down to an annual rate of 2.50% from 2002 through 2018. Among Black patients with epithelial ovarian cancer, incidence increased annually by 10.83% from 2000 through 2002 and 2.43% from 2006 through 2016 and declined annually by 0.82% from 2002 through 2006 and by 1.82% from 2016 through 2018. Incidence-based mortality of Black patients displayed a sharp annual increase of 63.70% from 2000 through 2002, then slowed to an annual rate of 1.90% from 2002 through 2018. **Conclusions:** Incidence-based mortality of specific ovarian epithelial cancer death decreased annually from 2005 through 2018. These results may be related to treatment advances of epithelial ovarian carcinoma, particularly surgical strategy and chemotherapy. Research Sponsor: Project of Experts of diagnosis and management of Gynecologic cancer and pelvic disease.

5541 **Poster Session**

Efficacy and toxicity of carboplatin and gemcitabine dosed on day 1/day 8 versus day 1 alone for platinum-sensitive recurrent epithelial ovarian cancer. *First Author: Erika Joelle Lampert, Cleveland Clinic Department of Obstetrics and Gynecology, Cleveland, OH*

Background: Carboplatin, gemcitabine +/- bevacizumab is a preferred regimen for recurrent, platinum-sensitive ovarian cancer (PSOC). A phase III trial established that the regimen of carboplatin on Day 1 (D1) and gemcitabine on D1 and Day 8 (D8) was associated with acceptable toxicity and improved progression free survival (PFS) compared to carboplatin alone. Treatment with gemcitabine on D8 incurs more exposure to cytotoxic therapy and increased burden on patients and the healthcare system, especially during the COVID-19 pandemic. However, it is unknown whether D1/D8 gemcitabine imparts an improvement in efficacy compared to D1 alone. Our objective was to compare efficacy and toxicity of carboplatin and gemcitabine D1/D8 (CG-D1/8) with a modified D1 regimen (CG-D1). **Methods:** A retrospective single-institution cohort study was performed in women with recurrent PSOC treated with carboplatin, gemcitabine +/- bevacizumab from 2009-2020. Data was analyzed by intention to treat comparing women who received CG-D1/8 vs CG-D1. Data was also analyzed by 3 groups: CG-D1/8 vs CG-D1/8 but dropped D8 vs CG-D1. The primary endpoint was response rate (RR), defined as complete or partial response at 6 cycles or maximum cycles if <6. Secondary outcomes included PFS, overall survival (OS), toxicity, Neulasta use and dose reduction. **Results:** Of 200 patients, 26% completed CG-D1/D8, 21.5% started CG-D1/D8 but dropped D8, and 52.5% received CG-D1. There were no significant differences in age, race, or ECOG between cohorts. Among CG-D1/D8, 45.3% dropped D8 primarily due to neutropenia (51.2%) or thrombocytopenia (30.2%). The RR at 6 cycles was 68.7% for CG-D1/8 completed, 70.7% for CG-D1/8 dropped D8, and 69.3% for CG-D1 (p=0.97). The median PFS was 13.1, 12.1 and 12.4 months for CG-D1/8 completed, CG-D1/8 dropped D8, and CG-D1, respectively (p=0.29). Similarly, median OS was 28.2, 33.5 and 34.3 months for the above groups respectively (p=0.42). While there was no difference in concurrent bevacizumab use for CG-D1/8 and CG-D1 (34.7% vs 29.5%, p=0.43), among the CG-D1/8 patients, a significantly higher proportion of patients who dropped D8 received bevacizumab (51.2% vs 21.2%, p=0.006). Table 1 lists secondary outcomes. **Conclusions:** There was no significant difference in RR, PFS or OS among women with PSOC receiving CG-D1/8 vs CG-D1, regardless of whether D8 was dropped. CG-D1/8 was associated with significantly greater hematologic toxicity. These findings suggest a modified D1 regimen may be a suitable alternative to standard CG-D1/8 treatment and warrant prospective validation. Research Sponsor: None.

	CG-D1/D8	CG-D1	p-value
Grade 3/4 hematologic toxicity	45 (47.8%)	33 (31.8%)	*0.005*[a]
Neulasta treatment	61 (65.6%)	51 (50.5%)	*0.033*[b]
Dose reduction	56 (58.9%)	35 (35.4%)	*<0.001*[b]

Statistics presented as N (column %). [a]Extrapolated from Wilcoxon Rank Sum test; [b]Pearson's chi-square test.

5542 **Poster Session**

Extracellular vesicle-based biomarker assay for the detection of early-stage ovarian cancer. *First Author: Laura Bortolin, Mercy BioAnalytics, Inc., Natick, MA*

Background: Detection of cancer with improved discrimination compared to current blood tests could be achieved using an approach that assesses extracellular vesicles (EVs). This approach should have high sensitivity (se) because of EVs abundance in blood and high specificity (sp) by assaying EVs with multiple cancer-related protein and glycosylation epitopes (PGEs) co-localized on their surfaces. We are developing a platform technology that detects multiple cancer-related PGEs co-localized on the same EV using immunoaffinity-capture and proximity-ligation qPCR. In this study, we compare the performance of this technology vs plasma CA125 for correctly categorizing early-stage high-grade serous ovarian cancer (HGSOC) vs healthy/benign ovarian tumors (OT). **Methods:** We evaluated our EV-based platform technology using 7 PGE combinations to discriminate HGSOC from benign adnexal masses. We first derived a prediction model on a retrospectively collected cohort of 42 HGSOC and 26 benign OT samples from 2 commercial vendors and 24 healthy controls (HC) using a machine-learning algorithm. We validated this model on an independent cohort [89 HGSOC: Stage I (17), II (35), III (37); 192 benign OT] from university-associated biobanks and 124 HC. We also assessed the assay's performance in plasma from 87 women with off-target cancers and 42 women with inflammatory conditions from commercial vendors. For each sample, we also measured CA125 levels using a commercial ELISA. **Results:** The prediction model distinguishes HGSOC from benign and HC with an AUC of 0.965 (95% CI 0.93-0.99), with 89.9% (0.82-0.95) se at 98% sp. For stage I/II HGSOC, the model achieves an AUC of 0.942 (0.9-0.99), with 84.6% (0.72-0.93) se at 98% sp. By comparison, CA125 achieves an AUC of 0.875 (0.81-0.94) and 44.2% (0.3-0.59) se at 98% sp. Direct comparison of CA125 and our model shows a significant difference at 98% sp for both all and stage I/II HGSOC (McNemar p-val < 0.001). When comparing HGSOC to HC, there is no significant difference between our model and CA125 (p-val = 1.0). There is a significant difference when comparing patients with all stage and stage I/II HGSOC to patients with benign OT (p-val < 0.001). Our assay had 1 false positive and CA125 had 3 false positives out of 42 inflammatory cases. **Conclusions:** These preliminary data suggest our platform technology for detecting PGEs co-localized on individual EVs may detect all stages of HGSOC from plasma with high se at a very high sp. Our assay may improve on CA125 by distinguishing stage I/II HGSOC from benign OT and could have clinical utility for both early detection and surgical referral recommendation for benign and malignant OT. While the diverse cohorts in this study may present challenges in interpretation, the reproducibility in an independent cohort is encouraging and supports further investigation using cases and controls from well-defined cohort studies. Research Sponsor: Mercy BioAnalytics, Inc.

5543 **Poster Session**

Efficacy and safety of pembrolizumab in combination with anlotinib in the treatment of refractory or recurrent high-grade serous ovarian cancer: A phase 2 nonrandomized clinical trial. *First Author: Man Jiang, The Affiliated Hospital of Qingdao University, Qingdao, China*

Background: Anlotinib, an oral multi-targeted receptor tyrosine kinase inhibitor (TKI), exhibits good safety and efficacy in many advanced refractory solid tumors. Previous studies have indicated that anlotinib has synergistic effects with anti–programmed death-1 antibodies via modulation of the tumor microenvironment. Our study aims to examine the efficacy and safety of anlotinib-pembrolizumab combination therapy as a treatment for refractory or recurrent High-Grade Serous Ovarian Cancer. **Methods:** Patients with refractory or recurrent High-Grade Serous Ovarian Cancer received pembrolizumab (200 mg, intravenously over 60 minutes, once every 3 weeks) plus anlotinib (12 mg/day, orally, 2 weeks on and 1 week off, every 3 weeks) therapy or pembrolizumab (200 mg, intravenously over 60 minutes, once every 3 weeks) monotherapy, respectively. Primary end points were progression-free survival (PFS) and overall survival (OS). The relationships of potential biomarkers with clinical efficacy were also evaluated. **Results:** A total of 33 patients were enrolled, with 15 participants received the anlotinib-pembrolizumab combination regime and 18 with pembrolizumab monotherapy, respectively. Grade 3 treatment-related adverse events (TRAEs) were recorded in 3 participants (20%) receive the combination treatment and 3 (16.7%) in the pembrolizumab monotherpay group, respectively. The PFS were 13.0 months and 8.0 months to anlotinib-pembrolizumab combination regime and pembrolizumab mono-treatment, respectively. And the OS of the two groups were equal as 31 months. In the anlotinib-pembrolizumab combination treatment group, patients with ARID1A mutation indicated a significantly survival benefit compared patient with the wide type (PFS: 12.5 VS. 7.0, P = 0.004). **Conclusions:** The anlotinib-pembrolizumab combination showed promising efficacy and favorable safety as treatment for refractory or recurrent High-Grade Serous Ovarian Cancer. The ARID1A are potential biomarkers for predicting the efficacy of this novel regimen. Research Sponsor: None.

5544 **Poster Session**

Efficacy and safety of rucaparib maintenance treatment in patients from ARIEL3 with platinum-sensitive, recurrent ovarian carcinoma not associated with homologous recombination deficiency. *First Author: Robert L. Coleman, U.S. Oncology Research, The Woodlands, TX*

Background: In ARIEL3 (NCT01968213), rucaparib maintenance treatment led to significant improvement vs placebo for the primary endpoint of investigator-assessed progression-free survival (PFS) in patients (pts) with platinum-sensitive, recurrent ovarian carcinoma responsive to the last line of platinum therapy (Coleman et al. *Lancet.* 2017;390:1949–61). The largest benefit was observed in pts with carcinomas with a BRCA mutation or high loss of heterozygosity (LOH), a marker of homologous recombination deficiency (HRD). However, rucaparib also improved PFS in pts with carcinomas negative by HRD test (ie, BRCA wild-type with low LOH), a subset of pts for which there is no identified molecular mechanism conferring PARP inhibitor sensitivity. Among these pts (rucaparib, n = 107; placebo, n = 54), median PFS was 6.7 vs 5.4 months, respectively (HR, 0.58 [95% CI 0.40–0.85]; *P*= 0.0049), and 31.8% vs 4.3% were progression-free at 1 yr. In this post hoc exploratory analysis, we further evaluated the efficacy of rucaparib maintenance vs placebo in this subset of pts. **Methods:** Pts were randomized 2:1 to oral rucaparib (600 mg BID) or placebo. For this analysis, investigator-assessed PFS and safety were evaluated in pts with HRD-negative carcinoma, defined as BRCA wild-type with genomic LOH < 16% using Foundation Medicine's T5 NGS assay. **Results:** Visit cutoff dates for efficacy and safety were Apr 15, 2017, and Dec 31, 2019. Across subgroups based on demographic or disease characteristics, the trend of rucaparib benefit vs placebo was consistently observed in pts with HRD-negative carcinoma (Table). The safety profile of rucaparib in the HRD-negative population was consistent with that of the overall safety population reported previously. **Conclusions:** Rucaparib maintenance reduced risk of progression in pts with ovarian carcinomas, including those not associated with HRD, regardless of clinical prognostic factors. Research Sponsor: Clovis Oncology, Inc.

Baseline Characteristic	Subcategory	HR (95% CI)	Subcategory	HR (95% CI)
Age	< 65 years (n = 86)	0.48 (0.25–0.90)	≥65 years (n = 75)	0.56 (0.31–1.03)
Race	White (n = 128)	0.64 (0.42–0.98)	Other/unknown (n = 33)	0.52 (0.22–1.23)
Measurable disease at baseline	Yes (n = 66)	0.60 (0.32–1.12)	No (n = 95)	0.53 (0.31–0.89)
Bulky disease at baseline	Yes (n = 36)	0.62 (0.25–1.54)	No (n = 125)	0.59 (0.39–0.91)
Number of prior chemotherapy regimens	2 (n = 112)	0.65 (0.42–1.03)	≥3 (n = 49)	0.48 (0.22–1.06)
Previous bevacizumab use	Yes (n = 40)	0.60 (0.25–1.45)	No (n = 121)	0.57 (0.37–0.88)
Number of prior platinum regimens	2 (n = 113)	0.64 (0.41–1.00)	≥3 (n = 48)	0.51 (0.23–1.15)
Time to disease progression with penultimate platinum	6–≤12 months (n = 57)	0.44 (0.23–0.85)	> 12 months (n = 104)	0.66 (0.42–1.05)
Response to last platinum	RECIST complete response (n = 56)	0.44 (0.22–0.91)	RECIST/CA-125 partial response (n = 105)	0.65 (0.41–1.01)

5545 **Poster Session**

Clinical implications of tumor-based next-generation sequencing in ovarian cancer. *First Author: Katherine Foster, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Epithelial ovarian cancer is genetically heterogeneous, both among and within histologic subtypes. Advances in next-generation sequencing have made it feasible to ascertain the somatic genetic signature of each patient, however, critical analysis of population-level sequencing results is required to maximize the potential of this technology. Here, we aimed to assess the clinical relevance of tumor-based next-generation sequencing (tbNGS) in a large cohort of patients with high-grade epithelial ovarian cancer. **Methods:** Our study population comprised patients with high-grade serous (n = 972), clear cell (n = 33), endometrioid (n = 28), mucinous (n = 4), and mixed (n = 34) or unspecified (n = 21) epithelial ovarian carcinoma diagnosed between April 2013 and September 2021. tbNGS results were identified within the electronic medical record using optical character recognition and natural language processing. Genetic, clinical, and demographic information was collected for patients who had undergone tbNGS. Progression-free survival (PFS) and overall survival (OS) were calculated from date of first treatment to date of first recurrence and date of death, respectively. Data were analyzed using descriptive statistics, univariate and multivariate Cox regression models, and clustering analyses. **Results:** Of 1092 patients in the described population, 409 (37.5%) had tbNGS results identified. Nearly all (96.1%) revealed one or more genetic aberrations. Most patients (74.6%) had an actionable mutation, defined as relaying eligibility for a targeted treatment or clinical trial. The most frequent alterations were *TP53, PIK3CA*, and *NF1* mutations; and *CCNE1* amplification. Ten different targeted institutional and commercial panels were employed, covering a range of 35 to 600+ gene loci. The median time from diagnosis to testing was 14.5 months, likely corresponding to time of recurrence. Though no standalone alterations were significantly related to survival, multivariate and clustering analyses identified several genetic patterns which corresponded to patient outcomes. Mutation of *BRAF, PIK3R1, NOTCH3, MET*, and/or *ATR* was correlated with shorter PFS (HR 1.84, p = 0.001); mutation of *ATM, RB1, CDKN2A, FGFR1*, and/or *FGFR2* was associated with improved PFS (HR 0.64, p = 0.04), as was mutation of *NBN* and/or *ATRX* (HR 0.54, p < 0.05). *MYC, NOTCH3*, and/or *CREBBP* mutations were significantly correlated with worse OS (HR 1.95, p = 0.02). In our population, 40 patients (9.78%) were enrolled in genotypically-relevant clinical trials. **Conclusions:** tbNGS is prevalent at our institution, and often yields actionable information. We identified several mutational patterns that correlate to patient survival. Detailed analysis of population-level tumor genomics may help to identify therapeutic targets and guide development of clinical decision support tools. Research Sponsor: MD Anderson Ovarian Cancer Moon Shot.

5546 **Poster Session**

Validation of the integrated prediction model algorithm for outcome of cytoreduction in advanced ovarian cancer. *First Author: Sabrina Piedimonte, University Health Network, Toronto, ON, Canada*

Background: In advanced ovarian cancer, the decision for primary cytoreductive surgery(PCS) or neoadjuvant chemotherapy(NACT) remains a challenge and may impact survival. We previously developed the integrated prediction model(IPM) using a 4-step algorithm of unresectable stage IVb, patient factors, surgical resectability and surgical complexity to predict outcome of optimal cytoreduction in advanced epithelial ovarian cancer(AEOC) and triage patients to NACT or PCS. The objective of the current study was to validate this model on a retrospective historical cohort of patients. **Methods:** This is a retrospective cohort study of 107 patients with AEOC treated at the Princess Margaret Cancer Centre between January 2017 and September 2018 undergoing PCS or NACT. All diagnostic imaging was retrospectively reviewed to assign surgical resectability score (SRS) for sites of disease and the surgical complexity score (SCS) for procedures anticipated to be required to achieve optimal cytoreduction based on preoperative imaging. Those scores were modified from previously validated tools. Patient factors (PF) included age, ECOG and albumin. We previously developed an IPM algorithm to achieve outcome of optimal cytoreduction and determined cut-offs using the Youden index J. Triaging patients to PCS without stage IVb unresectable disease, PF≤ 2, SRS≤5 and SCS≤ 9 led to an 85% specificity and 75% accuracy for outcome of optimal cytoreduction < 1 cm. The current validation study was performed reporting sensitivity, specificity, negative (NPV) and positive predictive value (PPV) on an external cohort. **Results:** Among 107 patients, 61 had PCS and 46 had NACT followed by ICS. Patients treated with NACT were significantly older (63.5 vs 61 years, p = 0.037), more likely stage IV (52% vs 18%, p < 0.001), had a higher proportion of ECOG > 1 (30% vs 11%, 0.045), a lower pre-operative album (37 vs 40, p < 0.001) and higher CA-125 (970 vs 227.5, p < 0.001) compared to PCS. They also had higher PF (2 vs 0, p = 0.013), SRS (4 vs 1, p < 0.001) and SCS (8 vs 5, p = < 0.001). There was no significant difference in outcome of cytoreduction; the optimal cytoreduction rate was 85% vs 87%, p = 0.12 between PCS and ICS patients. In this validation cohort, triaging patients without unresectable stage IVb disease, PF≤ 2, SRS≤ 5 and SCS≤ 9 to PCS had a sensitivity of 91% to correctly identify patients who will have optimal cytoreduction of < 1 cm at PCS and a specificity of 81%. The PPV was 83%, NPV was 90% and accuracy was 86%. Application of the IPM would have prevented 5 suboptimal patients and correctly triaged them to NACT. **Conclusions:** We validated a triage algorithm integrating patient factors, surgical complexity and surgical resectability for patients with AEOC to achieve optimal cytoreduction at PCS with high sensitivity and specificity. This may therefore be used in a clinical setting to decide between PCS and NACT. Research Sponsor: None.

5547 **Poster Session**

Copy number features as a novel biomarker of homologous recombination (HR) status in high-grade serous ovarian cancer (HGSOC). *First Author: Paula Romero Lozano, VHIO, Barcelona, Spain*

Background: Copy number alterations (CNA) arise as a result of somatic changes to chromosome structure, resulting in gain or loss of genomic regions. A likely source of copy number variation is an incorrect repair of DNA damage that causes chromosome instability (CI). Hence, many tumors with a high degree of CNAs suffer CI. This is the case of high grade serous ovarian cancer (HGSOC), where deficiency in homologous recombination (HRD) is highly prevalent, and so are CI and CNAs. Clinically, HR status in HGSOC is a biomarker of iPARP response and required for proper patient management. Available HRD tests measure genomic loss of heterozygosity (LOH) features, closely related to CI. Such features are complex to acquire in samples with low tumor content; overall, 15% of HGSOC specimens fail HR testing. CNA profiling is technically more amenable to lower tumor cellularity and may be captured by a wider range of techniques and applications (gene panels, low pass WGS...). We present here the analysis and identification of CNA features in HGSOC as a novel biomarker of HR status. **Methods:** A cohort of 123 primary HGSOC tumors were analysed with a custom hybrid capture-based NGS panel (VHIO-300) that provides, along mutations in 450 genes, genome-wide CNA profiles. B-allele fractions, obtained from single nucleotide polymorphisms also in the panel, allowed HRD-LOH score calculation (Marquard et al., 2015). 41 CNA segments correlated to HRD-LOH scores (proportions test, FDR < 0.001) and selected as features to calculate a CNA-HGSOC score (range 0-100). Among them, 10 segments appeared altered almost exclusively in *BRCA1/2* pathogenic/likely pathogenic mutant tumors. **Results:** The density plot of the CNA-HGSOC score showed a bimodal distribution with modes at 7 and 65. A cut-off value of 34 was selected based on the lowest density CNA-score value between the modes. Hence, high CNA-HGSOC was defined as tumors with scores ≥ 34. Our CNA-HGSOC score was strongly correlated as a continuous variable to HRD-LOH (Pearson correlation = 0.72; p < 0.0001) and ROC analysis (AUC = 0.84; CI 95% 0.77-0.91; p < 0.0001) demonstrated high predictability to classify tumors as if using an HRD-LOH test (HRD-LOH score; "very high": 100-75, "high": 74-50,"mid": 49-25 and "low": 24-0). BRCA mutation status was also accurately predicted using a subset of CNA features (AUC = 0.71; CI 95% 0.59-0.82; p < 0.0001). **Conclusions:** CNAs may provide a new powerful genomic resource to HRD determination. We identified 41 CNA features in tumors to inform HR status and a subset of 10 revealed mutation status of *BRCA1/2* in HGSOC. Upon further validation, a CNA-HCSOC score would be easily implemented in routine analysis pipelines in clinical labs, allowing HR testing or even broaden its application to emerging fields, such as liquid biopsy. Research Sponsor: Valle d'Hebron Oncology Institute, Instituto de Salut Carlos III (ISCIII).

5548 **Poster Session**

Genomic analysis of clear cell carcinoma. *First Author: Nirav Haribhakti, Department of Medicine, Brown University, Providence, RI*

Background: Clear cell carcinomas (CCC) are rare histologies outside of the kidney and are typically less sensitive to standard treatments. Genomic alterations in chromatin remodeling pathways involving ARID1A or the intracellular PI3K-mTOR signaling pathway are found in both renal and ovarian CCC. It is unclear whether CCCs originating from different anatomic sites share a common genomic landscape. This CARIS Precision Oncology Alliance project sought to determine whether CCC of different organs shared similar genomic signatures and to identify potential pathways that could be targeted in a tumor-agnostic clinical trial. **Methods:** CCCs (N = 861) from multiple primary tumor sites, including kidney (30.5%), ovary (39%), endometrium (23.9%), other gynecologic sites (e.g., cervix, fallopian tube, 3.3%), and miscellaneous (non-kidney or gynecologic sites, 3.3%) were analyzed at the Caris Life Sciences Laboratory (Phoenix, AZ). Using hierarchical clustering (HC) and principal component analysis (PCA), the samples were compared across 648 total genes from five metabolic gene sets consisting of angiogenesis, glycolysis, hypoxia, oxidative phosphorylation, and fatty acid metabolism. Gene Set Enrichment Analysis (GSEA) was further conducted on the samples across fifty hallmark gene sets representing specific biologic processes and expression. Samples were also analyzed for individual genomic alterations and immune-oncology associated biomarkers. PD-L1 (SP142) expression was evaluated by immunohistochemistry (positive threshold: 2+ stain intensity and ≥ 5% tumor cells). **Results:** HC and PCA demonstrated that renal CCC formed distinct clusters compared to non-renal CCC. Tumors from gynecologic sites could not be separated into distinct clusters. GSEA showed that the hypoxia gene set was significantly upregulated in the renal but not in non-renal CCCs. Mutations involving TP53, ARID1A, PIK3CA were found to be the most altered genes in endometrial (62%, 26%, 31%), ovarian (13%, 55%, 48%), other gynecological sites (33%, 38%, 44%), and non-gynecologic CCC (13%, 17%, 12%) respectively. PD-L1 expression, high tumor mutational burden (≥10 mutations/Mb), and deficient mismatch repair/microsatellite instability rates across sites were: kidney (11%, 2%, 2%), endometrium (13%, 12%, 7%), ovary (9%, 4%, 3%), other gynecological sites (31%, 11%, 11%), and miscellaneous sites (11%, 19%, 4%). **Conclusions:** Initial metabolic gene expression clustering analysis shows that CCCs do not separate by organ of origin beyond renal versus extra-renal. TP53, ARID1A, and PIK3CA were the most frequently altered genes in non-renal CCC. Out of fifty hallmark gene sets, only two were statistically significantly different among gynecological CCCs. This similarity between gynecological CCC can be leveraged by targeting pathways such as PI3K-AKT-mTOR, DNA repair, and MYC targets in a site agnostic manner. Furthermore, high PD-L1 expression is found in other gynecological sites. Research Sponsor: None.

5549 **Poster Session**

Prior authorizations for PARP inhibitors in ovarian cancer. *First Author: Audra Hugo, University of Pennsylvania, Philadelphia, PA*

Background: PARP inhibitors improve survival in ovarian cancer, especially in patients with BRCA 1/2 mutations or homologous recombination deficiency (HRD). However, these FDA-approved drugs cost $100,000 annually on average, and concerns have been raised about insurance barriers like prior authorization to such medications. Our objective was to examine the prevalence of prior authorization for PARP inhibitors in ovarian cancer overall, by frontline or recurrent maintenance, and by genetic status. **Methods:** We performed a retrospective cross-sectional study of ovarian cancer patients prescribed a PARP inhibitor within the University of Pennsylvania oncology practices from May 2020-2021. Using electronic medical records, we assessed the prevalence of prior authorization for PARP inhibitors overall, by frontline or recurrent maintenance, and by BRCA or HRD status. We then assessed the associated approval and appeal rates. **Results:** We identified 110 patients with ovarian cancer who were prescribed a PARP inhibitor. Of these, 67% (95%CI 57-75) experienced prior authorization for their PARP inhibitor. In contrast, 31 (95%CI 23-40) experienced prior authorization for other components of their gynecologic oncology care. Of patients in the frontline setting, 74 (95%CI 58-86) experienced prior authorization for FDA-approved PARP maintenance. Of patients prescribed PARP maintenance after recurrence, 58 (95%CI 45-71) experienced prior authorization. Of patients with germline BRCA, 70% (95%CI 47-85) experienced prior authorization for PARP inhibitors. Of patients with germline or somatic BRCA or HRD+, 76% (95%CI 61-87) experienced prior authorization. 95% (95%CI 86-94) of prior authorizations for PARP inhibitors were approved on their 1st appeal, and 99% (95%CI 95-100) were approved by the 2nd appeal. **Conclusions:** Two-thirds of patients of ovarian cancer patients who were prescribed PARP inhibitor experienced prior authorization, including equally high rates among women with germline or somatic BRCA mutations, as well as with HRD-deficient tumors. Given the nearly 100% approval after prior authorization, improvements in insurance processes are needed to streamline PARP inhibitor access in ovarian cancer. Research Sponsor: University of Pennsylvania Basser Center for BRCA, Other Foundation, Other Government Agency.

5550 **Poster Session**

Safety and efficacy of mitoxantrone hydrochloride liposome in patients with platinum-refractory or platinum-resistant ovarian cancer: A prospective, multicenter, open-label, single-arm, phase Ib clinical trial. *First Author: Yu Huang, Gynecological Oncology Center, Chongqing University Cancer Hospital, Chongqing, China*

Background: Platinum-refractory or platinum-resistant ovarian cancer remains unmet medical need with an unfavorable prognosis. Its treatment options are limited and sequentially with multiple single-agent regimens or bevacizumab plus single-agent regimens are recommended. Mitoxantrone hydrochloride liposome (PLM60) is the first approved mitoxantrone nano-drug, which has shown favorable pharmacokinetic characteristics with long circulation and high cumulation in tumor tissue, thus has a promising anti-tumor activity. This trial aimed to explore the efficacy and safety of PLM60 in patients with platinum-refractory or platinum-resistant ovarian cancer. **Methods:** In this multi-center, open-label, single arm study, patients with histologically confirmed, epithelial ovarian, fallopian tube, or primary peritoneal carcinoma, either platinum-refractory or platinum-resistant, with at least one measurable lesion were recruited. PLM60 20 mg/m^2 was administered on day 1 of each 21-day cycle for up to 8 cycles treatment or until disease progression or intolerable toxicities. The primary endpoint was safety, adverse events were graded according to CTCAE 5.0. Second endpoint included overall response rate (ORR), duration of response (DoR), disease control rate (DCR), progression free survival (PFS) and overall survival (OS) as per RECIST 1.1. **Results:** 47 eligible patients with a median age of 54 years (range, 35-67) were treated in 7 institutions in China, including 15 platinum-refractory patients and 32 platinum-resistant patients. 32 (68.1%) of 47 patients received at least 3 prior lines of therapy. Treatment related adverse events (TRAEs) of any grade occurred in 45 (95.7%) of 47 patients, in which 31 (66.0%) were ≥ grade 3. The most common ≥ grade 3 TRAEs (incidence ≥10%) were leucopenia (51.1%), neutropenia (40.4%), anemia (19.1%), lymphocytopenia (17.0%) and thrombocytopenia (17.0%). At the cut-off data of October 31 2021, 39 patients were evaluable for response. ORR was 17.9% (7/39, 95% CI:7.5-33.5%, 7 PRs) and DCR was 56.4% (22/39, 95% CI:39.6-72.2%, 15 SDs). Among 21 platinum-resistant patients with ≥3 prior lines, the median DoR was 4.6 month, 2 responders had a DoR of > 6 months. The ORR and DCR of this cohort were 28.6% (6/21, 95% CI: 11.3-52.2%, 6 PRs) and 61.9% (13/21, 95% CI: 38.4-81.9%, 7 SDs), respectively. Median PFS was 3.6 month (95% CI 1.4-4.6), OS data was not mature. Objective response was not observed in platinum-refractory patients. **Conclusions:** PLM60 had an encouraging efficacy especially in platinum-resistant patients who had received at least 3 prior lines with tolerable safety profiles. Clinical trial information: NCT04718376. Research Sponsor: CSPC Zhongqi Pharmaceutical Technology Co., Ltd.

5551 **Poster Session**

Efficacy of niraparib maintenance therapy in patients with newly diagnosed advanced ovarian cancer in phase 3 PRIME study: A subgroup analysis by response to first-line platinum-based chemotherapy. *First Author: Rutie Yin, Department of Gynecology and Obstetrics, and Key Laboratory of Obstetrics and Gynecologic and Pediatric Diseases and Birth Defects of the Ministry of Education, West China Second University Hospital, Sichuan University, Chengdu, China*

Background: In PRIME (NCT03709316), niraparib significantly reduced the risk of disease progression or death versus placebo (PBO) (hazard ratio [HR], 0.45; 95% confidence interval [CI], 0.34–0.60) in Chinese patients (pts) with newly diagnosed, advanced ovarian cancer (OC), regardless of biomarker status. As response to chemotherapy is deemed to be associated with prognosis in OC, this subgroup analysis of the PRIME study aims to better understand niraparib treatment effect in pts based on response to first-line platinum-based chemotherapy (1L CT). **Methods:** This randomized, double-blind, PBO-controlled, phase 3 trial enrolled adults with newly diagnosed, stage III or IV OC who achieved a complete response (CR) or partial response (PR) to 1L CT and received primary or interval cytoreductive surgery, irrespective of residual disease status after surgery. Pts were randomized (2:1) to receive niraparib or PBO, whose starting doses were individualized based on baseline bodyweight and platelet count, with stratification according to status of germline *BRCA* mutations (yes or no), tumor homologous recombination status (deficient or proficient), receipt of neoadjuvant chemotherapy (yes or no), and clinical response to 1L CT (CR or PR). This prespecified exploratory analysis reports progression-free survival (PFS) and HRs based on clinical response to 1L CT. The data cut-off date was 30 September 2021. **Results:** Of the 384 pts randomized, 315 (82.0%) and 69 (18.0%) had a CR (212 niraparib, 103 PBO) or PR (43 niraparib, 26 PBO) to 1L CT, respectively. Baseline characteristics are presented in the Table. The overall PFS median follow-up was 27.5 months. Niraparib significantly extended PFS compared with PBO: the median PFS was 29.4 months for niraparib versus 8.3 months for PBO (HR=0.45; 95% CI, 0.32–0.61; *P*<0.001) in the CR group and was 19.3 months for niraparib versus 8.3 months for PBO (HR=0.45; 95% CI, 0.23–0.86; *P*=0.014) in the PR group. **Conclusions:** In pts with newly diagnosed advanced OC, PFS was substantially prolonged with niraparib versus PBO, regardless of response to chemotherapy and biomarker status. Moreover, pts who achieved a CR appeared to receive larger PFS benefit from niraparib than those with a PR. Clinical trial information: NCT03709316. Research Sponsor: The study was funded by Zai Lab (Shanghai) Co. Ltd. This work was also partially supported by the National Major Scientific and Technological Special Project for "Significant New Drugs Development" in 2020, China [grant number 2020ZX09101-014].

Baseline characteristics.

Characteristic, n (%)		Complete response		Partial response	
		Niraparib (N=212)	Placebo (N=103)	Niraparib (N=43)	Placebo (N=26)
FIGO stage	III	156 (73.6)	79 (76.7)	26 (60.5)	15 (57.7)
	IV	56 (26.4)	24 (23.3)	17 (39.5)	11 (42.3)
Neoadjuvant chemotherapy	Yes	100 (47.2)	48 (46.6)	21 (48.8)	11 (42.3)
	No	112 (52.8)	55 (53.4)	22 (51.2)	15 (57.7)
Germline *BRCA* mutations	Yes	67 (31.6)	32 (31.1)	18 (41.9)	8 (30.8)
	No	145 (68.4)	71 (68.9)	25 (58.1)	18 (69.2)
Residual disease status after surgery	Optimal	167 (78.8)	86 (83.5)	26 (60.5)	19 (73.1)
	Suboptimal or missing	45 (21.2)	17 (16.5)	17 (39.5)	7 (26.9)

5552 **Poster Session**

Real-world use, tolerability, and dose modifications of PARP inhibitors in ovarian cancer. *First Author: David M. O'Malley, The Ohio State University, Columbus, OH*

Background: Tolerability is a key consideration when selecting a PARP inhibitor (PARPi) for ovarian cancer (OC). Here we expand on earlier work (Arend *et al* 2021) to further characterize real-world tolerability and dose modifications in US patients (pts) with OC receiving PARPi therapy. **Methods:** A retrospective cohort of OC pts starting olaparib (ola), niraparib (nir) or rucaparib (ruc) between Jan 2017 and Dec 2020 was identified from MarketScan® Commercial/Medicare Supplemental databases, increasing the period covered and number of pts included vs our previous analysis. Pts were followed up from first PARPi prescription (index) for ≥30 days until end of study period, disenrollment or death; baseline was 6 months pre-index. Clinical events of interest (CEIs; acute myeloid leukemia/myelodysplastic syndromes, anemia, leukopenia/neutropenia, thrombocytopenia, acute kidney injury, arthralgia, constipation, diarrhea, nausea, vomiting, dermatitis/rash/photosensitivity, fatigue, hypertension, infection, insomnia, pneumonitis, transaminitis) were identified via ICD-9/10 codes. Multivariable Cox regression compared the likelihood of CEIs, dose modifications and hospitalizations between PARPis, adjusting for baseline CEI, Charlson Comorbidity Index score, prior bevacizumab and cancer-related surgery. Persistence was defined as no PARPi treatment gaps of >90 days in pts with ≥6 months' continuous enrollment. **Results:** Overall, 637, 538 and 227 pts received ola, nir and ruc, respectively (median [IQR] follow-up 10.5 [13.4] months). Baseline characteristics were similar across groups. The proportion of pts initiating PARPi at the highest indicated dose was 89.2%, 57.6% and 89.9% for ola, nir and ruc, respectively; 22.6%, 34.8% and 28.6%, respectively, required dose decreases. The likelihood of experiencing CEIs varied across the PARPis after adjusting for *a priori* confounders as shown in the table. Persistence with index PARPi was higher with ola (83.4%) vs nir (73.3%; $P<0.001$) and similar vs ruc (80.2%; $P>0.05$). Among all pts, mean time to non-persistence was shorter with nir vs ola and ruc (6.4 vs 7.9 and 7.6 months, respectively; both $P<0.05$). CEIs by PARPi dose and calendar year will also be presented. **Conclusions:** This is the largest real-world comparison of PARPi use in OC pts reported to date. It supports differences between PARPis in persistence with therapy and risk of experiencing a CEI, even after adjusting for confounders. Research Sponsor: AstraZeneca.

Adjusted HR (95% CI)	Nir vs ola	Ruc vs ola	Nir vs ruc
Any CEI	1.34 (1.19–1.52)*	1.13 (0.96–1.33)	1.19 (1.01–1.40)‡
Any hematologic CEI	1.51 (1.30–1.77)*	1.18 (0.96–1.45)	1.28 (1.05–1.57)‡
Any non-hematologic CEI	1.27 (1.12–1.44)*	1.21 (1.03–1.43)‡	1.05 (0.89–1.23)
All-cause inpatient hospital admission	1.46 (1.15–1.84)†	1.38 (1.03–1.86)‡	1.05 (0.79–1.40)
Time to PARPi discontinuation	1.73 (1.47–2.02)*	1.35 (1.09–1.66)†	1.28 (1.05–1.57)‡

*$P<0.001$; †$P<0.01$; ‡$P<0.05$.

5553 **Poster Session**

Identification of patients with ovarian cancer who are experiencing the highest benefit from bevacizumab in first-line setting based on their tumor intrinsic chemosensitivity (KELIM): GOG-0218 validation study. *First Author: Benoit You, Institut de Cancérologie des Hospices Civils de Lyon (IC-HCL), Lyon, France*

Background: In patients with high-grade ovarian cancer in first-line setting, predictive factors of bevacizumab efficacy are needed, for selecting patients. In ICON-7 trial, a poor tumor intrisic chemosensitivity (defined by unfavorable modeled CA-125 kinetic ELIMination rate constant KELIM) was a predictive biomarker. Among patients with high-risk diseases, only those with unfavorable KELIM had survival benefit from bevacizumab (mOS: 29.7 vs 20.6 months, HR = 0.78)(Colomban. *JNCI CS* 2020). The objective was to perform an external validation in GOG-0218 trial (NCT00262847). **Methods:** In GOG-0218, 1,873 patients were treated with carboplatin-paclitaxel +/- concurrent bevacizumab/placebo followed by a 15 month maintenance. Patient KELIM values were estimated with longitudinal CA-125 kinetics during the first 100 chemotherapy days. The association between KELIM score (categorized as favorable ≥ 1, or unfavorable < 1) and efficacy of bevacizumab (bevacizumab-concurrent + maintenance, vs placebo) for PFS and OS was assessed using univariate/multivariate analyses, in a Training set with 2/3 patients managed the investigators, and then a Validation set with all patients, managed by NGR-GOG. **Results:** KELIM was assessable in 1,662 patients with ≥ 3 CA-125 available values. In both sets, the patients with unfavorable KELIM derived benefit from bevacizumab compared to placebo (Training: PFS, HR = 0.65 [0.54-0.80]; OS, HR = 0.80 [0.65-0.99]; Validation: PFS, HR = 0.69 [0.59-0.82]; OS, HR = 0.87 [0.73-1.03]), whilst those with favorable KELIM had no benefit from bevacizumab (Training: PFS, HR = 0.96 [0.75-1.23]; OS, HR = 1.05 [0.80-1.37]; Validation, PFS, HR = 0.96 [0.79-1.17]; OS HR = 1.11 [0.89-1.84]). The highest benefit was observed in patients with high-risk diseases (stage IV or sub-optimally resected stage III) characterized by unfavorable KELIM, for PFS (Learning (n = 276): mPFS: 9.0 vs 5.2 months, HR = 0.61 [0.48-0.78]; Validation (n = 433): mPFS: 9.1 vs 5.6 months, HR = 0.64 [0.53-0.78]), and for OS (Learning (n = 278): mOS: 38.9 vs 27.9 months, HR = 0.72 [0.56-0.93], Validation set (n = 438): mOS: 35.1 vs 29.1 months, HR = 0.79 [0.65-0.97]). **Conclusions:** This validation analysis of GOG-0218 trial confirms the outcomes of ICON-7 trial about the association between poor tumor chemosensitivity and benefit from concurrent + maintenance bevacizumab, suggesting that bevacizumab is mainly effective in patients with poorly chemosensitive diseases. No benefit was found in patients with favorable KELIM. The patients who derived the highest benefit from bevacizumab in PFS and OS (OS absolute benefit ~ 6 to 9 months) were those with high-risk diseases (stage IV, or incompletely resected stage III) associated with an unfavorable KELIM score (calculator on https://www.biomarker-kinetics.org/CA-125). Research Sponsor: GOG-0218 was funded by NRG-GOG.

5554 **Poster Session**

Immune tumor microenvironnement (iTME) post-neoadjuvant chemotherapy, beyond PD-L1: Novel immune targets in ovarian cancer, data from the CHIVA trial, a GINECO/GINEGEPS study. *First Author: Felix Blanc-Durand, Institut Gustave Roussy, Villejuif, France*

Background: Antibodies targeting PDL1 or PD1 have been disappointing so far in the treatment of ovarian cancer (OC). A greater understanding of the complex iTME and of the impact of chemotherapy on immune features could uncover promising immune targets. We previously reported that neoadjuvant chemotherapy (NACT) increased CD4+ and CD8+ immune cells (IC) and depleted FOXP3+ suppressive T-regs in OC iTME. Here we aimed to describe the expression of PDL1 as well as other co-regulatory molecules in OC and their changes under NACT. **Methods:** Tumor samples and clinical data were prospectively collected from patients (pts) in the randomized CHIVA trial of NACT +/- nintedanib. Samples were evaluable for immune profiling for 116-124 pts at diagnosis and 89-107 at surgery after 3 cycles of NACT. IC stained for CD4, CD8 were scored as number of IC+/mm^2. Expression of immune co-regulatory molecules PDL1, TIM3, LAG3 and IDO was scored as percentage of positive cells, and tumors were classified as PDL1/TIM3/IDO/LAG3 positive if > 1% of IC and/or tumor cells (TC) were positive. Highly sensitive pts, defined as objective response to NACT and prolonged median progression-free survival (mPFS > 24months), were compared to refractory pts (progressing during or within 3mo of platinum). **Results:** As expected, about one third (36%) of tumors were PDL1+ at diagnosis. In contrast, the prevalence of other co-regulatory molecules was higher with 52%, 54% and 93% of tumors being positive for IDO, LAG3 and TIM3, respectively. There was no significant change in PDL1 expression with NACT. However, in paired samples NACT significantly increased IDO and LAG3 expression ($p < 0.05$), such that 60% and 66% of tumors post-NACT were positive for IDO and LAG3, respectively. TIM3 expression remained high post-NACT with 92% of positive tumors. Highly sensitive tumors (vs refractory tumors) had significantly higher IC expression of TIM3 after NACT (24% vs 6%, $p = 0.005$), and were significantly more infiltrated by CD4+ (441 vs 228 cells/mm2, $p = 0.04$) and CD8+ (460 vs 225 cells/mm2, $p = 0.045$) T cells. **Conclusions:** Other immune targets beyond PDL1 are highly expressed in OC. In addition NACT appears to prime the iTME by increasing effector T cell infiltration and the expression of other relevant co-regulatory molecules (LAG3, TIM3 and IDO). Future studies could be performed by priming the iTME with NACT and testing novel immune therapies based on target expression in samples obtained at interval debulking surgery. Research Sponsor: ARCAGY-GINECO Grant.

5555 **Poster Session**

Real-world outcomes associated with bevacizumab combined with chemotherapy in platinum-resistant ovarian cancer. *First Author: Gordon Taylor Moffat, Queen's University, Kingston, ON, Canada*

Background: In the pivotal Aurelia study, addition of bevacizumab (bev) to physician's choice chemotherapy (paclitaxel, liposomal doxorubicin or topotecan) for platinum-resistant (PL-R) ovarian cancer (OC) was associated with improved progression-free survival (PFS; 6.7 vs 3.4 mos; hazard ratio (HR) 0.48, p = 0.001) but not overall survival (OS; 16.6 vs 13.3 mos HR 0.85, p = 0.174); the latter finding may relate to extensive crossover. In an exploratory subgroup analysis by treatment arm, benefits were particularly marked for bev + paclitaxel where median PFS (mPFS) increased from 3.9 to 10.4 mos (HR 0.46; 95%CI 0.30-0.71) and increases in OS approached statistical significance (HR 0.65; 95%CI, 0.42-1.02; 22.4 *v* 13.2 mos). Here we describe utilization of bev for PL-R OC and outcomes in routine clinical practice. **Methods:** The Ontario Cancer Registry and the New Drug Funding Program databases were utilized to identify all patients treated with bev plus chemotherapy (paclitaxel, liposomal doxorubicin or topotecan) for PL-R OC following its approval in 2017. Time on treatment (ToT) was defined as time from first to last bev treatment; this was used as a surrogate for PFS in routine practice. Median OS (mOS) was determined using the Kaplan-Meier method. Factors associated with ToT and OS were identified using a Cox proportional hazard model. A before and after comparison analysis was performed to determine mOS for patients treated pre- (2011-2017) and post-bev (2017-2019) approval. **Results:** From Oct 2017 to Dec 2019, 180 patients received bev + chemotherapy for first-line PL-R OC. Mean age was 63 years old, and 80% had serous OC. Bev was most often combined with liposomal doxorubicin (64 %) followed by paclitaxel (34%) and topotecan (2%). Median ToT was 3 months and OS was 11 months. ToT and OS were longer in patients who received paclitaxel as chemotherapy backbone (5 mos [ToT]; 14 mos [OS]) than those who received bev with liposomal doxorubicin (2 mos; 9 mos) or topotecan (2 mos; 6 mos). In multivariable models, ToT was superior in patients who received bev + paclitaxel than bev + liposomal doxorubicin (HR 0.40; 95%CI 0.28-0.57; p < 0.0001), and worse with longer time from diagnosis to bev start (1.03; 1.01-1.05; p = 0.0120). OS was also significantly longer in those who received paclitaxel vs liposomal doxorubicin (HR 0.54; 95%CI 0.30-0.98; p = 0.043). In a before and after analysis, patients treated in the pre- (n = 1290) and post-bev (n = 360) era had mOS of 8 and 9 months respectively. Post mOS increased for patients receiving paclitaxel (7 vs 12 months) but not with liposomal doxorubicin (9 vs 7 months). **Conclusions:** ToT and OS associated with bev for PL-R OC are shorter in a real-world population compared to results reported in AURELIA. ToT and OS were longer with bev + paclitaxel than with other chemotherapy agents. Research Sponsor: Queen's University Health Sciences Grant/Clare Nelson Bequest Fund.

5556 **Poster Session**

Prospective identification of prognostic factors for patients with early failure of advanced ovarian cancer who undergo primary cytoreductive surgery followed by chemotherapy: The AGO-OVAR 19/FRAGILE study (NCT02828618). *First Author: Felix Hilpert, Krankenhaus Jerusalem Hamburg, Hamburg, Germany*

Background: Standard treatment for advanced ovarian cancer (aOC) includes primary cytoreductive surgery followed by chemotherapy (PDS > CTX). There is strong evidence that this strategy is accompanied by high risk for early failure in some patients (pts) but prospective multicenter data for this specific question are lacking. **Methods:** 64 AGO-sites prospectively registered pts with suspected aOC and collected following variables prior to start of therapy: age, Charlson Comorbidity Index (CCI), timed up and go test (TUG), ASA and ECOG performance score, weight, height, estimated ascites, albumin, creatinine, hemoglobin, leucocytes, platelets, CA125, patient reported outcome measures according to EORTC QLQ-C30 and OV28, hospital anxiety and depression score (HADS), physician-assessed suspected FIGO IV stage, abdominal pain requiring treatment, abdominal bloating, dyspnea and required palliative paracentesis (ascites, pleural effusions). Treatment followed according to investigator's decision. Primary objective was to predict the unfavorable event of death or progression within 10 months after primary diagnosis. We applied univariate and multiple logistic regression with stepwise variable selection after multiple imputation of missing data in order to identify relevant predictors. **Results:** 223 pts with aOC FIGO IIIB to IVB and PDS were analyzed. Median age was 63 years (range 31-86). 52 (23.3%) pts experienced progression or death within 10 months from time of enrolment. In univariate regression, age (odds ratio (OR) 1.612 per 10 years), ASA (III vs I/II: OR 3.217), TUG (OR 1.087), body height (OR 0.541 per 10cm), ECOG (1 vs 0 OR 2.326, 2-3 vs 0 OR 4.102), estimated ascites (> 500cc vs. none OR 2.811), paracentesis (OR 1.991), platelets (upper limit of normal (ULN) vs norm or < lower limit of normal (LLN) OR 1.998), albumin (< LLN vs norm or > ULN OR 2.053), creatinine (> ULN vs norm OR 3.969) and baseline QoL single-item subscales appetite loss ("very much" vs "not at all" OR 2.611), constipation ("quite a bit" vs "not at all" OR 4.903), and multi-item subscales global health status (OR 0.982 per 1 point) and nausea/vomiting (OR 1.013 per 1 point) were significant ($p < 0.05$). Multiple logistic regression identified age (OR 1.459 per 10 years), ASA (III vs I/II: OR 2.427), constipation ("quite a bit" vs "not at all" OR 3.786) and global health (OR: 0.985 per 1 point) as independent predictors of progression or death within 10 months after primary diagnosis ($p < 0.05$). **Conclusions:** A significant proportion of aOC pts undergoing PDS > CTX are at high-risk for early failure. The finding of independent risk factors including self-ratings of QoL at time of diagnosis should be confirmed and tested against other models to facilitate a more tailored treatment of high-risk pts and design of future trials in aOC. Clinical trial information: NCT02828618. Research Sponsor: Roche Pharma AG, Grenzach-Wyhlen, Germany.

5557 **Poster Session**

Phase Ib INEOV neoadjuvant trial of durvalumab +/- tremelimumab with platinum chemotherapy for patients (pts) with unresectable ovarian cancer (OC): Final complete resection and pathological response rates. *First Author: Alexandra Leary, Medical Gynecology, Gustave Roussy, Villejuif, France*

Background: We have shown that neoadjuvant carboplatin and paclitaxel (NACP) increased tumor infiltrating lymphocytes and PDL1 expression in OC pts. INEOV evaluated NACP with durvalumab (D) +/- tremelimumab (T) in pts with unresectable OC. We previously reported that NACP with D+/-T was feasible and safe but the addition of T did not improve interval debulking surgery (IDS) rates after 3 cycles (C3) (ESMO 2021). Here we provide an update with longer follow up including data on delayed IDS performed after 6 cycles of neoadjuvant treatment. Key secondary endpoints include complete resection (CC0) and complete pathological response rates. **Methods:** Pts with stage IIIC/IV OC were randomized to NACP + D (1125mg) alone (arm A) or with T (75mg once at C2) (arm B). Interval debulking surgery (IDS) was planned after C3, or delayed after C6. Pts in arm A not operable after C3 crossed over to arm B, pts in arm B crossed over to standard of care (SOC). Pts were assessed for delayed IDS after C6. Complete pathological response (pCR) was defined as no residual tumor cells found on any surgical specimens, or no residual tumor cells on any samples outside the ovary at IDS. **Results:** Sixty four (N = 64) of 66 pts (IIIC/IV: 70%/30%) randomized were evaluable. After C3, 66% (21/32) of pts in arm A and 59% (19/32) in arm B had IDS. The 11 pts in arm A not candidate for IDS after C3 crossed over to arm B until C6 and 5/11 benefited from delayed IDS. The 13 pts in arm B inoperable at C3 went on to receive SOC (NACP +/- bevacizumab), and 5/13 became eligible for delayed IDS after C6. Overall, IDS was performed in 50 of 64 evaluable pts, and most (45/50) achieved macroscopically complete resection (CC0), so that the overall CC0 rate was 70% (45/64), with no significant difference between arms (CC0 = 75% vs 65% in arm A vs B). Among the 50 pts who had IDS, complete pathological responses were observed in 18% of pts. **Conclusions:** Taking into account the whole treatment strategy including delayed IDS after 6 cycles of neoadjuvant treatment, we have shown that neoadjuvant CP with D+/- T results in encouraging CC0 (70%) and pCR (18%) rates. However there was no apparent benefit to the addition of T to D. Studies are ongoing to describe the immune features predictive of pCR as well as the impact of treatment on the immune microenvironment. Clinical trial information: NCT03249142. Research Sponsor: AstraZeneca.

5558 **Poster Session**

OReO/ENGOT Ov-38 trial: Impact of maintenance olaparib rechallenge according to ovarian cancer patient prognosis—An exploratory joint analysis of the BRCA and non-BRCA cohorts. *First Author: Frédéric Selle, GINECO & Groupe Hospitalier Diaconesses Croix Saint Simon, Paris, France*

Background: In the Phase IIIb OReO/ENGOT Ov-38 trial (NCT03106987), maintenance olaparib (O) rechallenge significantly improved progression-free survival (PFS) vs placebo in patients (pts) with platinum-sensitive relapsed ovarian cancer (PSROC) regardless of their BRCA status (Pujade-Lauraine, ESMO 2021). The impact of prognostic factors on this PFS benefit were unknown. **Methods:** Pts had PSROC, one prior line of PARP inhibitor (PARPi) maintenance and were in response to platinum-based chemotherapy (Cx). Pts were enrolled into two cohorts – BRCA mutated (BRCAm) and non-BRCAm – and randomized to receive maintenance O (300 mg bid) or placebo. Primary endpoint was PFS. Post-hoc individual patient data meta-analysis was used to combine both cohorts using fixed and random effect models, interaction, and stratified tests in the Cox model. Stepwise Cox multivariate model for PFS and logistic regression models were used for late relapse, defined as disease progression occurring >24 weeks after randomization. Randomization stratification criteria and cohort effect were included in all models. **Results:** This study included 220 pts from the BRCAm (n=112) and non-BRCAm (n=108) cohorts recruited between October 3, 2017 and February 10, 2021. No heterogeneity was detected between cohorts: Cochran's Q test *P*=0.53 (fixed and random); interaction test *P*=0.63. The O effect was consistent, and no significant interactions were observed between subgroups. In the multivariate PFS analyses, the main independent factors for prognosis were CA-125 level, visceral disease (liver, lung, pleura, brain), and treatment arm. These factors were independent predictive factors for late relapse among the 181 evaluable pts with the opportunity of at least 6 months of follow-up (Table). **Conclusions:** In the OReO/ENGOT Ov-38 trial, CA-125 level and presence of visceral disease at baseline were the best predictors of patient outcome. Maintenance olaparib rechallenge was effective overall regardless of prognostic subgroup. Clinical trial information: NCT03106987. Research Sponsor: AstraZeneca, Pharmaceutical/Biotech Company.

	No patients	PFS univariate HR (95% CI)*	*P*	PFS multivariate HR (95% CI)*	*P*
Treatment (olaparib/placebo)	146/74	0.54 (0.39-0.73)	**<.01**	0.53 (0.38-0.73)	**<.0001**
CA-125 (>35/<35 U/mL)	64/152	1.75 (1.27-2.41)	**<.01**	1.50 (1.08-2.07)	**.015**
Visceral disease (yes/no)	61/159	1.82 (1.32-2.52)	**<.01**	2.04 (1.46-2.85)	**<.0001**
Prior bevacizumab (yes/no)	117/103	1.35 (1.01-1.82)	**.04**	1.35 (1.00-1.84)	.052
BRCA status (negative/positive)	108/112	0.99 (0.74-1.33)	.95		
Previous PARPi					
- Exposure (≤18/>18 months)	102/80	0.77 (0.56-1.07)	.12		
- Type (olaparib/others)	126/94	0.96 (0.71-1.30)	.81		
No of prior lines of Cx (≤3/>3)	141/79	1.05 (0.78-1.42)	.75		

		PFS at Placebo	24 weeks (%) Olaparib
Visceral disease (no)			
- CA-125 <35	96	28	53
- CA-125 ≥35	34	15	36
Visceral disease (yes)			
- CA-125 <35	32	0	23
- CA-125 ≥35	19	0	12

*Cox Proportional-Hazards Model.

5559 **Poster Session**

BRCA reversion mutations mediated by microhomology-mediated end joining (MMEJ) as a mechanism of resistance to PARP inhibitors in ovarian and breast cancer. *First Author: Natalia Lukashchuk, AstraZeneca, Cambridge, United Kingdom*

Background: PARP inhibitors exploit synthetic lethality in tumor cells with deficiency in homologous recombination repair (HRR). In line with this, most reported mechanisms of PARP inhibitor resistance restore HRR. Of multiple resistance mechanisms reported preclinically, reversion mutations in BRCA genes are the only confirmed mechanism of resistance to both platinum and PARP inhibitors in patients (pts) to date (Lin K *et al. Cancer Discov* 2019), with most studies focusing on ovarian cancer. MMEJ is an alternative DNA damage repair pathway, in which DNA polymerase θ (POLθ) has a key role; MMEJ has been suggested to play a role in BRCA reversion mutations (Tobalina L *et al. Ann Oncol* 2021). **Methods:** Targeted circulating tumor DNA (ctDNA) sequencing analyzed over 500 plasma samples collected at baseline and at progression to therapy in pts with ovarian or breast cancer and a mutation in *BRCA1* and/or *BRCA2* (BRCAm) who were treated with olaparib or chemotherapy in one of three Phase II/III clinical studies (LIGHT NCT02983799, SOLO3 NCT02282020, OlympiAD NCT02000622). Only pts with an original pathogenic BRCAm detected in ctDNA were evaluable. BRCA reversion mutations were identified using internal computational framework; DNA sequences surrounding BRCA reversion sites were analyzed for MMEJ signatures. **Results:** At baseline, in pooled data across treatment arms and across all available samples, BRCA reversion mutations were detected in 4/114 (3.5%) and 6/133 (4.5%) of breast and ovarian cancer pts, respectively, which may have developed on prior platinum therapy. At progression, BRCA reversion mutations were detected in 34/79 (43%) breast cancer pts and in 26/101 (26%) ovarian cancer pts who received olaparib, with at least 2/79 and 4/101 reversions already present at baseline, respectively. At progression, in the chemotherapy arm, BRCA reversion mutations were detected in 3/34 (9%) breast cancer pts and 1/29 (3%) ovarian cancer pts, with 2/34 and 0/29 reversions present at baseline, respectively. Reversion mutations varied in allelic frequency and were either present as single or multiple reversions, suggesting multiple events within the tumor were driving resistance. The location and type of reversion mutations reflected the functional importance of BRCA protein domains. A large proportion of BRCA reversion mutations (47/69 [68%] that were evaluable) were mediated by the MMEJ pathway based on the presence of MMEJ signatures around BRCA reversion sites. **Conclusions:** We detected BRCA reversion mutations in at least ~40% of breast and ~20% of ovarian cancer pts following treatment with olaparib. A large proportion of these reversion mutations are likely to have been mediated by MMEJ repair, suggesting that POLθ inhibitors in combination with platinum or PARP inhibitors might prevent or delay emergence of PARP inhibitor resistance. Clinical trial information: NCT02983799, NCT02282020, NCT02000622. Research Sponsor: This study was supported by AstraZeneca and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, who are codeveloping olaparib.

5560 **Poster Session**

Quality of life in patients with advanced high-grade ovarian cancer (HGOC) receiving maintenance therapies after first-line (1L) chemotherapy in the randomized phase III PAOLA-1/ENGOT-ov25 trial (NCT02477644). *First Author: Jean Emmanuel Kurtz, ICANS (Institut de Cancérologie Strasbourg Europe), Strasbourg, France*

Background: In the Phase III PAOLA-1/ENGOT-ov25 trial, maintenance olaparib + bevacizumab (bev) provided a significant progression-free survival (PFS) benefit vs placebo (pbo) + bev in patients (pts) with newly diagnosed advanced ovarian cancer in response to platinum-based chemotherapy. Subgroup analyses revealed a substantial PFS benefit in homologous recombination deficiency (HRD)-positive (including BRCA1/2 mutation) pts, leading to US/EU labels for this combination. Preliminary analyses reported that olaparib did not alter global health-related quality of life (G-HQoL; Ray-Coquard I *et al. NEJM* 2019). We analyzed HQoL by domains and molecular subgroups and explored the impact of disease progression (DP) on HQoL in the 1L setting. **Methods:** Eligible pts with newly diagnosed advanced (FIGO stage IIIIV) HGOC were randomized 2:1 to maintenance olaparib + bev or pbo + bev. Pts completed European Organisation for Research and Treatment of Cancer QLQ-C30 and QLQ-OV28 HQoL questionnaires at baseline and every 12 weeks for 2 years follow-up, irrespective of DP. The minimal important difference for clinically relevant change was fixed at 10 points. Longitudinal data were analyzed by mixed model for repeated measures (MMRM) and time until definitive deterioration (TUDD). Analyses were in the intent-to-treat population and HRD-positive subgroup. HQoL analyses at DP (± 60 days) were explored. **Results:** 806 pts were randomized to olaparib + bev (n=537) or pbo + bev (n=269). 465 pts had DP over 2 years follow-up. Compliance to HQoL questionnaires was high at baseline (95%) and over time (>70%). MMRM models by HQoL domain did not reveal a clinically relevant difference between treatment arms over time. TUDD of G-HQoL did not differ between arms (hazard ratio [HR] 0.88, 95% confidence interval [CI] 0.721.07). In the HRD-positive subgroup (n=372), we observed no difference by HQoL domain between treatment arms. Interestingly, TUDD of G-HQoL was statistically significantly in favor of olaparib + bev compared with pbo + bev (HR 0.70, 95% CI 0.520.93). We also observed a clinically significant deterioration in emotional (mean change −12.30 points, 95% CI −16.46 to −8.13) and social (−11.17 points, 95% CI −16.21 to −6.12) functioning in both treatment arms at DP, among 103 pts with HQoL questionnaires at DP. **Conclusions:** The substantial PFS benefit provided by maintenance olaparib + bev in the newly diagnosed setting was achieved without detrimental effect on HQoL domains, even with longer TUDD of G-HQoL in the HRD-positive subgroup. Use of an effective maintenance therapy (ie one with a significant PFS benefit) in HGOC patients in the 1L setting is likely to delay the clinically significant deterioration in emotional and social functioning we identified in patients at DP across PAOLA-1 treatments arms. Clinical trial information: NCT02477644. Research Sponsor: ARCAGY Research, Pharmaceutical/ Biotech Company.

5561 **Poster Session**

Identifying disparities in gynecologic cancer: Results and analysis from a patient preference survey. *First Author: Eloise Chapman-Davis, Division of OB/GYN and Gynecologic Oncology, Weill Cornell Medicine-New York Presbyterian Hospital, New York, NY*

Background: Health disparities exist in gynecologic cancers, with data revealing lower survival among certain racial/ethnic groups. Studies suggest underrepresented patients of color with gynecologic cancers may not receive guideline-concordant care to adequately manage their disease, including molecular testing. We conducted a patient preferences survey evaluating treatment choices and provider interactions influencing adherence to guideline-based care. **Methods:** From July 7 to August 18, 2021, a survey was sent to women with gynecologic cancers who participate in the SMART Patients advocacy group. Survey questions covered topics of preparedness to discuss care with provider, biomarker testing specific to gynecologic tumor type, patients' considerations informing treatment choices, and confidence to work with providers to improve their clinical and survival outcomes. Information regarding cancer diagnosis, stage, race, ethnicity, treatment, and genetic testing was obtained. Survey responses between non-Hispanic White patients (W) versus non-White (NW) underrepresented patients of color were compared and analyzed using descriptive statistics. **Results:** A total of 89 women with gynecologic cancers (67% ovarian, fallopian tube, and peritoneal; 21% endometrial; 9% vulvar or vaginal; and 2% cervical) participated in the patient survey. Amongst responders, 55% had localized disease while 36% indicated they had metastatic disease, and 9% did not know. Overall, 86.5% were W and 13.5% were NW (Asian, Black/ African American, Native American or Pacific Islander, Hispanic, or mixed race). A higher proportion of NW compared to W patients said they were not at all prepared to discuss cost of treatment (18.2% vs 9.5%), treatment options (12.5% vs 4.5%), and side effects of treatment (20% vs 0%) with their provider; 31% of W patients discussed genetic testing and received resources from their provider compared with only 16.7% of NW patients, and a higher proportion of NW compared to W patients (37.5% vs 28.1%) indicated they were not confident in their ability to work with providers to improve their cancer treatment outcome. **Conclusions:** While a limitation of this study was low participation from diverse populations, the findings indicate that underrepresented NW patients felt less prepared to discuss treatment-related issues compared to W patients. Moreover, a large proportion of all patients with OC were not informed and/or aware about genetic testing, and approximately a third of participants were not confident in their ability to interact with provider to improve their outcomes. The results highlight opportunities to enhance health care provider education and community outreach to reduce gaps in care delivery. Research Sponsor: None.

5562 **Poster Session**

Time without symptoms or toxicity (TWiST) in patients with newly diagnosed advanced ovarian cancer receiving maintenance olaparib or placebo plus bevacizumab: Analysis of PAOLA-1/ENGOT-ov25 phase III trial. *First Author: Florence Joly, Centre François Baclesse, Caen, France*

Background: In the Phase III PAOLA-1/ENGOT-ov25 trial (NCT02477644), maintenance olaparib plus bevacizumab (bev) provided a significant progression-free survival (PFS) benefit, compared with placebo plus bev, in patients (pts) with newly diagnosed advanced ovarian cancer in response after platinum-based chemotherapy (Ray-Coquard *et al. NEJM* 2019). A subgroup analysis revealed a substantial PFS benefit in HRD-positive (including *BRCA1/BRCA2* mutation) pts (median PFS 37.2 vs 17.7 months) leading to US and EU labels for this combination. We analyzed TWiST in PAOLA-1, using several definitions of toxicity (TOX) and by molecular subgroups. **Methods:** Pts were randomized 2:1 to maintenance olaparib (300 mg bid) plus bev (15 mg/kg, Day 1, q3w) or placebo plus bev, stratified by first-line treatment outcome and tumor BRCAm status. TWiST is defined as PFS minus time with TOX after randomization and before disease progression or censoring for progression, and was a prespecified exploratory endpoint. Definitions of significant symptoms or TOX were explored using the following approaches: 1) all grade ≥2 adverse events (AEs); and 2) all grade ≥2 AEs selected to be correlated to olaparib (fatigue, nausea, vomiting, and anemia). Area under PFS curve was split into TOX:TWIST ratio and compared between the two arms. **Results:** Between May 7, 2015 and August 31, 2017, 806 eligible pts were randomly assigned to olaparib plus bev (n = 537) or placebo plus bev (n = 269), with a median duration of treatment with olaparib of 17.3 months (range 0.0333.0) for olaparib plus bev arm and 15.6 months (range 0.0726.2) for placebo plus bev at data cutoff for primary endpoint analysis. In the Intent-to-treat population, median duration of TWiST for all grade ≥2 AEs for olaparib plus bev vs placebo plus bev arms was 14.1 months (95% confidence interval [CI] 12.516.1) vs 7.7 months (95% CI 5.99.1), respectively; and 21.9 months (95% CI 20.222.5) vs 16.6 months (95% CI 14.618.0) considering only grade ≥2 AEs linked to olaparib. The difference was particularly significant within the HRD-positive subgroup where median duration of TWiST was 24.4 months (95% CI 19.3not evaluable [NE]) vs 7.4 months (5.811.2) for TOX linked to all grade ≥2 AEs, and 36.6 months (95% CI 31.9NE) vs 17.4 months (15.119.4) linked to olaparib AEs only for the olaparib plus bev and placebo plus bev arms, respectively. **Conclusions:** The substantial PFS benefit provided by maintenance olaparib plus bev vs placebo plus bev in pts with newly diagnosed advanced ovarian cancer was supported by significant TWiST benefit. TWiST analyses, including all grade ≥2 symptoms or toxicity related to treatment, confirmed the clinically meaningful benefit from the combination, notably in the HRD-positive subgroup. Clinical trial information: NCT02477644. Research Sponsor: ARCAGY Research, Pharmaceutical/Biotech Company.

5564 **Poster Session**

Potential indicators in circulating cell-free DNA for monitoring PARP inhibitor resistance in high-grade serous ovarian cancer. *First Author: Gang Chen, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China*

Background: Although the clinical application of PARP inhibitors (PARPis) has brought great survival benefits to patients with high-grade serous ovarian carcinoma (HGSOC), its resistance has gradually become a major challenge for clinicians with the widespread use of PARPis. Unfortunately, there are no effective, non-invasive means for monitoring PARPis resistance in time during maintain therapy. **Methods:** We collected peripheral blood samples (n = 37) from 37 healthy subjects and a series of longitudinal peripheral blood samples (n = 61) of 25 platinum-sensitive HGSOC patients undergoing Olaparib maintenance therapy. The genome of white blood cell and cfDNA in plasma was extracted for germline and somatic mutation detection by Circular Ligation Amplification and sequencing (CLAmp-seq) based on a targeted 42-gene panel, respectively. Before cfDNA mutation analysis, background noise introduced by random NGS error was removed and clonal hematopoietic mutations were filtered. Variant-supporting reads > 2 and without germline mutations were defined as the criterion for somatic mutations. Progression-free survival (PFS) was collected through regular follow-up. We analyzed the dynamic changes of cfDNA mutation profiles, the correlation between cfDNA mutations and the prognosis of patients, and screened specific mutation sites that closely associated with Olaparib resistance. **Results:** The elevation of maximum mutant allele frequency (Max MAF) in cfDNA during Olaparib maintenance therapy predicted a poor prognosis of patients (P = 0.0043). Pathogenic germline mutations in *BRCA1/2 or RAD51* were strongly associated with longer PFS (P = 0.0229) and acquired new *MRE11A* mutations significantly shortened the PFS in patients (P = 0.0005). Dynamic fluctuations of somatic mutation sites in *CHEK2:p.K373E* (P = 0.0091) and *CHEK2:p.R406H* (P = 0.0002) can be used to evaluate the therapeutic efficacy of patients. Remarkably, *MRE11A:p.K464R* may be a vital driving factor of Olaparib resistance and all patients who acquired new *MRE11A:p.K464R* in post-treatment cfDNA developed resistance to Olaparib and had significantly shorter PFS than those without it (P = 0.0005). Besides, the combination of *CHEK2:p.R406H* and acquired new *MRE11A:p.K464R* in post-treatment improved the predictive efficiency of patients' prognosis compared with them alone (P < 0.0001). **Conclusions:** Olaparib resistance was robustly associated with the mutation load of tumor cells, and analysis of mutation profiles in cfDNA can be accurately monitor the status of Olaparib resistance in patients with HGSOC. Acquired new *MRE11A:p.K464R* may be a vital driver of Olaparib resistance and is expected to be a target for anti-tumor drug development. Research Sponsor: the Nature and Science Foundation of China, Other Government Agency.

5565 **Poster Session**

A multicenter phase II randomized trial of durvalumab (D) versus physician's choice chemotherapy (PCC) in patients (pts) with recurrent ovarian clear cell adenocarcinoma (MOCCA/APGOT-OV2/GCGS-OV3). *First Author: David Shao Peng Tan, National University Cancer Institute, Singapore and Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore*

Background: The optimal treatment of recurrent ovarian clear cell carcinoma (rOCCC) remains unknown. Prior data suggests rOCCC is a chemo-resistant disease that may respond to programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) immune checkpoint inhibition (ICI). We aimed to determine the efficacy of D versus PCC in pts with rOCCC. **Methods:** In this multicentre, open-label, randomised phase 2 trial, 9 academic centres across Singapore, South Korea and Australia, enrolled rOCCC (determined histologically) and Eastern Cooperative Oncology Group performance status (PS) 0-2 pts, who had recurred after prior platinum-based chemotherapy and had not received more than 4 prior lines of systemic therapy, nor prior ICI therapy. Eligible pts were randomly assigned (2:1), using dynamic block randomization with block size of 6, and stratification by ECOG PS, to receive D (1500mg on day 1, in 28-day cycles) or PCC until disease progression (PD), intolerable toxicity or withdrawal of consent. Pts with PD on PCC were allowed to crossover to D. The primary endpoint was investigator-assessed progression-free survival (PFS) by RECIST version 1.1 and analyses included pts who had commenced at least 1 cycle of study treatment. **Results:** Between 7 Nov 2017 and 17 Feb 2020, 57 pts were assessed for eligibility, of whom 47 (PS 0-1) were randomly assigned to treatment with D (31 pts) or PCC (16 pts). At the data cut-off date (10 Jan 2022), the median follow-up was 83.0 weeks (IQR: 54.1—97.0) in the PCC group and 107.0 weeks (IQR: 82.7—116.4) in the D group. Median PFS was 7.4 weeks (IQR: 6.0—16.0) in the D group and 14.0 (IQR: 7.0—28.6) in the PCC group (HR 1.5 [95% CI 0.8-2.8], log-rank p = 0.89). The objective response rate (ORR) was 10.7% in pts randomised to D and 18.8% in the PCC group (p = 0.884). Clinical benefit rate (CR/PR/SD for ≥16weeks) was similar for PCC (37.5%) and D (32.1%) (p = 0.756). 9 pts on PCC crossed over to receive D, with 2 of the 8 evaluable pts achieving partial response (PR). When crossover D pts were included, ORR to D was 13.9% (5/36) with a clinical benefit rate of 30.6% (11/36). Median duration of response was 44 weeks for the 3 PCC responders (PR to gemcitabine 24.9wks, PR to liposomal doxorubicin 65.7wks, CR to carboplatin/liposomal doxorubicin 44wks), and 18 weeks (range 2.1-45.3) for the 5 responders to D . Frequency of adverse events (AEs) across all grades was 68.8% for PCC and 38.7% for D. Grade 3/4 AEs were observed in 37.5% of PCC pts and 9.7% of D pts. **Conclusions:** No significant differences in PFS, ORR or clinical benefit rate were observed between D and PCC treatment in rOCCC. Treatment with D was associated with less grade 3-4 adverse events. Correlative translational analyses to elucidate predictive biomarkers of response and resistance are ongoing. Clinical trial information: NCT03405454. Research Sponsor: Astra Zeneca, Other Foundation, National Medical Research Council Singapore.

5566 **Poster Session**

Breast cancer incidence in patients with *BRCA*-related advanced ovarian cancer receiving olaparib-based maintenance therapy: A pooled analysis from phase III clinical trials. *First Author: Michele Bartoletti, Unit of Medical Oncology and Cancer Prevention, Department of Medical Oncology, Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano, Italy*

Background: As the prognosis of *BRCA*-related advanced ovarian cancer (AOC) continues to improve thanks to the introduction of targeted therapies like poly ADP-ribose polymerase inhibitors (PARPi) and bevacizumab, the occurrence of second primary tumors, in particular breast cancer (BC), is assumed to be more common. Despite this, data on the incidence of BC in this population are poor and guidelines for BC screening or risk reducing strategies are lacking. **Methods:** Published data from recent PARPi-based, phase III clinical trials involving germline *BRCA* mutated AOC were reviewed and analyzed. Only studies in which the incidence of at least one second primary solid tumor was reported were included. Cases of second primary BC cancers were pooled to calculate cumulative incidence according to the median follow-up period for each trial. 95% confidence interval (CI) was considered. **Results:** Four trials (SOLO1, PAOLA1, SOLO2 and SOLO3) involving 1186 germline *BRCA* 1-2 mutated AOC patients were included (*BRCA1*, n = 816; *BRCA2*, n = 360; *BRCA1* + *BRCA2*, n = 4; missing, n = 6). In all trials, patients were randomized to receive olaparib +/- bevacizumab (n = 788) versus placebo or standard therapies (n = 398). Median age at diagnosis of AOC was 56 years (range, 29-87). With a follow-up ranging from 3.9 months to 5 years, 16 new cases of BC were recorded, 10 in PARPi-based arms and 6 in control arms. Only two patients had a previous history of BC. The total cumulative incidence of BC was 1.37% (95% CI, 0.77-2.18), while cumulative incidences were 1.26% (95% CI, 0.61-2.31) and 1.51% (95% CI, 0.55-3.25) in PARPi-based arms and control arms, respectively. In a sensitivity analysis excluding the SOLO3 trial with the shortest follow-up, the total cumulative incidence was 1.63% (95% CI, 0.92-2.67). Other 20 cases of second primary solid tumors were registered, including 4 cases of non-small cell lung cancer. **Conclusions:** Patients with germline *BRCA*-related AOC receiving PARPi-based maintenance therapy can be reassured about the risk of second primary BC and intensive screening should be avoided at least in early treatment phase. More data with long term follow-up are needed. Research Sponsor: None.

5567 **Poster Session**

A phase Ib study of IN10018 in combination with pegylated liposomal doxorubicin (PLD) in patients with platinum-resistant ovarian cancer. *First Author: Lingying Wu, Cancer Hospital Chinese Academy of Medical Sciences, Beijing, China*

Background: IN10018 is a highly potent and selective oral inhibitor of focal adhesion kinase (FAK). IN10018 is synergistic with PLD against ovarian cancer in PDX models. This study evaluated the safety, tolerability, and antitumor activities of IN10018 in combination with PLD in patients with platinum-resistant ovarian cancer (PROC). **Methods:** This is an open-label phase Ib trial in patients with PROC (high-grade serous carcinoma only). Patient were treated with IN10018 in combination with PLD. This study has a dose-confirmation part and a dose-expansion part. Dose-expansion part was conducted at RP2D dose level to evaluate the primary endpoint of objective response rate (ORR). Secondary endpoints included disease control rate (DCR, CR + PR + SD ≥ 6 weeks), duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** As of December 31, 2021 (cutoff date for all assessments), a total of 42 PROC patients were enrolled. 92.9% (39/42) patients had 1-3 prior lines of therapy and 14.3% (6/42) had prior bevacizumab use. The RP2D of the combination was determined as IN10018 100 mg QD in combination with PLD 40 mg/m^2 Q4W in the dose-confirmation part since no DLTs were observed in 6 patients treated. The safety profile of the combination is comparable to these single agents alone without additive toxicities. No IN10018 related death was observed, and 9.5% (4/42) patients reported IN10018 related SAEs which were also PLD related. The most frequently reported IN10018 related AEs were proteinuria, decreased appetite, fatigue and AEs of gastrointestinal origin such as nausea, diarrhea, vomiting. Majority of these IN10018 related AEs were CTCAE grade 1 and 2, and 14.3% (6/42) had grade 3 AEs. No IN10018 related grade 4 or 5 AEs were reported. Proteinuria was noted asymptomatic, reversible, could be managed with appropriate dose interruption/reduction and only one proteinuria event resulted in IN10018 dose reduction. Antitumor response (as assessed by investigator) was evaluable in 30 patients. 17 patients had best overall response of PR including 13 confirmed PRs and 4 unconfirmed (2 in follow-up to be confirmed). No patient had CR and 9 patients had SD. The ORR is 56.7% (95% CI: 37.4%, 74.5%), the DCR is 86.7% (95% CI: 69.3%, 96.2%), and the median DOR was 4.5 months (95% CI: 2.7 months – NA) and is continuing to mature. Among the 20 efficacy evaluable patients who had at least 6 months of follow up, the ORR is 65.0% (13/20, 95% CI: 40.8%, 84.6%) and the DCR is 90.0% (18/20, 95% CI: 68.3%, 98.8%). In all 42 enrolled patients, the observed median PFS is 6.2 months (95% CI: 6.2 months - NA) and maturing. **Conclusions:** The combination of IN10018 with PLD showed promising antitumor activities and manageable safety profile in PROC patients. This combination warrants further confirmation in a randomized controlled trial. Research Sponsor: InxMed (Shanghai) Co., Ltd.

5570 **Poster Session**

Cisplatin-induced nephrotoxicity in hyperthermic intraperitoneal chemotherapy (HIPEC) is mitigated by sodium thiosulfate: Clinical and toxicotranscriptomic results of a prospective trial. *First Author: Nicole Lugo Santiago, City of Hope National Medical Cente, Chicago, CA*

Background: Hyperthermic intraperitoneal chemotherapy (HIPEC) with cisplatin confers a survival benefit in epithelial ovarian cancer (EOC). Unfortunately, cisplatin is associated with significant renal toxicities. Sodium thiosulfate (ST) has been suggested as a nephroprotectant for patients undergoing HIPEC with cisplatin. **Methods:** A feasibility trial (*ClinicalTrials.gov: NCT01970722*) evaluated safety outcomes of HIPEC with cisplatin 75 mg/m^2 during optimal cytoreductive surgery (CRS) in patients with EOC and endometrial cancer (n = 40), with or without ST. Twenty-one patients received no sodium-thiosulfate (nST group), and nineteen patients received sodium thiosulfate (ST group). Toxicities were reported according to CTCAE v. 5. Progression-free survival was followed. Normal tissue biopsies were collected intra-operatively immediately following HIPEC and cisplatin exposure in a subset of patients (n = 21), and profiled with transcriptomic sequencing to identify RNAseq signatures correlating with toxicities. Hierarchical cluster analyses identified distinct transcriptomic signatures in post-HIPEC normal samples of patients with renal AEs (rAEs) compared to no renal AEs (nrAEs). KEGG pathway analysis identified up- or downregulated gene sets using GSEA. **Results:** Forty patients had HIPEC at time of optimal CRS. Renal toxicities were higher in the nST group (no sodium thiosulfate) compared to the ST group. nST patients had 17% any grade, and 9% Grade 3 AEs for acute and chronic kidney injuries. In contrast, ST patients suffered 0% renal AEs. rAE patients demonstrated upregulation of immune signaling pathways (Toll-like receptor, Natural killer cell, Nod-like receptor); and downregulation of metabolic pathways. Top upregulated genes in rAE patients included immune (e.g. neutrophil) related genes, while downregulated genes included metabolism genes. Kaplan-Meier curves demonstrated improved PFS in primary ovarian cancer patients undergoing HIPEC who were treated with ST vs no ST (p = 0.04, NR vs 13.4 mo). **Conclusions:** HIPEC with cisplatin results in significant renal toxicities. The mechanisms of cisplatin-induced nephrotoxicity in HIPEC are immune-related and reflect reduced metabolism. Sodium thiosulfate abrogated renal toxicities and did not decrease PFS. Clinical trial information: NCT01970722. Research Sponsor: U.S. National Institutes of Health.

5571 **Poster Session**

Efficacy of maintenance olaparib plus bevacizumab in patients with newly diagnosed advanced ovarian cancer according to BRCA mutation genotype in the phase III PAOLA-1/ENGOT-ov25 trial.

First Author: Sana Intidhar Labidi-Galy, Department of Oncology, Hôpitaux Universitaires de Genève, Genève, Switzerland

Background: In the Phase III PAOLA-1/ENGOT-ov25 trial, the addition of maintenance olaparib (ola) to bevacizumab (bev) in patients (pts) with newly diagnosed advanced high-grade ovarian cancer (HGOC) resulted in prolonged progression-free survival (PFS), particularly for pts with HRD-positive tumors including a *BRCA1/BRCA2* mutation (BRCAm; Ray-Coquard *et al. NEJM* 2019). Preclinical data suggest that pts with mutations (mut) in the RING domain of *BRCA1* are less sensitive to ola. The magnitude of benefit from ola + bev, according to the location of mut in the functional domains (FD) of BRCA, remains to be explored. **Methods:** Pts with newly diagnosed advanced HGOC in response after platinum-based chemotherapy + bev received maintenance bev (15 mg/kg q3w for 15 months [mo]) + either ola (300 mg bid for 24 mo) or placebo (pbo). In this *post hoc* exploratory analysis, PFS was analyzed in pts with BRCAm according to mut location in the FDs of *BRCA1* (RING, DNA-binding domain [DNA-BD], or *BRCA1* C terminus [BRCT]) and *BRCA2* (RAD51-BD; DNA-BD). **Results:** Among the 806 randomized pts, 235 (29.2%) harbored a BRCAm: 160 (19.9%) with a *BRCA1* mut and 76 (9.4%) with a *BRCA2* mut. *BRCA1* mut in FDs of RING, DNA-BD and BRCT were detected in 19 (11.8%), 41 (25.6%) and 34 (21.2%) pts, respectively. *BRCA2* mut were detected in FDs of RAD51-BD and DNA-BD in 37 (48.7%) and 14 (18.4%) pts, respectively. With a median follow-up of 25.5 mo, 24-mo PFS rates and hazard ratios (HRs) according to mut locations are reported in the Table. In pts with a *BRCA1* DNA-BD mut, 24-mo PFS was 89% and 14% (ola + bev vs pbo + bev; HR 0.08, 95% confidence interval [CI] 0.02–0.26) compared with 64% and 24% for pts with mut in RING + BRCT + other domains (HR 0.33, 95% CI 0.19–0.57). In pts with *BRCA2* mut, 24-mo PFS for pts with mut in the DNA-BD was 91% vs 100% (ola + bev vs pbo + bev) compared with 82% and 44% for pts with mut in RAD51-BD + other domains (HR 0.21, 95% CI 0.08–0.54). **Conclusions:** In this exploratory analysis, pts with newly diagnosed advanced HGOC and a BRCAm had a PFS benefit from maintenance ola + bev regardless of mut locations in *BRCA1/BRCA2*. Sensitivity to ola + bev maintenance was particularly high for pts with mut in the DNA-BD of *BRCA1*. Pts with a mut in the DNA-BD of *BRCA2* commonly had excellent outcomes. Clinical trial information: NCT02477644. Research Sponsor: ARCAGY Research, Pharmaceutical/Biotech Company.

PFS according to *BRCA1/BRCA2* mut location.

	Pbo events, n/N	Ola events, n/N	Pbo 24-mo PFS, %	Ola 24-mo PFS, %	HR (95% CI)	*P*
***BRCA1* FD**						
RING (n=19)	3/6	6/13	40	66	0.38 (0.07–2.13)	0.273
DNA-BD (n=41)	15/17	4/24	14	89	0.08 (0.02–0.26)	<0.001
BRCT (n=34)	7/10	10/24	27	59	0.55 (0.20–1.56)	0.265
Other (n=68)	12/17	17/51	18	67	0.24 (0.11–0.51)	<0.001
***BRCA2* FD**						
RAD51-BD (n=37)	10/15	5/22	33	76	0.31 (0.11–0.92)	0.034
DNA-BD (n=14)	0/3	1/11	100	91	NC	NC
Other (n=25)	7/11	1/14	55	93	0.09 (0.01–0.75)	0.025

NC, not calculated.

5572 **Poster Session**

Potential clinical activity of pembrolizumab monotherapy in ovarian sex cords, rare epithelial carcinoma, and other rare ovarian tumor histotypes: The French AcSé pembrolizumab study from Unicancer.

First Author: Isabelle Laure Ray-Coquard, Centre Léon Bérard, University Claude Bernard, Lyon, France

Background: AcSé Pembrolizumab is a Phase 2, non-randomized parallel arms, multicentric basket trial investigating the efficacy and safety of pembrolizumab monotherapy in different cohorts of patients with rare cancers (NCT03012620). Here we report the results in the rare ovarian tumors cohort. **Methods:** Selected histotypes were all rare ovarian cancers (incidence < 6/100,000/year). Main inclusion criteria were age > 18, ECOG PS≤1, resistant disease to platinum based chemotherapy, and systematic histological central review by expert pathologist from TMRG network. Patients (pts) received pembrolizumab 200 mg IV on Day 1 of every 21-day cycle for a maximum of 2 years. The primary endpoint was the confirmed objective response rate according to RECIST v1.1 at 12 weeks. Secondary endpoints included best response rate, duration of response, progression-free survival (PFS), overall survival (OS), and safety. The 7 subgroups of pts analyzed were carcinosarcoma (CS), clear cell carcinoma (CCC), low grade serous carcinoma (LGSC), mucinous carcinoma (MEOC), sex cord tumors (SCT), germ cell tumor (GCT), and smarcA4 deficient hypercalcemic ovarian tumor (SCHOCCT). **Results:** 62 pts from 22 centers, were included from 08/2017 to 12/2020. Median Age was 53.5 years old [36-64]. Median number of previous lines of chemotherapy was 2 (range 1-4). The median number of cycles was 8 (range, 1-35) with 44 pts (70.9%) who discontinued the trial after a mean number of 6.8 cycles. There were 2 pts (3.2%) with partial response (PR) at 12 weeks. The best response in ITT was complete response (CR) in 1 patient (1%), PR in 3 (14.3%), and stable disease (SD) in 21 (33.8%). The occurrence of best response depended on the histotype with 1 CR (33%) in GCT (cancerized teratoma), 2 PR (20%) in CCC, and 1 PR (4%) in LGSC. 4/4 pts (100%) reported PD as best response in SCOOHT (Table 1). Median duration of response or stabilized disease was 7.8 months [IQR, 4.1 to 9.0]. At the data cut off, 6-month PFS was 29% [19.7-42.8] and 6-month OS was 77.8% [67.7-89.3] on the overall population. Outcomes differed according to subgroups and will be presented. There were a total of 62 adverse events (AEs) reported in 28 pts. For 5 pts (8%) AEs lead to drug discontinuation. AEs were of grade 1 (n = 9), grade 2 (n = 8), or grade ≥ 3 (n = 45: 42 grade 3, 2 grade 4, and 1 grade 5). **Conclusions:** Pembrolizumab is safe and well tolerate in this population of rare ovarian cancer pts. AcSé study reports prolonged responses in very selected subtypes of rare ovarian tumor (CCC, cancerized teratoma, and LGCS). Acknowledgements: TMRG (national cancer network dedicated to rare gynecological tumors), GINECO group for partnership, La Ligue Nationale contre le Cancer, INCa and MSD. Clinical trial information: NCT03012620. Research Sponsor: La Ligue Nationale Contre le Cancer, Other Government Agency, Pharmaceutical/Biotech Company.

Tumor type	PD	SD	PR+CR	NE	Total (pts)
CS	3	1	0		4
CCC	5	3	2		10
LGSC	9	11	1	2	23
MEOC	3	2	0		5
SCT	10	3	0		13
GCT	1	1	1		3
SCOOHT	4	0	0		4
Total	**35**	**21**	**4**	**2**	**62**

5573 **Poster Session**

MOONSTONE/GOG-3032: Interim analysis of a phase 2 study of niraparib + dostarlimab in patients (pts) with platinum-resistant ovarian cancer (PROC).

First Author: Leslie M. Randall, Massey Cancer Center, Richmond, VA

Background: PROC is poorly responsive to anticancer therapy. PARP inhibitors such as niraparib may increase neoantigen load and synergize with anti-PD-1 agents. TOPACIO reported a preliminary objective response rate (ORR: 18%) and disease control rate (DCR: 65%) to niraparib + pembrolizumab in pts with OC of any *BRCA* status. MOONSTONE sought to determine efficacy in pts without *BRCA* mutation (*BRCA*m). **Methods:** In this phase 2 open-label, single-arm study, eligible pts received 1–3 prior lines of therapy including platinum, taxane, and bevacizumab, had RECIST v1.1 radiographic progression within 6 mo of last platinum line and had no known germline *BRCA*m. Pts were treated with niraparib 300/200 mg PO daily (based on weight/platelets) and 500 mg dostarlimab IV Q3W (cycles 1–4) followed by 1000 mg Q6W until disease progression, toxicity or consent withdrawal. Programmed death-ligand 1 (PD-L1) positive status was determined by Ventana SP263 assay using visually-estimated combined positive score ≥5%. The primary endpoint was investigator-assessed ORR per RECIST v1.1. Secondary endpoints included duration of response (DOR), progression-free survival (PFS), DCR, and safety. Futility was prespecified as ≤5 responses in the first 40 pts. **Results:** At interim analysis (data cutoff Oct 6, 2021), 41 pts were enrolled; median age was 65.0 y (range 35–77). At baseline, 8 (20%)/22 (54%)/11 (27%) pts had received 1/2/3 prior lines of therapy, respectively; 26 (63%) pts had primary resistance to platinum therapy and 15 (37%) were sensitive to first platinum treatment. Overall, tumors were PD-L1+/PD-L1–/unknown in 13 (32%)/25 (61%)/3 (7%), respectively. Efficacy results are shown in the Table. Treatment-related adverse events were reported in 95% of pts, most commonly nausea (56%), fatigue (34%), vomiting (32%), and anemia (29%). **Conclusions:** PROC remains difficult to treat; the ORR observed with niraparib + dostarlimab did not reach the threshold for 2nd-stage accrual in this cohort of pts with PROC, no known *BRCA*m, and prior bevacizumab treatment. PD-L1 status did not predict response; HRD testing is in process. Although DCR was 29%, futility was declared based on low ORR. The safety of the combination was similar to the safety profile of each monotherapy. Clinical trial information: NCT03955471. Research Sponsor: GlaxoSmithKline.

Best overall response, n (%)	Overall N=41	PD-L1+ n=13	PD-L1– n=25
Complete (CR)	0	0	0
Partial (PR)	3 (7.3)	1 (7.7)	2 (8.0)
Stable disease (SD)	9 (22.0)	4 (30.8)	5 (20.0)
Progressive disease	24 (58.5)	7 (53.8)	15 (60.0)
Efficacy, n (%) [95% CI]*	3 (7.3) [1.5–19.9]	1 (7.7) [0.2–36.0]	2 (8.0) [1.0–26.0]
ORR (CR + PR)	12 (29.3)	5 (38.5)	7 (28.0)
DCR (CR + PR + SD)	[16.1–45.5]	[13.9–68.4]	[12.1–49.4]
DOR, mo		3.8+	3.0, 9.2+
Median PFS, mo (95% CI)	2.1 (2.0–2.2)	2.2 (1.6–not evaluable)	2.1 (1.8–2.2)

*Clopper-Pearson method.

5574 **Poster Session**

Integrated safety summary of single-agent mirvetuximab soravtansine in patients with folate receptor α (FRα)-positive recurrent ovarian cancer: Phase 1 and 3 clinical trials.

First Author: Kathleen N. Moore, Division of Obstetrics and Gynecology, Department of Gynecologic Oncology, University of Oklahoma Health Science Center, Stephenson Cancer Center, Oklahoma City, OK

Background: Available chemotherapies for platinum-resistant ovarian cancer (PROC) have limited clinical activity and considerable toxicity. Mirvetuximab soravtansine (MIRV) is a first-in-class antibody drug conjugate (ADC) comprising a folate receptor alpha (FRα)-binding antibody, cleavable linker, and the maytansinoid payload DM4, a potent tubulin-targeting agent that has demonstrated significant anti-tumor activity in this difficult to treat population. The objective is to characterize the tolerability profile of MIRV in a pooled analysis of experience when administered as monotherapy in patients (pts) with FRα positive recurrent ovarian cancer. **Methods:** Retrospective pooled analysis included pts enrolled across three studies: phase 1 first-in-human, phase 3 FORWARD I, and phase 3 SORAYA. Analysis included pts with FRα positive recurrent ovarian cancer and those pts with low, medium, and high FRα expression by immunohistochemistry (Roche FOLR1 Assay ≥ 25% of cells with PS2+ staining intensity). All pts received intravenous MIRV at 6 mg/kg, adjusted ideal body weight, on Day 1 of a 21-day cycle until disease progression or unacceptable toxicity. **Results:** 464 pts were included from 15 countries, with key characteristics: median age 63 yrs, 87% 1-3 prior therapies, 91% platinum free interval ≤6 months, 65% prior bevacizumab, and 25% prior PARPi. The most common treatment-related adverse events (TRAE) (all grade, grade 3+) included blurred vision (42%, 3%), nausea (40%, 2%), diarrhea (33%, 2%), fatigue (31%, 2%), keratopathy (26%, 3%), and dry eye (22%, 1%). TRAEs leading to a dose delay or reduction occurred in 33% and 21% of pts, respectively. Seven % discontinued due to a TRAE. Four pts (< 1%) discontinued MIRV due to an ocular event. Ninety % of pts with a grade 2+ blurred vision resolved to grade 0 or 1, 93% of pts with grade 2+ keratopathy resolved to grade 0 or 1. No corneal ulcers or perforation have been reported and no patient with a serious ocular event has been reported to have permanent sequelae. **Conclusions:** In a pooled analysis of 464 patients, MIRV monotherapy has a differentiated and predictable safety profile consisting primarily of low grade and reversible gastrointestinal and ocular events. These events were managed with supportive care and dose modifications if needed, with a low rate of treatment-related discontinuation. The safety profile of MIRV in recurrent ovarian cancer along with the anti-tumor activity in PROC (32.4% ORR Matulonis SGO 2022) support a favorable benefit/risk in this population. Clinical trial information: NCT01609556, NCT04296890, NCT02631876. Research Sponsor: ImmunoGen.

5575 **Poster Session**

PemBOv trial: Pembrolizumab plus bevacizumab with or without pegylated liposomal doxorubicin-based chemotherapy in patients with platinum-resistant ovarian cancer.

First Author: Judith Michels, Gustave Roussy Comprehensive Cancer Center, Villejuif, France

Background: Few platinum resistant ovarian cancer (PROvC) patients respond to anti-PD1 monotherapy (ORR 7.6%) with little impact on survival (OS 10.1 mo). Among responders the median duration of response is impressive (18.7 mo) (Hamanishi 2021). **Methods:** We have evaluated the combination of pembrolizumab (200mg), with bevacizumab (400mg) for 6 cycles plus minus peglyated liposomal doxorubicin (PLD) q3w in PROvC patients with no limit in previous treatment lines, allowed to be previously treated with bevacizumab. An initial safety run evaluated the dual combination of pembrolizumab plus PLD (cohort A). The triple combination was evaluated at MTD-1 and at MTD of PLD (30mg/m^2 q3w) (cohort C). The dual combination of pembrolizumab + bevacizumab was run in parallel (cohort B). This is an open label phase I trial with a modified toxicity probability interval design. The evaluation criteria endpoints were safety and efficacy. Pharmacokinetics of bevacizumab were evaluated. NCT03596281 **Results:** A total of 47 patients (pts) were enrolled between January 2019 and February 2021. Median age was 70 years (38-77). 30/12 pts (63.8/25.5%) had an initial FIGO stage III/IV, 44 pts (93.6%) had a HGSOC. 40 pts (85.1%) underwent surgery, out of which 13 pts (32.5%) had a primary debulking. BRCA mutations were present in 9 pts (19.1%). Pts had a median of 3 previous treatment lines (0-13), including pretreatment with antiangiogenic agents in 36 (76.6%) and PARP inhibitors in 21 pts (44.7%). No DLT was reported. Grade 3/4 treatment-related adverse events were reported in 2 pts (30%), 4 (20%) and 11 (50%) in cohorts A, B and C respectively. The ORR was 0, 26.3 (95% CI 6.5-46.1) and 30% (9.9-50.1) with a DCR of 0, 78.9 and 75% in cohorts A, B and C respectively. According to investigator assessment, the median PFS was 2.1, 4.7 and 4.8 mo (table). The blinded independent central review is currently under evaluation. A large inter-patient variability in bevacizumab plasma concentrations was observed among patients. The 400 mg flat dosing achieved residual concentrations similar to that of 5 mg/kg Q2W or 7.5 mg/kg q3w (51± 30 μg/ml in cohort B and 63 ± 55 μg/ml in cohort C (p>0.05) after C1). Overall, 22 % of pts of cohort B and 18 % of cohort C showed trough levels below the targeted threshold (i.e. < 25 μg/ml). Correlative studies are ongoing. **Conclusions:** Short-term flat dose bevacizumab potentiates the response to anti-PD1 therapy even in the absence of chemotherapy in heavily pre-treated PROvC patients. The long-term treatment with bevacizumab could potentially improve the outcome. The combination of anti-PD-1 plus anti-angiogenic agents should be a backbone for the treatment of PROvC patients. Clinical trial information: NCT03596281. Research Sponsor: MSD, Other Foundation.

Progression-free survival (months).

	Cohort A n=6	Cohort B n=19	Cohort C n=19
PFS	2.1	4.7	4.8
95% CI	1.3 - NR	2.1 - 7.6	2.1 - 7.5
median Follow-up	21.1	7.9	17.8
min max	5.8 - 30.1	2.9 - 29	2.6 - 19

5576 **Poster Session**

Landscape of homologous recombination reversion mutations in gynecologic malignancies.

First Author: Susan M. Domchek, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Background: Homologous recombination (HR) reversion mutations (REV) are biomarkers for predicting resistance to platinum and PARP inhibitor therapies. The biologic diversity of REV represents a diagnostic challenge. An automated computational approach was used to detect REV for analysis of genomic features of REV-positive ovarian epithelial, fallopian tube, and peritoneal cancers. **Methods:** Retrospective study of tissue (n = 23,612) and liquid biopsy (n = 869) samples from patients undergoing hybrid-capture comprehensive genomic profiling during routine clinical care 11/2012-03/2021. A proprietary algorithm tested for seven distinct REV mechanisms in *BRCA1*, *BRCA2*, *PALB2*, *RAD51C*, or *RAD51D*. For subjects with multiple samples, the earliest REV-positive sample was used for downstream analyses. **Results:** Among 23,866 ovarian epithelial, fallopian tube, and peritoneal cancers, 16.4% (n = 3,920) had at least one pathogenic variant (PV) in *BRCA1* (10%, n = 2,383), *BRCA2* (5.5%, n = 1,320), *PALB2* (0.67%, n = 160), *RAD51C* (0.64%, n = 152), or *RAD51D* (0.47%, n = 113). 3.9% (154/3,920) of patients with one or more PV had REV. REV were found in tumors with PV in *BRCA2* at twice the frequency of *BRCA1* (6.0%, [79/1,320] vs 3.0% [71/2,383]; p < 0.001). REV involving *RAD51D* (1.8%, 2/113), *RAD51C* (0.7%, 1/152), or *PALB2* (0.6%, 1/160) were rarer. A total of 193 REV pairs were identified. The most frequent REV mechanism was an exonic non-frameshift deletion completely encompassing a PV (45%, 87/193). Other recurrent mechanisms included restoration of the reading frame of a frameshift PV (21%, 42/193), replacement of a PV with a benign missense substitution at the same codon (16%, 32/193), and deletion with intronic breakpoints encompassing a PV (15%, 29/193). REV were significantly more prevalent in liquid biopsies than in tissue samples with PV (16% [20/124] vs. 3.5% [134/3,796]; p < 0.001). A range of 1-6 REV pairs were found per sample (liquid: 1-6, tissue: 1-3). Multiple REV per sample was more common in liquid biopsies (35% [7/20] vs. 11% [15/134]; p = 0.011). These differences likely reflect stage of disease and sampling of multiple subclones. **Conclusions:** *BRCA2* PV are most frequently reverted in gynecologic tumors. REV are also common in tumors with BRCA1 PV and can more rarely occur in other HR genes. Liquid biopsy is enriched for detection of polyclonal resistance. Diverse REV mechanisms highlight a need for robust detection to incorporate REV in identifying treatment resistance and guiding downstream therapy selection. Research Sponsor: Foundation Medicine.

5577 **Poster Session**

CeNtuRIOn: Rucaparib (R) with nivolumab (N) and ipilimumab (I) in patients (pts) with relapsed ovarian cancer (ROC)—Results of an initial safety cohort.

First Author: Marcia Hall, Mount Vernon Cancer Centre, Northwood, United Kingdom

Background: There is an urgent need to improve outcomes for ROC pts; progression free (PFS)/overall survival (OS) are 4-9 months (mo), 12-20mo respectively. ~50% ROC pts harbour homologous repair deficiencies (HRD), identified by *BRCA* mutations (m) & Loss of Heterozygosity (LoH). R, a PARP inhibitor (PARPi) has demonstrated efficacy when used as maintenance after chemotherapy (CT), and is superior to CT if used as treatment for ROC *BRCA*m pts. However repeating PARPi, even in highly selected *BRCA*m/HRD pts has limited benefit (1.5-2.5mo extra PFS). Single agent immunotherapy (PD-1/PD-L1/CTLA4 antibodies (Ab)) in ROC pts has been disappointing. Response rate to combined PD-1/CTLA4 Ab in ROC pts is 31.3%. *In vitro* evidence suggests that combinations of PD-1/CTLA4 Ab /PARPi may be more effective. CeNtuRIOn aims to explore the activity/toxicity of repeat PARPi (R) versus R+I (CTLA4 Ab) versus R+I+N (PD-1 Ab). Here we report safety data from the run-in cohort of 15 ROC pts treated with the triplet combination, RNI. **Methods:** Eligible pts had received ≥1 and <3 lines CT, were > 3 to <12 months from last platinum CT. Only 1 pt could experience a dose limiting toxicity (DLT) over initial 6 weeks of treatment. Pts received N 240mg q14 days, I 1mg/kg q42 days intravenously for up to 12mo and R orally, 600mg bd continuously. All bar 1 of 7 pts (recruited 06/19–12/19) received N+I to meet DLT evaluability, but 5 of remaining 6 received < 43% R during safety period. 6 further pts were recruited (08/20-06/21), with ≥60% starting dose R in first 6 weeks now required for evaluability. Review of toxicity/tolerability prompted reduction of R starting dose to 400mg bd and ipilimumab limited to 4 cycles for the last 4 pts. **Results:** Of all 15 recruits, median age was 64. Adverse events (AE)s are detailed in Table. 7 pts were evaluable for safety assessment: n = 4 started on 600mg bd and n = 3 on 400mg bd R. Median R dose intensity in these 7 was 82.5%. There was 1 DLT: G3 nephritis on day 18. 1 pt died of E. Coli sepsis related to colitis. Outcome data will be presented. **Conclusions:**R (400mg bd)+N+I (4 cycles only) will be taken forward to phase II. Pts will be randomised 1:1:2 to single agent R, R+I or RNI. Pts recruited to R alone are eligible for 2nd randomisation (1:1) to add I or N+I at progression. Clinical trial information: ISRCTN10490346. Research Sponsor: Clovis Oncology, BMS, Cancer Research UK.

	Any Grade		TRAEs, Any G		Grade ≥3		TRAEs, G≥3	
AEs and relationship to treatment (TRAEs) where available*	**Eval n = 7**	**Non-E n = 8**	**Eval n = 7**	**Non-E n = 8**	**Eval n = 7**	**Non-E n = 8**	**Eval n = 7**	**Non-E n = 8**
Fatigue	7 (100%	7 (88%)	7 (100%)	7 (88%)	3 (43%)	1 (13%)	2 (29%)	1 (13%)
Diarrhoea/colitis	6 (86%)	4 (50%)	6 (86%)	4 (50%)	2 (29%)	2 (25%)	2 (29%)	2 (25%)
Dyspnoea	6 (86%)	7 (88%)	5 (71%)	3 (38%)	1 (15%)	1 (13%)	0	1 (13%)
Rash	5 (71%)	3 (38%)	5 (71%)	3 (38%)	2 (29%)	0	2 (29%)	0
Lymphopenia	4 (57%)	5 (63%)	-	-	4 (57%)	4 (50%)	-	-
Hyponatraemia	3 (43%)	5 (63%)	-	-	2 (29%)	2 (25%)	-	-
Hypo-phosphataemia	6 (86%)	3 (38%)	-	-	4 (57%)	0	-	-
Anaemia	4 (57%)	3 (38%)	-	-	2 (29%)	0	-	-
Myocarditis	1 (14%)	0	-	-	0	0	-	-

5578 **Poster Session**

Mutational landscape of low-grade serous carcinoma of the ovary.

First Author: Julian C. Schink, Cancer Treatment Centers of America, Part of City of Hope, Zion, IL

Background: Tumor genomic profiling is a critical component of precision oncology allowing the detection of genomic alterations (GA) that are potential therapeutic targets. We present an analysis of comprehensive genomic profiling (CGP) of a large series of low grade serous ovarian carcinoma patients assayed in a nationwide cancer network. **Methods:** 40 Pts with advanced low grade serous ovarian carcinoma (LGSOC) underwent hybrid-capture based CGP for up to 324 cancer-related genes on archival tumor tissue or 62 genes on circulating tumor DNA ordered during clinical care for treatment decision-making between 01-2013 thru 06-2021. Clinically relevant genomic alterations (CRGA) were defined as associated with targeted therapies or mechanism-driven clinical trials. The treatment histories for these patients were obtained with IRB-approved retrospective review. **Results:** Median age was 44 years (range, 25-65), 68% were White and 23% were Black. Genomic alterations (GA) were identified in 80% (32/40) of LGSOC, of which 22 (55%) had a clinically relevant genomic alteration (CRGA). There were no apparent racial differences between mutation frequencies. The table below details the frequency of the most common of these clinically relevant mutations. Additionally, 1 patient had an ESR1 activating mutation commonly seen in acquired hormone therapy resistance in breast cancer; and single cases of the following mutations were also noted: *TSC1, PTCH1, PTEN, FGFR1,* and *AKT2.* **Conclusions:** In a large series of Low Grade Serous Ovarian Cancer patients assayed with CGP, 55% of pts had mutations potentially targeted by precision medicine therapy. The most common target is *KRAS*, seen in 33% of patients, these are potentially treatable with FAK and MEK inhibitors. Another 10% of patients had either a *BRCA* or *ATM* mutations making PARP inhibitor therapy an additional targeted treatment option. While mutations in the *RAS* pathway are most common in LGSOC they are not the only actionable target. Furthermore, this approach might also help identify baseline or acquired resistance to the hormone therapies often used to treat this cancer. The results of this study demonstrate the significant heterogeneity of genomic alterations in this rare cancer and highlight the importance of genomic profiling in this cancer which has a marked propensity for recurrence. Research Sponsor: None.

Gene	**White (n = 27)**	**Black (n = 9)**	**Hispanic (n = 1)**	**Other (n = 2)**
KRAS	8 (30%)	4 (44%)	1 (100%)	1 (50%)
BRAF	1 (4%)	1 (11%)	0 (0%)	1 (50%)
BRCA1	4 (15%)	0 (0%)	0 (0%)	0 (0%)
NRAS	2 (7%)	0 (0%)	0 (0%)	0 (0%)
NF1	1 (4%)	1 (11%)	0 (0%)	0 (0%)
MTOR	1 (4%)	0 (0%)	0 (0%)	0 (0%)
BRCA2	1 (4%)	0 (0%)	0 (0%)	0 (0%)
PIK3CA	1 (4%)	0 (0%)	0 (0%)	0 (0%)
EGFR	0 (0%)	1 (11%)	0 (0%)	0 (0%)
ATM	1 (4%)	1 (11%)	0 (0%)	0 (0%)

5579 **Poster Session**

Pharmacokinetic and pharmacodynamic analysis of adavosertib in advanced ovarian cancer. *First Author: Amit M. Oza, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada*

Background: Adavosertib (AZD-1775) is a potent small molecule inhibitor of Wee-1, currently in clinical development. In a double-blind, placebo-controlled, phase 2 trial (NCT02151292), adavosertib and gemcitabine significantly prolonged progression-free survival (PFS) and overall survival (OS) in patients with recurrent platinum-resistant or platinum-refractory high grade serous ovarian cancer (HGSOV) compared to gemcitabine alone. We investigated whether plasma and intra-tumoral adavosertib concentrations correlated with survival in these patients. **Methods:** Adavosertib was administered orally on Days 1, 2, 8, 9, 15 and 16 at 175 mg per day, and gemcitabine was administered on Days 1, 8 and 15 at 1000 mg/m^2 every 28 days. Serial blood samples were collected on Day 1 of cycle 1 after adavosertib administration. Tumor biopsies were taken 1-2 weeks after initiation of study treatments. Plasma and tumor adavosertib concentrations were determined using validated HPLC-MS/MS. Patients were divided into groups with plasma or tumor adavosertib concentrations above or below the biologically active concentration (BAC) of 125 ng/ml (Leijen et al, J Clin Onco 2016). Survival was described using the Kaplan-Meier method. **Results:** Among 61 HGSOV patients who received adavosertib, plasma samples were available in 47, and tumor samples were available in 31 patients. Among 25 non-HGSOV patients (exploratory cohort), plasma and tumor samples were available in 21 and 17 patients respectively. The mean maximum adavosertib concentration (Cmax) was 355.3 ± 120.9 ng/ml and 358.6 ± 117.9 ng/ml respectively. Cmax was above BAC in all patients. The mean tumor adavosertib concentration was 609.2 ± 1129.2 ng/ml (range: 0.47 – 5501 ng/ml) for HGSOV patients, and 964.2 ± 1611.2 ng/ml (range: 0.22 – 6116 ng/ml) for non-HGSOV patients. There was no correlation between Cmax and tumor adavosertib concentrations. In HGSOV, the median PFS was 5.8 months for patients with tumor concentrations above BAC, and 3.5 months for those with tumor concentrations below BAC (Hazard ratio (HR): 0.46, 95% confidence interval: 0.19 – 1.14, p = 0.06). No difference in PFS was seen in non-HGSOV patients according to tumor adavosertib concentration. Tumor adavosertib concentration did not correlate with OS. **Conclusions:** Although Cmax was above BAC in all patients, there was a high variability in tumor adavosertib concentrations. In HGSOV, higher tumor adavosertib concentration was associated with a trend towards improved PFS, but not OS. Our results indicate that the current adavosertib dosing regimen may not produce the desired concentrations in tumors for some patients, and further optimization may be needed. Research Sponsor: None.

5580 **Poster Session**

Exploring the nuances between BRCA1 and 2: A multiomic analysis. *First Author: Radhika Gogoi, Wayne State University, Detroit, MI*

Background: Emerging data suggests that key differences exist between BRCA1 and BRCA2 associated OC, including response to therapy and survival. The purpose of this study was to identify the gene expression profiles, interacting pathways and immune microenvironment of BRCA1 mutant (BRCA1mut), BRCA2 mutant (BRCA2mut) and homologous recombination wild-type (HRwt) associated high grade serous OC (HGSOC). **Methods:** Next-generation sequencing (592, NextSeq; WES, NovaSeq) and Whole Transcriptome Sequencing (NovaSeq) (Caris Life Sciences, Phoenix, AZ) were performed in 8196 OC tumors classified into 3 groups: BRCA1mt; BRCA2mt; and HRwt. BRCA mutations were defined as variants that result in loss-of-function of the BRCA protein and HRwt was defined as samples negative for aberrations in both BRCA1 and BRCA2, as well as for 28 other homologous recombination genes Microsatellite instability (MSI) was tested by fragment analysis, IHC and NGS. Tumor mutational burden (TMB) was measured by totaling somatic mutations (TMB-H: >10 mutations/MB). LOH cut-off >16%. Immune cell infiltrates were calculated by XCell. Differential gene expression was calculated using Limma. Significance was determined using chi-square and Wilcoxon rank sum test and adjusted for multiple comparisons (q-value < 0.05). **Results:** We identified 677 BRCA1mt, 439 BRCA2mt, and 7080 HRwt OC tumors. HGSOC made up the largest portion of BRCA1mt (523; 77%), BRCA2mt (306; 70%), and HRwt (4281; 60%) tumors. TP53 was most commonly mutated gene in all three groups. LOH (>16%) was highest in BRCA1mt (86.8%) compared to BRCA2mt (74.8%) and HRwt (38.4%). TMB-H was highest in BRCA2mt (6.29%) than in BRCA1mt (1.35%) and HRwt (0.91%) HGSOC (all q < 0.05). Expression of immune checkpoint genes *CD80, CD86, CD274, CTLA4, HAVCR2/TIM3*, *IFNG*, *IDO1*, *LAG3*, *PDCD1* and *PDCD1LG2* were significantly higher in BRCA1 and BRCA2 mt compared to HRwt HGSOC (FC: 1.12-1.59, q < 0.05). HRwt tumors had decreased infiltration of Activated Dendritic cells compared to BRCA1mt, and lower Macrophage M1 compared to both BRCA1mt and BRCA2mt (all q < 0.05). Additionally, T-inflamed score was higher in BRCA1mt compared to HRwt, while IFN score was higher in BRCA1mt compared to both BRCA2mt and HRwt (all q < 0.05). From 17,408 genes with measured expression. 522 (3.0%) differentially expressed genes (DEG) were found between BRCA2mt vs BRCA1mt; 1487 (8.54%) between BRCA2mt vs HRwt; and 9297 (53.4%) between BRCA1mt and HRwt HGSOC. Pathway analysis identified Fatty Acid Metabolism, Myc targets, ROS pathway, Oxidative Phosphorylation, and Wnt B-catenin signaling pathways as differentially regulated between the 3 groups. **Conclusions:** We describe the genomic, pathway and immunologic analyses in the largest cohort of BRCA1 and 2 mutated HGSOC to date. Both metabolic and immune response pathways are differentially regulated between the groups. Results can potentially inform targeted therapeutic studies based on unique BRCA genotype. Research Sponsor: Michigan Ovarian Cancer Alliance.

5581 **Poster Session**

Trends in frontline PARP inhibitor maintenance in advanced epithelial ovarian cancer across the United States. *First Author: Erica Huelsmann, Fox Chase Cancer Center, Philadelphia, PA*

Background: Advanced epithelial ovarian cancer (AEOC) is the fifth commonest cancer mortality among women in the United States. Despite 80% initial treatment response, most recur within two years and succumb from disease. Prolonging disease free interval with maintenance therapy is of interest. Options include Poly-(ADP) ribose polymerase inhibitors (PARPi's) and Bevacizumab, an anti-angiogenesis agent; eligibility criteria are based on clinical trials. Here we examine national approach to front line maintenance therapy following treatment in AEOC with focus on PARPi use. **Methods:** Protocol for data collection was IRB approved and institutional IRB approved. A retrospective, observational cohort study using Flatiron Health electronic health record (EHR)-derived, de-identified database patients diagnosed with AEOC between March 2017-June 2020, following FDA approval of PARPi use in AEOC. Demographics were summarized using descriptive statistics by use of maintenance treatment, and associations were tested using ANOVA and Chi-squared tests. Trends in use and type of maintenance therapy were summarized by year. Time trends assessed by Cochran–Armitage tests. **Results:** 1196 patients met inclusion criteria: Age>18, Stage III-IV, 90-day gap rule, systemic therapy after diagnosis. Majority were >65, White, Stage III with ECOG 0 at diagnosis. Only 31.6% of patients received maintenance after frontline therapy. Single agent PARPi was most used (12.9%), and Olaparib was most used PARPi (57%). Use of maintenance therapy significantly differed by ECOG value at diagnosis (p=.005), region of practice (p=.003), use of surgery (p=<.001) and extent of debulking (p=.002). Maintenance therapy was used more often when ECOG low at diagnosis, optimal debulking achieved and with treatment in the Southern US. Maintenance therapy significantly increased by year (p=<0.001); highest in 2020 (46.9%). Type of maintenance therapy had a significantly different trend by year with PARPi becoming more common (p=<.001). **Conclusions:** Despite known high rates of response to maintenance PARPi and increased use over time, less than 50% of patients with AEOC receive this regimen. Reasons for low adoption of maintenance PARPi in this population with poor prognosis deserves further investigation. Olaparib, approved for single use in BRCA mutation carriers in the front-line maintenance setting was used more often than Niraparib, approved for all comers. Research Sponsor: IVV Young Investigator Pilot Project.

Trends in use of maintenance therapy.

Any maintenance therapy	2017	2018	2019	2020
Yes (N=366)	26 (18.2%)	60 (17.3%)	134 (37.7%)	146 (46.9%)
No (N=789)	117 (81.8%)	286 (82.7%)	221 (62.3%)	165 (53.1%)
P-value				< 0.0011
Maintenance Type				
Bevacizumab only (N=117)	8 (30.8%)	23 (38.3%)	58 (43.3%)	28 (19.2%)
PARPi only (N=147)	7 (26.9%)	17 (28.3%)	50 (37.3%)	73 (50.0%)
Other maintenance (N=102)	11 (42.3%)	20 (33.3%)	26 (19.4%)	45 (30.8%)
P-value (bevacizumab vs PARPi)				< 0.0011

5582 **Poster Session**

Bevacizumab combined with platinum-based chemotherapy in patients with primary or relapsed ovarian cancer: Meta-analysis and literature review. *First Author: Faith Abodunrin, Department of Internal Medicine, Creighton University School of Medicine, Omaha, NE*

Background: Epithelial ovarian cancer has the highest mortality rates among all gynecological malignancies and is the fifth leading cause of cancer-related deaths in females. Previously, the treatment of ovarian cancers included cytoreductive surgery in combination with platinum-based chemotherapy. While this treatment regimen initially resulted in a good response, most of the patients subsequently relapsed. Given the role of Vascular Endothelial Growth factor (VEGF) and angiogenesis in the progression of ovarian cancer, VEGF inhibitors such as Bevacizumab were considered in the treatment of advanced or relapsed ovarian cancer patients. We conducted a meta-analysis to compare the efficacy of Bevacizumab with platinum-based chemotherapy to platinum-based chemotherapy. **Methods:** A thorough systematic literature review identified five eligible studies reporting the efficacy of bevacizumab with platinum-based chemotherapy in the treatment of advanced or recurrent Ovarian cancer as compared to control group receiving platinum-based chemotherapy alone. These studies were randomized Phase III clinical trials, one of which was recently published in 2021. Summary estimates of the clinical endpoints were calculated with risk ratio (RR) and 95% confidence intervals using the random-effects model. Heterogeneity between studies was examined with COCHRAN'S Q based 12 statistics. The primary endpoint was progression free survival at 12 months while secondary endpoints were overall survival and certain adverse effects. **Results:** Our pooled analysis from the five studies included 4,648 patients. 2,641 were in the Bevacizumab and platinum-based treatment group while 2007 patients in sole-platinum based chemotherapy group. There was a statistically significant difference in primary outcome of progression free survival at 12 months was noted (RR = 1.56 (95% CI: 1.09 to 2.24; p = 0.020). 33,4% of patients in the treatment group as compared to 22.9% observed in the control group attained PFS at 12 months. The secondary outcome of overall survival at 12 months was seen in 76.7% patients in treatment group as compared to 73.02% observed in control group. This was no statistically significant difference in this case (RR = 1.04 (95% CI: 0.96 to 1.12; p = 0.34). Adverse effects including hypertension, proteinuria, arterial and venous thromboembolism, posterior reversible leukoencephalopathy syndrome occurred more frequently in the treatment group. **Conclusions:** Results from our meta-analysis support the superiority of Bevacizumab with platinum-based chemotherapy over platinum-based chemotherapy with regards to PFS. However, the OS benefit remains questionable. Research Sponsor: None.

5583 **Poster Session**

Dysfunctional CD8+ T cells in the tumor microenvironment are associated with response to nivolumab in mismatch repair deficient (dMMR) or hypermutated ovarian (OVCA) or endometrial cancer (EC). *First Author: Claire Frances Friedman, Memorial Sloan Kettering Cancer Center and Weill Medical College at Cornell University, New York, NY*

Background: EC and a subset of OVCA are associated with high rates of dMMR and are responsive to PD-1 blockade. It is unknown what additional biomarkers beyond dMMR may enrich for benefit in these patients (pts). **Methods:** This was an investigator-initiated, single-arm, phase II study. Eligible pts had recurrent EC or OVCA that met one of the following criteria: 1) dMMR, as determined by immunohistochemical loss of expression of 1+ MMR genes; 2) MSI-H, as determined by next generation sequencing (MSK-IMPACT); or 3) hypermutated, defined as 20+ non-synonymous somatic mutations. Pts received nivo 240mg IV every 2 weeks or 480mg IV every 4 weeks until toxicity or progression. The co-primary endpoints were 1) the progression-free survival (PFS) rate at 24 weeks (PFS24) and 2) the objective response rate (ORR) by RECIST v1.1. The study was designed using Simon's two-stage design, with a sample size of 40 pts based on a promising ORR of 25% with a type I error rate of 0.025 and a type II error rate of 0.05. Overall survival (OS), PFS and duration of response (DOR) were calculated using the method of Kaplan-Meier. Adverse events (AEs) were graded per CTCAE and tabulated. Biomarker analyses on the available archival tissue were performed using multiplex immunofluorescence (mIF) labeling for CD8, PD-1, TOX, PD-1, PD-L1, and FoxP3. Quantification of immune phenotypes and interaction studies between CD8+ T cells and PD-L1+ cells was performed in HALO. **Results:** Between 9/2017 and 5/2021, 35 pts were enrolled; the study closed early due to slow accrual. The median duration of follow-up was 33.2 months. The median age was 64 years (range 36-87); 82% of pts were white, 54% had high grade EC, and 65% had confirmed MLH1 hypermethylation. The ORR was 57.1% (97.5% CI 39.4-100%) [37% PR, 20% CR]. The PFS24 was 62.9% and median PFS was 26.7 months (95% CI 4.9-NE). Neither median DOR nor OS was reached. OS at 1 year was 76.4% (95% CI 58.2-87.4%). The ORR in patients with MLH1 hypermethylation was 52%; 4 of 5 patients with confirmed germline MMR alterations had a response by RECIST. AEs were consistent with the reported literature. Notable treatment related AEs included Grade 4 myocarditis with associated grade 4 AV block, grade 2 extraocular paresis, grade 3 Type 1 diabetes mellitus, and grade 3 elevations in AST/ALT. On mIF analysis, PD-L1 expression did not distinguish responders from non-responders, though interaction between $CD8^+$ T cells and $PD\text{-}L1^+$ cells was associated with CR/PR. Increase in relative fraction of dysfunctional $CD8^+$ T cells (characterized by $CD8^+TOX^+PD\text{-}1^+$ phenotype) was also associated with CR/PR. **Conclusions:** Nivo is an effective and tolerable treatment option for patients with MMR-D/MSI-H or hypermutated EC or OVCA. Presence of dysfunctional $CD8^+$ T cells in the tumors was associated with response, while expression of PD-L1 was not predictive. Clinical trial information: NCT03241745. Research Sponsor: Stand Up to Cancer, Pharmaceutical/Biotech Company.

5584 **Poster Session**

Clinicopathologic and molecular features associated with response to anti-HER2 therapy in endometrial cancer. *First Author: Sherry Shen, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Endometrial cancer (EC) is the most common gynecologic malignancy in the United States. Human epidermal growth factor 2 (HER2) overexpression or gene amplification occurs in 10-60% of EC. The addition of trastuzumab to carboplatin-paclitaxel chemotherapy improves survival in women with HER2-positive serous EC. However, criteria for assessment of HER2 status in EC are not standardized, and furthermore, intratumor heterogeneity may impact therapeutic efficacy. We aimed to identify factors associated with treatment response and survival outcomes in a retrospective cohort of ECs treated with anti-HER2 therapy. **Methods:** Patients with advanced/recurrent EC treated with trastuzumab or trastuzumab emtansine alone or in combination with chemotherapy from 2013-2021 at our institution were identified. Clinical and treatment information were retrieved from medical records. Central pathology review, HER2 immunohistochemistry (IHC) and fluorescence in-situ hybridization (FISH) were performed. HER2 IHC was scored using modified ASCO/CAP 2007 guidelines for breast cancer. HER2 expression heterogeneity was defined as a 2-degree difference in staining intensity in ≥5% of tumor cells or discordant IHC score on different specimens. *HER2* amplification (tumor/normal fold change) was also estimated from targeted next-generation sequencing (NGS). Best response was assessed by RECIST v1.1 as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD), with clinical benefit defined as CR/PR/SD. **Results:** Among 39 patients included, median age was 69. Histologic subtypes included serous (n = 18, 46%), carcinosarcoma (n = 7, 18%), high-grade EC with ambiguous features (n = 13, 33%) and low-grade endometrioid carcinoma (n = 1, 3%). HER2 IHC results were 0 or 1+ (n = 2, 5%), 2+ (n = 17, 46%), 3+ (n = 18, 49%), with HER2 heterogeneity in 15 cases. By FISH, the HER2/CEP17 ratio was ≥2.0 in 34 (92%) and < 2.0 in 3 (8%); HER2 copy number (CN) was ≥6.0 in 25 (68%) and < 6.0 in 12 (32%). HER2 copy number ≥6.0 was significantly correlated with *HER2* amplification by NGS (p< 0.001). 18 (49%) patients had a co-existing somatic *PIK3CA* mutation. Amongst parameters assessed, only higher level of *HER2* amplification by NGS was significantly associated with clinical benefit (p= 0.036). None of these features were associated with progression-free survival. Notably, 2 patients with IHC 0/1+ had PD and 1 patient with IHC 3+, but non-amplified by FISH, achieved PR. **Conclusions:** In our cohort of EC patients treated with anti-HER2 therapy, higher level of *HER2* amplification was associated with clinical benefit. Further studies with larger sample sizes are needed to determine whether any additional characteristics are associated with treatment response and survival. Research Sponsor: None.

5585 **Poster Session**

Outcomes of recurrent and metastatic endometrial cancer (RMEC) treated with systemic progestins. *First Author: Anjali Kulkarni, Ottawa Hospital Research Institute, Ottawa, ON, Canada*

Background: Recurrent endometrial cancer has a poor prognosis with limited treatment options. Systemic therapy for RMEC includes chemotherapy, immunotherapy and hormonal therapy. Although studies on hormonal therapy have described modest results, agents such as megestrol acetate (megace) continue to be used mainly for low grade, ER+/PR+ve tumors in the advanced and recurrent setting. Overall response rates have been reported in the range of 20-25% with responses up to 25-35% in ER+/PR+ve tumors. Despite comparative response rates to chemotherapy, the use of hormonal therapy in clinical trials in RMEC is hampered by a lack of clear progression-free survival (PFS) data. The primary objective of this study is to determine the PFS in RMEC patients treated with progestins. **Methods:** A retrospective chart review on RMEC was conducted at The Ottawa Hospital with data sourced from medical records. Main inclusion criteria were a diagnosis of RMEC between 2000 and 2019, endometrioid histology, and ≥1 one line of progestin treatment. PFS was the time from initiation of progestin therapy until progression of disease (PD) by imaging, biopsy or death. Overall survival (OS) was the time from initiation of progestins until death. Median time to PFS and OS were estimated using the Kaplan-Meier method and compared using a Log-rank Test with 95% confidence interval (CI). **Results:** Of 2342 cases reviewed, 75 met inclusion criteria. The mean age at the time of primary diagnosis was 66.7 years and the range of follow-up was 1-199 months (mo). Sixty-six (88.0%) patients received megestrol acetate and 9 (12.0%) received a progestin alternative. The distribution of all patients by grade was: 1: 25 (33.3%), 2: 30 (40.0%) and 3: 20 (26.7%). The median PFS for all patients with grade 1 and 2 RMEC was 15.7 mo (95% CI: 8.0, 19.5), compared to 5.0 mo (3.0, 23.0) for grade 3 disease (p=0.28). The median OS for all patients with grade 1 and 2 versus grade 3 RMEC, was 25.9 mo (15.3, 40.3) versus 12.5 mo (5.7, 35.9), respectively (p=0.12). The number of patients treated with 0 and ≥1 line of chemotherapy was 34 (45.3%) and 41 (54.7%). The median PFS for patients who were naïve to chemotherapy was 17.9 mo (14.3, 27.0), compared to 6.2 mo (3.9, 14.8) for patients who had received ≥1 prior lines of treatment (p=0.09). The median OS was 29.1 mo (17.9, 61.1) for patients who were naïve to chemotherapy, versus 23.0 mo (10.5, 37.6) for patients who were previously exposed (p=0.64). **Conclusions:** This real-world data suggests that progestins for RMEC have comparable outcomes to other systemic therapies in chemotherapy-exposed patients. Progestins such as megestrol acetate may be considered in the design of RMEC clinical trials. Research Sponsor: AstraZeneca.

5586 **Poster Session**

The ENSURE trial for women with low-risk, early-stage endometrial cancer: A randomized controlled trial comparing the effect of a reduced (4 visits/3 yr) versus usual (8-11 visits/3 yr) follow-up schedule on patient satisfaction, health care use, and disease perception. *First Author: Lonneke V van de Poll-Franse, Division of Psychosocial Oncology and Epidemiology, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: Research suggests that most early-stage endometrial cancer patients do not need intensive follow-up to detect recurrences, improve survival, or discuss consequences of treatment. However, a minimal number of follow-up visits is needed to support necessary patient counselling and information provision. The aim of the ENSURE (ENdometrial cancer SURvivors' follow-up carE) trial was to compare, for three years after diagnosis, satisfaction with care between women who received reduced follow-up (FU) care (4 visits) and women who received usual FU care according to the Netherlands guideline (8-11 visits). **Methods:** In this multicenter non-inferiority trial from the Netherlands, 316 women from 42 hospitals with FIGO stage IA/B low-risk endometrial cancer were randomized after treatment. Women allocated to reduced FU (n = 160) and usual FU (n = 156) completed questionnaires at baseline (after surgery), and after 6, 12 and 36 months. The primary outcome was satisfaction with FU care (Patient Satisfaction Questionnaire III total scale: PSQ-III). The predefined noninferiority margin was 6 points. Mixed linear regression and intention-to-treat analyses were used. Secondary outcomes were health care utilization, disease perception (Brief Illness Perception Questionnaire: BIPQ) and cancer recurrence. **Results:** 299 (95%) women completed the questionnaire at baseline; 291 (92%) at 6-months; 272 (86%) at 12 months and 222 (70%) at 36 months. Overall satisfaction with care was similar in the reduced FU (average 82; SD = 15) and usual FU (average 80; SD = 15) group. At 6, 12 and 36 months, more women (93%, 94% and 90%) in the reduced FU group were satisfied with their FU schedule than patients in usual FU group (79%, 79% and 82%; p < 0.001; p < 0.001; p = 0.050). During three years of FU care, women in the reduced FU group had an average of 3.8 (SD = 1.5) visits with their specialist/nurse compared to 6.8 (SD = 2.4) visits for women in the usual FU group. We observed a non-significant trend of less severe disease perception in patients in the reduced vs. the usual FU group: impact on life (M = 1.8; SD = 2.2 vs. M = 2.5; SD = 2.8); concern about disease (M = 1.5; SD = 2.1 vs. M = 2.3; SD = 2.9); emotional impact (M = 1.4; SD = 2.1 vs. M = 2.2; SD = 2.9). Nine women in the reduced FU group and five in the usual FU group developed a recurrence within three years after diagnosis (n.s.). **Conclusions:** Women with low-risk, early-stage endometrial cancer receiving reduced follow-up care were just as satisfied with their care as those women receiving follow-up care according to Netherlands guidelines. Compared with usual care, women in the reduced care group had fewer medical visits and, at the same time, more often reported being satisfied with this reduced frequency. Clinical trial information: NCT02413606. Research Sponsor: Dutch Cancer Sciety.

5587 **Poster Session**

Efficacy of next line of therapy after treatment with lenvatinib (LEN) in combination with pembrolizumab (pembro) versus treatment of physician's choice (TPC) in patients (pts) with advanced endometrial cancer (aEC): Exploratory analysis of Study 309/KEYNOTE-775. *First Author: Vicky Makker, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: In the multicenter, open-label, randomized, phase 3 Study 309/KEYNOTE-775, LEN + pembro had significant PFS and overall survival benefits, and improved objective response rate vs TPC in pts with aEC following systemic platinum-based treatment (Makker 2022, *NEJM*). These results were seen in all-comer pts and in pts with DNA mismatch repair proficient (pMMR) disease. Here, we assessed PFS on next line of therapy (PFS2) of each arm. **Methods:** Pts with aEC and 1 prior platinum-based chemotherapy regimen (or up to 2 if 1 was given in neoadjuvant/adjuvant setting) were randomized (1:1) to receive LEN 20 mg orally QD + pembro 200 mg IV Q3W or TPC (doxorubicin at 60 mg/m^2 IV Q3W or paclitaxel at 80 mg/m^2 IV QW [3 weeks on; 1 week off]). Randomization was stratified by MMR status (determined centrally); pts with pMMR tumors were further stratified by Eastern Cooperative Oncology Group performance status, geographic region, and history of pelvic radiation. In this prespecified exploratory analysis, PFS2 (defined as the time from randomization to disease progression on next line of treatment or death, whichever came first) was analyzed per investigator assessment in the pMMR and all-comer populations. **Results:** 827 Pts (pMMR, n=697; MMR deficient [dMMR], n=130) were randomized to LEN + pembro (n=411) or TPC (n=416). At data cutoff (October 26, 2020), 567 pts (LEN + pembro, n=282; TPC, n=285) had discontinued study treatment and 315 (LEN + pembro, n=115; TPC, n=200) had received a subsequent systemic anticancer therapy (Table): most commonly doxorubicin (n=58) in the LEN + pembro arm and paclitaxel (n=57) in the TPC arm. Median PFS2 was longer in the LEN + pembro arm vs the TPC arm in the pMMR population (14.4 vs 9.8 mo; HR 0.62, 95% CI 0.50–0.75) and in the all-comer population (16.0 vs 9.5 mo; HR 0.56, 95% CI 0.46–0.67). Additionally, the PFS2 rate at 6 months favored LEN + pembro vs TPC in the pMMR population (82.0% vs 74.8%) and in the all-comer population (81.7% vs 72.5%). **Conclusions:** Clinically meaningful improvements in PFS2 were seen in the LEN + pembro group compared with TPC in pMMR and all-comer pts. Clinical trial information: NCT03517449. Research Sponsor: Eisai Inc., Nutley, NJ, USA, and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co. Inc., Kenilworth, NJ, USA.

	pMMR		All-comers	
	LEN + pembro (n = 346)	TPC(n = 351)	LEN + pembro (n = 411)	TPC(n = 416)
Subsequent anticancer therapy, n (%)	109 (31.5)	176 (50.1)	115 (28.0)	200 (48.1)
Chemotherapy	92 (26.6)	119 (33.9)	97 (23.6)	129 (31.0)
VEGF/VEGFR inhibitor	10 (2.9)	43 (12.3)	10 (2.4)	46 (11.1)
PD1/PD-L1 checkpoint inhibitor	4 (1.2)	42 (12.0)	4 (1.0)	53 (12.7)
2 Subsequent therapy lines	81 (23.4)	134 (38.2)	85 (20.7)	152 (36.5)
≥3 Subsequent therapy lines	55 (15.9)	78 (22.2)	58 (14.1)	85 (20.4)
Median PFS2, mo (95% CI)	14.4 (12.1-17.3)	9.8 (8.7-11.1)	16.0 (13.0–19.5)	9.5 (8.6–10.7)
PFS2 HR (95% CI); *P*-value	0.62 (0.50–0.75); <0.0001		0.56 (0.46–0.67); <0.0001	

5588 **Poster Session**

HER2 in endometrioid endometrial adenocarcinoma (E-EMCA): Defining incidence, molecular profiles, and outcomes. *First Author: Shaina F. Bruce, Washington University School of Medicine, Saint Louis, MO*

Background: Immunohistochemistry (IHC) for HER2 in E-EMCA is not standard of care. We aimed to establish the correlation of HER2 transcript to IHC expression in the much more frequently tested uterine serous carcinoma (USC). We applied the threshold calculated in USC to E-EMCA and compared molecular and immune profiles among HER2+ and HER2- E-EMCA tumors, which may affect response to targeted therapy. **Methods:** 1462 E-EMCA tumors were analyzed using next-generation sequencing (592, NextSeq; WES, NovaSeq), WTS (NovaSeq) (Caris Life Sciences, Phoenix, AZ). PD-L1 was tested by IHC (SP142, >1%). Microsatellite instability (MSI) was tested by FA, IHC and NGS. TMB was measured by totaling somatic mutations per tumor (TMB-H: >10 mutations/MB). LOH cut-off was > 16%. HER2+ cut-off by WTS was determined by Receiver Operator Characteristic (ROC) analysis in USC tumors by comparing to HER2 IHC/CISH results using 2018 Breast Cancer ASCO/CAP Guidelines. Immune cell infiltrates were calculated by Quantiseq. Real world overall survival (OS) was extracted from insurance claims data and calculated using Kaplan-Meier survival curves for molecularly defined cohorts. Significance was determined using chi-square and Wilcoxon rank sum test and adjusted for multiple comparisons (q-value < 0.05), $p < 0.05$ but $q > 0.05$ was considered a trend. **Results:** We determined a cut-off of > 62.99 TPM for HER2+ with a sensitivity of 81.5%, specificity of 87.6% and AUC of 0.92 in Uterine Serous. When this cut-off is applied to E-EMCA, 76 of 1462 (5.2%) E-EMCA tumors were HER2+. HER2+ tumors had fewer mutations (mt) in *PI3KR1*, *PTEN* and *CTNNB1* but higher mts in *TP53* and more frequent LOH (q < 0.05). HER2+ tumors had a trend towards decreased MSI-H status (22.4% vs 39.1%; $p = 0.003$, $q = 0.058$) and TMB-H (25.4% vs 41.5%; $p = 0.007$, $q = 0.084$). MSS HER2+ E-EMCA had a similar mutational profile compared to all HER2+ tumors; MSI-H HER2+ E-EMCA had a trend towards higher DDR pathway gene mts compared to MSI-H HER2- EMCA tumors. HER2+ tumors had increased Dendritic cell (3.84% vs 2.97%) but decreased Neutrophil (2.66% vs 5.20%) and T-reg (1.38% vs 2.07%) infiltration (q < 0.01). HER2+ tumors had higher immune checkpoint gene expression of *CD80, HAVCR2* and *PDCD1LG2* (q < 0.01), and increased T-cell inflamed and MAPK activation score (q < 0.01). MSS HER2+ E-EMCA tumors had a similar immune profile when compared to all HER2+ tumors; MSI-H HER2+ E-EMCA tumors had increased Treg infiltration and MAPK activation score. Median OS was significantly worse for HER2+ pts compared to HER2- (64.3 vs. 23.6 months, HR: 1.93(1.32-2.80), $p < 0.001$). **Conclusions:** Using a WTS cutoff from USC, we found 5% of E-EMCA are HER2+ and showed distinct molecular and immune profile compared to HER2- tumors. HER2+ confers a worse OS compared to HER2- tumors. Furthermore, HER2+ tumors demonstrate an immune hot phenotype suggesting that immunotherapy may be a potential therapeutic option. Research Sponsor: None.

5589 **Poster Session**

A phase II trial of IDO-inhibitor, BMS-986205 (IDO), and PD-1 inhibitor, nivolumab (NIVO), in recurrent or persistent endometrial cancer (EC; CA017-056). *First Author: Chrisann Kyi, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Indoleamine 2,3-dioxygenase 1 (IDO1) allows tumor escape through kynurenine production, which induces regulatory T cells and suppresses effector T-cell proliferation. NIVO, an anti-PD-1 inhibitor can upregulate IDO1, supporting the rationale for combining NIVO with IDO. We report results of NIVO as monotherapy and in combination with IDO inhibitor BMS-986205 in the treatment of pts with recurrent EC. **Methods:** In this single-institution, randomized phase 2 study, eligible pts must have received 1-4 prior lines of chemotherapy and have measurable disease by RECIST v 1.1. All EC histologies, including carcinosarcoma, were allowed. Pts with microsatellite insufficient (MSI-H) or mismatch repair (MMR)-deficient tumors were excluded. Pts were randomized to NIVO 480mg IV every 4 weeks (wks) with or without IDO 100mg orally daily. Primary endpoints were Overall Response Rate [ORR = Complete Response (CR) + Partial Response (PR)] by RECIST v 1.1. Secondary objectives were duration of response (DOR), median progression free survival (mPFS), PFS rate at 24 wks (PFS_{24wks}) and safety. Overall survival (OS) was also evaluated. **Results:** Between 10/2019 and 11/2021, pts were randomized to receive either NIVO (n = 12) or NIVO + IDO (n = 12). Median age was 67 years (range 48-82) and median number of prior lines of therapy was 2 (range 1-3). Histologies included serous (n = 5, 21%), endometrioid (n = 10, 42%), clear cell (n = 1, 4.2%), carcinosarcoma (n = 6, 25%), undifferentiated (n = 1, 4.2%), and mucinous (n = 1, 4.2%). In the NIVO + IDO arm, 1 pt achieved partial response (8.3%, CI: 0.9-100%) with DOR of 17.6 months. In the NIVO arm, no responses were observed. Efficacy outcomes are summarized in the table. Treatment-related adverse events (TRAEs) grade ≥ 3 in the NIVO arm included acute kidney injury (n = 1, 8.3%), hypokalemia (n = 1, 8.3%), and thromboembolic event (n = 1, 8.3%). In the NIVO + IDO arm, TRAEs grade ≥ 3 included fatigue (n = 1, 8.3%), and elevated liver function (n = 1, 8.3%). No TRAEs led to study-drug interruption or dose reductions. **Conclusions:** NIVO monotherapy and in combination with IDO showed acceptable safety in pts with recurrent EC. NIVO in combination with IDO showed ORR of 8.3%. No responses were observed with NIVO monotherapy. The trial closed to accrual due to lack of observed clinical efficacy. Clinical trial information: NCT04106414. Research Sponsor: Bristol-Myers Squibb.

Arm	Evaluable (N)	ORR	DOR (months)	mPFS (wks)	PFS at 24wks	mOS	OS at 24wks
NIVO alone	12	0%		7.3(6.4-15.1)	16.7% (5.8-32.3%)	27.5(17-NE)	58.3% (38.2-74%)
NIVO + IDO	12	8.3% (0.9-100%)	17.6	12.3(4.1-22.1)	25% (11.1-41.8%)	Not Reached	66.7% (46.2-80.8%)

Primary objective ORR is reported as 1-sided 90% CI. All other secondary objectives are 2-sided 80% CI per protocol.

5590 **Poster Session**

HER2 in uterine carcinosarcoma: Testing platforms and implications for targeted therapy. *First Author: Navin Maredia, University of Minnesota, Minneapolis, MN*

Background: Uterine carcinosarcomas (UCS) are rare, aggressive tumors accounting for 5% of all uterine cancers. Recurrence rates are high and 5-year survival is only 18-39%. HER2 is an emerging prognostic and therapeutic target in uterine cancer including UCS. Testing algorithms and platforms in breast and gastric cancers are well studied and validated, but optimal HER2 testing in uterine cancer is not yet established. We aimed to determine HER2 prevalence in UCS and the concordance of chromogenic in situ hybridization (CISH), immunohistochemistry (IHC), and next generation sequencing (NGS) platforms to aid in the development of UCS specific testing guidelines. We also evaluated the rate of downstream mutations and immune biomarkers that may affect response to HER2 directed therapy. **Methods:** Eight hundred and seventy-five UCS tumor samples (primary 81.4%; metastatic 17.1%; unknown 1.5%) were analyzed using NGS (592, NextSeq; WES, NovaSeq, Caris Life Sciences, Phoenix, AZ). A subset of tumors with HER2 positivity were tested with IHC (4B5, Ventana) and/or CISH (INFORM DUAL HER2 ISH Assay, Ventana) based on 2018 ASCO/CAP HER2 Breast Cancer guidelines. Amplification of ERBB2/HER2 by NGS used a copy number cut-off >6. PD-L1 expression was analyzed by IHC (SP142, positive cut-off ≥1%, Ventana). Tumor mutational burden (TMB) was measured by counting all somatic mutations found per tumor (TMB high cut-off > 10 mutations per Mb). Microsatellite instability (MSI) was tested by fragment analysis (FA), IHC and NGS. **Results:** Rates of HER2 positivity were 3.4% (28/820) by NGS. Among the IHC/CISH-tested cohort, 7.2% was positive (10/139) by IHC, and 19.5% (27/133) by CISH. In the 105 samples tested with both IHC and CISH, the concordance was 100%. Specifically, 9/105 patients (8.6%) were IHC+/CISH+ and 96 patients (91.4%) were IHC-/CISH-. The concordance between CISH and NGS (N = 127) was 90.6% (sensitivity 100% and specificity 89.3%). Common gene alterations in CISH HER2+ UCS tumors that may implicate resistance to HER2 targeted therapy included mutations in *TP53* (100%), *FBXW7* (22.2%), *PIK3CA* (33.3%), *PIK3R1* (18.5%), *PTEN* (3.7%) and *KRAS* (3.7%) and gene amplification of *KRAS* (11.1%). CISH+ HER2+ UCS tumors had low immunotherapy biomarker prevalence (0% MSI-H, 0% TMB high, 7.7% PD-L1+). **Conclusions:** Increased HER2 positivity was detected via CISH testing compared to IHC and NGS, which may reflect the heterogeneity of HER2 amplification due to mixed histology between the sarcoma and carcinoma portion of the tumor. High concordance rates were observed between CISH and IHC. These testing platforms need to be validated by response to HER2 targeted therapies in order to develop UCS specific testing guidelines. Research Sponsor: None.

5591 **Poster Session**

Camrelizumab plus apatinib in patients with advanced or recurrent endometrial cancer after failure of at least first-line therapy: Interim results of a single-arm phase II trial. *First Author: Huaying Wang, Department of Gynecologic Oncology, Fudan University Shanghai Cancer Center; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China*

Background: For advanced or recurrent endometrial cancer (EC), therapeutic options remain scarce. Immune or antiangiogenic monotherapy has shown moderate efficacy in EC. Preclinical and clinical data showed that camrelizumab (an anti-PD-1 antibody) plus apatinib (a selective VEGFR2 inhibitor) markedly enhanced anti-tumor efficacy in multiple solid tumors. This study was designed to assess the efficacy and safety of the combination of camrelizumab and apatinib as second-line or above therapy for advanced or recurrent EC. **Methods:** This was an open-label, single-arm, phase II trial conducted in China. Patients with advanced or recurrent EC who progressed after at least first-line therapy received camrelizumab (200 mg, intravenously, q2w) plus apatinib (250 mg, orally, qd). Using a minimax Simon two-stage design, 21 patients were enrolled at stage I and if a complete or partial response was observed in at least four patients, the enrollment would be continued to 40 patients. The primary endpoint was the objective response rate (ORR) per RECIST version 1.1. Secondary endpoints included time to objective response (TTR), disease control rate (DCR), duration of Response (DoR), progression-free survival (PFS), overall survival (OS), time to treatment failure (TTF) and safety. Here, the results of stage I are reported. **Results:** Between January 20, 2020 and July 8, 2021, 21 patients were enrolled. The median age was 57 years (range 29–72). Thirteen patients (61.9%) had ECOG PS of 0, and eight patients (38.1%) received at least two prior therapies. As of November 9, 2021, the median follow-up time was 13.5 months (IQR 11.3-16.3). Among 21 evaluable patients, the confirmed ORR was 47.6% (95% CI 25.7%-70.2%) with complete response in one patient (4.8%) and partial response in nine patients (42.9%); eight patients had stable disease for a DCR of 85.7% (95% CI 63.7%-97.0%). The median PFS was 11.8 months (95% CI 5.2-14.4). Treatment-related adverse events (TRAEs) of any grade and of grade ≥ 3 were reported in 21 (100%) patients and 10 (47.6%) patients, respectively. The most common grade ≥ 3 TRAEs included gamma-glutamyltransferase increased (six [28.6%]), direct bilirubin increased (four [19.0%]), alanine aminotransferase increased (three [14.3%]), aspartate aminotransferase increased (three [14.3%]) and hyperglycaemia (three [14.3%]). Four patients (19.0%) experienced reactive cutaneous capillary endothelial proliferation, all of which were grade 1-2. No treatment-related deaths were reported. **Conclusions:** Camrelizumab plus apatinib demonstrated promising antitumor activity and a manageable safety profile in patients with advanced or recurrent EC after failure of at least first-line therapy. Clinical trial information: ChiCTR2000031932. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

5592 **Poster Session**

Cell-free DNA analysis as a molecular tool to monitor response to immune checkpoint inhibition in endometrial cancer. *First Author: Beryl Manning-Geist, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Immune checkpoint inhibitors (ICI) targeting PD-1 have meaningful activity in microsatellite instability high (MSI-H), hypermutated or mismatch repair deficient (dMMR) advanced endometrial cancer (EC). We investigated if high-depth circulating cell free (cf)DNA sequencing can be used to assess MSI status and monitor ICI response in EC patients enrolled in a phase II trial (NCT03241745). **Methods:** Patients with recurrent/persistent MSI-H/dMMR/hypermutated EC with measurable disease and ≥1 prior lines of cytotoxic therapy were treated from 06/2018-01/2022 with nivolumab until progression of disease (PD) or unacceptable toxicity. Radiologic tumor response was assessed every 12 wks by RECIST 1.1 criteria.Pre-treatment ECs and matched normal blood-derived DNA were subjected to whole-exome sequencing (WES); cfDNA from plasma at baseline, 2 wks and every 6 wks thereafter was subjected to high-depth MSK-ACCESS sequencing (129 genes). MSI in WES and cfDNA was calculated by MSIsensor and ADMIE, respectively. **Results:** Ten patients with ≥10 ng cfDNA at baseline and 2 weeks after nivolumab initiation were included. Most (80%) had grade 3 endometrioid EC; 70% had *MLH1* hypermethylated EC. Two patients had partial response (PR), 3 had stable disease (SD) and 5 had PD on nivolumab. A high-depth sequencing assay captured somatic mutations in cfDNA at baseline in all patients (median, 29.5; range, 2-75). Median circulating tumor (ct)DNA fraction in cfDNA was 13.1% at baseline (range, 0.0-86.0%). In 8 cases, ctDNA fraction was sufficient to perform MSI assessment. Liquid biopsy MSI status matched tumor MSI status assessed by WES: in 7 patients with MSI-H disease by tumor WES, cfDNA MSI status was also MSI-H (> 0; range, 0.21-5.46); in 1 patient with MSI-low but hypermutated tumor, cfDNA MSI was 0.0. In all cases, changes in ctDNA fractions reflected ICI response. Median ctDNA fraction percent change from week 0 to week 8 was -51.6% (IQR, -6.2, -85.1) in patients with PR and SD vs +17.7% (IQR, -6.6, +356.6) in patients with PD (p = 0.08). In patients with PR, ctDNA fraction decreased at week 2 and stayed low at week 8 and weeks 32-55 of nivolumab in concordance with ongoing response. In 3 patients with SD, ctDNA fractions decreased by week 2. In 1 patient with SD at week 8 and PD at week 22, ctDNA fraction increased from week 8 to week 20. In 5 patients with PD, 4 had increased ctDNA fraction by week 8. The last patient had a stable ctDNA fraction but increasing allele frequency of 2 truncating *B2M* alterations, possibly associated with ICI resistance. **Conclusions:** In patients with advanced hypermutated ECs, cfDNA sequencing can be used to accurately detect MSI status. Early changes in ctDNA fraction may be associated with durable response to ICI or may anticipate radiological progression. Future studies may use ctDNA to assess mechanisms of ICI resistance and offer opportunities for adaptive therapy intervention. Clinical trial information: NCT03241745. Research Sponsor: None.

5593 **Poster Session**

Survival outcomes for dostarlimab and real-world (RW) treatment (tx) paradigms in post-platinum patients (pts) with advanced/recurrent (A/R) endometrial cancer (EC): The GARNET trial versus an external control arm from the Flatiron Health database. *First Author: Robert L. Coleman, Texas Oncology, US Oncology Research, The Woodlands, TX*

Background: There are limited treatment options for pts with A/R EC progressing on or after platinum-based chemotherapy (PBCT) and their prognosis is poor. This study compared the efficacy of the anti-programmed death (PD)-1 antibody dostarlimab evaluated in the single-arm, Phase I GARNET trial with current RW tx. Overall survival (OS) of pts with A/R mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) EC receiving dostarlimab in Cohort A1 of the GARNET trial was compared with an equivalent RW cohort receiving non-anti-PD-(ligand [L])1 tx. **Methods:** The dostarlimab arm was the GARNET (Cohort A1) dMMR/MSI-H EC safety population. For the external control arm, a RW cohort was constructed using the Flatiron Health database and aligning eligibility criteria with those for GARNET, including pts with A/R EC, Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤1, who had received ≤2 lines of chemotherapy (≥1 line PBCT) and no anti-PD-(L)1 therapy. GARNET pts who received anti-PD-(L)1 therapy following dostarlimab (n=5/129) were excluded. Inverse probability of tx weighting (IPTW) was performed based on propensity scores constructed from key prognostic factors identified by literature review and clinical experts. With IPTW, Kaplan–Meier curves were created, OS rates estimated, and adjusted hazard ratios (HR) estimated by a Cox regression model. MMR/MSI status, only partially available in Flatiron and considered not significantly prognostic for OS as per a recent meta-analyses, was not included in the IPTW. **Results:** Baseline characteristics for GARNET (N=124) and RW (N=185) after IPTW are shown in the Table. Dostarlimab was associated with a 44% lower risk of death compared with RW tx (OS HR [95% confidence interval {CI}] 0.56 [0.385–0.812]; p=0.002) (see Tablefor median OS). Survival rates (95% CI) were higher for dostarlimab than RW tx at 12 months (mos) (72% [57%–82%] vs 51% [43%–59%]), 18 mos (57% [41%–70%] vs 40% [32%–48%]), and 24 mos (53% [37%–67%] vs 34% [26%–42%]). **Conclusions:** These results indicate that pts with A/R EC receiving dostarlimab in the GARNET trial had significantly lower risk of death than those receiving current non-anti-PD-(L)1 tx in the RW. Research Sponsor: GlaxoSmithKline.

Baseline characteristic after IPTW (*included in model)	GARNET (N=124)	RW (N=185)
Age group at index, % ≥65 years	52.3	55.6
ECOG PS 1 (%)*	48.8	52.7
Tumor histology – endometrioid (%)*	69.1	61.9
International Federation of Gynecologic Oncology stage III/IV at diagnosis (%)	60.9	53.8
Tumor grade 3 at diagnosis (%)*	22.9	24.4
≥2 prior PBCTs in A/R setting (%)*	10.5	13.3
Outcome after IPTW		
Median OS, (95% CI), mos	NE (15.4–NE)	13.1 (8.3–15.9)

NE, not estimable.

5594 **Poster Session**

Identification of a novel subtype of endometrial cancer with unfavorable outcome using artificial intelligence-based histopathology image analysis. *First Author: Amirali Darbandsari, University of British Columbia, Vancouver, BC, Canada*

Background: Molecular subtyping of endometrial cancer (EC), unlike histopathological evaluation, offers an objective and reproducible classification system that has strong prognostic value and therapeutic implications. The Proactive Molecular risk classifier for Endometrial cancer (ProMisE) was developed by our team as a pragmatic, cost-effective, and clinically applicable molecular classifier for EC patients. ProMisE has four subtypes: (i) *POLE* mutant (*POLE*mut), (ii) mismatch repair deficient (MMRd), (iii) p53 abnormal (p53abn) by immunohistochemistry, and (iv) NSMP (No Specific Molecular Profile), lacking any of the defining features of the other three subtypes. While ProMisE subtypes are associated with clinical outcomes, within each subtype, there are clinical/prognostic outliers. This is particularly true within the largest ProMisE subtype; NSMP (representing ~50% of ECs), where a subset of patients experience a very aggressive disease course, comparable to what is observed in patients with p53abn ECs. **Methods:** We hypothesized that objective assessment of the digitized hematoxylin and eosin (H&E)-stained histopathology slides of the largest and most diverse EC subset, NSMP, could potentially identify clinical outcome outliers. As such, we developed an artificial intelligence (AI)-based image analysis model to identify the NSMP cases that had similar histopathological features to the p53abn subtype, as assessed by H&E stain. We used a discovery cohort of 182 and an external validation cohort of 195 NSMP ECs. **Results:** Our AI-based image analysis model, based on deep convolutional neural networks, identified 21 (11.5%) out of the 182 NSMP cases with similar histopathological features as p53abn cases. We refer to these cases as 'p53abn-like' NSMPs. Compared to the rest of the NSMP cases, these cases had markedly inferior disease-specific survival (DSS) (10-year DSS 58.9% vs. 93.1% (p<3.44e-8)) and progression-free survival (PFS) (10-year PFS 55.1% vs. 91.4% (p<3.76e-6)). These findings were confirmed in our validation cohort, with 10.7% of the 195 patients categorized as 'p53abn-like' tumors with 10-year DSS of 82% vs. 51.3% (p<5.28e-5) and PFS of 89.3% vs. 56.6% (p<2.15e-4). **Conclusions:** Utilizing an AI-based approach for histopathology image analysis, we have discovered 'p53abn-like' NSMPs, a novel subtype of NSMP ECs with morphological features similar to p53abn cases. 'p53abn-like' NSMPs exhibit similar clinical behavior as p53abn, having noticeably inferior outcome compared to the rest of the NSMP cases in two independent cohorts. These findings warrant further molecular investigation of this novel subtype of EC to identify the biological underpinning and future therapeutic strategies. Research Sponsor: CCSRI, MSFHR.

5595 **Poster Session**

Interaction of race and socioeconomic status as risk modulators of treatment delay and cancer-specific mortality in uterine cancer. *First Author: Larissa H Mattei, Wayne State University, Detroit, MI*

Background: The majority of studies of uterine cancer combine high and low-grade histologies and do not sample a diverse cohort of patients. In many studies race is treated as biologic construct, when it may be better thought of as a proxy for socioeconomic inequity and deprivation. Socioeconomic (SE) deprivation may play a significant role in the disease trajectory of women with uterine cancer. **Methods:** Data were drawn from the Metropolitan Detroit Cancer Surveillance System which covers a tri-county area of approximately 4 million people. We included non-Hispanic Black (NHB) and White (NHW) women diagnosed with uterine cancer between 2010 and 2018. Poorly differentiated and undifferentiated endometrioid, serous, clear cell, mixed, carcinosarcoma and mucinous histologies were considered high grade. Patients diagnosed by death certificate, or with unknown stage or histology were excluded. Socioeconomic status was assessed using the Yost Score, an area-level composite measure of socioeconomic deprivation derived from census-tract data at cancer diagnosis. Lower Yost quintile indicates higher deprivation. Competing risk analysis was used to determine risk of uterine cancer specific mortality (reported as subdistribution hazard ratio [SHR]) and to assess statistical interaction between race and Yost score. **Results:** A total of 4,840 patients were identified. Race conferred significant increased risk of cancer-specific mortality (SHR 2.11, $p < 0.0001$). Race and Yost score interacted to increase risk of cancer-specific mortality in NHB women in the lowest Yost quintile (SHR 2.23, $p < 0.0001$) compared to NHW and NHB women in the highest quintiles. The interaction between race and Yost score persisted only among women with low grade cancers (SHR 1.7, $p = 0.04$). Time from diagnosis to surgery increased as Yost score decreased. Women in the lowest Yost quintile had lower likelihood of receiving surgery within 6 weeks of diagnosis (OR 0.74, $p = 0.001$). This effect persisted among women with low grade cancer (NHB OR 0.75, $p = 0.014$; lowest Yost quintile OR 0.68, $p < 0.0001$). An association between race, Yost score and delays in time to surgery was not seen among women with high grade cancers. **Conclusions:** Race and Yost score, an area-based measure of socioeconomic deprivation, are associated with increased cancer-specific mortality risk among women with low grade cancer. NHB race and high socioeconomic deprivation are associated with delayed primary surgery. The interaction between race and socioeconomic deprivation may underlie known disparities in uterine cancer survival, particularly in low grade disease where there is the greatest opportunity for timely curative surgery. Research Sponsor: None.

5596 **Poster Session**

Biomarker associations of immune checkpoint inhibitor versus chemotherapy effectiveness in first-line metastatic endometrial carcinomas: A real-world study. *First Author: Alessandro Santin, Yale University School of Medicine, New Haven, CT*

Background: Limited evidence exists comparing outcomes of single-agent anti-PD1 immune checkpoint inhibitors (ICPI) vs. chemotherapy in the 1st line among metastatic endometrial carcinoma (mEC) patients. dMMR, MSI status, and Tumor Mutational Burden (TMB) have been characterized as predictive biomarkers of ICPI response in many solid tumors, including mEC. We sought to evaluate ICPI vs. chemotherapy effectiveness in 1st line mEC, stratified by TMB ≥ 10 mut/MB and MSI as assessed by next-generation sequencing. **Methods:** Following a prespecified analysis plan, this study used the nationwide (~280 US cancer clinics) de-identified, EHR-derived, Flatiron Health-Foundation Medicine mEC clinico-genomic database (FH-FMI CGDB), with tissue CGP between 1/2011 - 6/2021. Cohort inclusion criteria: recurrent mEC patients with stage I-III at original diagnosis, 1st line ICPI or platinum chemotherapy treatment with TMB and MSI assessments available. Adjusted hazard ratios (aHR) from multivariable Cox proportional hazard models were utilized for time to next treatment (TTNT) and overall survival (OS) comparisons between 1L chemotherapy and 1L ICPI from start of 1L treatment stratified by TMB (≥ 10 vs. < 10) and adjusted for ECOG, BMI, and stage at diagnosis. **Results:** Among the 1st line cohort, patients received either Chemotherapy (n = 139, 87%) or first-line ICPI (n = 20, 13%). While the overlap between the TMB ≥ 10 (n = 46) population and MSI-H (n = 39) populations was high, with 38/46 (83%) of TMB ≥ 10 classified as MSI-H and 38/39 (97%) of MSI-H with a TMB ≥ 10, there were also 8 (17%) TMB ≥ 10 patients who were MSS. TMB ≥ 10 was associated with more favorable TTNT (aHR: 0.11 [0.03 - 0.44]) and OS (aHR: 0.1 [0.01 - 0.82]) on single-agent ICPIs vs. chemotherapy; however, TMB < 10 patients exhibited no observed differences in TTNT (aHR: 1.66 [0.79 - 3.48]) or OS (aHR: 1.79 [0.66 - 4.8]) between treatments. MSI-H pts were associated with more favorable TTNT (aHR: 0.1 [0.02 - 0.39]) and OS (aHR: 0.1 [0.01 - 0.86]) on single-agent ICPIs over chemotherapy; however, MSS pts did not observe differences in TTNT (aHR: 1.5 [0.65 - 3.5]) or OS (aHR: 2.14 [0.63 - 7.26]) between ICPI vs. chemotherapy. **Conclusions:** Recurrent 1st line mEC patients with TMB ≥ 10 and/or MSI-H exhibit more favorable outcomes on single-agent ICPI than standard chemotherapy in real-world settings. These findings warrant prospective randomized validation. Future studies should assess the utility of a combined biomarker approach across TMB and MSI status to identify the broadest group of patients who might benefit from ICPI. Research Sponsor: Foundation Medicine.

5597 **Poster Session**

Impact of molecular features on outcome in African American or Black women with type 1 endometrial cancer. *First Author: Roy Khalife, Protean BioDiagnostics, Orlando, FL*

Background: Among women with endometrial cancer (EC), African American or Black (AAoB) population share a disproportionate burden of cancer deaths. Previous research exploring genetic and molecular explanations revealed White (W) women with EC are more likely to have mutations in PTEN, while AAoB women have higher rates of mutations in p53. However, these studies did not stratify EC by subtype, which occur at different rates among racial groups. Here, we aim to focus on molecular differences between racial groups, specifically in Type 1 EC (T1EC). **Methods:** Molecular data from TCGA Uterine Corpus Endometrial Carcinoma datasets on cBioPortal was used. Cancer type was filtered to Uterine Endometrioid Carcinoma Type 1 and separated by race. A total of 711 cases were analyzed for gene alterations, expression versus copy number variations, survival curves, and OncoPrints; significant findings and differences between racial groups were noted. The Surveillance, Epidemiology, and End Results (SEER) database was used to access the frequency, rate, and survival of AAoB and W with EC. **Results:** The genes analyzed on cBioPortal (575 W, 136 AAoB) depicted a similar alteration rate between the two groups, except for the most altered gene, PTEN (66% altered in W, 38% in AAoB). W women with a PTEN and PIK3CA alterations had significantly increased 5-year survival periods (P-value = 1.573e-3), while these alterations had no effect survival in AAoB. Six of the ten most altered genes between the two subgroups, and 6 of the 17 most actionable genes, were statistically significant for W but not for AAoB. SEER analyses depicted a frequency of 51,677 W and 3,915 AAoB, with a rate of 5.7% and 3.9%, respectively. The observed survival was 96.1% after 1 year and 85.6% after 5 years for W, compared to 92.8% after 1 year and 76.9% after 5 years for AAoB. **Conclusions:** Based on 5 years of data, overall survival (OS) rates among W women with T1EC are better than AAoB. PTEN mutation confers a survival advantage in W but not in AAoB, indicating that in AAoB, PTEN may play a different role or other factors may override the PTEN advantage. Additional analyses revealed non-remarkable findings, suggesting that molecular factors play a minor role in T1EC disparities or that a larger AAoB sample size is necessary. A better understanding of the downstream signaling pathways of common mutations in T1EC is necessary to further elucidate factors that contribute to racial disparities in T1EC. Research Sponsor: None.

Genes	OS in W (P-value)	OS in AAoB	Actionable for T1EC
PTEN	Increased (0.0391)	Unchanged	Yes
PIK3CA	Increased (3.161e-5)	Unchanged	No
ARID1A	Increased (2.124e-3)	Unchanged	Yes
TTN	Increased (0.0197)	Unchanged	Yes
MET	Increased (0.0247)	Unchanged	Yes
KRAS	Increased (9.769e-3)	Unchanged	Yes
MTOR	Increased (0.0121)	Unchanged	Yes
NF1	Increased (3.387e-3)	Unchanged	Yes

5598 **Poster Session**

Stage 1 results of BrUOG 354: A randomized phase II trial of nivolumab alone or in combination with ipilimumab for people with ovarian and other extra-renal clear cell carcinomas (NCT03355976). *First Author: Don S. Dizon, Lifespan Cancer Institute and Brown University, Providence, RI*

Background: Clear Cell Carcinoma (CCC) outside the kidney is a rare tumor that can arise from multiple organs, including the ovary, endometrium and cervix. Extra-renal CCC is chemoresistant and has a poor prognosis. Data suggest that CCC of the gynecologic tract resembles the genomic profile of Renal Cell Carcinoma (RCC), which is responsive to immune checkpoint inhibition (ICI) therapy. We are conducting a two-stage phase 2 trial evaluating immunotherapy for extra-renal CCC. The primary objective is to assess overall rate of response (ORR); Progression-Free (PFS), Overall Survival (OS), and correlative biomarker studies are secondary. Here we present the results of Stage 1. **Methods:** This is a randomized two-stage non-comparative phase II study evaluating nivolumab (240mg IV every two weeks) alone (N) and in combination with ipilimumab (1mg/kg every six weeks, [N+I]) in patients with relapsed extra-renal CCC after at least one prior chemotherapy (no prior ICI), and measurable disease. Treatment was continued until disease progression or unacceptable toxicity. Stage 1 of this trial called for up to 30 volunteers (15 per arm) after which the study was closed. Consideration to reopen to stage 2 called for two or more responses in either arm. Here we present the completion of Stage 1; the release of results was approved by Brown University Oncology Group (BrUOG) Data Safety and Monitoring Committee. **Results:** Between July 2018 and October 2021, 30 patients were enrolled and 29 were treated (Table). The majority (83%) had CCC of the ovary (n=24). The ORR with N and N+I was 14.2 and 26.7%, respectively. The 6 month PFS rate was 19.1 and 43.8%; median PFS was 2.7 (95%CI 1.3-5.1) and 5.1 months (95%CI 0.9-NR), respectively. Grade ≥3 treatment-related toxicities occurred in 4 (28.6%) on N and 5 (33.3%) on N+I. There were no treatment-related deaths and no new safety signals. One volunteer enrolled on N+I stopped treatment after two years and remains in CR to date. **Conclusions:** Although sufficient activity was seen in CCC in both arms, the single-agent activity of N is similar to published reports in platinum-resistant epithelial ovarian cancer and decision made not to pursue it further. However, the combination of ipilimumab and nivolumab warrants additional investigation, and the second stage of this study will enroll 14 more patients to receive N+I. Clinical trial information: NCT03355976. Research Sponsor: Bristol Myers Squibb.

Best Response	Nivolumab (n, %) n=13*	Nivolumab + Ipilimumab (n,%) n=15
CR	0	3 (20)
PR	2 (15.4)	1 (6.7)
SD	3 (23.8)	6 (40)
PD	8 (61.5)	5 (33.3)

*One patient receiving nivolumab was not evaluable.

5599 **Poster Session**

Immune phenotypes and T-cell density at the invasive margin correlate with prognosis in epithelial vulvar cancer. *First Author: Eike Burandt, University Medical Center Hamburg-Eppendorf, Hamburg, Germany*

Background: Tumor infiltrating lymphocytes (TILs) in the cancer microenvironment are of prognostic value in many solid tumors. However, only little is known about TILs infiltration and its predictive value in vulvar cancer. **Methods:** Immunohistochemistry and automated digital image analysis was applied to measure the densities of $CD3^+$ (DAKO, Santa Clara, US; #IR503) and $CD8^+$ (DAKO, Santa Clara, US; #IR623) TILs at the invasive margin (IM) and in the center of 530 vulvar carcinomas. **Results:** At the IM the mean immune cell density was significantly higher compared to the center of the tumor (CD3: 1772±1105, CD8: 769±644 cells/mm^2 vs. CD3: 518±570, CD8: 301±445 cells/mm^2, $p \leq 0.0001$). An elevated density of $CD3^+$ T-cell at the IM was significantly associated with low tumor stage ($p = 0.0012$). The 2-years OS and PFS rate was significantly different between the group with a high (OS: 82%, PFS: 65%), moderate (OS: 76%, PFS: 55%), or low $CD3^+$ T-cell density at the IM (OS: 64%, $p = 0.008$, PFS: 44%, $p = 0.02$). The prognostic impact of $CD3^+$ cells in the center of the tumor was weaker compared to the IM (OS $p = 0.046$, PPS $p = 0.031$) and lacking for $CD8^+$ T-cell densities at any location ($p \geq 0.14$ each). Unsupervised clustering of $CD3^+$ and $CD8^+$ T-cell densities identified three major subgroups corresponding to the immune desert (137 patients), immune excluded (220 patients) and immune inflamed phenotypes (133 patients). Survival analysis revealed a particular poor prognosis for the immune desert phenotype for OS (0.0071) and PFS (0.0027). **Conclusions:** This study demonstrates a prognostical relevance of the immunphenotype and the distribution of CD3+ T-cells in vulvar cancer. Their value for therapeutic decision making has to be determined in the future. Research Sponsor: None.

5600 **Poster Session**

Racial differences in the mutational landscape of serous endometrial cancer. *First Author: Julian C. Schink, Cancer Treatment Centers of America, Part of City of Hope, Zion, IL*

Background: Tumor comprehensive genomic profiling (CGP) identifying genomic alterations (GA) that have diagnostic, prognostic and are potentially therapeutically targetable is essential to precision oncology. 2022 NCCN Uterine Neoplasm guidelines recommend tumor genetic evaluation as part of initial evaluation. As racial disparities in endometrial cancer outcomes have been widely reported, we analyzed our CGP results from a large series of serous endometrial cancer patients treated in a nationwide cancer network to identify GA differences that may contribute to worse prognosis and help inform better therapy selection. **Methods:** 86 Pts with serous endometrial underwent hybrid-capture based CGP for up to 324 cancer-related genes of archival tumor tissue or 62 genes on circulating tumor DNA ordered during clinical care for treatment decision-making between 01-2013 to 07-2021. Clinically relevant genomic alterations (CRGA) were defined as associated with targeted therapies or mechanism-driven clinical trials. Statistical analysis performed with Fisher Exact test comparing Black and White women. **Results:** Median age was 63 years (range, 38-85), 37% were White, 58% were Black and 5% were Asian. GA were identified in 94% (81/86) of these patients. TP 53 mutations which is characteristic of serous cancer were present in 80 of 86 patients (93%). GA predicted to activate PI3-Kinase pathway signaling (*PIK3CA, PIK3R1, PTEN*) were significantly more common in White women occurring in 13 of 32 (41%), compared with 8 of 50 (16%) of Black women ($p < 0.02$). An important, but not statistically significant trend of greater percentage of CCNE1 amplification in Black women is also noted, see table below: Mutation frequencies were similar between Black and White women for the following genes: *PPP2R1A* 23%; *MYC* 19%; *FBXW7* 14%; *ARID1A* 9%. **Conclusions:** In this 86 patient series of women with Serous Endometrial Cancer we note that PIK3CA mutations, an important resistance factor in anti-HER2 therapy, were significantly more common in White women (41%) compared with Black women (16%) ($p < 0.02$) and ERBB2 mutations occurred in 19% of White women and only 10% of Black women. This study cohort also identified a larger percentage of black women with CCNE1 amplification. Increased CCNE1 amplification has been linked to the racial disparities in cancer outcomes and may explain the disparities seen with endometrial cancers. Research Sponsor: None.

Gene/Race	Black (n = 50)	White (n = 32)	Asian (n = 4)	Total (n = 86)	p values
MSI status	Stable – 35 (70%) High – 1 (.02%)	Stable – 22 (69%) High – 0 (0%)	Stable – 2 (50%) High – 0 (0%)	Stable – 59 (67%) High – 1 (.01%)	NS
TMB >10	2 (.04%)	0 (0%)	0 (0%)	2 (.02%)	NS
TP53	48 (96%)	30 (94%)	2 (50%)	80 (93%)	NS
PI3K Pathway					
****PIK3CA***	**8 (16%)**	**13 (41%)**	**0 (0%)**	**21 (24%)**	***p*= 0.019**
****PIK3R1***	5 (10%)	4 (13%)	1 (25%)	10 (12%)	NS *p*= 0.73
****PTEN***	5 (10%)	4 (13%)	0 (0%)	9 (10%)	NS *p*= 0.73
CCNE1 (AMP)	11 (22%)	3 (9%)	2 (50%)	16 (19%)	NS *p*= 0.23
ERBB2	5 (10%)	6 (19%)	1 (25%)	12 (14%)	NS *p*= 0.32

TPS5601 **Poster Session**

Surgical window-of-opportunity study of megestrol acetate compared with megestrol acetate and metformin for endometrial intraepithelial neoplasia. *First Author: Yanfei Xu, Northwestern University, Chicago, IL*

Background: Endometrial Intraepithelial Neoplasia (EIN) is a precursor lesion to endometrial carcinoma (EC), the most common gynecologic cancer among women in the US. The current standard of care for women with EIN is hysterectomy. Non-surgical treatments are needed for women desiring fertility preservation, and for those who are medically unfit for a major surgical procedure. Progestin therapy is the cornerstone of current nonsurgical management of EIN. However, approximately 30% of patients with EIN do not respond to progestin therapy, or respond incompletely. EIN is closely related to insulin resistance and metabolic syndrome with evidence that increased insulin resistance is a significant risk factor for development of EC. Metformin, an inhibitor of insulin/PI3K/AKT pathway, has been demonstrated to reduce endometrial proliferation *in vitro* and *in vivo*. We hypothesize that the combination of metformin and progestin therapy may synergize to arrest EIN progression and prevent the development of EC. **Methods:** This is a randomized pre-surgical window of opportunity study, comparing a commonly used oral progestin, megestrol acetate (MA), to MA and metformin (M). Patients with pathologically confirmed EIN or complex atypical hyperplasia (CAH) who present for hysterectomy will be approached. After enrollment, participants will receive MA 80mg PO BID ± M 500mg BID for 4 ± 1 weeks pre-operatively. Post-therapy endometrial biopsy will be obtained in the operating room prior to the hysterectomy, and compared to the pre-therapy diagnostic endometrial biopsy sample. The primary endpoint is the change in the percentage (%) of Ki-67 expressing cells (%Ki-67) between the pre- and post-treatment biopsies. Based on a two-sample *t*-test comparing the pre- to post-treatment changes in %Ki-67 between the two arms, a sample size of 21 patients per arm achieves 80% power with two-sided $\alpha = 0.05$ to detect an absolute reduction in %Ki-67 of 10% vs. 17.6% in the MA vs. MA + M arms. An interim analysis is planned after enrollment of 32 patients, and an internal pilot approach based on variance re-estimation will be used to increase the sample size if needed, to maintain the original planned power. Secondary endpoints will include comparison of changes in protein expression of ER, PR, PTEN/PAX2, markers of the PI3K/AKT/MTOR pathway, cell death and intratumoral insulin signaling. We will randomize 50 subjects at five sites: Northwestern University, Cedars-Sinai (Los Angeles), Duke University, University of Colorado, and University of North Carolina. Participants will be randomized 1:1 and stratified by menopausal status to ensure balance between the two arms. Since September 2021, four sites have opened and 22 patients have been pre-screened. Three participants were enrolled and two have completed intervention. The study is expected to complete accrual by the end of 2023. Clinical trial information: NCT04576104. Research Sponsor: U.S. National Institutes of Health.

TPS5602 **Poster Session**

A phase 1 adoptive cell therapy using drug-enhanced, tumor-infiltrating lymphocytes, DeTIL-0255, in adults with advanced malignancies. *First Author: Eugenia Girda, Rutgers Cancer Inst of New Jersey, New Brunswick, NJ*

Background: Tumor-infiltrating lymphocytes (TIL) are a heterogeneous population of T cells that recognize multiple endogenous tumor antigens but may have developed an exhausted phenotype due to the tumor microenvironment. While existing TIL therapies produce durable responses in patients with melanoma, cervical, and head and neck cancers, poor in vitro cell expansion, limited short-lived in vivo persistence, and diminishing potency restrict this approach's broader application. DeTIL-0255 (drug-enhanced TIL [DeTIL]) is an autologous adoptive cell therapy (ACT) derived from a patient's tumor and expanded *ex vivo* with NX-0255, a small-molecule inhibitor of the E3 ligase, Casitas B-lineage lymphoma proto-oncogene B (CBL-B). CBL-B is expressed in T cells, where it functions as a regulator of immune cell activation, in part by requiring CD28 co-stimulation in addition to T-cell receptor activation. Desirable properties enhanced by DeTIL-0255 when compared with TIL include increased number of stem-like CD39-/CD69-, and CD8+ T cells associated with persistence, as well as enhanced cytolytic function. ACT with T cells expanded *ex vivo* using NX-0255 demonstrated increased anti-tumor activity, longer survival, increased stem-like phenotype, and persistence of tumor antigen-specific T cells in mouse tumor models. Adoptive cell transfer of DeTIL-0255, therefore, may exhibit broader functional activity than conventional TIL, potentially conferring improved anti-tumor activity and response. **Methods:** NX-DeTIL-0255-201 is a Phase 1 multicenter, open-label study of DeTIL-0255 administered with systemic high-dose IL-2 following nonmyeloablative lymphodepleting chemotherapy in patients with advanced gynecological malignancies for whom standard therapy with proven clinical benefit does not exist, is no longer effective, or is inappropriate. The primary objectives are to evaluate the safety, tolerability, and preliminary antitumor activity of DeTIL-0255. A safety run-in will consist of 3 to 6 patients treated with DeTIL-0255 and evaluated for dose-limiting toxicity (DLT). The DLT period starts with DeTIL-0255 infusion and ends after a total of 28 days. The safety run-in will investigate DeTIL-0255 at a dose range of 1 to 150 x 109 CD3+ T cells (exact dose varying based on expansion potential of DeTIL-0255 from tumor biopsies). Following the safety run-in, cohort expansion will further evaluate the safety and antitumor activity of DeTIL-0255 in patients with recurrent/persistent platinum-resistant epithelial ovarian cancer, cervical carcinoma, and endometrial cancer. Key eligibility criteria include measurable disease, a resectable lesion for TIL harvest, ≥2 prior lines of therapy, and an Eastern Cooperative Oncology Group performance status 0 or 1. The study is expected to enroll ~54 patients in ~10 sites across the United States. Clinical trial information: NCT05107739. Research Sponsor: Nurix Therapeutics, Inc.

TPS5603 **Poster Session**

Trial in progress update on ENGOT-cx8/GOG-3024/innovaTV 205: Addition of a new cohort with first-line (1L) tisotumab vedotin (TV) + pembrolizumab (pembro) + carboplatin (carbo) ± bevacizumab (bev) in recurrent/metastatic cervical cancer (r/mCC). *First Author: Ignace Vergote, Belgium and Luxembourg Gynaecological Oncology Group (BGOG), Leuven Cancer Institute, and University Hospital Leuven, Leuven, Belgium*

Background: Despite the use of platinum-taxane doublets ± bev in eligible patients (pts), overall survival (OS) outcomes for pts with r/mCC remain poor. With the US approval of pembro + chemotherapy ± bev in the 1L setting for r/mCC with ≥1% of programmed death ligand 1–positive cells in the tumor, an unmet need remains for pts who do not meet this threshold and for pts who progress or are intolerant to standard treatment (tx). TV is a tissue factor–directed antibody–drug conjugate that has been granted accelerated approval in the United States for the tx of adults with r/mCC with disease progression on or after chemotherapy. To develop more effective treatments, we investigated TV in combination with agents with known activity in cervical cancer. We conducted a 2-part, multicohort phase 1b/2 trial, ENGOT-cx8/GOG-3024/innovaTV 205 (NCT03786081), to evaluate TV in combination with bev, pembro, or carbo. The phase 1b dose-escalation phase of innovaTV 205 established the recommended phase 2 dose (RP2D) and the feasibility of these doublet combinations (Monk et al, IGCS 2021). Moreover, we recently reported encouraging antitumor activity from the dose-expansion cohort of TV + carbo (1L; confirmed objective response rate [ORR], 55%; median duration of response [DOR], 8.3 mo) and TV + pembro (second-line; confirmed ORR, 38%; median DOR, 13.8 mo) (Vergote et al, ESMO 2021). The current report describes the design of a new, ongoing dose expansion cohort in the innovaTV 205 study to evaluate the combinations of TV, pembro, and carbo ± bev. **Methods:** A new cohort has been added to the innovaTV 205 study, comprising adult pts with recurrent or stage IVB squamous, adenosquamous, or adenocarcinoma of the cervix with no prior systemic therapy and an Eastern Cooperative Oncology Group score of 0 or 1. Pts will be treated with the RP2D of TV (2.0 mg/kg) + carbo (AUC 5 mg/mL), pembro (200 mg), and bev (15 mg/kg) every 3 weeks or with TV + carbo (AUC 5 mg/mL) and pembro (200 mg). To assess the regimen's initial tolerability, there will be a dose-limiting toxicity evaluation period that will consist of completion of 1 tx cycle of 21 days for 6 pts enrolled to receive the quadruplet combination. The primary endpoint of this dose expansion phase is confirmed ORR per RECIST v1.1; secondary endpoints include DOR, time to response, progression-free survival, OS, and safety. Enrollment is ongoing in the United States and Europe, with additional sites planned globally. Clinical trial information: NCT03786081. Research Sponsor: Genmab A/S and Seagen Inc. in collaboration with Merck & Co., Inc.

TPS5604 **Poster Session**

Randomized controlled trial of the efficacy of lymph node dissection on stage IIICr of cervical cancer (CQGOG0103). *First Author: Misi He, Chongqing University Cancer Hospital, Chongqing, China*

Background: In FIGO 2018, allowing assessment of retroperitoneal lymph nodes by imaging and/or pathological findings and, if deemed metastatic, the case is designated as stage IIIC (with r and p notations). Patients with lymph node metastases have lower overall survival (OS), progression free survival (PFS), and survival after recurrence, especially those who have unresectable macroscopically positive lymph nodes. Retrospective analysis suggests that there may be a benefit to debulking macroscopic nodes that would be otherwise difficult to sterilize with standard doses of radiation therapy. No prospective study reported that resecting macroscopic nodes before Concurrent chemoradiation therapy (CCRT) would improve PFS or OS of cervical cancer. The CQGOG0103 study is a national, prospective, multicenter and randomized clinical study evaluating lymph node dissection on stage IIICr of cervical cancer. **Methods:** Eligible patients are histologically confirmed cervical squamous cell carcinoma, adenocarcinoma, adeno-squamous cell carcinoma. Stage IIICr (confirmed by CT/MRI/PET/CT) and the short diameter of image-positive lymph node ≥15mm. 452 patients will be equally randomized to receive either CCRT (Pelvic EBRT/Extended-field EBRT + cisplatin (40mg/m2) or carboplatin (AUC = 2) every week for 5 cycles + brachytherapy) or Open/minimally invasive pelvic and para-aortic lymph node dissection followed by CCRT. Randomization is stratified by status of para-aortic lymph node. The primary endpoint is PFS. Secondary endpoints are OS and surgical complications. The sample size calculation of 346 patients provides 80% power to detect a difference in survival at the two-sided 5% significance level using the log-rank test, considering a 20% reduction, a total of 452 patients are required. This study began in January 2021 and will be accrued within 4 years. Enrollment is ongoing. Research Sponsor: None.

TPS5605 **Poster Session**

ROCC/GOG-3043: A randomized non-inferiority trial of robotic versus open radical hysterectomy for early-stage cervical cancer. *First Author: Kristin Leigh Bixel, The Ohio State University Wexner Medical Center and James Cancer Hospital, Columbus, OH*

Background: Minimally invasive surgery (MIS) is associated with improved perioperative safety outcomes, but, in 2018, the Laparoscopic Approach to Cervical Cancer (LACC) trial, a non-inferiority study comparing laparoscopic versus open radical hysterectomy for early stage cervical cancer, reported significantly worse disease-specific (DSS) and overall survival (OS) in the MIS group. Criticisms of the LACC trial include lack of proper preoperative imaging and assessment, use of transcervical uterine manipulators, and lack of proper tumor containment leading to peritoneal contamination. Subsequent retrospective studies have reported conflicting results. Given the potential benefit of MIS, the ROCC trial seeks to address the limitations of the LACC trial. **Methods:** ROCC is a multi-center, prospective, randomized, non-inferiority trial. The primary objective is to determine whether robotic-assisted (RBT) radical hysterectomy is not inferior to abdominal (OPEN) approach with respect to 3-year disease-free survival (DFS). Secondary objectives include DSS, OS, patterns of recurrence, peri- and postoperative complications, long-term morbidity, impact on patient-reported outcome (PRO) measures and development of lower extremity lymphedema (LEL). Key inclusion criteria include patients with histologically confirmed adenocarcinoma, squamous cell, and adenosquamous cell carcinoma of FIGO 2018 stage IA2-IB2. All patients must have a preoperative pelvic MRI confirming that the cervical tumor is < 4 cm in size, no obvious evidence of extracervical extension and no nodal or other regional metastasis. Intraoperatively, the use of transcervical uterine manipulators is not allowed and specific detailed surgical techniques for proper tumor containment is required. Photographic evidence of specimen with tumor contained is mandated. We estimate the 3-year DFS to be 92% in the control (OPEN) arm. If the DFS does not differ by more than 7% and the one-sided 95% CI does not cross the non-inferiority boundary, then the RBT arm will be deemed non-inferior. 840 patients will be enrolled (420 per arm, 89 events total), which provides 90% power to exclude an absolute decrease in DFS by 7% (HR < = 1.375) with a log-rank test for non-inferiority with a one-sided alpha of 0.05. The primary analysis will be conducted in all randomized patients (ITT). Given the LACC findings of worse oncologic outcomes with MIS, a formal DSMC will conduct periodic reviews of safety including two planned formal interim analyses for futility (harm) after accrual of 370 and 640 patients using an aggressive Lan-DeMets beta-spending function similar to a Pocock boundary. Results of this trial may be practice changing and will either support or refute the findings of the LACC trial. The study is currently activating sites for enrollment. Clinical trial information: NCT04831580. Research Sponsor: Intuitive Foundation, GOG Foundation.

TPS5606 **Poster Session**

Pivotal study of ofra-vec (VB-111) combined with paclitaxel versus paclitaxel for treatment of platinum-resistant ovarian cancer (OVAL, VB-111-701/GOG-3018). *First Author: Richard T. Penson, Harvard Medical School, Massachusetts General Hospital, Boston, MA*

Background: Ofranergene obadenovec (Ofra-vec, VB-111) is an anti-cancer gene based immune activator and targeted vascular disruptor. The dual mechanism of action triggers a broad antiangiogenic effect and induces of a tumor directed immune response. A phase II trial in patients with platinum resistant ovarian cancer (PROC) demonstrated that ofra-vec in combination with weekly paclitaxel was well tolerated and associated with a CA-125 Objective Response Rate (ORR) of 58%, a trend for improved survival and induction of an immunotherapeutic effect of tumor infiltration with CD-8 T cells. Based on these observations, a pivotal phase III study was initiated in collaboration with the GOG Foundation, Inc. **Methods:** Study NCT03398655 is an international, randomized, double-blind, placebo-controlled, phase III study. Eligible patients have recurrent PROC and may have been previously treated with up to 5 prior lines of therapy (but not >2 for PROC). Patient are randomized 1:1 to receive ofra-vec ($1x10^{13}$ Viral Particles) with weekly paclitaxel ($80mg/m^2$), or weekly paclitaxel with placebo. Randomization is stratified by number of prior treatment lines, prior antiangiogenic therapy and platinum refractory disease status. The dual primary endpoints are OS and PFS. A pre-planned interim analysis of CA-125 response (GCIG) performed by the DSMC met the pre-defined criteria showing that CA-125 ORR in the treatment arm was at least 10% higher than in the control arm. Study is enrolling in the US, EU, Japan and Israel, with 90% enrollment to date. Completion of accrual is anticipated in Q1 2022. Clinical trial information: NCT03398655. Research Sponsor: VBL therapeutics.

TPS5607 **Poster Session**

Frontline therapy of anlotinib combined with carboplatin/paclitaxel and maintenance anlotinib in patients with newly diagnosed advanced ovarian cancer: A phase II, single-arm, multicenter study. *First Author: Yi Jiang, Jiangsu Province Hospital, Nanjing, China*

Background: It has been reported that antiangiogenic drug combined with chemotherapy as first-line treatment, and subsequent antiangiogenic drug as maintenance therapy for ovarian cancer can achieve better clinical benefits. Anlotinib is a highly effective VEGFRs, FGFRs, PDGFRs and c-kit multi-target tyrosine kinase inhibitor which has been approved for the treatment of several solid tumors in China. This single arm, multicentric, phase II study is expected to investigate the efficacy and safety of anlotinib combined with carboplatin/paclitaxel as front-line treatment in patients with advanced ovarian cancer. **Methods:** Eligible patients with FIGO stage III–IV primary epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer and ECOG PS 0-1 undergo primary debulking surgery or interval debulking surgery, will receive 6-8 cycles of chemotherapy (paclitaxel 175 mg/m2 + carboplatin area under the curve [AUC] 5 q3w) and anlotinib (12 mg po qd, days 1-14, 21 days per cycle, anlotinib will be omitted from the first treatment cycle to prevent delayed wound healing). Anlotinib as maintenance monotherapy will be continue until disease progression, unacceptable toxicity, or death. Patients with prior anti-angiogenic therapy and major surgical procedure within 28 days before the first date of anlotinib therapy will be excluded. This study will recruit approximately 56 patients. The primary endpoint is progression free survival. Key secondary endpoints include overall response rate, disease control rate per RECIST1.1, overall survival, safety. The study began enrolling patients in August 2021 and is ongoing. Clinical trial information: NCT04807166. Research Sponsor: None.

TPS5608 **Poster Session**

SCOUT-1: Prospective non-interventional study in patients with *BRCA*/HRD-tested ovarian cancer (OC) eligible for first-line (1L) platinum-based chemotherapy (NOGGO ov54). *First Author: Pauline Wimberger, North-Eastern German Society of Gynecological Oncology (NOGGO) and Department of Gynecology and Obstetrics, University Hospital Carl Gustav Carus, TU Dresden, Dresden, Germany*

Background: Two third of patients with OC, have an advanced stage at initial diagnosis accompanied with poor prognosis. Results from landmark trials of maintenance therapy (MTX) with poly ADP ribose polymerase inhibitors (PARPi), especially in tumors associated with homologous recombination deficiency (HRD), like *BRCA*-mutated tumors, led to the strong recommendation on testing and treatment procedures in the clinical routine in patients newly diagnosed with advanced high-grade epithelial OC. The translation of these guidelines into clinical routine affects care management and therefore needs to be evaluated. This study aims to gain new insights into current real-world biomarker testing and 1L-treatment patterns together with clinical and patient-reported outcomes of patients with newly diagnosed advanced OC in Germany and to capture the influence of 1L treatment (with or without PARPi MTX) on medical routine and patient needs. **Methods:** SCOUT-1 is a national prospective, observational study (NCT04830709) to collect clinical real-world and patient-reported outcome (PRO) data in patients newly diagnosed with histologically confirmed advanced (FIGO stage III or IV) high-grade epithelial ovarian, fallopian-tube, or primary peritoneal cancer in Germany. Selection criteria include written informed consent, completed surgery (if applicable), eligible for platinum-based chemotherapy, *BRCA*1/2 mutation tested and willingness/ability to report PROs electronically. About 750 patients are planned to be included in up to 80 sites (hospitals or office-based). The primary objective is to determine the effectiveness of standard treatment sequences by estimating progression-free survival according to investigator's assessment. Further focus is to describe biomarker-testing algorithm, patient selection and to assess patients' QoL, symptoms, needs, as well as patients' expectations. Importantly, SCOUT-1 will help to collect long-term data as patients will be followed for up to 7 years. First-subject-was included in the study in June 2021. Study completion date is planned in Q2 2032. Research Sponsor: AstraZeneca, in cooperation with North-Eastern German Society of Gynecological Oncology (NOGGO e.V.).

TPS5609 **Poster Session**

ARTISTRY-7: A phase 3, multicenter study of nemvaleukin alfa in combination with pembrolizumab versus chemotherapy in patients (pts) with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer. *First Author: Thomas J. Herzog, University of Cincinnati, University of Cincinnati Cancer Institute, Cincinnati, OH*

Background: ARTISTRY-7 will evaluate the novel engineered cytokine nemvaleukin alfa (nemvaleukin, ALKS 4230) in pts with gynecologic cancers. Epithelial ovarian cancer (OC) is the 7th most common cause of cancer mortality in women. OC is an area of high unmet need, as many pts become resistant or refractory to frontline platinum-based chemotherapy. Nemvaleukin was designed to selectively bind to the intermediate-affinity interleukin-2 (IL-2) receptor, preferentially activating and expanding antitumor $CD8^+$ T and NK cells with minimal expansion of T_{regs}. This selectivity may provide enhanced tumor killing and improved safety/tolerability compared with high-dose IL-2. In clinical studies, nemvaleukin, as monotherapy and in combination with pembrolizumab, has shown evidence of clinical benefit in multiple tumor types, including OC. In ARTISTRY-1, 4 responses were observed in pts with OC, including 2 complete responses, 1 in a pt with platinum-resistant OC and 5 prior lines of therapy, and 2 partial responses. **Methods:** ARTISTRY-7 is a phase 3, multicenter, open-label randomized study of nemvaleukin and/or pembrolizumab vs chemotherapy. Eligible pts are women (≥18 y) with histologically confirmed epithelial OC (high-grade serous, endometrioid, clear cell), fallopian tube cancer, or primary peritoneal cancer. Pts must have received ≥1 prior line of systemic therapy in the platinum-sensitive setting, ≤5 prior lines in the platinum-resistant setting, and prior bevacizumab, with radiographic progression on most recent therapy. Primary platinum-refractory disease (progression on first-line platinum therapy) or primary platinum resistance (progression < 3 months after completion of first-line platinum therapy) is exclusionary. Pts must have ECOG performance status of 0 or 1, estimated life expectancy of ≥3 months, and adequate hematologic reserve and hepatic and renal function. Approximately 376 pts will be randomized (3:1:1:3) to receive nemvaleukin 6 μg/kg IV on days 1-5 and pembrolizumab 200 mg IV on day 1 of each 21-day cycle, pembrolizumab monotherapy, nemvaleukin monotherapy, or chemotherapy (pegylated liposomal doxorubicin, paclitaxel, topotecan, or gemcitabine) and stratified according to PD-L1 status, histologic subtype (high-grade vs non–high-grade serous), and chemotherapy (paclitaxel vs other). Pts will continue treatment until disease progression or intolerable toxicity (maximum 35 cycles for pembrolizumab; nemvaleukin can be continued). The primary endpoint is investigator-assessed PFS (RECIST v1.1) in the nemvaleukin/pembrolizumab vs chemotherapy group. Secondary/exploratory endpoints include overall survival, other antitumor measures, safety, health-related quality of life, and pharmacokinetic/pharmacodynamic effects. Clinical trial information: NCT05092360. Research Sponsor: Alkermes, Inc.

TPS5610 **Poster Session**

A single-arm, phase II study of niraparib and bevacizumab maintenance therapy in patients with platinum-sensitive, recurrent ovarian cancer previously treated with a PARP inhibitor: Korean Gynecologic Oncology Group (KGOG 3056)/NIRVANA-R trial. *First Author: Jung-Yun Lee, Department of Obstetrics and Gynecology, Institute of Women's Life Medical Science, Yonsei University College of Medicine, Seoul, South Korea*

Background: Given the expanding clinical use of poly(adenosine diphosphate [ADP]-ribose) polymerase inhibitors (PARPis), there is a significant need for optimal strategies with which to treat patients whose cancer progresses while using a PARPi. However, the treatment consensus after PARPi has not been established. The aim of the Korean Gynecologic Oncology Group (KGOG) 3056/NIRVANA-R trial is to investigate the efficacy of niraparib in combination with bevacizumab as a maintenance therapy in platinum-sensitive ovarian cancer patients who were previously treated with a PARPi. **Methods:** The KGOG 3056/NIRVANA-R is a multi-centre, investigator-initiated, single-arm, phase II trial of patients with platinum-sensitive recurrent ovarian cancer recruited from seven KGOG sites. This study included patients with platinum-sensitive recurrent epithelial ovarian cancer who received at least 2 previous courses of platinum-containing therapy and had been treated with a PARPi. Mucinous histology type was excluded. Patients who had responded to the last platinum regimen (either complete or partial response) were eligible to participate in this study. Forty-four patients will be recruited. All enrolled patients are treated with niraparib and bevacizumab for maintenance therapy until disease progression, unacceptable toxicity, or withdrawal of patient consent. The primary endpoint of the study is 6-month progression-free survival rate and 4 of planned 44 patients have been enrolled. Clinical trial information: NCT04734665. Research Sponsor: Takeda.

TPS5611 **Poster Session**

AGO-OVAR 2.29 (ENGOT-ov34): Atezolizumab in combination with bevacizumab and chemotherapy versus bevacizumab and chemotherapy in recurrent ovarian cancer (ROC). *First Author: Philipp Harter, AGO Study Group & Department of Gynecology and Gynecologic Oncology, Ev. Kliniken Essen-Mitte, Essen, Germany*

Background: Paclitaxel or pegylated liposomal doxorubicin in combination with bevacizumab constitutes a standard treatment option in patients with relapsed ovarian cancer who are not considered candidate for platinum, but responses are short-lived. Immune checkpoint inhibitors like atezolizumab as single agents have limited activity in ovarian cancer. There is a biologic rationale to combine checkpoint inhibitors with chemotherapy and bevacizumab, however, the role of such combination for the management of ovarian cancer is so far undefined. Because of the intimate relationship between angiogenesis and immunosuppression, it is expected that the inhibition of both pathways could lead to synergism and more durable clinical benefit. The addition of a chemotherapeutic agent is expected to lead to the release of tumor antigens and enhance the efficacy of immunotherapy in turn. Therefore, we aim to test the efficacy of atezolizumab in combination with non-platinum-based chemotherapy and bevacizumab vs the combination of a non-platinum-based chemotherapy and bevacizumab alone. **Methods:** AGO-OVAR 2.29 is a randomized (1:1), double blinded, phase III trial evaluating the efficacy and safety of atezolizumab plus bevacizumab and chemotherapy (weekly paclitaxel or pegylated liposomal doxorubicin) compared with placebo plus bevacizumab and chemotherapy in patients with recurrent ovarian, fallopian tube, or primary peritoneal cancer with 1st or 2nd relapse within 6 months after completing platinum-based chemotherapy or 3rd relapse. A de novo tumor biopsy to determine the PD-L1 expression status prior to randomization for stratification is mandatory. Patients are treated with chemotherapy plus bevacizumab + atezolizumab/placebo until progression or unacceptable toxicity. Co-primary endpoints are overall survival and progression-free survival. It is planned to randomize approximately 664 patients. Safety interim analyses were performed after inclusion of 24 and an additional 60 and 120 patients who had completed at least one treatment cycle. As of 09th February 2022, 461 patients have been randomized. Clinical trial information: NCT03353831. Research Sponsor: F. Hoffmann-La Roche Ltd.

TPS5612 **Poster Session**

AGO-OVAR 28/ENGOT-ov57: Niraparib versus niraparib in combination with bevacizumab in patients with carboplatin-taxane based chemotherapy in advanced ovarian cancer—A multicenter, randomized, phase III trial. *First Author: Florian Heitz, AGO Study Group & Ev. Kliniken Essen-Mitte, Essen, Germany*

Background: Standard of care chemotherapy in patients (pts) with advanced ovarian cancer (AOC) is the combination of carboplatin and paclitaxel. Data from the PRIMA trial has shown a significant benefit in pts by the addition of a maintenance treatment (MT) with niraparib irrespective of BRCA or HRD-status in high-grade ovarian cancers (OC). The PAOLA-1 trial evaluated MT in pts with AOC with the combination of olaparib and bevacizumab and has also shown a significant benefit compared to bevacizumab monotherapy. However, it is unclear if a PARP-inhibitor (PARPi) MT monotherapy is sufficient or if the addition of bevacizumab is needed. Therefore, we investigate, if the treatment strategy of carboplatin / paclitaxel / bevacizumab / PARPi is superior to the treatment of carboplatin / paclitaxel / PARPi in an all-comer population. **Methods:** AGO-OVAR 28/ENGOT-ov57 (NCT05009082; EudraCT Number: 2021-001271-16) is an Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) Study Group led, international, multicenter, randomized, prospective phase III trial within the ENGOT trial network. The trial population is composed of adult pts with newly diagnosed, advanced high-grade epithelial OC, primary peritoneal cancer or fallopian tube cancer FIGO III/IV (except FIGO IIIA2 without nodal involvement). All pts should have completed the first cycle of chemotherapy (carboplatin and paclitaxel) as part of Study Run-In-Period. Prior to day1 of cycle2, pts with a valid central tumor BRCA (*tBRCA*) test result will be randomized 1:1 into either Arm1 and will receive 5 additional cycles of carboplatin and paclitaxel, q21d followed by niraparib for up to 3 years; or into Arm2 where pts will receive 5 additional cycles of carboplatin and paclitaxel plus bevacizumab, q21d followed by bevacizumab, q21d (for up to 1 year) and niraparib for up to 3 years. Patients who are scheduled for neoadjuvant chemotherapy and interval debulking surgery are also allowed to be included in the trial. The primary objective is progression free survival (PFS). Secondary objectives include but are not limited to: PFS according to *tBRCA*-status, overall survival, PFS2, safety and tolerability, and quality of life. The trial will start in Q1/2022 with First Patient First Visit expected in Q2/2022. It is planned to recruit 970 patients. Clinical trial information: NCT05009082. Research Sponsor: GlaxoSmithKline (GSK).

TPS5613 **Poster Session**

PERCEPTION: Phase II investigational study of pembrolizumab combination with chemotherapy in platinum-sensitive recurrent low-grade serous ovarian cancer— A NOGGO trial. *First Author: Jacek P. Grabowski, North-Eastern German Society of Gynaecological Oncology (NOGGO) and Department of Gynecology with Center for Oncological Surgery, Charité-University Medicine of Berlin, Campus Virchow Klinikum, Berlin, Germany*

Background: Low-grade serous ovarian cancer (LGSOC) represents a minority within the group of invasive epithelial ovarian malignancies. Recent analyses showed a very limited responsiveness to chemotherapy in LGSOC. Since bevacizumab many years ago, none other agents have been approved in LGSOC. There is a high demand of new therapy combinations with modern substances to improve the response rate and prognosis in this group of patients. Immune check-point inhibitors provide a new possibility which showed to be effective in different malignant diseases as well as in selected ovarian cancer patients. In this study, the standard chemotherapy is going to be combined with pembrolizumab in recurrent LGSOC cases with therapy free interval (TFI) over 6 months after last platinum-based chemotherapy. To the authors knowledge no comparable studies have been performed or planned. If our trial should show pembrolizumab effectivity in LGSOC, it would be a signal and impulse for future clinical studies in this rare disease. **Methods:** PERCEPTION/NOGGO-ov44 (NCT04575961) clinical trial is a multicenter, single-arm phase 2 study to evaluate pembrolizumab therapy concomitant to platinum-based chemotherapy (carboplatin plus pegylated liposomal doxorubicin, carboplatin plus gemcitabine or carboplatin monotherapy) and as maintenance in recurrent low-grade serous ovarian cancer cases. LGSOC patients with progression or recurrence at least six months after most previous platinum-containing therapy and in good general performance (ECOG 0 or 1) are eligible to participate in this clinical trial. The primary objective is the 12 months progression free survival (PFS) rate. Secondary end-points include overall survival, response rate (RR), PFS and RR according to Ki67 expression levels, time to first subsequent therapy (TFST) and its response, safety and quality of life. The trial is planned according to Simon's two-stage design with total sample size up to 33 patients. The null hypothesis is PFS-rate after 12 months of 20%. In the first phase 18 patients will be enrolled and if at least 5 patients show PFS after 12 months the study is going to be continued with an additional 15 patients. The trial is claimed successful, if at least 11 patients show PFS after 12 months. Assuming a true PFS-rate of 40%, this trial has 5% type I error rate and 80% power. Clinical trial information: NCT04575961. Research Sponsor: MSD Sharp & Dohme GmbH.

TPS5614 **Poster Session**

TEDOVA/GINECO-OV244b/ENGOT-ov58 trial: Neo-epitope based vaccine OSE2101 alone or in combination with pembrolizumab versus best supportive care (BSC) as maintenance in platinum-sensitive recurrent ovarian cancer with disease control after platinum. *First Author: Alexandra Leary, Gustave-Roussy Cancer Campus, Villejuif, and Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens, Villejuif, France*

Background: Besides PARP inhibitors and bevacizumab, there are no approved maintenance therapies after platinum based chemotherapy for patients with a platinum sensitive relapsed epithelial ovarian cancer (OC). Immune checkpoint inhibitors (ICI) as single agents have limited activity in OC. One attractive strategy is to turn OC from immunogenic "cold" to "hot" tumors via vaccination with tumor-associated antigens (TAAs). OSE2101 is a multiple-neoepitope vaccine restricted to HLA-A2-positive patients (45% of OC patients) targeting 5 TAAs: TP53, MAGE2, MAGE3, CEA and HER2. These neo-epitopes are modified to increase both major histocompatibility complex and the T cell receptor binding affinity. The proof of concept for this approach was recently demonstrated with OSE2101 improving overall survival in a phase III trial in lung cancer progressing after ICI (Besse *et al.* 2021). The combination of OSE2101 with an ICI may most effectively harness anti-tumor immunity. **Methods:** TEDOVA is an international randomized open-label, phase II trial evaluating the benefit of maintenance by OSE2101 alone or in combination with PD1 inhibition (pembrolizumab) after platinum based chemotherapy in relapsed OC, previously treated with bevacizumab (if eligible) and a PARP inhibitor (if eligible). Patients (N=180) with CR/PR/SD at the end of chemotherapy are randomized (1:1:2) to: Observation/BSC (Arm A), OSE2101 alone (Arm B), or OSE2101 in combination with pembrolizumab (Arm C). Experimental treatments are continued until progression, or intolerance, for up to 2 years. The primary endpoint is progression-free survival (PFS). Secondary endpoints include overall response rate, safety, time to subsequent first or second treatment (TTST-1, TTST-2) and overall survival. 180 HLA-A*02 positive patients will be randomized. HLA-A*02 negative patients will be followed in a separate observational cohort. The sample size is calculated to provide 90% power to detect an improvement in PFS for Arm C vs Arm A with a HR of 0.57. Three one-sided Log-rank tests will be considered in a pre-defined sequence: H1: C (OSE2101+pembrolizumab) vs A (BSC); H2: C (OSE2101+pembrolizumab) vs B (OSE2101) and H3: B vs A. The type I error will be α=5%. The type II error will be β=10%. Tests will be one-sided. Status: The TEDOVA/GINECO-OV244b/ENGOT-ov58 trial is currently recruiting. Clinical trial information: NCT04713514. Research Sponsor: OSE Immunotherapeutics, Pharmaceutical/Biotech Company.

TPS5615 **Poster Session**

ENGOT-ov60/GOG-3052/RAMP 201: A phase 2 study of VS-6766 (RAF/MEK clamp) alone and in combination with defactinib (FAK inhibitor) in recurrent low-grade serous ovarian cancer (LGSOC). *First Author: Susana N. Banerjee, The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, National Cancer Research Institute (NCRI), London, United Kingdom*

Background: Low-grade serous ovarian cancer (LGSOC) constitutes up to 10% of all ovarian cancer and has clinical and molecular characteristics distinct from high-grade serous ovarian cancer. Approximately a third of patients (pts) with recurrent LGSOC harbor KRAS mutations (mt) and pts with KRAS wild-type (wt) LGSOC may have mutations in NRAS, BRAF, or other RAS pathway-associated genes. Prior clinical studies with single agent MEK inhibitors have shown response rates of 16-26% in recurrent LGSOC. VS-6766 is a unique small molecule RAF/MEK clamp that inhibits both RAF and MEK activities by trapping them in inactive complexes. This mechanism of blockade has been shown to limit compensatory MEK activation, thereby potentially enhancing efficacy of MEK inhibition. Focal adhesion kinase (FAK) activation is a putative resistance mechanism to RAF and MEK inhibition, and defactinib, a small molecule inhibitor of FAK, has shown synergistic anti-tumor activity with VS-6766 in preclinical models, including organoids from LGSOC pts. Furthermore, FAK inhibition combined with VS-6766 induces tumor regression in a KRAS mt ovarian cancer xenograft model. The combination of VS-6766 and defactinib is currently being evaluated in the ongoing Investigator Sponsored FRAME study (NCT03875820). In this proof-of-concept study, durable objective responses (ORR = 46%; 11/24) have been reported in recurrent LGSOC pts, including pts who have had a prior MEK inhibitor (Banerjee ESMO 2021) and the combination of VS-6766 + defactinib has received FDA Breakthrough Therapy Designation for recurrent LGSOC. These initial preclinical and clinical results support the ongoing phase 2 ENGOT-ov60/GOG-3052 in recurrent LGSOC. **Methods:** This is an international phase 2, adaptive, multicenter, randomized, open label study designed to evaluate the efficacy and safety of VS-6766 vs VS-6766 in combination with defactinib currently open to enrollment (NCT04625270). The study will be conducted in two parts. Part A will determine the optimal regimen based on confirmed overall response rate (independent radiology review) in KRAS mt and KRAS wt LGSOC. Part B will determine the efficacy of the optimal regimen identified in Part A in KRAS mt and KRAS wt LGSOC. The minimum expected enrollment is 104 pts, 52 pts with KRAS mt and 52 KRAS wt (64 pts in Part A and 40 pts in Part B). Pts will be randomized to receive VS-6766 (4.0 mg orally (PO), twice weekly 3 wks on, 1 wk off) or VS-6766 with defactinib (VS-6766 3.2 mg PO, twice weekly + defactinib 200 mg PO BID 3 wks on, 1 wk off) till progression. Key inclusion criteria include histologically confirmed LGSOC, known KRAS mutation status, prior systemic therapy including platinum for metastatic disease and up to 1 prior line of MEK inhibitor therapy permitted. Part A of this study has completed enrollment and Part B is currently enrolling pts. Clinical trial information: NCT04625270. Research Sponsor: Verastem.

TPS5616 **Poster Session**

GRN300–001: Phase 1/1B evaluation of the safety, pharmacokinetics, and efficacy of GRN-300, a salt-inducible kinase inhibitor, alone and in combination with paclitaxel, in recurrent ovarian, primary peritoneal, and fallopian tube cancers. *First Author: Siqing Fu, Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Salt-induced kinase 2 (SIK2) is a serine-threonine kinase that regulates centrosome splitting, activation of PI3 kinase and phosphorylation of Class IIa HDACs. SIK2 is overexpressed in 30% of ovarian cancers and associated with decreased progression-free survival (Ahmed et al., 2010). Treatment with GRN-300, an orally bioavailable small-molecule inhibitor of SIK2, was shown to improve the response to paclitaxel in human ovarian cancer cells grown in culture and in immunocompromised mice (Zhou et al., 2017). **Methods:** Part 1 of the study will evaluate the safety, MTD, RP2D (Recommended Phase 2 Dose), and PK of daily GRN-300 monotherapy. For the dose-escalation enrollment of patients with advanced solid tumors of any histology, four dose levels of GRN-300 are planned: 100, 200, 300, and 400 mg BID. Subsequently, GRN-300 will be administered at the determined RP2D in an ovarian cancer expansion cohort. Part 2 will evaluate the safety, PK, and preliminary clinical activity in an open-label study of the combination of GRN-300 and paclitaxel weekly x3. Paclitaxel will be administered in one of two different dosing levels: 60 mg/m2 initially, then dose escalated to 80 mg/m2. In the combination regimen, GRN-300 will be administered at the RP2D dose as determined in Part 1 of this study. The two dose findings will be conducted independently using the BOIN design (Liu 2015, Yuan 2016). Study drug may be administered per protocol for continuous 28-day cycles until disease progression, adverse events, or other criteria as described in the protocol. Tumor biopsies and blood plasma samples including peripheral blood mononuclear cells (PBMCs) will be collected for exploratory biomarker analysis to predict and to monitor responses to GRN-300 treatment. Major eligibility criteria At least 18 years of age. Recurrent or persistent, locally non-resectable or metastatic ovarian, primary peritoneal or fallopian tube epithelial cancer (advanced solid tumors of any other histology only for the monotherapy dose escalation enrollment in Part 1) In Part 2, diagnosis of recurrent or persistent, locally non-resectable or metastatic ovarian, primary peritoneal or fallopian tube epithelial cancer for which treatment with paclitaxel is indicated. Received at least one prior second-line treatment. The first 3 dose groups (100, 200, and 300 mg BID of GRN-300) have been completed without DLT and preliminary PK analysis indicate dose proportionality. Enrollment to dose group 4 (400 mg BID) began in February 2022. Clinical trial information: NCT04711161. Research Sponsor: GreenfireBio LLC.

TPS5617 **Poster Session**

ENGOT-ov65/KEYNOTE-B96: Phase 3, randomized, double-blind study of pembrolizumab versus placebo plus paclitaxel with optional bevacizumab for platinum-resistant recurrent ovarian cancer. *First Author: Nicoletta Colombo, University of Milan-Bicocca, European Institute of Oncology (IEO) IRCCS, Milan, Italy*

Background: Despite therapeutic advances in ovarian cancer, platinum-resistant recurrent ovarian cancer (PROC) remains an area of high unmet clinical need and there is an urgent need for new treatments to further improve clinical outcomes. Addition of bevacizumab to non-platinum-based chemotherapy significantly improved PFS in patients with PROC but did not show a clear OS benefit. Thus far, the combination of paclitaxel and bevacizumab has shown the most promise in treatment of PROC, although the proportion of patients eligible for bevacizumab is limited by treatment-associated toxicities. Combination of the anti-PD-1 antibody pembrolizumab with weekly paclitaxel showed antitumor activity and manageable toxicity in patients with PROC in a single-arm, phase 2 study (Wenham *Int J Gynecol Cancer* 2018). The current study ENGOT-ov65/KEYNOTE-B96 (NCT05116189) compares the efficacy and safety of the addition of pembrolizumab to standard of care chemotherapy (weekly paclitaxel) with/without bevacizumab vs placebo plus weekly paclitaxel with/without bevacizumab in patients with PROC. **Methods:** In this randomized, placebo-controlled, double-blind, phase 3 study, eligible patients are aged ≥18 y with histologically confirmed epithelial ovarian, fallopian tube, or primary peritoneal carcinoma with 1-2 prior lines of systemic therapy, including at least 1 prior platinum-based therapy with ≥4 cycles in first line. Patients must have platinum-resistant disease (radiographic evidence of PD ≤6 mo after last platinum-based therapy dose), be eligible for paclitaxel (with/without bevacizumab per investigator discretion), have ECOG PS ≤1, radiographically evaluable disease per RECIST v1.1, and have a tumor sample for central evaluation of PD-L1 status. Approximately 616 patients will be randomized 1:1 to receive pembrolizumab 400 mg IV or placebo Q6W for up to 18 cycles (~2 y) plus paclitaxel 80 mg/m^2 on days 1, 8, and 15 of each Q3W cycle (with/without bevacizumab 10 mg/kg Q2W per investigator discretion) until PD or unacceptable toxicity. Randomization is stratified by planned bevacizumab use (yes vs no), region (US vs Europe vs rest of world), and PD-L1 status (combined positive score [CPS] < 1 vs CPS 1- < 10 vs CPS ≥10). Tumor PD-L1 status is determined using the PD-L1 IHC 22C3 pharmDx (Investigational Use Only) diagnostic kit. Tumor imaging is performed Q9W from randomization to week 54 and Q12W thereafter. The primary endpoint is PFS per RECIST version 1.1 by investigator review in patients with tumor PD-L1 CPS ≥1 and in all patients. Secondary endpoints are OS in patients with tumor PD-L1 CPS ≥1 and in all patients, PFS per RECIST version 1.1 by blinded independent central review in patients with tumor PD-L1 CPS ≥1 and in all patients, safety, and patient-reported outcomes. Enrollment is ongoing. Clinical trial information: NCT05116189. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

TPS5618 **Poster Session**

A randomized phase II trial of mirvetuximab soravtansine (IMGN853), in folate receptor alpha (FRα)-high recurrent ovarian cancer eligible for platinum-based chemotherapy. *First Author: Fabian Trillsch, University Hospital LMU Munich, Munich, Germany*

Background: Despite radical primary surgery and carboplatin/paclitaxel-based chemotherapy in combination with anti-angiogenic bevacizumab and/or PARP inhibitors (PARPi), most patients (pts) with advanced ovarian cancer (OC) will relapse. Following the implementation of these targeted therapies to first-line treatment, repeated use of bevacizumab and/or PARPi is often not approved nor has conclusively been proven efficacious for all pts with recurrent OC. New combination partners for platinum-based chemotherapy remain important to improve outcome. The antibody-drug conjugate Mirvetuximab soravtansine (MIRV) is comprised of a folate receptor alpha (FRα)-binding antibody, cleavable linker, and the maytansinoid DM4, a potent tubulin-targeting agent. Results from the phase III trial FORWARD I revealed in an exploratory analysis that pts with high FRα expression following PS2+ Scoring (cut off: ≥75% of tumor cells with FRα membrane staining and ≥ 2+ intensity) had significant progression-free survival (PFS) improvements with a hazard ratio of 0.55 compared to mono-chemotherapy (median PFS 5.6 vs 3.2 months, P=0.015) and high activity was most recently confirmed in the SORAYA trial with an overall response rate (ORR) of 32.4%. Preliminary data for the combination of MIRV with carboplatin exist from the Phase 1b FORWARD II trial, which resulted in an ORR of 71%, observed in 17 pts with a median PFS of 15 months, and an ORR of 80% in the FRα medium/high (>50% PS2+) subset of 10 pts. MIRV is well-tolerated with a manageable safety profile. **Methods:** Eligible pts for this multicenter, randomized, two-arm, open-label, comparative phase II trial must have recurrent, FRα high epithelial cancer of the ovary, fallopian tube or peritoneum and have measurable disease. Pts are eligible for platinum-based chemotherapy with a platinum-free interval of more than 3 months and had at least one prior chemotherapy, but are not candidates to receive bevacizumab for the current relapse. Pts can be included irrespective of wildtype BRCA1/2 mutation status, pts with a deleterious mutation are required to have received prior PARPi therapy. Following pre-screening for high FRα expression in FFPE tumor tissue according to PS2+ scoring, 136 pts are randomized (1:1) to: a) Control arm: Platinum-based combination chemotherapy (for 6 cycles) followed by PARPi if indicated or standard of care or b) Experimental arm: Carboplatin + MIRV 6 mg/kg adjusted ideal body weight (AIBW) IV d1 (6 cycles q21d) followed by MIRV monotherapy 6 mg/kg AIBW IV q21d until disease progression. The primary endpoint of PFS will be assessed by modified RECIST 1.1. Key secondary endpoints include overall survival, ORR, and quality of life. Enrollment started in September 2021. Clinical trial information: NCT04274426. Research Sponsor: ImmunoGen.

TPS5619 **Poster Session**

FLORA-5/GOG3035: Frontline chemo-immunotherapy (paclitaxel-carboplatin-oregovomab [PCO] versus chemotherapy (paclitaxel-carboplatin-placebo [PCP]) in patients with advanced epithelial ovarian cancer (EOC)—Phase III, double-blind, placebo-controlled, global, multinational study. *First Author: Angeles Alvarez Secord, Duke Cancer Institute, Duke University Medical Center, Durham, NC*

Background: Oregovomab, a murine IgGκ1 monoclonal antibody, has high affinity binding to tumor associated antigen CA125, thus, rendering the target antigen CA125 more immunogenic or "neoantigen-like" through altered and enhanced antigen processing and presentation to specific T cells. This phenomenon is hypothesized to bypass tumor-associated immune suppression when oregovomab is combined with chemotherapy. In a randomized phase II study, oregovomab in combination with paclitaxel and carboplatin (PC) induced tumor immunity and demonstrated significant improvement in median PFS (41.8 months(m) PCO vs 12.2 m PC, HR 0.46, p=0.0027) and median OS (N.E. PCO vs 43.2 m PC, HR 0.35, p=0.043) in patients with previously untreated EOC. Oregovomab combined with PC had a favorable toxicity profile. FLORA-5/GOG3035, the definitive confirmatory global registration trial, is currently recruiting patients in the front-line setting. **Methods:** The study is a phase 3, multicenter, double-blind, placebo-controlled trial. Optimally debulked patients with FIGO III/IV EOC and serum CA125 ≥ 50 U/ml receiving adjuvant (Cohort 1) or patients receiving neoadjuvant chemotherapy post-interval cytoreductive surgery (Cohort 2) will be randomized to PC + oregovomab or placebo (PCO vs. PCP). Patients with germline *BRCA1/2* mutations are excluded. Chemotherapy will be administered every 3 weeks in both cohorts. Oregovomab/placebo is administered simultaneously at cycles 1, 3, and 5 of chemotherapy with an additional dose at 12 weeks following cycle 5 in Cohort 1. Neoadjuvant patients will be administered oregovomab/placebo after debulking surgery at cycles 4 and 6 with two additional doses at 6- and 18-weeks following cycle 6 in Cohort 2. No other front-line maintenance therapy is permitted. The primary objective is PFS determined by RECIST 1.1. Cohort 1 will recruit 372 patients with a 90% power to detect a difference with an alpha of 0.025 and a hazard ratio of 0.65 when 252 PFS events have been observed. Cohort 2 will be analyzed separately recruiting 232 patients with a 90% power to detect a difference with an alpha of 0.025 and a hazard ratio of 0.60 when 165 PFS events have been observed. An interim futility analysis will be performed. Secondary objectives include OS, frequency and severity of AEs, and QoL. Exploratory objectives include iRECIST, TFST, TSST, PFS2, and evaluation of correlative biomarkers. The study is actively enrolling in the US, Canada, Belgium, Italy, Spain, Czech Republic, Hungary, Poland, Korea, Taiwan, Mexico, Argentina, and Chile. 179 patients were enrolled at time of submission. Clinical trial information: NCT04498117. Research Sponsor: OncoQuest Pharmaceuticals, Inc.

TPS5620 **Poster Session**

ROSELLA: A phase 3 study of relacorilant in combination with nab-paclitaxel versus investigator's choice in advanced, platinum-resistant, high-grade epithelial ovarian, primary peritoneal, or fallopian-tube cancer. *First Author: Alexander Olawaiye, University of Pittsburgh, Pittsburgh, PA*

Background: Chemotherapy resistance is a major concern in the treatment of advanced platinum-resistant and platinum-refractory ovarian cancer. One mechanism of resistance is driven by cortisol, which can suppress the apoptotic pathways that chemotherapy agents rely upon, eg, suppression of BCL2 and FOXO3a pathways. Preclinical and clinical data indicate that glucocorticoid receptor (GR) antagonism may reverse the anti-apoptotic effects of cortisol, thereby restoring the efficacy of cytotoxic agents. Relacorilant is a selective GR modulator that has shown promise in overcoming resistance when combined with taxanes (particularly nab-paclitaxel) in preclinical models (Greenstein & Hunt 2021) and early-phase clinical studies (Munster et al. 2019) in various solid tumors. A randomized, controlled phase 2 study of relacorilant + nab-paclitaxel found clinically meaningful improvements in progression-free survival (PFS) and duration of response (DOR) without increased side effect burden in patients with recurrent, platinum-refractory and platinum-resistant ovarian cancer (Colombo et al. 2021). The aim of this phase 3 study is to confirm these phase 2 findings in a larger patient population. **Methods:** ROSELLA (EudraCT 2022-000662-18, NCT pending) is a phase 3, randomized, 2-arm, open-label, multicenter study of relacorilant + nab-paclitaxel compared to investigator's choice of chemotherapy agents in patients with confirmed high-grade serous epithelial ovarian, primary peritoneal, or fallopian tube cancer. The trial is being conducted at multiple sites in North America and Europe and has a planned enrollment of 360 patients. Patients are randomized 1:1 to either relacorilant (150 mg the day before, day of, and day after nab-paclitaxel infusion) + nab-paclitaxel (80 mg/m^2 on days 1, 8, and 15 of each 28-day cycle) or investigator's choice of chemotherapy (liposomal doxorubicin, paclitaxel, topotecan, or nab-paclitaxel). Randomization is stratified by prior lines of therapy (1 vs > 1), region of world (North America vs Europe), and prior bevacizumab (yes/no). Adult female patients with platinum-resistant disease (progression within 6 months of completion of platinum-containing therapy), excluding patients with primary platinum refractory disease, who have received 1–3 lines of prior systemic anticancer therapy and at least 1 prior line of platinum therapy are being enrolled. Life expectancy ≥3 months, adequate organ function, and ECOG performance status of 0 or 1 are required. The primary study endpoint is PFS by blinded independent central review. Key secondary endpoints include overall survival, PFS by investigator, overall response rate, best overall response, DOR, clinical benefit rate, safety, quality of life, CA-125, pharmacodynamics, and pharmacokinetics. Clinical trial information: 2022-000662-18. Research Sponsor: Corcept Therapeutics.

TPS5621 **Poster Session**

OZM-114: Phase Ib expansion study of CX-5461in patients with solid tumors and *BRCA2* and/or *PALB2* mutation. *First Author: Husam Alqaisi, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Pre-clinical and clinical data demonstrate that CX-5461 selectively kills HR deficient cancer cells through stabilizing G4 structures and inducing replication-dependent DNA damage. Phase 1 studies suggest CX-5461 has clinical activity and warrants further investigation in HR-deficient tumors, including those with pathogenic *BRCA2* and *PALB2* mutation. The recommended phase 2 dose (RP2D) requires further refinement to establish the chronic tolerable dose for further phase 2 trials, particularly regarding the incidence of ocular toxicity. The doses of 325mg/m2 and 250mg/m2 were selected for this study expansion cohorts because it is well within the efficacy range and below the first occurrence of ocular toxicity in a previous study. **Methods:** This is an open-label, multi-center, phase 1b study designed to determine a tolerable dose of CX-5461 in patients with ovarian, pancreatic, prostate, and breast cancers for Phase II trials. Eligible patients will be enrolled into two cohorts: A) Main cohort (target accrual: 32 patients) and B) Exploratory cohorts (target accrual: 20 patients), see table-1 below. The primary outcomes include assessment of: 1) Safety and tolerability of CX-5461, in particular to determine late onset ocular toxicity 2) Anti-tumor activity of CX-5461 in patients with solid tumors and germline *BRCA2* and/or *PALB2* mutation, and 3) Effect of CX-5461 on Quality of Life measures. Secondary outcomes include evaluation of :1) Safety: CTCAE v 5.0, SAEs, dose modifications due to AEs, 2) Activity: best overall response from tumor evaluations performed every 2 cycles, according to RECIST v1.1, and duration of response., and 3) patient-reported outcomes: PRO (PRO-CTCAE v1.0 questionnaires to evaluate cutaneous, gastrointestinal, visual/perceptual, cardio/circulatory, sleep/wake and miscellaneous symptoms. Exploratory Objectives include assessment of: 1) anti-tumor activity of CX-5461 in patients with ovarian cancer and pathogenic/likely-pathogenic *BRCA1* mutation and/or other HRD-associated somatic mutation, and 2) molecular profile of tumors and predictive value of mutational signatures in predicting response or resistance to CX-5461. Clinical trial information: NCT04890613. Research Sponsor: Senhwa Biosiences.

Study cohorts and treatment arms.

Main study cohort	Exploratory cohort
histologically-confirmed pancreatic, ovarian, prostate, or breast cancers with pathogenic/likely-pathogenic germline *BRCA2* and/or *PALB2* mutation.	women with ovarian cancer and pathogenic/likely-pathogenic *BRCA1 and/*or other HRD-associated mutation.
Arm A	**Arm C**
N=16	N=10
IV CX-5461	IV CX-5461
250mg/m^2, Day 1 and 8 of a 28-day cycle	250mg/m^2, Day 1 and 8 of a 28-day cycle
Safety cohort review every 4 weeks.	
Arm B	**Arm C**
N=16	N=10
IV CX-5461	IV CX-5461
325mg/m^2, Day 1 and 8 of a 28-day cycle	325mg/m^2, Day 1 and 8 of a 28-day cycle
Safety cohort review every 4 weeks.	

TPS5622 **Poster Session**

STRO-002-GM2: A phase 1, open-label, safety, pharmacokinetic, and preliminary efficacy study of STRO-002, an anti-folate receptor alpha (FolRα) antibody-drug conjugate (ADC), in combination with bevacizumab in patients with advanced epithelial ovarian cancer (EOC, including fallopian tube or primary peritoneal cancers). *First Author: R. Wendel Naumann, Levine Cancer Institute, Atrium Health, Charlotte, NC*

Background: STRO-002 is a novel FolRα targeting ADC, generated using cell-free antibody production and site-specific conjugation technology. STRO-002 demonstrates potent *in vitro* cytotoxicity in EOC cell lines and anti-tumor activity in xenograft models, including induction of immunogenic cell death. STRO-002 is currently being studied as a single agent in ovarian and endometrial cancer (Phase 1 Study STRO-002-GM1; NCT03748186). Preliminary efficacy data in relapsed/progressive platinum resistant EOC compared favorably to standard chemotherapy (Naumann W., *et al*, ASCO 2021). Pre-clinical models tested with STRO-002/bevacizumab combinations demonstrated additive anti-tumor activity compared to monotherapy. This study is a first in human study of STRO-002 plus bevacizumab in patients with advanced ovarian cancer that have progressed on standard therapy. **Methods:** STRO-002-GM2 is a Phase 1, open-label, multicenter, dose escalation study with a standard 3+3 design with a 21-day dose-limiting toxicity (DLT) assessment period followed by dose expansion. The study will assess safety, establish recommended phase 2 dose (RP2D), and preliminary efficacy of STRO-002/bevacizumab combination in patients with recurrent high-grade EOC. Bevacizumab will be administered at the labeled dose of 15 mg/kg given with STRO-002 starting at 3.5 mg/kg, both administered IV q 3 weeks. Planned dose escalation doses of STRO-002 include 3.5, 4.3, and 5.2 mg/kg and will continue until MTD/MAD is reached. Additional intermediate dose level cohorts may be added for RP2D optimization. Once a cohort is cleared per dose escalation rules, up to 10 additional subjects may be enrolled and treated at that cleared dose level in order to obtain additional safety and efficacy data for RP2D determination and ungating of the expansion stage. Dose expansion will enroll approximately 40 patients treated at the RP2D. The patient population is relapsed high-grade EOC with up to 4 prior regimens. Subjects with primary platinum refractory disease will be enrolled in dose escalation only. Key inclusion criteria include: measurable disease, adequate bone marrow and renal function. Key exclusion criteria include: contraindication to receive bevacizumab and prior treatment with a FolRα ADC or ADC containing a tubulin inhibitor. Efficacy evaluation is per RECIST v1.1. Tumor tissue (archival or fresh biopsy) is required. Study oversight includes a Safety Evaluation Team. Samples will be collected to assess the PK and immunogenicity. No formal statistical hypothesis testing will be conducted in this study. This study is currently open for enrollment in the U.S. Clinical trial information: NCT05200364. Research Sponsor: Sutro Biopharma.

TPS5623 **Poster Session**

KEYNOTE-C93/GOG-3064/ENGOT-en15: A phase 3, randomized, open-label study of first-line pembrolizumab versus platinum-doublet chemotherapy in mismatch repair deficient advanced or recurrent endometrial carcinoma. *First Author: Brian M. Slomovitz, Division of Gynecologic Oncology, Mount Sinai Medical Center, Miami Beach, FL*

Background: Carboplatin-paclitaxel chemotherapy (with trastuzumab for HER2+ uterine serous carcinoma) is the standard of care first-line systemic treatment for recurrent or metastatic endometrial carcinoma (EC), which has a 5-year relative survival rate of only 17%. Worse survival outcomes have been shown for the mismatch repair deficient (dMMR) subtype of EC. Pembrolizumab (pembro), an anti-PD-1 antibody, showed compelling antitumor activity in previously treated, advanced MSI-H/dMMR EC in the phase 2 KEYNOTE-158 study (ORR, 48%; median duration of response [DOR], not reached; O'Malley *JCO* 2022). KEYNOTE-C93/GOG-3064/ENGOT-en15 (NCT05173987) is a phase 3, randomized, open-label study evaluating first-line pembro versus carboplatin-paclitaxel chemotherapy in patients with dMMR advanced or recurrent EC. **Methods:** Patients aged ≥18 years with histologically confirmed stage III/IV recurrent EC including carcinosarcoma (mixed Mullerian tumor), radiographically evaluable disease (measurable or nonmeasurable per RECIST v1.1), no prior systemic therapy (prior radiation with or without radiosensitizing chemotherapy > 2 weeks before first dose or prior hormonal therapy ≥1 week before randomization is permitted), and an ECOG PS ≤1 are eligible. Patients must have central confirmation of dMMR status. Approximately 350 patients will be randomized 1:1 to receive pembro 400 mg IV Q6W for 18 cycles (~2 years) or carboplatin AUC 5 or 6 mg/mL/min IV Q3W and paclitaxel 175 mg/m^2 IV Q3W for 6 cycles (with option for > 6 cycles). Trastuzumab is permitted for patients in the chemotherapy arm with HER2+ serous EC. Randomization is stratified by disease status (newly diagnosed advanced EC vs recurrent EC) and histology (endometrioid vs nonendometrioid). Treatment will continue for the specified number of cycles or until PD or unacceptable toxicity. Patients in the chemotherapy arm have the option to receive pembro following confirmed PD by blinded independent central review (BICR). Tumor imaging will be performed Q9W from randomization to week 54 and Q12W thereafter. AEs will be assessed from randomization to 30 days (90 days for serious AEs) after treatment discontinuation and graded per NCI CTCAE version 5.0. Dual primary endpoints are PFS per RECIST v1.1 by BICR and OS. Secondary endpoints are ORR, disease control rate, and DOR per RECIST v1.1 by BICR; PFS per RECIST v1.1 by investigator review; PFS2 (ie, time from randomization to PD per investigator assessment or death from any cause after start of subsequent anticancer therapy); safety; and patient-reported outcomes. PFS and OS will be estimated by the Kaplan-Meier method, with treatment differences assessed by the stratified log-rank test and HRs with 95% CIs determined using a Cox proportional hazard model. Enrollment is ongoing. Clinical trial information: NCT05173987. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

TPS5624 **Poster Session**

Trial in progress: Phase II activity trial of high-dose radiation and chemosensitization in patients with macrometastatic lymph node spread after sentinel node biopsy in vulvar cancer: Groningen International Study on Sentinel Nodes in Vulvar Cancer III (GROINSS-V III/NRG-GY024). *First Author: Lilian T. Gien, Sunnybrook Odette Cancer Centre, Toronto, ON, Canada*

Background: Early stage invasive squamous cell carcinoma of the vulva is treated by radical excision of the primary tumor combined with a sentinel node (SN) procedure for the groins. GROINSS-VI and GOG-173 demonstrated that if there is no metastasis to the SN, then standard of care is observation. GROINSS-VII/GOG-270 demonstrated that micrometastatic disease (<2mm) to the SN requires standard radiotherapy (50 Gy) without the need for an inguinofemoral lymphadenectomy (IFL). This study also found that patients with macrometastasis (> 2mm) required IFL in order to have an acceptably low groin recurrence rate. However, IFL is associated with significant morbidity such as lymphedema, wound healing issues, and recurrent infections. It is hypothesized that for those with macrometastasis (> 2 mm) in the SN, the efficacy of treatment can be increased by giving a higher dose of radiotherapy along with chemosensitization. **Methods:** This is an international multicenter single-arm phase II prospective clinical trial. The primary objective is to investigate the safety of replacing IFL by chemoradiation in early-stage vulvar cancer patients with a macrometastasis (> 2mm) and/or extracapsular extension in the SN. The primary endpoint is the groin recurrence rate in the first two years after primary treatment. Secondary endpoints are short and long-term morbidity associated with the SN procedure and chemoradiation and quality of life as measured by EORTC-QLQc30. Patients with invasive (> 1mm) squamous cell carcinoma of the vulva, stage T1, tumor size < 4 cm diameter and no suspicious lymph nodes by imaging of the groins will proceed with SN detection. Institutions enrolling patients must demonstrate prior surgical experience with SN detection with the submission of at least 10 successfully completed cases in vulvar cancer. Patients with SN metastases > 2mm and/or with extracapsular extension or those with > 1 SN with micrometastases will be eligible for this study. Treatment will consist of chemoradiation with a dose of 56 Gy to the groin combined with weekly cisplatin 40 mg/m2 IV on days 1, 8, 15, 21 and 29 of radiotherapy. One hundred and fifty-seven patients in Europe, United States and Canada will be enrolled. The study includes continuous monitoring of groin recurrences with stopping rules. Results of this trial may be practice changing and eliminate the need for IFL in all women with clinically early stage vulvar cancer. The study is currently open for enrollment. Clinical trial information: NCT05076942. Research Sponsor: Dutch Cancer Society, U.S. National Institutes of Health.

6000 **Oral Abstract Session**

Radiotherapy alone versus concurrent chemoradiotherapy in intermediate risk nasopharyngeal carcinoma: A multicentre, open-label, noninferiority, randomised phase III trial. *First Author: Jun Ma, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: The benefit of concurrent chemotherapy to treat intermediate-risk (stage II and T3N0M0) nasopharyngeal carcinoma (NPC) remains controversial. We aimed to assess whether concurrent chemotherapy can be omitted safely for intermediate-risk NPC patients treated with intensity-modulated radiotherapy. **Methods:** This multi-centre, noninferiority, open-label, randomised controlled, phase III trial was done at 4 hospitals in China. Patients aged 18–65 years, with histologically confirmed, stage T1-2N1/T2-3N0M0, a Karnofsky score of at least 70 were randomly assigned (1:1) to receive either concurrent chemoradiotherapy (CCRT) (cisplatin 100 mg/m^2 on days 1, 22, and 43) or radiotherapy alone (RT). Key exclusion criteria included: maximal axial diameter of neck lymph node ≥30mm, positive neck lymph node at level IV or lower, pretherapy plasma EBV DNA level ≥4000 copy/ml. Randomisation was performed with a random number code stratified by treatment centre and stage. The primary endpoint was failure-free survival （FFS) .The calculated sample size was 169 per group, with an 80% power (one-sided α 0.05). **Results:** Between November 11, 2015 and August 4, 2020, 341 NPC patients were randomly assigned to receive either RT (n=172) or CCRT （n=169). After a median follow-up of 41 months, intention-to-treat analysis showed that 3-year FFS was 90.7% (95% CI 86.2–95.2) in the RT group, and 92.1% (95%CI 88.8–96.4) in the CCRT group, with a difference of -1.4% (upper limit of the one-sided 95% CI 4.5; $p_{non\text{-}inferiority}$=0.00017). Similarly excellent FFS was found in the per-protocol analysis: 3year FFS for RT versus CCRT was 90.3% (95% CI 85.6–95.0) and 92.1% (95% CI 87.8–96.4), respectively, with a difference of -1.8% (upper limit of the one-sided 95% CI 4.3; $p_{non\text{-}inferiority}$=0.00014). No differences were observed between groups in terms of overall survival, locoregional relapse and distant metastasis. Patients in the CCRT group developed significantly more grade 3-4 hematologic and nonhematologic adverse events such as vomiting (CCRT group 14.8% vs. RT group 1.2%), anorexia (29.9% vs. 4.8%), mucositis (18.9 % vs. 9.7%) and weight loss(4.7% vs. 0.6%) . No patients died from treatment-related causes. **Conclusions:** Radiotherapy alone provides comparable disease control or survival and less toxicity compared to CCRT in the intermediate risk NPC. Clinical trial information: NCT02633202. Research Sponsor: Sun Yat-sen University Clinical Research 5010 Program.

	RT group(%)	CCRT group (%)	P value
Intention-to-treat population	n = 172	n = 169	
3-yr overall survival	98.7	99.4	0.178
3-yr distant metastasis-free survival	95.6	98.1	0.136
3-yr locoregional recurrence-free survival	94.4	93.9	0.975
Per-protocol population	n = 165	n = 169	
3-yr overall survival	98.7	99.4	0.159
3-yr distant metastasis-free survival	95.4	98.1	0.118
3-yr locoregional recurrence-free survival	94.2	93.9	0.890

6001 **Oral Abstract Session**

Nimotuzumab plus chemoradiotherapy versus placebo plus chemoradiotherapy in patients with locally advanced nasopharyngeal carcinoma (NPC): A prospective, randomized-controlled, double-blinded, multicenter phase III clinical trial. *First Author: Yan Sun, Beijing Cancer Hospital, Beijing, China*

Background: Epidermal growth factor receptor (EGFR) is highly expressed in most NPC, and it is also an essential factor of prognosis for NPC. nimotuzumab is a humanized anti-EGFR monoclonal antibody. Retrospective clinical studies showed that nimotuzumab combined with chemo-radiotherapy had better survival benefits in locally advanced NPC. The present study is a confirmatory study that aims to assess the clinical efficacy of long-term survival and safety of nimotuzumab combined with chemo-radiotherapy in locally advanced NPC patients. **Methods:** Patients with locally advanced NPC were randomized (3:1) to receive nimotuzumab (200 mg, weekly, 7-8 weeks) plus chemo-radiotherapy (Arm A) versus chemo-radiotherapy (intensity-modulated radiation therapy or conventional radiotherapy, cisplatin100mg/m^2/d, 21days/cycle, three cycles) plus placebo (Arm B) as front-line therapy. The primary endpoint was a 5-year OS rate, and the secondary endpoints included disease-free survival and safety. **Results:** 482 patients in 24 study sites were enrolled (361 in Arm A vs. 121 in Arm B). Both groups were well balanced regarding age, gender, race and ethnicity. The 5-year OS rate was 76.9% in Arm A compared to 64.3% in Arm B (log-rank=4.125, p=0.042). The median DFS was 50.6 months and 42.6 months in Arm A and B, respectively. The 5-year DFS rate was 40.0% in Arm A compared to 14.4% in Arm B (log-rank=1.701, p=0.192). The combination of nimotuzumab plus chemo-radiotherapy was well tolerated. The incidence of adverse drug reactions (ADRs) in Arm A was similar to Arm B (35.7% vs. 42.1%, p=0.207), and the grade 3-5 ADRs as well (17.7% vs.15.7%, p=0.609). **Conclusions:** Nimotuzumab plus chemo-radiotherapy increase 5-year OS of NPC patients with good safety profile. Clinical trial information: 01074021. Research Sponsor: None.

6002 **Oral Abstract Session**

Reduced-dose radiotherapy for pretreatment EBV DNA selected low-risk stage III nasopharyngeal carcinoma: A single-arm, phase II trial. *First Author: Hai-Qiang Mai, Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: The radiotherapy (RT)-related toxicities of nasopharyngeal carcinoma (NPC) caused by the standard dose of 70 Gy still remained a critical issue. It is necessary to select optimal candidates for reduced-dose RT. The pretreatment Epstein-Barr virus (EBV) DNA level has been universally applied to select low-risk NPC patients and the response to induction chemotherapy (IC) can be used to screen patients sensitive to RT. In this trial, we assessed whether RT dose of 60Gy was noninferior to standard dose in low-risk stage III NPC patients with favorable response to IC. **Methods:** We did a single-arm, single-center, phase II clinical trial in Sun Yat-sen University Cancer Center in China. Patients aged 18-70 with low-risk (EBV DNA level < 4,000 copies/ml) stage III NPC were treated with two cycles IC of TPF regimen (paclitaxel liposome 135 mg/m^2 on days 1, cisplatin 25 mg/m^2 on days 1-3, fluorouracil 750 mg/m^2 as a continuous 120 hours infusion on days 1-5) intravenously given every 3 weeks. Patients with complete/partial response (CR/PR) and undetectable EBV DNA level were assigned 60Gy intensity modulated RT, currently with 100 mg/m^2 cisplatin intravenously on days 1, 22, and 43. The primary end point was 2-year progression-free survival (PFS). The second end points included: overall survival (OS), locoregional relapse-free survival (LRRFS) and distant metastasis-free survival (DMFS), etc. The trial was registered with ClinicalTrials.gov, number NCT 03668730. **Results:** Between Nov 19, 2018, and Mar 13, 2020, a total of 216 patients were enrolled in this study, and 1 patient withdrew from the informed consent. 215 patients completed two cycles IC, after which 116 (54.0%) and 99 (46.0%) patients were assigned 60Gy and 70Gy RT, respectively. For patients treated with 60 Gy RT, 2-year PFS, OS, LRRFS and DMFS were 94% (95% confidence interval [CI], 89 to 99), 100%, 95% (95%CI, 91 to 99) and 97% (95%CI, 93 to 100), respectively, with the median follow-up of 25.8 months (interquartile range 22-28). During RT, the most common toxicity was nausea, with the proportion of 61% (71/116), 5% (6/116) for grade 1-2 and 3. The major grade 3-4 toxicities were leucopenia, neutropenia, mucositis and pain, which were reported in 16 (14%), 16 (14%), 13 (11%) and 15 (13%) patients, respectively. The most common late toxicity was grade 1-2 dry mouth with the incidence of 54% (63/116). No grade 3+ long-term adverse event was observed and no patients died from treatment-related causes. All quality of life items, domains, and symptom scores returned to baseline by 6 months, with the exception of dry mouth and sticky saliva. **Conclusions:** Our findings show that reduced-dose RT (60Gy) is associated with favorable survival outcomes and limited treatment-related toxicities for low-risk stage III NPC patients sensitive to IC. Clinical trial information: 03668730. Research Sponsor: None.

LBA6003 **Oral Abstract Session**

Results of phase 3 randomized trial for use of docetaxel as a radiosensitizer in patients with head and neck cancer unsuitable for cisplatin-based chemoradiation. *First Author: Vijay Maruti Patil, Tata Memorial Centre, Mumbai, India*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

6004 **Oral Abstract Session**

An open-label, noninferiority phase III RCT of weekly versus three weekly cisplatin and radical radiotherapy in locally advanced head and neck squamous cell carcinoma (ConCERT trial). *First Author: Atul Sharma, All India Institute of Medical Sciences, New Delhi, India*

Background: CCRT using 3 weekly cisplatin (DDP) 100mg/m^2 is considered standard nonsurgical option for LAHNSCC. Many prefer DDP 40 mg/m^2 weekly assuming this to be non inferior, with better radio sensitization, and less toxic but without robust supporting evidence. We designed this non inferiority trial to compare 3 weekly DDP to weekly DDP. **Methods:** Multicentric non inferiority RCT to compare DDP 100 mg/m^2 (Control as C) 3 weekly x 3 times to 40 mg/m^2 (Test as T) weekly DDP x7 times with concurrent RT as definitive therapy in non nasopharyngeal LAHNSCC. Primary objective was 2 years loco regional control (LRC) rates. Secondary endpoints included OS, PFS, toxicity, compliance, others. Assuming LRC of 60%, power of 80%, alpha error of 5%, and non inferiority margin of 10% 143 patients in each arm were required (including 10% non evaluable etc). **Results:** Between April 2018 and January 2021, 278 were randomised. Median age was 56 years (range 19-70), 89.6% were males. Primary sites were, oropharynx (59.6%), larynx (17.5%), hypopharynx, and oral cavity (11.6%) each. TNM stage was, stage III (29.1%), stage IVA (50.5%), and IVB (20.4%). 13% of oropharyngeal who were tested for p16 were found positive. ECOG PS was 0-1 in 78.9%. 135 in each arm were eligible for treatment and 132 received some form of treatment. Baseline characteristics (Chi square/Fisher's exact test) were well balanced except higher number of patients with LVEF <50% in T arm (p=0.035). 87.2% of patients in C arm, and 81.6% in T arm received ≥ 60 Grays (p=.94), 78.6% in C and 81.6% patients in T arm received ≥ 200 mg/m2 of DDP (p=.31). There were more treatment delays in treatment in C arm (p=NS). Treatments interruptions (p=0.035), hospitalizations (p=0.004), use of additional IV fluids (p= <.001), mucositis (p=.029), myelosuppression (P=.021), renal toxicity (p=<.001), vomiting ((p=.002), hyponatremia (p=.004) were all significantly more in C arm. There were 10 toxic deaths in C arm and 7 in T arm. 81.6% in C arm and 85.4% patients in T arm achieved CR+PR (p=.055). LRC rates at 2 years were 57.69% in C arm and 61.53% in T arm, with an absolute difference of 3.84% and (one sided 95% CI= -6.15, 13.80) which is within the pre defined non inferiority margin of -10%. Cumulative 2 year LRC rates were 52.6% in T and 47.4% in C (log-rank p=0.426; HR 0.86 [95%CI: 0.60-1.23]) by parametric survival estimates with an absolute difference of 5.2% (95%CI= -7.7, 18.2) again within pre defined margin. There was no significant difference in median time to loco-regional failure (C=21.23 months and T= NR; p=.45), OS (C=30.50 months and T= 25.46; p=.59) and PFS (C=20.60 months and T= 20.66; p=.46). **Conclusions:** This academic trial confirms that CCRT with weekly DDP is non inferior to 3 weekly DDP, is better tolerated with less interruptions, hospitalizations, and toxicity and should now be considered as one of the standards. Clinical trial information: CTRI/2018/03/012422. Research Sponsor: None.

6005 **Oral Abstract Session**

ROMAN: Phase 3 trial of avasopasem manganese (GC4419) for severe oral mucositis (SOM) in patients receiving chemoradiotherapy (CRT) for locally advanced, nonmetastatic head and neck cancer (LAHNC). *First Author: Carryn M. Anderson, The University of Iowa Hospitals & Clinics, Iowa City, IA*

Background: Intensity-modulated radiotherapy (IMRT) plus cisplatin is an established treatment for LAHNC, but ~70% of patients develop SOM (WHO grade 3 or 4), limiting their ability to eat solids (grade 3) or liquids (grade 4), and often requiring nutrition by feeding tube. Management focuses on symptoms and supportive care (Elad 2020). There are no US-approved drugs to reduce SOM in LAHNC. A radiotherapy (RT)-induced burst of superoxide initiates oral mucositis (OM) development (Sonis 2004). Avasopasem (GC4419, AVA) is an investigational selective small molecule dismutase mimetic designed to convert superoxide to hydrogen peroxide, which may protect normal cells from, and potentially sensitize cancer cells to, radiation (Riley DP 2006, El-Mahdy 2020). In a randomized, double-blind phase 2b trial, AVA reduced duration and incidence of SOM due to CRT for LAHNC vs placebo (PBO) (Anderson 2019). The present trial (NCT03689712) further assessed safety and efficacy of AVA to reduce SOM due to CRT for LAHNC of the oral cavity (OC) or oropharynx (OP). **Methods:** Double-blind, PBO-controlled trial; patients receiving 60-72 Gy of IMRT (>50 Gy to ≥2 oral mucosal sites) plus cisplatin (weekly or q3 weeks) were randomized 3:2 to AVA 90 mg vs PBO by 60-minute IV infusion, M-F before each RT fraction. OM by the WHO scale was assessed by trained evaluators biweekly during RT & weekly for 2 weeks thereafter. Primary endpoint: SOM (WHO grade 3 or 4) incidence through the end of IMRT. Secondary endpoints included SOM duration through 2 weeks post-IMRT and grade 4 OM incidence through the end of IMRT. **Results:** N = 407 (241 AVA/166 PBO); median age 61; 86% male; 82% OP. Statistically significant 16% relative reduction in SOM incidence (54% vs 64%; p= 0.045) and 56% relative reduction in SOM duration (median, 8 vs 18 days; p= 0.002) were observed. Grade 4 incidence was reduced 27% (p= 0.052). Improvement was seen in multiple secondary and exploratory endpoints (table). Adverse event frequencies (all grade, grade 3+, serious) were comparable between treatment groups without clear AVA-specific toxicity or increase in cisplatin-attributable toxicity. **Conclusions:** AVA produced statistically significant, clinically meaningful improvement of SOM vs PBO that was consistent across multiple measures of SOM, and was well tolerated, with an adverse event profile consistent with expectations for IMRT/cisplatin in LAHNC. Clinical trial information: NCT03689712. Research Sponsor: Galera Therapeutics, Inc.

	PBO	AVA	AVA vs PBO	
			Relative Δ	p value
SOM incidence through IMRT	64%	54%	16%	0.045*
SOM duration through f/u, median days	18	8	56%	0.002*
Gr 4 OM incidence through IMRT	33%	24%	27%	0.052
SOM incidence through 50 Gy	45%	28%	38%	< 0.001
SOM incidence through 60 Gy	58%	42%	28%	0.002
SOM incidence through f/u	71%	58%	18%	0.012
SOM onset, median days	38	49	29%	0.002

*statistically significant.

6006 **Oral Abstract Session**

Association of plasma tumor tissue modified viral HPV DNA (TTMV) with tumor burden, treatment type, and outcome: A translational analysis from NRG-HN002. *First Author: Sue S. Yom, University of California-San Francisco, San Francisco, CA*

Background: NRG-HN002 was a phase II trial that randomized patients with p16-positive oropharynx cancer to 60 Gy IMRT with concurrent cisplatin (IMRT-C) or 60 Gy accelerated IMRT. The protocol specified plasma collection at pretreatment (t0), intratreatment (20-28 Gy, t1), and 2 weeks to 1 month posttreatment (t2); at these timepoints, TTMV was assayed. A prespecified analysis evaluated: association of t0 TTMV to gross tumor volume (GTV) of primary and lymph nodes; t0-t1 decrease in TTMV; and association of t2 TTMV to treatment and outcome. **Methods:** TTMV was quantified as fragments/mL of plasma. If TTMV-HPV16 was not detected (<5 fragments/mL) or was a low value, the specimen was tested for TTMV-HPV18, -HPV31, -HPV33, and -HPV35. The distribution of t0 TTMV fragments was highly skewed, so these data were log-transformed; their correlation to GTV was measured by Pearson coefficient. Paired and two-sample t-tests were used to compare t0 and t1 log-transformed fragments within and between arms. Proportions of TTMV detection at t2 between arms were compared using Fisher's exact test. Rates of undetectability and fragment clearance (≥94% reduction from t0) at t2 were estimated. The negative predictive value (NPV) was estimated for 2-year locoregional failure (LRF) and progression-free survival (PFS). **Results:** Of 306 eligible patients, 164 (53.6%) donated at least one specimen. The median collection time/RT dose was -2.6 days before RT (Q1-Q3, -4.0-0.0), at 24 Gy (22-28), and 25.5 days after RT end (18-31). The t0, t1, and t2 patient participation rates were 53.6%, 45.4%, and 42.5%. Zero TTMV fragments were detected in 10.4% at t0, 19.4% at t1, and 93.1% at t2. At t0, t1, and t2, 83.5%, 79.1%, and 6.2% had detectable TTMV; 78.0%, 73.4%, and 5.4% had TTMV-HPV16. In correlating GTV to t0 TTMV fragments, the Pearson coefficient was 0.30 (95% CI 0.15-0.44). In a linear model, T stage (p=0.01) and N stage (p=0.004) were positively associated with t0 TTMV fragments. On the IMRT-C arm, the t0-to-t1 mean change was -1.06 (p=0.0009), and for IMRT, it was -0.22 (p=0.35) (p=0.03 between arms). The t2 TTMV detectability rate was 3.3% for IMRT-C vs 8.7% for IMRT (p=0.28). The t2 TTMV undetectability rate was 93.8% and the fragment clearance rate was 95.4%. Two-year LRF and PFS were 6.2% and 91.4%. The NPV of t2 undetectability was 95.0% (95% CI 89.4-98.1) for 2-year LRF and 93.3% (95% CI 87.3-97.1) for 2-year PFS, and for fragment clearance was 94.3% and 92.7%. **Conclusions:** Feasibility of the TTMV-HPV assay in clinical trial specimens was established. About 10% of p16-positive patients had zero TTMV fragments at baseline. Among those with TTMV detectability, 6.6% had types other than TTMV-HPV16. T and N stage were positively associated with TTMV fragments. The IMRT-C arm achieved rapid TTMV undetectability unlike IMRT. The NPV of posttreatment undetectability was 93-95% for 2-year LRF and PFS. Research Sponsor: U.S. National Institutes of Health.

6007 **Oral Abstract Session**

A randomized phase II study evaluating concurrent or sequential fixed-dose immune therapy in combination with cisplatin and intensity-modulated radiotherapy in intermediate- or high-risk, previously untreated, locally advanced head and neck cancer (LA SCCHN). *First Author: David Anthony Clump, UPMC Hillman Cancer Center, Pittsburgh, PA*

Background: Optimal timing, either concurrent or sequential, of anti-programmed death (PD)-1 antibody with chemoradiotherapy (CRT) for LA SCCHN is unknown. Recently, JAVELIN-100 showed no benefit of adding concurrent avelumab to CRT. **Methods:** In this randomized, phase 2 study, patients (pts) with intermediate risk human papillomavirus (HPV) positive oropharyngeal (> 10 pack years or T4 or N3) or HPV negative previously-untreated LA SCCHN of the oropharynx, hypopharynx, larynx, or oral cavity (unselected PD-L1 status) were randomized 1:1 (stratified by HPV and nodal stage) to receive CRT (cisplatin 40 mg/m^2 weekly + radiation therapy consisting of 70 Gy in 35 fractions and concurrent or sequential pembrolizumab (pembro) 200 mg q 3 week X 8 doses total . Pembro was started 1 week prior to CRT and 2 weeks after CRT in the concurrent and sequential arms respectively. The primary objective was to evaluate two schedules of pembro (concurrent vs. sequential) combined with CRT in order to recommend the regimen to be tested subsequently. The study was powered to detect a signal of antagonism, defined as a 1-year local failure rate exceeding 60% and each arm had to meet all of the following: dose limiting toxicity (DLT) rate £ 20%, 1-year local failure rate (LRF) < 60%, and 1-year PFS ^{3} 60%. If all three were met the arm with a numerically superior 1-year PFS would be selected for further study. Extensive correlatives were collected and will be reported in the future. **Results:** Between 05/2016 and 05/2021, 80 patients were randomized, 41 participants received concurrent while 39 patients received sequential pembro along with CRT. Minimum follow-up is 9 months with a median > 24 months. Both treatment schedules met the predefined composite endpoints of rate of DLT, LRF, and 1-year PFS. The 1 and 2-year PFS for sequential pembro of 89% was numerically higher than that of 82% and 78% for concurrent pembro. OS at 1 and 2 years was 94% for sequential and 82% and 78% for concurrent pembro. Median PFS and OS was not reached in either arm. 3-year PFS and OS will be reported along with PD-L1 status and other exploratory correlatives. Grade 3 adverse events were 76.7% with concurrent vs 58.9% with sequential pembro added to CRT. There were 2 Grade 5 events with sequential and 3 Grade 5 with concurrent pembro. **Conclusions:** This randomized phase II trial evaluated fixed-dose concurrent versus sequential pembro added to standard CRT in LA SCCHN. Sequential pembro had a numerically superior 1 and 2-year PFS compared to concurrent therapy. Sequential pembro is the preferred regimen to compare with standard of care CRT for LA SCCHN in a phase III trial. Clinical trial information: NCT02777385. Research Sponsor: Merck, Inc.

6008 **Oral Abstract Session**

A phase II trial of pembrolizumab and cabozantinib in patients (pts) with recurrent metastatic head and neck squamous cell carcinoma (RMHNSCC). *First Author: Nabil F. Saba, Winship Cancer Institute Emory University School of Medicine, Atlanta, GA*

Background: Pembrolizumab (pembro) is an immune checkpoint inhibitor (ICI) approved for treating pts with recurrent/metastatic (RM) HNSCC. Cabozantinib (cabo) is a multiple receptor tyrosine kinase inhibitor (TKI) targeting MET and VEGFR2 shown to reduce tumor growth, metastasis, and angiogenesis and has immuno-modulatory properties. **Methods:** This is a phase II, open label multi-center, single arm trial evaluating the tolerability and clinical benefit of pembro administered at 200 mg/m2 every 3 weeks and cabo 40 mg daily for pts with RM HNSCC who have not received prior ICI. It had a lead-in safety cohort allowing reduction of cabo dose to 20mg daily. Eligible pts had RM HNSCC, deemed incurable, with a tumor PD-L1 CPS > 1, RECIST 1.1 measurable disease, a life expectancy of > 3 months, an Eastern Cooperative Group (ECOG) Performance Status (PS) of 0-1. Enrollment was initiated in March of 2019. We estimated that the ORR will improve to 35% with pembro+ cabo (from a historic of 18%) with a significance level of 0.05 and 80% power. **Results:** A total of 47 pts were screened, 13 screen failures [cavitation on scan (4), inability to swallow pills (2), other exclusions (7)]; 34 pts were enrolled, 32 were dosed and 31 evaluable (at least one follow-up scan). Pts had cancers of the oropharynx (21, 65%), nasopharynx (6, 19%), larynx/hypopharynx (4, 13%) and oral cavity (1,3%). 32 patients received cabo at 40 mg daily; 13 patients (41%) were dose reduced to 20mg daily [mucositis, increased liver function (LFT) tests, diarrhea]; males (n=29, 90%), median age 63 years (range 53-67); presence of distant metastases (34, 100%); prior radiation (29, 90%), chemotherapy (14, 43%); ECOG PS =0 (16, 50%), 1 (16,50%); HPV/p16 positive (17, 53%), negative (5, 16%), not applicable (10, 29%); the most frequent adverse event (AE) (all grades) was fatigue (16,50.0%), grade 3 or 4 treatment-related AE were increased LFTs, hyponatremia (3, 9.3% each). With a median follow up of 12.7 months (mos) (range 6.9- 20.5 mos), a RECIST 1.1 overall response rate ORR= 45.2% (CR=0; PR=14, 45.2%; SD =14, 45.2%; PD=3.0, 10%) with an overall clinical benefit of 90.4% were observed; The 1-yr OS was 67.7% (95% CI, 42.9%-83.6%; median 22.3 mos) and 1-yr PFS was 51.8% (95% CI, 28.8%-70.7%; median 14.6 mos). **Conclusions:** This phase II trial of pembro + cabo met its primary endpoint of ORR. The regimen is well-tolerated with very encouraging clinical activity in RM HNSCC and warrants further exploration in this disease. The study was supported by a grant from Exelixis to NFS. Clinical trial information: NCT03468218. Research Sponsor: exelixis.

6009 **Poster Discussion Session**

Deintensification of postoperative radiotherapy in head and neck cancer independent of human papillomavirus status: Results of a prospective multicenter phase II trial. *First Author: Marlen Haderlein, Universitaetsklinikum Erlangen, Erlangen, Germany*

Background: Long-term toxicity is highly relevant for cancer survivors. Therefore, in a clearly defined patient population with HNSCC individualized risk-adapted De-intensification of radiotherapy(RT) should be investigated to reduce long-term toxicity without compromising locoregional control rates (LRRR). **Methods:** Patients with newly diagnosed HNSCC after surgery with the following tumor stages (TNM 7th Edition) were eligible for the study: Oral cavity, oropharynx, larynx: pT1-3, pN0-pN2b. Hypopharynx: pT1-2; pN1, resection margin (R) ≥1mm, cM0.Patients were treated in 3 different arms adapted to tumor stage and quality of surgery performed (table below). Concomitant chemotherapy was applied according to standard. Primary endpoint was the LRRR after 2 years (y). After 2y a LRRR up to 10% was expected and an additionally LRRR in non-irradiated or dose-reduced areas of 6% would be accepted. The calculated sample size was 150 patients. Secondary endpoints were overall(OS)/ disease-free(DFS) survival and late toxicity according to CTC-AE v4.0. **Results:** Between Oct 2014 and March 2021 150 patients were enrolled. 8 (5%) patients were treated in arm A, 88 (59%) in arm B and 54 (35%) in arm C. Median age was 59 years. Tumor localisation was: 35% oral cavity, 63% oropharynx (82% HPV-positive), 1% Hypopharynx, 1% Larynx. 61 patients (41%) were stage IVA, 81 (54%) stage III and 8(5%) stage II. Median follow up was 36 months. LRRR after 2 and 3y was 6% (95%-CI 2-10%), and 7% (CI 3-12%). LRRR in not irradiated or dose-reduced regions was 4 % (CI 1-7%) after 2 and 5 % (CI 1-9%) after 3y. The 2 and 3y DFS rates were 90% (CI 85-95%) and 88% (CI 82-94%) and the OS rates were 94% and 94% (CI 90-98%). Late dysphagia was as follows: 0°: 55%, I°: 29%, II°: 9%, III°: 3%. Other grade ≥3 toxicities: Xerostomia 1%, esophageal stenosis 2%, osteonecrosis of the mandible 1%. **Conclusions:** The trial met its primary endpoint. De-intensification of RT independent of HPV status in a pre-defined low-risk patient population is safe and results in very low rates of late toxicity. Clinical trial information: NCT02528955. Research Sponsor: None.

ARM	Pathologic Tumor stage	Intervention
A	≤ pT2, R ≥ 5 mm, L0, Pn0 and >3 LN (lymph node) metastasis or ≤ 3 unilateral LN metastasis and a bilateral primary tumor without adequate contralateral neck dissection	***Dose reduction in primary tumor region to 56 Gy*** Elective RT: both neck sides
B	> pT2 and/or R < 5mm and/or L1 and/or Pn1 and ≤ 3 ipsilateral LN metastasis, contralateral pN0 or contralateral cN0 in unilateral oral cavity or oropharyngeal cancer	64 Gy in primary tumor region ***Reduction of target volume: elective RT: ipsilateral neck only***
C	≤ pT2, R ≥ 5 mm, L0, Pn0 and ≤ 3 ipsilateral LN metastasis, contralateral pN0 or contralateral cN0 in unilateral oral cavity or oropharyngeal cancer	***Dose reduction in primary tumor region to 56 Gy*** ***AND*** ***Reduction of target volume: elective RT: ipsilateral neck only***

6010 **Poster Discussion Session**

Effectiveness of adjuvant chemoradiotherapy for oral cavity squamous cell carcinoma with minor and major extranodal extension: A multi-institutional consortium study. *First Author: Mirko Manojlovic Kolarski, University of Toronto, Toronto, ON, Canada*

Background: Extranodal extension (ENE) in oral cavity squamous cell carcinoma (OSCC) is a poor prognostic feature and an indication for adjuvant chemoradiotherapy. Recent pathology reporting guidelines recommend stratifying ENE into minor (≤2mm) or major (>2mm) extent. Prior studies have suggested that the addition of chemotherapy to adjuvant radiation may not improve oncologic outcomes in minor ENE. We evaluated this through a large multi-institutional cohort study. **Methods:** Surgically resected primary T1-4,N1-N3,M0 OSCC with pathologic nodal disease treated between 2005-2018 from four institutions in three countries were included. Extent of ENE was re-classified by pathologists on archived tissue. Adjuvant radiotherapy or chemoradiotherapy was recommended as per standard guidelines, unless contraindicated. Uni- (UVA) and Multivariable analysis (MVA) assessed the effect of chemotherapy on survival and disease control in minor and major ENE subgroups. Outcomes were also assessed in propensity score matched cohorts for each subgroup. **Results:** A total of 764 patients were included, of whom 126 (16%) had minor ENE and 242 (32%) had major ENE. Adjuvant chemoradiotherapy was given in 51 (40.5%) with minor ENE and 115 (47.5%) with major ENE. On MVA, chemotherapy was not associated with improved overall survival (OS) (HR 0.97, 95% CI 0.55-1.73, p=0.92) for patients with minor ENE, however, there was significant OS benefit for patients with major ENE (HR 0.61, 95% CI 0.38-0.98, p=0.041) after adjusting for age, T-category, N-category, margin status, adjuvant radiation, LN ratio, LVI, PNI, and ECOG status. Patients with major ENE receiving adjuvant chemoradiotherapy had improved locoregional control (LRC) (HR 0.67, 95% CI 0.42-1.09, p=0.1) although this did not reach statistical significance. Propensity score matched analysis found that patients with minor ENE who did and did not receive chemotherapy had no difference in OS (52% vs. 52%, p=0.85), but those with major ENE did (44% vs 13%, p=0.008). **Conclusions:** In OSCC, the addition of chemotherapy to adjuvant treatment is beneficial in major ENE, but our group failed to demonstrate a benefit for minor ENE. The benefit of chemotherapy in major ENE may result from improved LRC. Minor ENE is a clinically relevant subgroup in OSCC that warrants distinctive adjuvant treatment considerations. Research Sponsor: None.

6011 **Poster Discussion Session**

Swallowing and quality-of-life outcomes of response adaptive de-escalated therapy following nivolumab-based induction for HPV+ oropharyngeal cancer. *First Author: Ari Rosenberg, University of Chicago, Department of Medicine, Chicago, IL*

Background: Despite the survival benefit of anti-PD1 therapy in recurrent/metastatic head and neck cancer, its role in locoregional disease remains undefined. Swallowing and quality of life (QoL) outcomes for patients with human papillomavirus associated (HPV+) oropharyngeal cancer (OPC) treated with de-intensified local therapy following anti-PD1 based induction is unknown. Here we report functional swallowing and QoL outcomes with response-adaptive de-escalation after induction chemoimmunotherapy in the context of a prospective investigator initiated trial, OPTIMA II. **Methods:** OPTIMA II enrolled locoregionally advanced HPV+ OPC. Treatment consisted of induction therapy with 3 cycles of nivolumab, nab-paclitaxel, and carboplatin, followed by risk and response de-escalated local therapy. High-risk (HR) included: T4, N2c-N3 (AJCC 7th edition), > 20 pack year smoking history, or non-HPV16 subtype; All others were low-risk (LR). Single-modality de-escalation received radiation (RT) alone to 50 Gy or transoral robotic surgery, and was administered to LR with ≥50% post-induction shrinkage by RECIST. Intermediate-dose de-escalation received chemoradiation (CRT) to 45-50Gy and was administered to HR with ≥50% shrinkage or LR with < 50% shrinkage. All others received regular-dose CRT to 70-75 Gy. Adjuvant nivolumab was administered for 6 months. Swallowing and QoL was assessed with the Rosenbek score and EORTC QLQ-C30 questionnaires, respectively. Higher values indicated greater degree of swallowing dysfunction and worse QoL, respectively. **Results:** Seventy-three eligible patients (pts) initiated treatment on protocol. Median age 61 (range 37-82). Primary site was tonsil in 70% and base of tongue in 29%. T3 or T4 primary tumor in 30%. De-escalated therapy was administered in 62 pts, of which 28 pts received single-modality and 34 pts received intermediate-dose. Rosenbek mean and standard deviation (SD) at baseline among single-modality, intermediate-dose, and regular-dose, was 1.3 (SD 0.6), 1.7 (SD 1.3), and 1.4 (SD 0.7), respectively. Rosenbek mean at 1 month following local therapy (n = 45) among single-modality, intermediate-dose, and regular-dose was 2.3 (SD 1.6), 3.8 (SD 2.5), and 4.7 (SD 2.1), respectively (p = 0.06). Feeding tube rates at the end of local therapy among single-modality, intermediate-dose, and regular-dose was 7%, 44%, and 75% respectively (p < 0.01). QoL scores (n = 30) were worse among regular-dose as compared with de-escalated treatment for activities of daily living (p = 0.01), neuropathy (p = 0.01), and eating in social settings (p = 0.09). **Conclusions:** Response adaptive de-escalated treatment for HPV+ OPC following nivolumab/nab-paclitaxel/carboplatin induction is associated with improved swallowing function, reduced rates of enteral feeding, and an improvement in QoL across several domains. Clinical trial information: NCT03107182. Research Sponsor: Bristol Myers Squibb.

6012 **Poster Discussion Session**

Efficacy and safety of camrelizumab and apatinib combined with induction chemotherapy and concurrent chemoradiotherapy for stage $T_{any}N3M0$ nasopharyngeal carcinoma: A phase II QUINTUPLED trial. *First Author: Hu Liang, Department of Nasopharyngeal Carcinoma, Sun Yat-Sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou, China*

Background: Prognosis of nasopharyngeal carcinoma (NPC) with stage $T_{any}N3M0$ remains unsatisfactory due to high-risk of distant metastasis, indicating the need of more comprehensive treatment strategy. Synergistic effects are observed when immune checkpoint blockade anti-PD-1 is combined with chemotherapy or anti-angiogenic agents. This trial investigated the efficacy and safety of anti-PD-1 camrelizumab and anti-angiogenic agent apatinib in combination with induction chemotherapy and concurrent chemoradiotherapy (CCRT) in patients with $T_{any}N3M0$ NPC. **Methods:** In this phase II trial, patients with $T_{any}N3M0$ NPC (AJCC 8th edition) were enrolled and treated with induction chemotherapy (NAB-paclitaxel, 200 mg/m^2, day 1; cisplatin 60 mg/m^2, day 1; and capecitabine, 1000 mg/m^2, orally twice a day, days 1-14; every 21-day for 3 cycles) and apatinib (250 mg, 5 days/week, for up to 8 weeks), followed by CCRT (cisplatin, 100 mg/m^2, day 1, every 21-day for 2 cycles and IMRT). Camrelizumab (200 mg once every 3 weeks) was given from the first cycle of induction chemotherapy until one year. Prescribed radiation doses were 68-72 Gy, 64-68 Gy, 60-64 Gy, and 54-58 Gy in 30-33 fractions for PTVnx, PTVnd, $PTV_{high\text{-}risk}$, and $PTV_{low\text{-}risk}$, respectively. Primary endpoint was 1-year distant metastasis-free survival (DMFS). Patient's response to the therapy was evaluated using RECIST 1.1. **Results:** From May 2020 to July 2021, 50 eligible patients were enrolled. Median age was 45 years (range 20-65), median EBV DNA concentration was 4520 copy/ml (IQR 1595-17550), and 13 patients (26%) were female. Among 50 patients evaluable for response assessment after induction therapy, all patients had overall response, including 12 patients (24%) with complete response (CR). After 1-3 cycles of induction therapy, 84.8% (28/33 available) patients achieved negative pathological finding in the primary tumor site from endoscopic biopsy and 50% (17/34 available) from lymph nodes biopsy. Except one patient achieved regional partial response and one patient died from liver and bone metastases, the other patients all achieved CR at 3 months after radiotherapy. One-year DMFS rate was 98% (95% CI 96-100) with a median follow-up of 12.3 months (range 6.4-20.2). Grade ≥3 toxicity appeared in 32 (64%) of 50 patients and mainly consisted of nausea/vomiting (9 [18%]), neutropenia (8 [16%]), leukopenia (7 [14%]), anemia (7 [14%]), rash (5 [10%]) and thrombocytopenia (5 [10%]). Safety profile was anticipated without treatment or immune-related deaths. **Conclusions:** Camrelizumab and apatinib combined with induction chemotherapy of NAB-paclitaxel, cisplatin and capecitabine and CCRT shows excellent distant metastatic control with acceptable safety, which is a new promising and effective systemic therapy regimen for high-risk of metastatic NPC patients. Clinical trial information: ChiCTR2000032317. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd., Other Foundation.

6013 **Poster Discussion Session**

Phase 3 randomized study comparing docetaxel-platinum with docetaxel-platinum-5 fluorouracil as neoadjuvant chemotherapy in technically unresectable oral cancer. *First Author: Ajaykumar Singh, Tata Memorial Centre, Mumbai, India*

Background: Neoadjuvant chemotherapy (NACT) with DCF (Docetaxel, Cisplatin, and 5FU) is one of the treatment options in very locally advanced oral cancer (LAOC) and has a survival advantage over the CF (Cisplatin and 5FU) regimen. DC regimen (Docetaxel, Cisplatin) had shown promising results in small series, with a lower rate of adverse events but has never been compared with DCF. **Methods:** This was a phase 3 open-label superiority randomized study. Adult patients with very LAOC (technically unresectable), ECOG PS 0-2 and adequate organ function were eligible. They were randomly assigned in a 1:1 fashion to either DCF or DC regimen. After the administration of 2 cycles, these patients were evaluated in the multidisciplinary clinic. Based on the response, further treatment either surgery followed by adjuvant or radical chemoradiation or palliative therapy was planned. The primary endpoint was overall survival (OS). The key secondary endpoint was adverse events. **Results:** 495 patients were randomized in this study, 250 patients in arm A and 245 in arm B. At a median follow-up of 39.5 months. The 2-year OS was 29.1% in the DCF and 23.5% in the DC arm respectively (HR=0.81; 95%CI 0.66-0.99, P-value= 0.043). Grade 3 or above adverse events were higher in the DCF arm - oral mucositis (10.6% versus 1.2%), diarrhea (13.6% versus 9.6%), febrile neutropenia (23.2% versus 2.6%), hyponatremia (40.8% versus 20.8%), and hypokalemia (17.9% versus 1.6%). **Conclusions:** NACT with DCF has a survival benefit over DC in oral cancers but it comes at the cost of an increment in acute adverse events. Clinical trial information: CTRI/2016/04/006804. Research Sponsor: Tata memorial center research administrative council.

6014 **Poster Discussion Session**

Dose-finding and efficacy confirmation trial of the superselective intra-arterial infusion of cisplatin and concomitant radiotherapy for locally advanced maxillary sinus cancer (JCOG1212): Results of the efficacy confirmation phase in the T4a cohort. *First Author: Akihiro Homma, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan*

Background: The JCOG1212 trial seeks to evaluate the safety and efficacy of the superselective intra-arterial infusion of high-dose cisplatin with concomitant radiotherapy (RADPLAT) for patients (pts) with T4aN0M0 or T4bN0M0 maxillary sinus squamous cell carcinomas (MS-SCC). T4aN0M0 MS-SCC requires radical surgery with or without complete resection of the orbital contents as a standard treatment, which results in disfigurement and functional impairment. We herein report the results of the efficacy confirmation phase in the T4a cohort. **Methods**: Eligible pts with T4aN0M0 MS-SCC were registered and received cisplatin 100 mg/m^2 intra-arterially weekly for 7 weeks with concomitant radiotherapy (total 70 Gy) as determined by the results of the previous dose-finding phase. The trial investigated the 3-year overall survival (3yr OS) of RADPLAT to demonstrate its non-inferiority to surgery, the current standard of care, and its superiority to IV-CRT, which is used for pts refusing surgery. From the results of observational study undertaken by our group, the historical control for the 3yr OS was set at 80% for surgery and 65% for IV-CRT. A margin of 15% was set to demonstrate its non-inferiority to surgery and superiority to IV-CRT. Thus, when the lower boundary of the two-sided 90% confidence interval (CI) exceeds the threshold of 65% for 3yr OS, RADPLAT will be confirmed as the new standard. A sample size of 62 was required to achieve 80% power with a one-sided 5% significance level. **Results**: From April 2014 to August 2018, 65 pts were registered in the T4a cohort from 18 institutions, consisting of 54 males and 11 females with a median age of 64 years (range, 40-78 years) and ECOG PS 0/1 (58/7). After the exclusion of one ineligible patient, 64 pts were included in the primary analysis of efficacy and safety. The complete clinical remission rate was 73.4% (47/64, 95% CI, 60.9%-83.7%), with 15 showing CR and 32 showing good PR. The median follow-up was 4.5 years in all eligible pts and the primary endpoint for 3yr-OS was 82.8% (90% CI, 73.4%-89.2%), which met the prespecified hypothesis. The 3yr event-free survival and 3yr local event-free survival were 60.9% (95% CI, 47.9%-71.7%) and 65.6 % (95% CI, 52.5%-75.8%), respectively. With regard to acute adverse events, neutropenia (≥ grade 3), increased creatinine (≥ grade 2), hearing impairment (≥ grade 2), mucositis (≥ grade 3), and stroke (≥ grade 2) were observed in 14.1%, 3.1%, 3.1%, 20.3%, and 1.6% of pts, respectively. One treatment-related death due to a thromboembolic event was reported. **Conclusions**: RADPLAT is non-inferior to surgery and superior to IV-CRT for pts with T4aN0M0 MS-SCCs and showed manageable toxicities. Therefore, RADPLAT, as well as surgery, should be considered the new standard treatment option for these pts. Clinical trial information: UMIN000013706. Research Sponsor: Japan Agency for Medical Research and Development.

6015 **Poster Discussion Session**

Refining nodal category in TNM staging with extent of extranodal extension for oral cavity squamous cell carcinoma. *First Author: John R de Almeida, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: The TNM 8th edition N classification (TNM-8-N) has limitations based on evidence that: (1) extent of extranodal extension (ENE), classified as minor($_{min}$) (≤ 2mm) or major ($_{maj}$)(> 2mm), is prognostic, and (2) N3a category (i.e. lymph node (LN)s > 6 cm, no ENE) is rare and redundant. Refining N classification may improve staging performance. **Methods:** Patients with surgically resected T1-4,N0-3 OCSCC at four centers between 2005 - 2018 were included. Pathologists were asked to measure extent of ENE on archived slides for all cases. Thresholds for stratification of adverse LN features were determined using the Contal O'Quigley method. Multivariable analyses for overall survival (OS) were performed using Cox proportional hazard models. Two new N classification proposals were created based on LN features using (1) adjusted hazard ratios (aHR) and (2) recursive partitioning analysis (RPA). These were ranked against two published proposals and TNM-8-N with the following criteria: hazard consistency, hazard discrimination, explained variance, likelihood difference, sample size balance. **Results:** In total, 1460 patients were included, 764 (52%) were LN positive, and 135 (18%) had contralateral LNs. The following TNM-8-N subgroups were rare and had poor prognosis: LN between 3-6 cm without ENE (N2a) [n=4] and LN(s) > 6 cm without ENE (N3a) [n=1]. All 5 either recurred or died. TNM-8-N N2b and N2c categories had disordered 5-year OS (45% vs. 67%). Thresholds for stratification of LN features, rounded to the nearest whole number, were <=1 vs >1 for number of LNs; ≤ 3 vs. > 3 cm for size of largest LN, and ≤ 2 mm vs. > 2 mm for extent of ENE. Significant predictors of OS included (1) the presence of ENE_{maj} and no ENE vs. ENE_{min} (HR 1.37; 95% CI 1.03-1.82 and HR=0.66, 95%CI 0.49-0.88), (2) multiple LNs vs. 1 LN (HR 1.72; 95% CI, 1.33-2.22), and (3) size of largest LN > 3 cm vs. <=3 (HR 1.86; 95% CI 1.42-2.43), but contralateral LN(s) vs. ipsilateral LN(s) was not (HR 1.08; 0.83-1.40). The aHR proposal ranked highest (table). **Conclusions:** A new N-classification proposal based on aHR provides improved staging information. Major changes include: (1) stratification by ENE extent (2) elimination of N2c (3) stratification of multiple LNs without ENE by size, and (4) elimination of the 6 cm threshold. New TNM iterations may incorporate these changes. Research Sponsor: None.

	TNM-8-N	aHR	RPA	Liao et al.	Ho et al.
N1	1 LN, ≤ 3cm, no ENE	**same**	Same	same	1 LN, no ENE
N2a	1 LN, ≤ 3 cm, with ENE OR 1 LN, 3-6 cm, no ENE	1 LN, ≤ 3 cm, with ENE	1 LN, any size, with ENE	same	1 LN, with ENE OR 2 LNs
N2b	>1 LN, ≤ 6 cm, no ENE	> 1 LNs,≤ 3 cm, no ENE	>1 LN, ≤ 3 cm, no ENE	same	
N2c	Contralateral LN(s), ≤ 6 cm, no ENE	*	*	same	
N3a	LN(s) > 6 cm, no ENE	LN(s) > 3 cm, no ENE OR 1 LN, > 3 cm, ENE_{min} OR > 1 LNs, ENE_{min}	LN (s) > 3 cm, no ENE OR >1 LN, ENE_{min}	≤ 7 LNs, OR ≤ 4 LNs with ENE	3-7 LNs
N3b	1 LN, > 3 cm, any ENE OR >1 LN(s), any ENE	1 LN > 3 cm, ENE_{maj} OR >1 LNs, ENE_{maj}	> 1 LN, ENE_{maj}	≥ 8 LNs OR ≥5 LNs with ENE	≥ 8 LNs
Ranking	5	1	2	4	3

*eliminated

LBA6016 **Poster Discussion Session**

Phase 3 randomised study evaluating the addition of low-dose nivolumab to palliative chemotherapy in head and neck cancer. *First Author: Vijay Maruti Patil, Tata Memorial Centre, Mumbai, India*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

6017 **Poster Discussion Session**

Liquid Biopsy for Minimal Residual Disease Detection in Head and Neck Squamous Cell Carcinoma (LIONESS): A personalized cell-free tumor DNA analysis for patients with HNSCC. *First Author: Susanne Flach, Hospital of the University of Munich, München, Germany*

Background: Despite improvements in multimodal treatment options for patients with head and neck squamous cell carcinoma (HNSCC), survival has only improved modestly over the past decades as patients frequently develop recurrences. Detection of cell-free circulating tumor DNA (ctDNA) post-operatively and during clinical follow-up has the potential to identify patients with molecular residual disease (MRD) or who are at an increased risk of relapse, and who may therefore benefit from personalized treatment strategies. **Methods:** We conducted LIONESS, a single-center prospective cohort study to investigate ctDNA in patients with HNSCC who received primary surgical treatment with curative intent. 58 patients have been recruited as of January 2022, with disease stage I (15.5%), II (13.8%), III (36.2%) and IV (34.5%). Whole exome sequencing was performed on FFPE tissue. RaDaR, a highly sensitive personalized assay using deep sequencing of tumor-specific variants, was used to analyze serial pre- and post-operative plasma samples for evidence of molecular residual disease and recurrence. In addition, pre-operative saliva samples were collected for detection of tumor DNA in saliva. **Results:** 236 longitudinal plasma samples from 35 patients have been analyzed so far, using personalized panels designed targeting a median 48 (20-60) somatic variants. Preliminary data shows 94.28% ctDNA detection in baseline samples taken prior to surgery. In post-surgery samples, ctDNA could be detected at levels as low as 0.0005% variant allele fraction (eVAF). Survival analysis showed a significant difference (p-value = 7e-7) in recurrence rates between patients who tested ctDNA+ during follow-up (8/11, 72.7%) and those who were negative for ctDNA (0/24, 0%). In all eight cases with clinical recurrence, ctDNA was detected prior to progression, with lead times ranging from 56 to 265 days. Patients were followed for clinical recurrence with a median follow-up of 9.5 months to date, but longer follow-up is necessary for patients who may be at increased risk of recurrence. Work is ongoing for analysis of the full cohort of plasma and saliva samples, which will be presented at the congress. **Conclusions:** In this prospective observational study, detection of residual disease using ctDNA was associated with poorer progression-free survival and much earlier detection of disease prior to clinical relapse. The implementation of a highly sensitive ctDNA assay such as RaDaR into clinical practice has the potential to tailor personalized treatment strategies for molecular residual disease and recurrence in patients with HNSCC. In future, ctDNA analysis with subsequent ctDNA-guided treatment may reduce morbidity for HNSCC patients. Research Sponsor: None.

6018 **Poster Discussion Session**

Phase II study of trastuzumab-pkrb and docetaxel anhydrous combination therapy in recurrent or metastatic salivary ductal carcinomas (KCSG HN18-08/KM11). *First Author: Jiyun Lee, Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea*

Background: Salivary gland cancers (SGCs) are relatively rare, accounting for 1-6% of all neoplasms of the head and neck, have diverse disease course with respect to origin and pathology. Salivary duct carcinoma (SDC) is the most aggressive tumor subtype of primary SGC, showing high rates of local recurrence and distant metastases. In regard to previous studies which reported a high prevalence of HER2 positivity in SDCs, we conducted a single-arm, phase II study to evaluate the antitumor activity and safety of Herzuma (a trastuzumab biosimilar which demonstrated an equivalent efficacy to reference trastuzumab) in combination with docetaxel anhydrous (Nanoxel) in patients with HER2-positive advanced SDCs. **Methods:** Eligible patients had histologically confirmed HER2-positive (defined as IHC≥2+ and/or FISH HER2/CEN17 ratio ≥2.0) recurrent/metastatic SDC, or subtypes of SGC that were pathologically similar to SDC (excluding ACCs). They received Herzuma (8mg/kg i.v. loading dose, followed by 6mg/kg i.v.) and Nanoxel (75mg/m2 i.v.) every 3 weeks. The primary endpoint was the investigator-assessed objective response rate (ORR) according to RECIST v1.1. Secondary endpoints were overall survival (OS), progression-free survival (PFS), and safety. The calculated sample size was 43 patients for H1 of ORR ≥40%. Safety was evaluated by CTCAE v4.0. **Results:** A total of 43 patients were enrolled. Patient characteristics included: median age 60 (range 35–81); 86% male; 84% ECOG1; 84% SDC, 9% adenocarcinoma, 2% high grade mucoepidermoid carcinoma, and 5% other subtypes. Confirmed ORR was seen in 67% (95% CI, 52–81). No patient had a complete response as their BOR, 29 (67%) had a partial response, 11 (26%) had stable disease, 1 (2%) had progressive disease, and 2 (5%) were unevaluable. The DCR was 93% (95% CI, 81–99). The median PFS and OS were 8.2 months (95% CI, 6.7–9.7) and 23.3 months (95% CI, 19.9–26.7), respectively. Thirty-eight (88%) patients experienced a treatment-related AE (TRAE), with 15 (35%) patients experiencing ≥grade 3 TRAE including: neutropenia (10), febrile neutropenia (4), anemia (1), sepsis (1), anaphylaxis (1), decreased LVEF (1). There were no treatment-related deaths. **Conclusions:** The study met the primary endpoint of ORR. Herzuma and Nanoxel combination therapy demonstrated a promising treatment outcome in patients with HER2-positive recurrent/metastatic SDC. Clinical trial information: NCT03614364. Research Sponsor: Celltrion, Samyang.

6019 **Poster Discussion Session**

A phase 2 clinical trial of axitinib and avelumab in patients with recurrent/metastatic adenoid cystic carcinoma (ACC). *First Author: Renata Ferrarotto, Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: ACC is a heterogeneous neoplasm and there is no standard treatment for patients (pts) with recurrent/metastatic (R/M) disease. Vascular endothelial growth factor receptor inhibitors (VEGFRi) are frequently used to treat R/M ACC rendering mostly disease stabilization. ACC is resistant to PD-1/PD-L1 inhibitors (PD-L1i), consistent with its low mutational burden and uninflamed immune microenvironment. We hypothesized that the immunomodulatory role of VEGFRi (axitinib) would enhance PD-L1i (Avelumab) activity and be a more effective therapy for R/M ACC. **Methods:** Eligible pts had R/M ACC with radiological or clinical progression within 6 months (mos) of enrollment. Treatment consisted of axitinib 5 mg PO bid and avelumab 10 mg/Kg IV every 2 weeks. Primary endpoint was objective response rate (ORR) per RECIST 1.1; secondary endpoints included duration of response (DOR), progression-free survival (PFS), overall survival (OS), and toxicity. Simon 2-stage design was applied to test the null hypothesis of ORR ≤ 5% versus the alternative ORR ≥ 20%; ≥ 4 responses out of 29 pts was required to reject the null hypothesis. **Results:** 41 pts enrolled from 07/24/19 to 06/29/21; 28 were evaluable for the primary endpoint (7 screen failures, 6 evaluable for safety only due to loss of insurance/logistics issues related to COVID-19 pandemic); 16 pts were treated in first-line. Mutation data was available for 23 of 28 evaluable pts; 7 had *NOTCH1* activating mutations. The ORR was 17.9% (5/28, 95%CI: 6.1-36.9%). One response was unconfirmed (pt progressed in non-target lesions 2 mos after achieving a PR), for a confirmed ORR of 14.3% (95%CI: 4-32.7%). The median follow-up time for the 15 alive pts was 11.6 mos (min-max: 7.7-29.2 mos). Median PFS was 7.2 mos (95%CI: 3.7-11.7 mos) with a 6-mos PFS rate of 57% (95%CI: 41-79%). Median OS was 17.4 mos (95%CI: 13-NA). 5 pts remain on therapy, 2/5 with a PR. The median DOR for the 5 responders was 5.2 mos (95% CI: 3.7–NA mos). The most common treatment-related adverse events (TRAEs) were fatigue (62%), hypertension (32%), diarrhea (29%), and stomatitis (29%). Serious TRAEs occurred in 8 (24%) pts, all grade 3 and manageable. 4 (15%) pts discontinued avelumab and 9 (32%) underwent axitinib dose reduction due to toxicity. **Conclusions:** The study reached its primary endpoint with ≥ 4 responses out of 28 evaluable pts (ORR of 17.8%; confirmed ORR of 14.3%). The ORR and 6-mos PFS rate of 57% with axitinib and avelumab compares favorably with single agent axitinib and warrants further study of the combination. Clinical trial information: NCT03990571. Research Sponsor: Pfizer, Other Foundation.

6020 **Poster Discussion Session**

A phase 2 study of the oral vascular endothelial growth factor receptor 2 (VEGFR2) inhibitor, rivoceranib, for recurrent or metastatic (R/M) adenoid cystic carcinoma (ACC). *First Author: Hyunseok Kang, Hematology/Oncology, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA*

Background: ACC is a rare tumor that overexpresses VEGF, primarily affecting salivary glands. Often indolent, it can progress, with metastases common in lungs, liver, and bone. There are no FDA-approved systemic treatments (tx) for R/M ACC. Rivoceranib is an oral tyrosine kinase inhibitor (TKI) that potently and selectively inhibits VEGFR2. **Methods:** In this single-arm, open-label trial, patients (pts) with R/M ACC with evidence of ≥20% progression by RECIST v1.1 or new lesions within the preceding 6 mo were eligible; there was no limit on prior tx. Pts received rivoceranib 700 mg once daily until progression or withdrawal with pre-planned dose reductions for toxicity. Primary endpoint was objective response rate (ORR) per RECIST v1.1 by investigator (PI) and by Independent Review Committee (IRC). Secondary endpoints included duration of response (DoR), progression-free survival (PFS), time to progression (TTP), overall survival, and safety. Exploratory analysis included disease control rate (DCR), and ORR using CHOI criteria by IRC. **Results:** 80 pts (72 evaluable) were enrolled at 11 sites in the US and Korea (53% male; median age: 55 yr). Primary tumor sites: major (34%) and minor (59%) salivary glands and other (8%). 5 (6%) pts had locoregional disease only and 74 (93%) had metastatic disease. Most had prior surgery (89%) and radiation (96%); 53% had prior systemic tx (44% chemotherapy; 18% VEGFR TKI). Median follow-up was 15 mo (2–19); 20 pts remain on tx. PI-assessed efficacy data are listed in the table. ORR in pts with or without prior systemic tx was 13.9% and 16.9%, respectively. ORR by CHOI was 50.8% overall (51% VEGFR TKI-naive and 50% VEGFR TKI treated). 18% of pts discontinued tx, 74% had at least 1 dose reduction, and 93% dose interruption for adverse events (AEs). All pts had ≥1 AE and 80% had Grade ≥3 AEs, including 3 Grade 5 AEs (2 epistaxis [1 related], 1 acute respiratory failure). Common (> 30%) AEs were hypertension (65%), fatigue (61%), nausea and headache (50%), stomatitis (46%), diarrhea (40%), decreased appetite (38%), proteinuria (36%) and palmar-plantar erythrodysesthesia syndrome (34%). Grade ≥3 AEs in ≥5% of pts were hypertension (43%), stomatitis (8%), fatigue and anemia (6%), and back pain and pneumothorax (5%). **Conclusions:** In this population of R/M ACC with unmet medical need, rivoceranib showed promising antitumor activity, particularly among VEGFR TKI-naïve pts. The safety profile was consistent with other VEGFR TKIs. Clinical trial information: NCT04119453. Research Sponsor: Elevar Therapeutics.

	Total (N = 72)	VEGFR TKI-Naïve (n = 59)	VEGFR TKI Prior Tx (n = 13)
ORR* (%)	10 (13.9)	10 (16.9)	0
95% CI	6.9-24.1	8.4-29.0	
Median (m) DOR (mo)	12.0	12.0	-
6, 9, 12 mo DOR (%)	100, 88.9, 59.3	100, 88.9, 59.3	-
DCR (%)	43 (59.7)	33 (55.9)	10 (76.9)
95% CI	47.5-71.1	42.4-68.8	46.2-95.0
mTTP (mo)	10.9	9.0	16.4
mPFS (mo)	9.0	9.0	9.1
6, 9, 12 mo PFS rate (%)	76.7, 53.2, 43.0	74.9, 51.1, 41.3	84.6, 61.7, 49.4

*All partial responses.

6021 **Poster Session**

Predicting emergency department use and unplanned hospitalization in patients with head and neck cancer: Development and validation of a machine learning algorithm. *First Author: Christopher W Noel, Department of Otolaryngology Head and Neck Surgery, Faculty of Medicine, University of Toronto, Toronto, ON, Canada*

Background: We recently demonstrated that patient reported symptom burden is strongly associated with emergency department use and unplanned hospitalization (ED/Hosp) in head and neck cancer (Noel et. al 2021 J. Clin Oncol - DOI: 10.1200/JCO.20.01845). We hypothesized that symptom scores could be used to build a tool that would accurately risk stratify patients. **Methods:** This was a population-based study of patients diagnosed with head and neck cancer between 2007 and 2018. All outpatient clinical encounters were identified. Edmonton Symptom Assessment Scores (ESAS) and clinical and demographic factors were abstracted. Training and test cohorts were randomly generated in a 4:1 ratio. Various machine learning algorithms were explored including: (1) logistic regression, (2) random forest, (3) gradient boosting machines (4) k-nearest neighbors and an (5) artificial neural network. Our main outcome was any 14-day ED/Hosp event following symptom assessment. The performance of each risk model was assessed on the test cohort using the area under the receiver operator characteristic (AUROC) curve and calibration plots. Shapley values were used to identify the variables with greatest contribution to the model. **Results:** The training cohort consisted of 9,409 patients undergoing 59,089 symptom assessments (80%). The remaining 2,352 patients and 14,193 symptom assessments were set aside as the test cohort (20%). Several models had high predictive accuracy, particularly the gradient boosting machine algorithm (validation AUROC 0.80 [95%CI 0.78-0.81]). A Youden-based cut-off corresponded to a validation sensitivity of 0.77 and specificity of 0.66. A second model built only with symptom severity data had an AUROC of 0.72 [95%CI 0.70-0.74]. **Conclusions:** Machine learning approaches can be used to predict ED/Hosp in head and neck cancer patients. This tool can risk stratify patients and may help direct targeted intervention. Research Sponsor: Challenge Grant, CIHR Terry Fox New Investigator Award.

6022 **Poster Session**

Preliminary safety and efficacy of toripalimab combined with cetuximab in platinum-refractory recurrent or metastatic head and neck squamous cell carcinoma (R/M-HNSCC): A phase Ib/II clinical trial. *First Author: Ye Guo, Shanghai East Hospital, School of Medicine, Tongji University, Shanghai, China*

Background: PD-1 inhibitors and EGFR inhibitors are effective and may provide potential synergy in R/M HNSCC. We launched an open-label, single-arm, multicenter phase Ib/II study of toripalimab (a humanized IgG4K monoclonal antibody specific for PD-1) with cetuximab in platinum-refractory R/M-HNSCC (NCT04856631). We report the results of the phase Ib portion of this study. **Methods:** Eligible patients with R/M HNSCC progressed upon 1st-line platinum-containing treatment or developed R/M disease within 6 months of platinum-containing neo-adjuvant/adjuvant or chemo-radiation therapy were enrolled in this study. Exclusion criteria included prior immunotherapy or EGFR inhibitors therapy. Toripalimab was administered at 240mg intravenously Q3W and cetuximab was given as a loading dose of 400mg/m^2 IV followed by 250mg/m^2 QW. Dose-limiting toxicities (DLTs) and de-escalating dose were evaluated by a Safety Monitoring Committee (SMC). If less than 2 DLTs were observed in the first 6 patients, 6 more patients were enrolled to confirm safety. If 2 or more DLTs were observed, the next 6 patients would be enrolled at a lower dose level. The primary endpoint was safety. Secondary endpoints included determination of recommended phase 2 dose (RP2D), ORR, DCR, DOR, and PFS by an independent review committee (IRC) per RECIST v1.1, OS, and PK. **Results:** A total of 13 patients were enrolled in the phase Ib portion, including 11 (84.6%) male and 2 (15.4%) female patients. The median age was 58 (range 36-74) years. 7 (53.8%) patients had distant metastases and 9 (69.2%) were PD-L1 CPS ≥1. By the data cutoff date of Dec 21, 2021, the median follow-up was 19.3 (1.6-36.3) weeks. No DLT was observed, and the initial dose was chosen as RP2D. 10 (76.9%) patients experienced TRAEs; the most common TRAEs were rash (46.2%) and paronychia (38.5%). 5 (38.5%) patients experienced irAEs, including immune-related skin adverse reactions, hypothyroidism, thyroid function abnormal and duodenitis. No Grade≥3 TRAEs or irAEs occurred. No TRAEs led to discontinuation of study drug. 2 patients reported fatal AEs, both of which were caused by tumor hemorrhage and were judged not related to the study treatment by the SMC. Among 12 patients with at least one post-treatment tumor assessment, 6 confirmed PR (ORR 50%) and 6 SD (DCR 100%) were observed as assessed by the IRC. By the cutoff date, 5 patients have ongoing responses, with 3 over 12 weeks. **Conclusions:** Toripalimab combined with cetuximab were well tolerated and showed preliminary clinical efficacy in patients with R/M HNSCC. Clinical trial information: NCT04856631. Research Sponsor: Shanghai Junshi Biosciences, Pharmaceutical/Biotech Company.

6023 **Poster Session**

Neoadjuvant toripalimab combined with gemcitabine and cisplatin in resectable locally advanced head and neck squamous cell carcinoma (NeoTGP01): An open-label, single-arm, phase Ib clinical trial. *First Author: Zhigang Liu, Cancer Center, The Fifth Affiliated Hospital of Sun Yat-sen University, Zhuhai, China*

Background: The positive outcome of first-line programmed death receptor-1 (PD-1) inhibitors has been revealed in recurrent/metastatic head and neck squamous cell carcinoma (HNSCC). Researches about neoadjuvant immunotherapy for resectable locally advanced HNSCC have been proceeding continuously, however the optimal regimen was inconclusive. Here, we combined a powerful chemotherapy regime, gemcitabine plus cisplatin (GP), and a PD-1 inhibitor to treat the potentially resectable locally advanced HNSCC followed by operation for exploring the safety and efficacy of the combination regime in this phase I trial. **Methods:** This was an open-label, single-arm, phase Ib clinical trial. Untreated patients, aged 18-70, with histologically confirmed localized advanced HNSCC (stage III-IVB), were enrolled. The eligible patients are scheduled to administered PD-1 inhibitor (Toripalimab) 240 mg on day 1, gemcitabine 1000 mg/m^2 on days 1 and 8, and cisplatin 80 mg/m^2 on day 1 every 21 days for two cycles. Radical resection was performed in 4-6 weeks after the first day of the second cycle. The primary endpoints were safety and no surgical-delay rate. Safety evaluation was performed in total participants in 90 days from the first day of treatment (or 30 days after surgery). The second endpoints consisted pathological complete response (pCR) rate, major pathological response (MPR) rate, objective response rate (ORR) and R0 resection rate. **Results:** By December 10, 2021, twenty-three patients were enrolled. Up to now, 18 out of 23 patients successfully finished the operation on schedule. Grade 3/4 adverse events (AEs) occurred in totally 3 patients (13.0%), 2 (8.7%) case of neutropenia, and one each of fatigue (4.3%), hyperglycemia (4.3%), vomiting (4.3%) and diarrhea (4.3%). The most shared adverse events of grade 1/2 were anorexia (30.4%), fatigue (21.7%), vomitting (17.4%) and hyperglycemia (17.4%). The median interval between second administration and surgery was 33 days. For the 20 patients with available radiological examination at pre- and post-neoadjuvant therapy, the assessment per RESCIST criteria was as follow: 1 (5.0%) CR, 7 (35.0%) PR, 12 (60.0%) SD. R0 resection rate reached 100% in a total of 18 patients with complete surgical resection. Three patients achieved pCR at primary site (viable tumor = 0), 5 achieved MPR (0 < viable tumor≤10%) and 2 among 5 were near-pCR (viable tumor = 1%), and the other 11 patient did not reach MPR. **Conclusions:** Triweekly neoadjuvant Toripalimab plus GP was generally tolerated by the locally advanced HNSCC and contributed to a major pathological response in 44.4% patients at present. Research Sponsor: Shanghai Junshi Biosciences Co., Ltd. Clinical trial information: NCT04947241. Research Sponsor: None.

6024 **Poster Session**

A phase Ib study of SHR-1701, a bifunctional fusion protein targeting PD-L1 and TGF-β, in patients with recurrent or metastatic nasopharyngeal carcinoma (RM-NPC). *First Author: Yunpeng Yang, Medical Oncology Department, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Immune checkpoint inhibitors (ICIs) demonstrated favorable antitumor activity in RM-NPC. However, only a subset of patients derived benefits. Combining ICIs with agents blocking immunosuppressive pathway may expand the clinical benefit of ICIs to more patients. Transforming growth factor β (TGF-β) participates in tumor immune escape. SHR-1701 is a bifunctional fusion protein composed of a mAb against PD-L1 fused to the extracellular domain of TGF-β receptor II. Here, we report the safety and efficacy of SHR-1701 in RM-NPC patients. **Methods:** This is an ongoing, multicenter, open-label, phase Ib study (NCT04282070). Patients with confirmed RM-NPC who failed prior platinum-based chemotherapy (Arm 1) or both platinum-based chemotherapy and anti-PD-1/PD-L1 antibody treatment (Arm 2) were enrolled to receive SHR-1701 30 mg/kg intravenously once every three weeks until disease progression, unacceptable toxicity, or patient withdrawal. The primary endpoint was safety. The secondary endpoints were objective response rate (ORR), duration of response (DoR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS). **Results:** 54 patients with RM-NPC were enrolled (Arm 1, n = 30; Arm 2, n = 24). All patients had stage IVb disease and 34 (63%) had received ≥2 lines prior therapies. At data cutoff on Nov 19, 2021, the median SHR-1701 exposure was 6.7 cycles (range 2-23) in Arm 1 and 2.1 cycles (range 1-17) in Arm 2. Grade ≥3 treatment-related adverse events (TRAEs) were observed in 10 patients (18.5%), with the most common being anemia (7.4%) and hemoptysis (3.7%). Two patients (3.7%) discontinued study treatment due to AEs (peripheral nerve injury and epistaxis, n = 1 each), and 10 patients (18.5%) had dose delay caused by AEs. Investigator reported immune related AEs (irAEs) of grade ≥3 occurred in five patients (9.3%). One death (1.9%) from unknown cause was observed, and the causality was deemed as not assessable. At data cutoff, the ORR was 33.3% (95% CI 17.3-52.8) in Arm 1 and 4.2% (95% CI 0.1-21.1) in Arm 2. Responses were ongoing in nine (90.0%) and no patients, respectively, and the median DoR was not reached in Arm 1 and 4.1 months in Arm 2. The DCR was 53.3% (95% CI 34.3-71.7) and 25.0% (95% CI 9.8-46.7), respectively. The median PFS was 5.3 months (95% CI 1.3-not reached) in Arm 1 and 1.4 months (95% CI 1.3-2.7) in Arm 2. At data cutoff, five patients (16.7%) in Arm 1 and eight patients (33.3%) in Arm 2 had died, and the median OS was not reached in both Arms. The 12-month OS rate was 79.9% (95% CI 53.2-92.3) and 71.9% (95% CI 47.6-86.4), respectively. **Conclusions:** SHR-1701 showed tolerable toxicity profile and promising antitumor activity in patients with RM-NPC who failed prior platinum-based chemotherapy. Clinical trial information: NCT04282070. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

6025 **Poster Session**

Efficacy and safety of chemotherapy plus subsequent locoregional radiotherapy and toripalimab in de novo metastatic nasopharyngeal carcinoma. *First Author: Si-Yuan Chen, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Approximately 50% of primary metastatic nasopharyngeal carcinoma (mNPC) patients who received sequential chemoradiotherapy experience disease progression within one year. Improvements in therapy are greatly needed. This phase II study aimed to investigate the efficacy and safety of programmed cell death protein-1 (PD-1) inhibitor combined with sequential chemoradiotherapy in de novo mNPC. **Methods:** Patients who demonstrated complete or partial response following 3 cycles of cisplatin and fluorouracil (PF) were enrolled. Eligible patients received 3 more cycles of PF and subsequent radiotherapy plus toripalimab every three weeks at a fixed dose of 240 mg. The primary end point was objective response rate (ORR) at three months after radiotherapy, and the secondary end points were progression-free survival (PFS), disease control rate (DCR) and safety profiles. Exploratory study included biomarker analysis and efficacy comparation based on a historical cohort. A Simon's two-stage optimal design with one-sided type I error rate of 5% and power of 80% was utilized to compare a null hypothesis ORR of 54% against an alternative of 80%. Target accrual was a minimum of 22 patients (stage 1 and 2 combined). **Results:** Of the 22 enrolled patients (7 women and 15 men; median age of 54.5 years [IQR 40.5-57.5 years]), the ORR at three months after radiotherapy was 81.8% (22.7% complete response, n = 5; 59.1% partial response, n = 13), and the DCR was 81.8%. The median PFS was 19.4 months (95% CI 10.8-NR). Grade 3-4 adverse events occurred in 15 (68.2%) patients; two patients (9.1%) had grade 2 or 3 immune-related adverse events and discontinued toripalimab. This trial met its primary objective of demonstrating a significant ORR versus historical controls (81.8% vs. 54%, $P = 0.024$). Elevation of plasma EBV DNA post radiation was associated with worse median PFS (10.5 vs. 19.4 months; hazard ratio = 4.23, 95% CI 1.0-17.9; $P = 0.033$). **Conclusions:** The addition of toripalimab to sequential chemoradiotherapy displayed promising tumor response and manageable safety profile in primary mNPC. These results support a potential role of PD-1 inhibition as consolidation therapy in the first-line treatment of primary mNPC. Clinical trial information: NCT04398056. Research Sponsor: the National Natural Science Foundation of China, Other Foundation.

6026 **Poster Session**

A new prognostic model in patients with recurrent or metastatic head and neck cancer treated with chemotherapy: An analysis of ECOG-ACRIN E1305. *First Author: Athanassios Argiris, Department of Medical Oncology, Thomas Jefferson University, Philadelphia, PA*

Background: We examined a large patient dataset based on E1305, a completed phase III randomized trial of platinum-based chemotherapy with or without bevacizumab (Argiris et al. JCO 2019), to evaluate prognostic factors in the first-line treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck (RM SCCHN) and expand on our previous observations in cooperative group trials (Argiris et al. Cancer 2004). **Methods:** All 403 patients enrolled in E1305 were analyzed. Overall survival (OS) was the outcome of interest. Clinical and tumor characteristics were examined using Cox proportional hazards models. Variables which were significant in the univariate setting at a level of ≤ 0.10 were included in a multivariable model, and backwards selection was performed (threshold of $p \leq 0.05$). The final multivariable model was then applied to the two treatment arms, separately. Variables for which the hazards ratio (HR) within an arm was more than 10% different than that for the whole cohort, were removed from the final cohort model. **Results:** The median OS in the whole study cohort was 11.8 months. A prognostic score model for OS was built, using the 4 independent prognostic factors identified in the multivariable model: ECOG performance status (1 vs 0), prior radiation, primary region (non-oropharynx vs oropharynx), and metastatic disease bone or liver (vs other sites/no metastases). Prognostic score was dichotomized (0-2 and > 2). Patients with 0-2 risk factors (n = 249) had a median OS of 15.2 months (90% CI: 13.8, 18.1), while patients with > 2 risk factors (n = 154) had a median OS of 7.6 months (90% CI: 6.5, 9.3); HR of 2.14 (95% CI: 1.73, 2.66), $p < 0.0001$. Compared to our previous 5-factor model from analysis of older trials in a similar setting, the variable "bone/liver metastasis" is new, but "tumor cell differentiation" and "weight loss" were not significant and not included in the new model for OS. **Conclusions:** The new proposed model includes 4 prognostic factors for OS (performance status, primary site, prior radiation, presence of bone/liver metastasis) in the first-line treatment of RM SCCHN. Research Sponsor: U.S. National Institutes of Health.

6027 **Poster Session**

Penpulimab plus anlotinib in patients with recurrent or metastatic head and neck squamous cell carcinoma after the failure of first-line platinum-based chemotherapy: A single-arm, multicenter, phase 2 study. *First Author: Changgong Zhang, Department of Medical Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Clinical Study On Anticancer Molecular Targeted Drugs, Beijing, China*

Background: Penpulimab is a novel human immunoglobulin G1 (IgG1) anti-programmed cell death-1 (PD-1) antibody. The effect of antibody-dependent cell-mediated cytotoxicity and antibody-dependent cellular phagocytosis was eliminated completely by the modification of crystallizable fragment to avoid the FcγR binding. ALTN-AK105-II-01 (NCT04203719) is a single-arm, multi-cohort, multicenter phase 2 study to explore the efficacy and safety of penpulimab plus anlotinib, a multikinase inhibitor inhibiting angiogenesis and tumor cell proliferation simultaneously, in the treatment of various advanced cancers. Here we report the results of the cohort 1 for patients (pts) with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC). **Methods:** Eligible pts were diagnosed with histologically confirmed R/M HNSCC and had failed at least one line of platinum-based chemotherapy. Other inclusion criteria included aged 18 years or older, ECOG PS 0-1, and previous anti-angiogenic agents or immune checkpoint inhibitors treatment-naïve. Pts were given penpulimab 200mg intravenously on day 1 and oral anlotinib 12mg once daily from day 1 to day 14 every 3 weeks until disease progression or unacceptable toxicities. The primary endpoint was objective response rate (ORR) per RECIST 1.1. Secondary endpoints included progression-free survival (PFS), overall survival (OS), disease control rate (DCR), duration of response (DoR), and safety. **Results:** From June 1, 2020 to November 22, 2021, 38 pts were enrolled in 8 cencers in China. The sites of primary tumors included oral cavity (15/38, 42.9%), oropharynx (6/38, 15.8%), hypopharynx (4/38 4.5%), larynx (10/38, 26.3%) and others (3/38, 7.9%). As of January 6, 2022 (data cut-off),The study met its primary endpoint that 13 pts achieved partial response (PR) and the ORR (confirmed at least 4 weeks after initial response) was 34.21%. 14 pts obtained stable disease (SD) lasting for at least 4 weeks, given a DCR of 76.32%. After a median follow-up of 6.96 months (95%CI: 4.40, 8.80). PFS events were observed in 17 pts and the median PFS was 8.35 months (95%CI: 5.45, 13.11). The PFS at 6 months was 62.5%. 9 pts died and the median OS was not reached (95% CI: 9.43, NE). For pts with tumor response, the median DoR was not reached (95% CI: 2.37, NE). Treatment-related adverse events (TRAEs) occurred in 89.47% pts, TRAE of grade 3 or above occurred in 39.47% of pts. The most common TRAEs were hypertension (28.95%) and hypothyroidism (28.95%). **Conclusions:** The combination of penpulimab and anlotinib demonstrated promising efficacy and manageable toxicities in R/M HNSCC pts who failed standard first-line therapy. Further investigation is warranted. Clinical trial information: NCT04203719. Research Sponsor: None.

6028 **Poster Session**

Comprehensive immune landscape and molecular characteristics of clinical responses to chemotherapy, antiangiogenic agents, and PD-1 inhibitors in recurrent or metastatic nasopharyngeal carcinoma. *First Author: Mingyuan Chen, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: The role of a triple combination of gemcitabine (chemotherapy) plus apatinib (anti-VEGF) and toripalimab (anti-PD-1) (GAT) in recurrent/metastatic nasopharyngeal carcinoma is unclear. **Methods:** Between August 2019 and April 2020, 54 patients with recurrent or metastatic NPC were screened, of whom 41 eligible patients were enrolled and received study treatment. Patients were treated with gemcitabine (1000 mg/m^2) on days 1 and 8 once every 3 weeks for a maximum of 6 cycles plus toripalimab (240 mg) on day 1 once every 3 weeks and apatinib (orally administered at 250 mg) once a day until disease progression, death, dose-limiting toxicities, or at the patient's request to stop. The primary endpoint was the safety. The secondary endpoints included the objective response rate (ORR) and progression-free survival (PFS). **Results:** By the data cutoff date, the median follow-up time was 13.4 months. G3-4 hematologic, gastrointestinal and kidney toxicities were observed in no more than 3 (3/41, 7.3%) patients, while G3-4 nasopharyngeal wall necrosis was observed in 9 (9/41, 21.9%) patients. High-risk factors for nasopharyngeal necrosis, included repeated radiotherapy and an interval of less than 12 months from the last radiotherapy. Among all 41 patients, the ORR was 90.2% (95% CI: 76.9%-97.2%). The median PFS was 13.93 months (95% CI: NR-NR), and the 12-month PFS rate was 72.0% (95% CI: 57.1%-86.9%). A substantial increase of CD28+ and ICOS+ CD4+/CD8+ T cells and a decrease of PD1+ CD4+/CD8+ T cells were observed in the peripheral blood after the GAT treatment. 11q13.3 amplification and MRGPRF high expression in tumors correlated with poor PFS from the triple combination therapy. NPCs with 11q13.3 amplification was characterized by high epithelial mesenchymal transition (EMT) and immune suppressive transcriptional signatures. Furthermore, serial circulating tumor DNA (ctDNA) sequencing could predict PFS outcomes to combination therapy. **Conclusions:** The triple combination of GAT exhibits a promising antitumor activity and manageable toxicities in patients with recurrent/metastatic NPC. Patients with repeated radiotherapy and an interval of less than 12 months from the last radiotherapy should be carefully selected for antiangiogenic therapies. An integrated genomic and transcriptional analyses may aid to identify the beneficial patient populations in response to this novel combination therapy. Clinical trial information: NCT04073784. Research Sponsor: the National Natural Science Foundation of China.

6029 **Poster Session**

CA209-9KY: Results of a phase II study of intensity modulated radiotherapy (IMRT) re-irradiation and concurrent/adjuvant nivolumab (nivo) in patients with loco-regionally recurrent or second primary (RSPT) head and neck squamous cell carcinoma (HNSCC). *First Author: Nabil F. Saba, Winship Cancer Institute Emory University School of Medicine, Atlanta, GA*

Background: RSPT HNSCC within a previously irradiated field presents a technical challenge portending worse outcome. Anti-PD-1 therapy is an approved standard of care in the treatment of advanced HNSCC. CA209-9KY aimed to investigate the progression-free survival (PFS), tolerability, overall survival (OS) and patient reported outcomes (PRO) of nivo during and after IMRT re-irradiation. We report here the results for 51 enrolled and evaluable patients **Methods:** Following IRB approval at 3 participating institutions (Emory University, Cleveland Clinic, Medical College of Wisconsin), patients (pts) were enrolled if they had RSPT in a previously irradiated field (>40Gy) and met criteria for recursive partition analysis (RPA) classes I or II (Ward et al, IJROBP 2018). Salvage resection was allowed provided the presence of pos margins, ENE, pN2/3 or pT3/4 disease, multifocal PNI, or LVI. IMRT re-irradiation to a total of 60-66 Gy in 30-33 daily fractions were delivered over 6-6.5 weeks with nivo (240 mg) two weeks prior and every 2 weeks x 5 during IMRT then at 480 mg every 4 weeks up to 52 weeks. The primary endpoint was improvement in 1-yr PFS from 40% to 55% (one-sided alpha of 0.05 and an 85% power). **Results:** As of 1/2022, a total of 51 evaluable pts completed IMRT with nivo. Median age 62 (56-67), RPA status 1 (23, 46%), 2 (27, 54%), Males (41, 80%), ECOG performance status 0 (13, 25%) 1 (36, 71%), 2 (2, 4%); p16 pos (16, 31%), neg (9,18%), not applicable (26, 51%). With a median follow up of 12.5 mos (11.2-14.0) the 1- yr PFS was 57.8% (95% CI, 41.3-71.1%) and OS was 81.7% (95% CI, 65.2-90.9%). Among 38 pts with available flow cytometry, pts with a 1.5-fold increase in peripheral blood PD1+KI67+CD8+ T cells (baseline to weeks 2 or 4) had an OS of 19.3 mos (vs 13.3 mos) (p=0.1617). Adverse events (AEs) (CTCAE version 4.0) included fatigue(40, 78%), dermatitis (30,58%), dysphagia (28, 54%). Most frequent serious AEs were anorexia and dyspnea (2, 4% each). Treatment related >3 AEs were lymphopenia (2, 4%), colitis, diarrhea, mucositis and nausea (1, 2% each). FACT-G and FACT-H&N QOL scores remained stable and consistent across all time points (52 weeks) (Cronbach's alpha of > 0.7) (ASTRO 21, abstract # 2738). **Conclusions:** CA209-9KY met its primary endpoint of 1-yr PFS; IMRT reirradiation with concurrent and adjuvant nivo is clinically effective, well tolerated and deserves further exploration in patients with RSPT HNSCC. CA209-9KY was supported by a grant from BMS. Clinical trial information: NCT03521570. Research Sponsor: BMS.

6030 **Poster Session**

A retrospective analysis of patients administered neoadjuvant chemotherapy (NACT) with paclitaxel plus carboplatin with oral metronomic chemotherapy (OMCT) in locally advanced borderline resectable/technically unresectable head and neck cancers. *First Author: Shruti Pathak, Tata Memorial Centre, Mumbai, India*

Background: Neoadjuvant chemotherapy with TPF though the standard is seldom used in India due to its adverse events rate. Two drug regimen of Paclitaxel and Carboplatin (PC) though favoured has inferior outcomes. Hence, we did an analysis to estimate the efficacy and adverse event rate of addition of 3 drug metronomic schedule to PC. **Methods:** Patients of locally advanced head and neck cancer referred from multidisciplinary board for neoadjuvant chemotherapy and unsuitable for TPF were selected for this analysis. These patients had received 2 drug regimen of intravenous PC with 3 drug regimen of weekly methotrexate 9 mg per m2, Celecoxib 200 mg twice daily, erlotinib 150 mg once daily all administered orally. All patients underwent a response assessment at 5-7 weeks post start of therapy and we're discussed in MDT for further treatment. Adverse events were recorded in accordance with CTCAE version 4.03 and response in accordance with RECIST version 1.1. PFS and OS were estimated with Kaplan Meier method. **Results:** 72 patients were identified with the median age being 45 (27-80) and M:F ratio (67:5). The indication for NACT were borderline resectability in all patients. . The response rate was 61.1% and grade 3 and above adverse event rate was 33.5% . A total number of 34 among 40 borderline resectable patients underwent surgery. The overall estimated PFS and OS were 18.5 (95%CI = 14.4-22.7) months and 18.05 (95%CI = 14.2-21.8) months respectively. The three most adverse events observed were grade 3 thrombocytopenia in 2 patients (2.8%), grade 3 aspartate aminotransferase (AST) derangement in 4 patients (5.6%) and grade 3 alanine aminotransferase (ALT) in 4 patients (5.6%). **Conclusions:** The 5 drug combination regimen is safe, tolerable and seems to have similar efficacy as a three drug TPF regimen. Research Sponsor: None.

6031 **Poster Session**

Complications and severity of COVID-19 in patients with head and neck cancer (HNC): A COVID-19 and Cancer Consortium (CCC19) registry analysis. *First Author: Vidhya Karivedu, Division of Medical Oncology, Ohio State University, Columbus, OH*

Background: Patients with cancer have worse outcomes from COVID-19 infection. However, the specific impact of COVID-19 on patients with head and neck cancer (HNC) is largely unknown. The COVID-19 and Cancer Consortium (CCC19) maintains an international registry (NCT04354701) aimed to investigate the clinical course and complications of COVID-19 in patients with cancer. Here, we report severity of COVID-19 and its complications among HNC patients. **Methods:** The CCC19 registry was queried for patients with HNC and laboratory confirmed SARS-CoV-2 infection. The co-primary outcomes were severity of COVID-19 illness on an ordinal scale (0: no complications; 1: hospitalized, no oxygen (O2); 2: hospitalized, required O2; 3: ICU admission; 4: mechanical ventilation (MV); 5: death), and severity of complications (mild, moderate, serious). The outcomes were further stratified by demographics, recent treatment (systemic vs local; surgery, radiation (RT) vs systemic), treatment intent (palliative vs curative), and cancer status (remission, responding, stable, progressing). **Results:** From March 2020 to December 2021, 356 HNC patients were identified. Median age was 65 (interquartile range 58-74), 29% were female, 56% were white, 67% were former or current smokers, 20% had a BMI >30, 15% had an ECOG performance status >2, and 57% had >2 comorbidities. 154 (43%) had no complications, 61 (17%) were hospitalized without O2, 135 (38%) were hospitalized with O2, 50 (14%) required ICU, 32 (9%) required MV, and 74 (21%) died. 88 (25%) had mild, 59 (17%) had moderate, and 132 (37%) had serious complications. 33% of patients who received systemic therapy and 30% who received RT within 3 mo prior to COVID-19 diagnosis died. Mortality was higher in patients receiving palliative when compared to curative intent treatment (44% vs 16%). In addition, 50% of patients with actively progressing cancer, and 45% who had serious complications died. Importantly, 37 (n=12 palliative systemic therapy and n=25 local therapy) patients had a treatment delay due to COVID-19 diagnosis. **Conclusions:** Our study is the largest cohort to date describing COVID-19 outcomes in HNC patients and suggest a high rate of mortality even in those receiving local and curative intent treatment. Variables stratified by COVID-19 severity. Note: Ordinal levels 3 and 4 not shown due to small case numbers. Research Sponsor: Supported by Vanderbilt Institute for Clinical and Translational Research grant support (UL1 TR000445 from NCATS / NIH).

	Worst severity of COVID-19 illness			
Characteristics	0 (N=150) %	1 (N=51) %	2 (N=60) %	5 (N=74) %
Complication severity				
Mild	84	10	<8	<7
Moderate	25	37	27	8
Serious	<3	<10	8	45
ECOG>2	15	<10	19	52
Obesity (BMI >30)	49	10	25	10
Smoking				
Never	49	12	14	19
Former/current	38	16	19	21
Treatment intent				
Curative	48	16	19	16
Palliative	25	15	15	44
Treatment modality				
Systemic therapy	34	19	11	33
Local therapy	30	10	28	27
Cancer status				
Remission/NED	50	12	18	12
Responding/stable	39	18	24	16
Progressing	25	14	<8	50

Note: Ordinal levels 3 and 4 not shown due to small case number

6032 **Poster Session**

Leukocyte interleukin injection (LI) immunotherapy extends overall survival (OS) in treatment-naive low-risk (LR) locally advanced primary squamous cell carcinoma of the head and neck: The IT-MATTERS study. *First Author: Eyal Talor, Cel-Sci Corporation, Vienna, VA*

Background: The 3-week pre-surgery peritumoral/perilymphatic administration of an investigational proinflammatory cytokine complex biologic (LI) with CIZ (single low dose cyclophosphamide IV-bolus, 300 mg/m^2), indomethacin (po 25mg tid) and Zinc as multivitamins (po 15-45mg Zinc) + Standard of Care (SOC) to oral and soft-palate SCCHN subjects, resulted in early response (CRs/PRs) prior to surgery [RECIST] (confirmed at surgery by pathology) significantly prolonged OS in the NCCN-defined LR intent to treat (ITT) population vs SOC alone. Encouraging phase 2 OS and early responders results motivated this pivotal study IT-MATTERS Clinicaltrials.gov NCT01265849. No safety issues were noted for LI in this pivotal study or previous studies. **Methods:** Subjects (923 ITT; of which 380 LR ITT) meeting protocol entry criteria (including AJCC Stage III/IVa OSCC, soft-palate SCCHN, treatment naive) were randomized 3:1:3 to treatment arms LI (+/- CIZ) + SOC or to Control (SOC alone). LI treated were administered 200IU peritumorally and the same dose peri-lymphatically daily for 3-weeks before surgery. All study subjects were to receive SOC (per NCCN Guidelines). LR for recurrence subjects were to receive RTx while high risk subjects were to receive CRTx post-surgery. Follow-up was comparable (56-57 months median per treatment group). **Results:** Pre-surgery responders (PSR; CR/PR) in ITT LI treated (+/- CIZ) groups were 8.5% (45/529; overall LI) and 16% (34/212; LR LI) vs no SOC PSRs. Early response lowered death rate to 22.2% (ITT LI treated) vs 54.1% for non-PSRs (two-sided Fisher Exact (2FE) $p < 0.0001$), for ITT LR LI PSRs with 17.6% vs 42.7% (2FE $p = 0.0067$), and for ITT LR LI responders (LI+CIZ+SOC) 12.5% vs 41% (2FE $p = 0.0101$). Proportional hazard (PH) ITT LR LI treated HR = 0.348 (95% CI: [0.152, 0.801]), ITT LR LI+CIZ+SOC HR = 0.246 (95% CI: [0.077, 0.787]). For all ITT LR (n = 380), LI+CIZ+SOC demonstrated significant OS advantage vs SOC (log rank $p = 0.0478$; Cox HR = 0.68 (95% CI: [0.48-0.95]), Wald $p = 0.0236$ [controlling for tumor stage, tumor location and geographic region]. The absolute OS advantage in ITT LR LI+CIZ+SOC vs SOC was 4.9%/9.5%/14.1%, at 36/48/60 months (M), representing 72.4% vs 67.5% (36 M); 67.3% vs 57.8% (48 M), and 62.7% vs 48.6% (60 M) with a 46.5 M median OS advantage (101.7 M [LI+CIZ+SOC] vs 55.2 M [SOC]). Percent treatment emergent adverse events (TEAEs) were comparable among all treated groups. No excess safety was reported for LI treatment over SOC alone. **Conclusions:** LI immunotherapy did not add excess safety issues or TEAEs. Early LI response decreases mortality and is OS prognostic. ITT LR LI+CIZ+SOC absolute OS advantage over SOC alone increased over time; the 0.68 HR corresponds to a 47% prolongation of median survival in a population without any new therapy options in decades. Clinical trial information: NCT01265849. Research Sponsor: CEL-SCI Corporation.

6033 **Poster Session**

Four-year result of diffusion-weighted, MRI-guided, dose-painting radiotherapy following induction chemotherapy in patients with locally advanced recurrent nasopharyngeal carcinoma: A randomized controlled trial. *First Author: Feng Liu, Hunan Cancer Hospital and The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, China*

Background: We hypothesized that diffusion-weighted MR imaging (DWI) guided dose-painting radiotherapy (DP-RT) following induction chemotherapy (IC)was associated with improved local tumor control and progression-free survival compared with conventional MRI-based radiotherapy (RT) in locally advanced recurrentnasopharyngeal carcinoma (rNPC). The purpose of this randomized phase II trial was to compare the efficacy and toxicity of DWI guided DP-RT following IC versus standard conventional MRI-based radiotherapy following IC in locally advanced rNPC. **Methods:** Tow hundred and four patients with locally recurrent T3 to T4 NPC were randomly assigned to receive DWI-guided dose-painting radiotherapy (DP-RT) or conventional MRI-based radiotherapy. Patients in both groups received reirradiation using intensity modulated radiation therapy (IMRT) following cisplatin-based induction chemotherapy. In DP-RT group (group A, n = 102), subvolume GTVnx-DWI (gross tumor volume of nasopharynx in DWI) was defined as the areas within the GTVnx (gross tumor volume of nasopharynx) with an apparent diffusion coefficient (ADC) below the mean ADC (ADC < mean). The dose to GTVnx-DWI was escalated to DT 65.4 Gy/30 Fx in 2.18 Gy per fraction. In conventional MRI-based RT group (group B), PGTVnx was irradiated at DT 60.0 Gy/30 Fx in 2.0 Gy per fraction. This trial is registered with chictr.org.cn, number ChiCTR2100052340. **Results:** Compared with conventional MRI-based radiotherapy, DWI-guided DP-RT significantly improved 4-year progression-free survival (PFS, 48.0% vs. 33.3%; P = 0.033), local control rate (LC, 85.3% vs. 69.6%; P = 0.007), and overall survival (OS, 52.0% vs. 37.3%; P = 0.035). No statistically significant differences in acute and late toxic effects (mucosal necrosis, trismus, temporal lobe necrosis, and cranial nerve palsy) were observed between the two groups. Dose painting (DWI-guided DP-RT vs conventional MRI-based RT) was a significant independent prognostic factor for PFS and LC (P = 0.035 and P = 0.020, respectively). **Conclusions:** Diffusion-weighted MRI guided dose-painting radiotherapy following induction chemotherapy is associated with a considerable progression-free survival and local control benefit, without increasing toxicity, as compared with standard conventional MRI-based RT following IC, among patients with locally recurrent T3 to T4 nasopharyngeal carcinoma. Clinical trial information: ChiCTR2100052340. Research Sponsor: Hunan Provincial Science and Technology Department (NO. 2021JJ30426) (China), Other Foundation.

6034 **Poster Session**

Efficacy and safety of QL1706, a novel dual immune checkpoint blockade containing a mixture of anti-PD1 IgG4 and anti-CTLA4 IgG1 antibodies, for advanced nasopharyngeal carcinoma (NPC): Pooled cohort data from phase 1a/1b trials. *First Author: Hongyun Zhao, State Key Laboratory of Oncology in South China Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Additional anti-cytotoxic T lymphocyte antigen 4 (CTLA-4) antibody could increase the anti-tumor effect of anti-programmed cell death 1 (PD-1) antibody. QL1706 is a novel dual immune checkpoint blockade containing a mixture of anti-PD-1 IgG4 and anti-CTLA4 IgG1 antibodies produced by a single cell line. Here the pooled data from phase 1a/1b trials of QL1706 in advanced NPC were reported. **Methods:** In the phase 1a dose escalation and expansion study (NCT04296994), patients received intravenous QL1706 at 0.3, 1.0, 3.0, 5.0, 7.5, or 10.0 mg/kg q3w for dose escalation in an accelerated 3+3 design, and the dose expansion cohorts received selected doses. In phase 1b (NCT05171790), patients with advanced solid tumors were given intravenous QL1706 5.0 mg/kg q3w according to the data in phase 1a. Phase 1a was primarily aimed to define the safety, tolerability, and recommended phase 2 dose of QL1706, and phase 1b was to evaluate the preliminary efficacy. Pooled analyses were conducted in the NPC cohorts receiving QL1706 5 mg/kg. Additionally, dynamic changes of plasma EBV DNA level from baseline were determined in a part of patients during the studies. **Results:** As of Dec 31, 2021, totally 110 patients with NPC were included. Median follow-up was 7.7 months. 79 (71.8%) patients had ≥two prior treatment lines. 48 (43.6%) patients received previous immunotherapy. Confirmed overall response was reached in 27 patients (24.5%; 95% CI 16.8%-33.7%). In immunotherapy-naive patients with one and ≥two prior lines of treatment, overall response rates were 39.1% (9/23) and 38.5% (15/39), respectively. Three of 48 (6.3%) immunotherapy-treated patients had partial response. Disease control was observed in 54 (49.1%; 95% CI 39.4%-58.8%) patients. Median duration of response reached 11.7 months (95% CI 8.1-not estimable). Median progression-free survival was 2.0 months (95% CI 1.4-2.9). Overall survival data were immature. Patients with ≥50% decrease in EBV DNA level on day 43 had significantly better ORR than those with < 50% decrease (67% [8/12] versus 12% [2/17]; P = 0.0045). Treatment-related adverse events (TRAE) were reported in 85 (77.3%) patients. 14 (12.7%) experienced grade ≥3 TRAE. The most common TRAE were rash, hypothyroidism (25 [22.7%], each), and pruritus (22 [20%]). TRAE leading to dose interruptions occurred in 10 (9.1%) patients. No TRAE leading to dose discontinuation or death was reported. The immune-related TRAE and serious TRAE were observed in 51 (46.4%) and eight patients (7.3%), respectively. **Conclusions:** These preliminary results indicated QL1706 had impressive anti-tumor effects on advanced NPC, with acceptable tolerability and manageable toxicity. Further investigation of QL1706 in NPC is continuing. Clinical trial information: NCT04296994; NCT05171790. Research Sponsor: Qilu Pharmaceutical Co., Ltd.

6035 **Poster Session**

Infections and their impact on patients on pembrolizumab-based therapies for head and neck cancer. *First Author: Yuqi Zhang, Houston Methodist Hospital, Houston, TX*

Background: Immune checkpoint inhibitors (ICIs) stimulate the antitumor activity of the adaptive immune response and are used in combination with chemotherapy or as a monotherapy in metastatic head and neck squamous cell carcinoma (mHNSCC). Infections are known to impact outcomes in patients receiving chemotherapy, but the incidence and impact in patients receiving ICI is poorly defined. This analysis aims to identify the infectious burden and associated impact on clinical outcome in patients receiving pembrolizumab for mHNSCC. **Methods:** This is a retrospective study across 7 hospitals analyzing patients who received pembrolizumab from 1/1/2017-8/1/2021 and followed until 12/1/2021. Patients with mHNSCC that received pembrolizumab were dichotomized into infected and uninfected cohorts. Comparative covariates included gender, race, ECOG, comorbidities, anti-infectives use at ICI initiation, chronic infections, line of therapy (first or 1L, second or 2L, or > 2L). Risk factors for infections were assessed by univariable and multivariable analysis with reported odds ratio (OR) and 95% confidence intervals (CI). Morbidity and mortality was assessed by all-cause emergency department (ED), inpatient, and intensive care unit (ICU) admissions, median cycles of ICI-based therapy, and overall survival (OS). OS was assessed via Kaplan-Meier analysis. P-value < 0.05 was considered statistically significant. **Results:** Of the 45 evaluable patients with mHNSCC, 22 (48.9%) had at least one infection. Baseline characteristics and comorbidities were similar across cohorts. Risk factors for developing infection included anti-infective use at ICI initiation (OR 13.27, 95% CI: 1.13-156.53, p = 0.04). Fewer infections were observed with ICI as > 2L compared to 1L (OR 0.1, 95% CI: 0.01-0.91, p = 0.041). Infection was the primary cause of death in 2 (9.5%) patients. Compared to the uninfected, infected patients received fewer cycles of therapy (4 vs 7, p = 0.026), and were more frequently admitted to the hospital [20 (90.9%) vs. 8 (34.8%), p < 0.001)] and ICU [5 (11%) vs. 0, p = 0.022]. Number of ED visits were similar at 8 (36.4%) in the infected vs. 5 (21.7%) in the uninfected (p = 0.28). At median follow-up of 8 months, 13 (59.1%) in the infected cohort and 8 (34.8%) in the uninfected had died (p = 0.1). Median OS was significantly lower in the infected (9.2; 95% CI 4.9-12.8 months) compared to the uninfected (28.1; 95% CI 14.3-unreached months) (p = 0.009). **Conclusions:** For mHNSCC patients on pembrolizumab, infections are more common in the 1L setting and is associated with fewer treatment cycles, more hospitalizations, and significantly shorter OS. Risk factors for infection include anti-infective use at ICI initiation. Research Sponsor: None.

6036 **Poster Session**

Taxanes plus cetuximab with or without platinum chemotherapy after progression on immune checkpoint inhibitors in patients with squamous cell carcinoma of the head and neck. *First Author: Khalil Saleh, Departemnt of Hematology, Gustave Roussy Cancer Campus, Villejuif, France*

Background: Salvage chemotherapy after progression on immune checkpoint inhibitors (ICIs) was associated with an objective response rate (ORR) of 30% in patients (pts) with recurrent/metastatic squamous cell carcinoma of the head and neck (R/M SCCHN). We aimed to investigate the efficacy of taxanes + cetuximab (TC) +/- platinum chemotherapy in pts with R/M SCCHN who failed ICIs in palliative setting. **Methods:** A retrospective study was conducted at 7 French university hospitals. Eligibility criteria were pts treated with ICI for R/M SCCHN, who progressed after treatment with ICI and received TC +/- platinum salvage chemotherapy between August 2017 and December 2021. Clinical and radiological data and outcome were collected from review of medical records. **Results:** Ninety-nine pts met eligibility criteria: 63 pts received TC and 36 pts received triplet regimen (TR). The median age was 61 years (range 24-78) and 79% of pts were male. Forty-two pts (42%) had platinum-refractory disease (PRD) after multimodal treatment, 13 pts received prior taxanes and 24 pts received prior cetuximab. The median PS at salvage chemotherapy was 1 (range 0-3). ICIs were given as first-line treatment in 70% of pts including those with PRD. The ORR of the entire cohort was 62% (61/99) including 5 complete responses (CR) and the disease control rate was 79% (78/99). The median progression-free survival of the entire cohort was 4.4 months and the median overall survival (OS) was 7.5 months. The 5 pts who had CR as best response are still in remission after a median follow-up of 24 months (range 8-58). The ORR of TC subgroup was 57% (36/63) and the ORR of TR subgroup was 69% (25/36). Furthermore, the ORR in the PRD subgroup of pts was 54% (39/72), and the ORR in the subgroup of pts who were not chemo naïve was 54% (39/72). The ORR in pts who previously received cetuximab was 50% (12/24) vs 75% (49/75) in those who did not. The ORR in pts who previsouly received taxanes was 38% (5/13) vs 65% in those who did not. Finally, the ORR in PRD pts and treated with TR was 50% (7/14) and the ORR in pts who previously received platinum-based treatment or PRD and treated with TR was 55% (11/20). **Conclusions:** TC +/- platinum chemotherapy was highly effective in pts R/M SCCHN who progressed on ICIs with an ORR of 62% and DCR of 79%. Further investigations are warranted. Research Sponsor: None.

6037 **Poster Session**

Individualized prediction of distant metastases risk in oral cavity carcinoma: A validated predictive-score model. *First Author: Badr Id Said, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: We aimed to develop and validate a risk-scoring system for distant metastases (DM) in oral cavity carcinoma (OCC). **Methods:** In this IRB-approved retrospective study, OCC patients treated at 4 tertiary cancer institutions with curative surgery +/- postoperative radiation/chemo-radiation (PORT/PO-CRT) were divided into discovery and validation cohorts (randomly selected in 3:2 ratio). Staging was reviewed based on TNM 8th edition. Predictors of DM identified on multivariable analysis in discovery cohort were used to develop DM risk-score model to classify patients into risk groups using Contal and O'Quigley method for cut-off optimization. The utility of risk classification was subsequently evaluated in validation cohort. C-index was used to assess predictive ability of the continuous risk score. **Results:** Overall 2749 patients were analyzed (Table). Predictors (risk score coefficient) of DM in discovery cohort were: pT3-4 (0.4), pN+ (N1:0.8; N2:1.0; N3:1.5), histologic grade 3 (G3, 0.7) and lymphovascular invasion (LVI, 0.4). The DM risk groups were defined by cumulative sum of risk score coefficients: high risk (sum >2), intermediate risk (sum=1-2), and standard risk (sum<1). In the discovery cohort, 5-yr DM for high vs intermediate vs standard risk groups was 33% vs 19% vs 6%, p<0.001 (C-index=0.79). Similarly, in the validation cohort, 5-yr DM for high vs intermediate vs standard risk groups was 36% vs 23% vs 7%, p<0.001 (C-index=0.77). When applied to entire study population, this predictive model showed excellent discriminative ability in predicting DM only without locoregional failure (29% vs 18% vs 3%, p<0.001), late (>2 yr) DM (11% vs 5% vs 3%; p<0.001), DM in patients treated with surgery only (26% vs 11% vs 6%, p<0.001), PORT (37% vs 23% vs 7%, p<0.001), and PO-CRT (42% vs 29% vs 9%, p<0.001). Finally, 5-yr OS for high vs intermediate vs standard risk groups in the overall cohort was 24% vs 38% vs 66%, p<0.001. **Conclusions:** A predictive-score model for DM utilizing pT3-4, pN1/2/3, G3 and LVI demonstrated a validated utility in identifying patients at higher risk of DM who may be evaluated for individualized risk-adaptive treatment escalation and/or surveillance strategies. Research Sponsor: None.

Study cohorts and predictors of distant metastases in discovery cohort.

	Discovery (n=1650) N (%)	Validation (n=1099) N (%)	p
Median follow up	4.6 yr	4.5 yr	0.11
pT3-4	895 (54)	565 (51)	0.16
pN1/pN2/pN3	156(9)/ 258 (16)/ 280 (17)	99 (9)/ 159 (14)/ 196 (18)	0.78
G3	210 (13)	132 (12)	0.62
LVI	349 (22)	271 (25)	0.05
PORT/PO-CRT	873 (54)/ 220 (13)	567 (52)/ 150 (14)	0.48
5-yr DM (95% CI)	14% (12%-17%)	12% (11%-14%)	0.07
5-yr OS (95% CI)	55% (52%-59%)	53% (51%-56%)	0.38
Predictors of DM[@]	* pT3-4 (p=0.04) * pN+ (p<0.001) * G3 (p< 0.001) * LVI (p<0.01)	-	-

[@]variables included in multivariable analysis: age, gender, smoking history, subsite, pT, pN, grade, LVI, PNI, margin status, pN+ at level IV/VB, PORT and PO-CRT.

6038 **Poster Session**

Predictors of the survival for platinum-refractory head and neck squamous cell carcinoma by using contrast-enhanced magnetic resonance imaging. *First Author: Hsueh-Ju Lu, Division of Hematology and Oncology, Department of Internal Medicine, Chung Shan Medical University Hospital, Taichung, Taiwan*

Background: Platinum-refractory head and neck squamous cell carcinoma (HNSCC) was a poor prognosis. Under the treatment of immune checkpoint therapy, overall survival (OS) was still only 7.7 months. Moreover, the prognostic factors were unclear. **Methods:** For enrolled platinum-refractory HNSCC patients, the presented images of the axial, coronal, and sagittal planes from T1-Weighted Contrast-Enhanced Magnetic Resonance Imaging (T1 CE MRI) were independently reviewed by two physicians. First, the most representative characteristics of the recurrent tumor on the three planes were manually identified, and the intersection coordinate was calculated as a circle center by computerized methods. Then, the center delineated a region of interest (ROI) with a radius of 25 pixels on each representative slice and excluded the air areas. Descriptive features and four groups of texture features (Gray Level Co-occurrence Matrix [GLCM], Gray Level Run Length Matrix [GLRLM], Gray Level Size Zone Matrix [GLSZM], and Neighbouring Gray Tone Difference Matrix [NGTDM]) were derived from the ROI to depict MRI intensities' distribution and heterogeneity. **Results:** A total of 30 patients were retrospectively enrolled, including immune checkpoint therapy (N = 19) and cetuximab-based chemotherapy (N = 11) as front-line therapy. Median OS was 7.0 months with 17 death events during follow-up. The area size of ROI was not significantly associated with the death events. However, High Gray-level Run Emphasis (HGRE) and Short-Run High Gray-level Emphasis (SRHGE) of GLRLM as well as High Gray-level Zone Emphasis (HGZE) and Short-Zone High Gray-level Emphasis (SZHGE) of GLSZM were significant to predict the event of death. The area under the curve (AUC) of HGRE, SRHGE, HGZE, and SZHGE were 0.747 (P = 0.023), 0.842 (P = 0.002), 0.819 (P = 0.003), and 0.833 (P = 0.002) at discretization levels of 16, respectively. These features also significantly differed OS of platinum-refractory HNSCC (Table). **Conclusions:** Four texture features of GLRLM and GLSZM depicted the fragmentation of extracellular volume of the recurrent tumor on T1 CE MRI and significantly correlated with the outcomes of platinum-refractory HNSCC. However, future warranted studies were needed. Research Sponsor: None.

	1-year survival	Hazard ratio (95% CI)
High Gray-level Run Emphasis (HGRE)	54.5% vs. 9.7%	2.218(0.629-7.826)
Short-Run High Gray-level Emphasis (SHRGE)	65.9% vs. 0.0%	4.254(1.213-14.915)
High Gray-level Zone Emphasis (HGZE)	75.0% vs. 0.0%	8.741(1.134-67.397)
Short-Zone High Gray-level Emphasis (SZHGE)	100.0% vs. 0.0%	45.726(0.714-2927.085)

6039 **Poster Session**

Phase I results of gunagratinib (ICP-192), a highly selective irreversible FGFR 1-4 inhibitor in patients with head and neck cancer harboring FGF/FGFR gene aberrations. *First Author: Ye Guo, Oncology, Shanghai East Hospital, Tongji University, School of Medicine, Shanghai, China*

Background: The fibroblast growth factor (FGF) and FGF receptor (FGFR) signaling pathway has been evaluated as critical driver of carcinogenesis in multiple cancer types. However, primary results of several FGFR inhibitors showed no or limited response in head and neck cancer (HNC) with FGF/FGFR gene aberrations. Here, we evaluated the efficacy and safety of a novel irreversible pan-FGFR inhibitor gunagratinib in HNC in a first-in-human, phase I/IIa, dose escalation and dose expansion study (ICP-CL-00301 NCT03758664). **Methods:** In the dose-escalation stage of ICP-CL-00301 study, patients with advanced solid tumors (including HNC) with or without FGF/FGFR gene alterations were treated with escalating doses (range: 2mg-26mg) of gunagratinib once daily in 21-day cycles until disease progression or unacceptable toxicity. **Results:** 12 HNC patients with or without FGF/FGFR aberrations, including FGF amplification and FGFR mutation, were treated with escalating doses (range: 14mg-22mg) of gunagratinib. Among them, 9 patients harbored FGF/FGFR gene alterations with at least one tumor assessment. The median age of the 12 treated HNC patients was 56 (range: 44 to 75 years) with 75% male and ECOG performance status 1. Among the 9 HNC patients with FGF/FGFR gene aberrations who have completed at least one tumor assessment, 3 patients had partial response (PR), the overall response rate (ORR) was 33.3% (3 of 9 patients). The disease control rate (DCR) was 66.7% (6 of 9 patients). Total of 62 patients with solid tumor were enrolled in ICP-CL-00301 study. The most common treatment-related adverse events (TRAEs) (≥15%) included hyperphosphatemia, diarrhea, increased ALT or AST, increased alkaline phosphatase, hypercalcemia, increased serum creatinine, dry mouth, hypertriglyceridemia, anemia and hyperuricemia. In ICP-CL-00301 study, 3 serious TRAEs were reported, and no serious TRAE were reported in HNC patients. **Conclusions:** This study demonstrated the anti-tumor activity of gunagratinib in HNC patients carrying FGF/FGFR gene aberrations with an ORR of 33.3%. Gunagratinib is safe and well-tolerated in patients with advanced solid tumors including HNC. Clinical trial information: NCT03758664. Research Sponsor: Beijing InnoCare Pharma Tech Co., Ltd.

Tumor histological type and gene alteration type.

Histological Type	**N=12 [1]**
squamous cell cancer	8
Ameloblastic carcinoma	2
Nasopharyngeal carcinoma	3
Gene alterations Type	**N=10 [2]**
FGF	7
FGFR	3

[1]One patient was a nasopharyngeal carcinoma patient with tongue squamous cell cancer. [2]One patient had no imaging tumor evaluation.

6040 **Poster Session**

The impact of induction chemotherapy response to survival outcomes in oropharyngeal cancer. *First Author: Qixian Zhang, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: The role of induction chemotherapy (IC) in oropharyngeal squamous cell carcinoma (OPSCC) remains inconclusive. Previous randomized trials showed no survival advantage with IC in head and neck squamous cell carcinoma, including OPSCC. However, the impact of response to IC has rarely been considered in these trials. In this study, we aimed to investigate the prognostic value of IC response on HPV+ and HPV- OPSCC. **Methods:** Patients with stage II-IVB OPSCC (UICC 7th edition) who underwent IC (paclitaxel and platinum-based regimen for the most) and concurrent chemoradiotherapy during 2010 to 2020 were enrolled. HPV status was confirmed by p16 immunohistochemistry (p16 ≥ 70%). The clinical response to IC was assessed on MRI or CT images. Patients with complete response (CR) or major partial response (PR) (≥50% PR) were defined as sensitive subgroup (IC-s), while those with <50% PR, stable disease (SD) or progressive disease (PD) were deemed as resistant (IC-r). Progression-free survival (PFS) and overall survival (OS) were compared. **Results:** 51 HPV+ and 57 HPV- OPSCC patients were included. In the entire cohort, 55.6% patients were sensitive to IC. HPV+ OPSCC showed higher IC-s rate (62.7% vs. 49.1%) than HPV- subgroup. IC-s was associated with better clinical outcomes either in the whole cohort (3y-PFS 91.7%vs.43.7%, P < 0.001; 3y-OS 98.3% vs.67.4%, P = 0.002), the HPV+ subgroup (3-year PFS 94.7% vs. 47.9%, P < 0.001; 3-year OS 100% vs. 73.5%, P = 0.055) or the HPV- subgroup (3-year PFS 88.2% vs. 40.9%, P = 0.001; 3-year OS 96.4% vs. 63.1%, P = 0.026). Multivariate analysis demonstrated IC-s as an independent prognosticator for 3y-PFS (hazard ratio [HR], 0.088; 95% confidence interval [CI], 0.027-0.289; P < 0.001) and 3y-OS ([HR], 0.100; 95% CI, 0.021-0.477; P = 0.004) when adjusting for T, N, gender, age and smoking status. **Conclusions:** The response to IC exerts a critical predictive effect on survival outcomes in both HPV+ and HPV- OPSCC. Personalized treatment strategy based on IC response warrants further exploration in future studies. Research Sponsor: None.

Response to induction chemotherapy.

	All patients (n = 108)			HPV+ patients (n = 51)			HPV- patients (n = 57)		
	OP	LN	OP+LN	OP	LN	OP+LN	OP	LN	OP+LN
IC-s, n (%)	84 (77.8%)	64 (59.3%)	60 (55.6%)	44 (86.3%)	34 (66.7%)	32 (62.7%)	40 (70.2%)	30 (52.6%)	28 (49.1%)
CR	45 (41.7%)	21 (19.4%)	12 (11.1%)	26 (51.0%)	13 (25.5%)	7 (13.7%)	19 (33.3%)	8 (14.0%)	5 (8.8%)
Major PR	39 (36.1%)	43 (39.8%)	48 (44.4%)	18 (35.3%)	21 (41.2%)	25 (49.0%)	21 (36.8%)	22 (38.6%)	23 (40.4%)
IC-r, n (%)	24 (22.2%)	44 (40.7%)	48 (44.4)	7 (13.7%)	17 (33.3)	19 (37.3%)	17 (29.8)	27 (47.4%)	29 (50.9%)
Minor PR	14 (13.0%)	18 (16.7%)	20 (18.5%)	2 (3.9%)	5 (9.8%)	5 (9.8%)	12 (21.1%)	13 (22.8%)	15 (26.3%)
SD	9 (8.3%)	25 (23.1%)	27 (25.0%)	5 (9.8%)	12 (23.5%)	14 (27.5%)	4 (7.0%)	13 (22.8%)	13 (22.8%)
PD	1 (0.9%)	1 (0.9%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	1 (1.8%)	1 (1.8%)

Abbreviation: OP = oropharynx; LN = lymph node; ORR = objective response rate.

6041 **Poster Session**

PDS0101, a novel type I interferon and CD8 T-cell activating immunotherapy, in combination with pembrolizumab in subjects with recurrent/metastatic HPV16-positive head and neck squamous cell carcinoma (HNSCC). *First Author: Jared Weiss, University of North Carolina Hospitals, Chapel Hill, NC*

Background: Human papillomavirus (HPV) E6/E7 oncoproteins mediate immune evasion by down-regulating Type 1 interferons, TLR9, MHC Class I/II as well as other mechanisms, resulting in persistent infection and initiation of ~5% of all cancers globally. Similarly, established cancers evade immune surveillance utilizing parallel mechanisms including the expression of checkpoint proteins. PDS0101 is a molecularly targeted immunotherapeutic based on an enantiospecific cationic lipid nanoparticle platform containing HPV16 neoantigens that exhibits anti-tumor activity with checkpoint inhibitors (CPIs) by upregulating Type I interferons and promoting antigen processing and cross presentation. This allows generation of high levels of polyfunctional HPV16-specific CD8 and CD4 T cells *in vivo* as well as immune memory. VERSATILE-002 (NCT04260126) is a phase 2 study of the combination of PDS0101 and pembrolizumab in treatment of CPI naïve and refractory patients with recurrent or metastatic HPV16-related HNSCC. Herein, we report preliminary safety and efficacy data for CPI naïve patients at a prespecified interim analysis. **Methods:** Subjects are treated with pembrolizumab 200mg IV every three weeks plus SC PDS0101 following pembrolizumab on days one of Cycles1-4 and Cycle12; pembrolizumab continues up until 35 cycles, disease progression or intolerance to therapy. **Results:** Eighteen CPI naïve subjects with confirmed HPV16 tumors and a CPS score > = 1, median age 62 yrs (range 46-71), all male, 17 (94%) of whom were White and 16 (88.9%) not Hispanic or Latino, received at least one cycle of combination therapy. At the time of analysis, 17 (94%) subjects had received > = 4 doses of PDS0101 (median 4, range 1-5) and pembrolizumab (median 7, range 1-14). There were no Grade 3 or greater treatment-related toxicities and no drug discontinuation related to toxicity or immune-related AEs. Clinical activity (CR+PR+SD) was seen in 13 (72.2%) of 18 subjects, with best overall reponse per RECIST1.1 documenting: OR in 7 (38.9%; 2 CR, 5PR); stable disease (SD) in 6 (33.3%) and progressive disease in 3 (16.7%); 2 subjects had missing data. Tumor reduction was seen in 4 of 6 (67%) subjects with SD. Nine-month PFS and OS rates (95% CI) were 52% (22.5, 74.7) and 81% (37.8, 95.5) respectively; median PFS and OS have not been reached. **Conclusions:** The combination of PDS0101 and pembrolizumab demonstrates an excellent safety profile with preliminary evidence of clinical activity in the majority of CPI naïve patients with HPV-related HNSCC. Clinical trial information: NCT04260126. Research Sponsor: PDS Biotechnology.

6042 **Poster Session**

Efficacy and safety of camrelizumab combined with apatinib in previously treated recurrent or metastatic nasopharyngeal carcinoma: A phase II clinical trial. *First Author: Lin-Quan Tang, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: The synergistic antitumour effect immune checkpoint inhibitors combined with antiangiogenic targeted therapy in refractory RM-NPC patients remains unknown. This phase 2 trial assessed the efficacy and safety of camrelizumab (an anti-programmed death 1 [PD-1] inhibitor) plus apatinib (a VEGFR-2 tyrosine kinase inhibitor) after at least first-line therapy in refractory RM-NPC patients. **Methods:** We did a phase 2 single-armed study to evaluate the activity of camrelizumab plus apatinib in platinum-resistant (cohort 1) and PD-1 inhibitor resistant (cohort 2) NPC. Eligibility required measurable disease (RECIST 1·1), Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, age of 18-75 years, and disease progression on platinum but PD-1 inhibitor-naive (cohort 1) or disease progression on PD-1 inhibitor (cohort 2) after at least first-line therapy. Patients in cohort 1 received 200 mg intravenous camrelizumab every 3 weeks plus 250 mg oral apatinib daily. Patients in cohort 2 received apatinib monotherapy in the first two weeks to modify the immune-resistant microenvironment, and were then administered camrelizumab plus apatinib until disease progression or unacceptable toxicity. The primary endpoint was the objective response rate (ORR). This study was registered with ClinicalTrials.gov (NCT04547088, NCT04548271). **Results:** From August 20, 2020 to September 6, 2021, 72 patients were enrolled into the trial: 40 patients were enrolled in cohort 1 and 32 in cohort 2. Median follow-up was 13.1 months (IQR 10.0-15.2 months) for cohort 1 and 9.0 (5.9-10.7) months for cohort 2. Among the 40 evaluable patients in cohort 1, an objective response was achieved by 26 (65%; 95% CI, 49.6-80.4). A total of 16 (40%) patients had tumor progression, and the median PFS was not reached. Among the 32 evaluable patients in cohort 2, an objective response was achieved by 11 (34.4%; 95% CI, 17.0-51.8). A total of 22 (69%) patients had tumor progression, and the median PFS was 6.0 months (95% CI, 4.4 to 7.6). Grade ≥ 3 treatment-related adverse events (TRAE) were reported in 34 (47.2%) of 72 patients, with the most common TRAE being hypertension (18.1%), an increase of serum transaminase (13.9%) and hand and foot syndrome (12.5%). No treatment-related deaths occurred. **Conclusions:** In patients with platinum-resistant or PD-1 inhibitor resistant RM-NPC, camrelizumab plus apatinib achieved promising outcomes. Further studies of the camrelizumab plus apatinib treatment regimen are warranted in a phase 3 trial. Clinical trial information: NCT04547088, NCT04548271. Research Sponsor: None.

6043 **Poster Session**

Clinicopathologic characteristics of HRAS-mutant head and neck squamous cell carcinoma (HNSCC). *First Author: Coral Olazagasti, Sylvester Comprehensive Cancer Center, Miami, FL*

Background: RAS mutations are often associated with tumor development and immune evasion and therefore unfavorable clinical outcomes. Farnesyl transferase inhibitors (FTI) are an emerging therapeutic option for HRAS mutant HNSCC (Hm), thus understanding the genomic and immunologic landscape of Hm is important for further development of this therapeutic approach. **Methods:** A total of 2,407 HNSCC tissue went through tumor molecular profiling at Caris Life Science (Phoenix, AZ). Analyses included next-generation sequencing of DNA (NextSeq, 592 Gene or NovaSeq, WES) and RNA (NovaSeq, WTS), and immunohistochemistry (IHC). HPV 16/18 status was assessed using WES. MAPK pathway activation and the likelihood of a tumor's response to anti PD1 therapy were tested via MPAS and IFN signatures, respectively. Wilcoxon, Fisher's exact were used for statistical significance (p without and q values with multiple comparison correction). Overall survival was calculated from date of tissue collection to last contact from insurance claims data and compared using Kaplan-Meier method. All comparisons were made between Hm and the entire HNSCC general cohort (GC). **Results:** Of the 2,407 HSNCC tested, 69 (2.87%) were pathogenic/likely pathogenic Hm. The most prevalent mutation (mt) was G12 (34.8%), G12 (31.9%) and Q61 (30.3%). Hm significantly correlated with male gender (59.4%, q <0.01) and older age (median 68.6 vs 64.1, q <0.01). No difference in HPV status was observed. Hm had worse prognosis (HR 1.49, 95 CI: 1.03 -2.13, p<0.05) and correlated with more TERT, FAT1 mt, lower p16, PD-L1 expression and TMB-H (cutoff: >=10mt/MB) (Table). Interestingly, PIK3CA Hm were mutually exclusive with TMB-H tumors in Hm (p<.0001). All Hm had higher MPAS scores (all: 0.88, Q61: 0.88, G13: 1.07 vs -0.34, q <0.05) compared to GC. Hm showed higher immunogenicity, evidenced by higher IFN score (all: -0.1, G12: -0.04 vs GC: -0.21, q < 0.05), higher ratio of macrophage M(MM)1 to MM2 (Fold change = 2.27, q <0.0001), more CD8+ T cells and elevated expression level of MHC1 class I genes (Table). **Conclusions:** Hm was associated with poor outcomes, higher MAPK activation, PD-L1 levels, TMB and IFN scores. This points to the oncogenic and immunomodulatory role of HRAS in HNSCC. Our findings provide additional evidence for ongoing clinical trials on combinatorial immunotherapy or PI3KCA inhibitors with FTI and demonstrate unique landscape of different point mutations; further evaluation is warranted. Differentially regulated features between Hm and GC (*p<0.05, q<0.05) for all results. Research Sponsor: None.

alteration (%)	Hm	GC	TME	Hm	GC	genes (TPM)	Hm	GC
TERT	64.9	23.3	MM1	0.075	0.054	*HLA-A	234.4	185.0
FAT1	39.5	12.5	MM2	0.027	0.035	*HLA-B	251.1	199.2
***PIK3CA**	27.9	15.5	Neutrophil	0.068	0.054	*HLA-C	206.2	153.8
***CDK2A**	28.1	17.7	CD8+	0.016	0.011	*HLA-E	86.5	67.9
***p16 (IHC)**	23.4	42.0	NK	0.02	0.027	HLA-F	46.7	31.6
PD-L1	100.0	50.3	Bcells	0.038	0.053			
TMB-H	30.3	16.6	mDC	0.01	0.017			

6044 **Poster Session**

The effect of opioids on the efficacy of immunotherapy in recurrent/metastatic squamous cell carcinoma of the head and neck (R/M HNSCC). *First Author: Nicole N Scheff, UPMC Hillman Cancer Center, Pittsburgh, PA*

Background: HNSCC can cause severe pain, exceeding the levels seen in other cancers. Opioids, the mainstay for cancer pain treatment, can have an immunomodulatory effect. We hypothesized that immunotherapy efficacy is impaired by immunosuppressive actions of opioids. **Methods:** We conducted a retrospective analysis of R/M HNSCC patients who received anti-PD-1 mAb therapy in the first line or platinum failure setting at UPMC Hillman from 2015–2020. Pretreatment (most recent visit prior to day of treatment) and day of treatment opioid prescription, calculated as morphine milligram equivalent (MME) per day, were evaluated. Opioids were analyzed as a continuous and a categorical (yes/no) variable. CD8 T and T regulatory (Treg) cells in the tumor microenvironment (TME) were evaluated on archival tumor samples via immunofluorescent imaging via ImageJ software. Linear regression and logistic regression were used to determine the effect of opioids on oncologic factors, disease control rate (DCR) and TME, depending on the data types. Univariable and multivariable Cox Proportional Hazard models were used to identify factors associated with progression free survival (PFS) and overall survival (OS). **Results:** The 66 patients analyzed were 79% male, median age was 67, 26% were HPV positive oropharyngeal, and 56% were platinum failure. The median time between pretreatment and day of treatment visits was 29 days. 63.3% of patients were on opioids pretreatment and day of treatment; median MME/day was 60 mg and 85 mg, respectively. When measured as a continuous variable, increased opioid dosage was significantly associated with worse PFS and OS at pretreatment (PFS, $p = 0.002$; OS, $p < 0.001$) and day of treatment (PFS, $p = 0.021$; OS, $p = 0.017$). Multivariate analyses, which included significant variables from univariate analysis (neutrophil/lymphocyte ratio (NLR), platinum failure) revealed that opioid dose given pretreatment (PFS, $p = 0.047$, OS $p = 0.001$) and day of treatment (OS, $p = 0.019$) are independently associated with worse survival. Receipt of pretreatment opioids, assessed as a categorical variable, were associated with a significant decrease in CD8+ T cells ($p = 0.03$), and on day of treatment, a significant decrease in CD8 T cells ($p = 0.015$) and the ratio of CD8 T cells to Treg (CD8/Treg, $p = 0.011$) in the TME. There was no correlation of opioid variables with DCR, PD-L1 expression, or NLR. **Conclusions:** In our analysis, opioids were associated with significantly lower PFS and OS as well as decreased CD8 T cells and CD8/Treg ratio in the tumor microenvironment. To our knowledge, this is the first study of the effect of opioids on the efficacy of anti-PD-1 mAb treatment for R/M HNSCC as well as on the TME. Our findings suggest the need for further study into the impact of opioids on immunotherapy efficacy to improve patient outcomes. Research Sponsor: Virginia Kaufman Foundation.

6045 **Poster Session**

A phase 1 dose-escalation and expansion study of CUE-101, a novel HPV16 E7-pHLA-IL2-Fc fusion protein, given alone and in combination with pembrolizumab in patients with recurrent/metastatic HPV16+ head and neck cancer. *First Author: Christine H. Chung, Moffitt Cancer Center, Tampa, FL*

Background: Immuno-STATs are novel, modular fusion proteins designed to locally deliver cytokines for the selective activation of tumor-antigen specific CD8+ T cells. CUE-101, the first Immuno-STAT in clinical trials, is composed of a human leukocyte antigen (HLA) complex, HLA-A*0201, a peptide epitope derived from the HPV16 E7 protein, and 4 molecules of reduced affinity human interleukin-2 (IL-2) that is designed to bind, expand, and activate HPV16-specific CD8+ T cells for the treatment of HPV16+ cancers. **Methods:** CUE-101-01 is an ongoing first-in-human study in HLA-A*0201 patients with HPV16+ recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). Escalating doses of CUE-101 monotherapy or in combination with pembrolizumab was evaluated, followed by expanded enrollment at the recommended phase 2 dose (RP2D). Patients with R/M HNSCC refractory to ≥ 1 platinum- or pembrolizumab-based systemic therapies received CUE-101 monotherapy. Patients with previously untreated PD-L1+ R/M HNSCC received CUE-101 and pembrolizumab 200 mg as first-line treatment. Therapy was administered every 3 weeks until disease progression or toxicity. Objectives included evaluation of safety, pharmacokinetics (PK), pharmacodynamics (PD), and antitumor activity. **Results:** As of January 20, 2022, 53 patients received CUE-101 ranging from 0.06 to 8 mg/kg/dose. The most common adverse events included grade ≤ 2 fatigue (40%), anemia (28%), lymphopenia (23%), chills (23%), and hyponatremia (21%). In the monotherapy dose escalation cohort, a MTD was not identified. A RP2D of 4 mg/kg/dose was chosen based on PK, PD, and clinical data in the absence of an MTD. Dose escalation of CUE-101 from 1 to 4 mg/kg in combination with pembrolizumab is ongoing with no DLTs identified as of data cut-off. CUE-101 PK data demonstrated dose-dependent increases in drug exposure that were sustained upon repeat dosing. PD data demonstrated selected expansion of HPV-16 $E7_{11-20}$-specific CD8+ T cells, sustained increase in NK cells and transient increase in Treg cells. Of the 14 evaluable patients treated with CUE-101 monotherapy at the RP2D, there was 1 PR and 6 with SD for ≥ 12 weeks. Of the 7 evaluable patients treated with CUE-101 plus pembrolizumab, there were 2 PR (1 confirmed) and 2 with SD for ≥ 12 weeks. **Conclusions:** CUE-101 is a novel immunotherapeutic that facilitates the targeted delivery of high concentrations of IL-2 to relevant tumor-specific CD8+ T cells. We demonstrate safety and tolerability with encouraging PD signals and antitumor activity. Enrollment continues in the combination cohort. Other novel Immuno-STATs, targeting local delivery of IL-2 for selective expansion and activation of additional tumor-antigen specific T cells, are in development. Clinical trial information: NCT03978689. Research Sponsor: Cue Biopharma Inc.

6046 **Poster Session**

Results of ACCURACY: A phase 2 trial of AL101, a selective gamma secretase inhibitor, in subjects with recurrent/metastatic (R/M) adenoid cystic carcinoma (ACC) harboring Notch activating mutations ($Notch^{mut}$). *First Author: Renata Ferrarotto, Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Notch signaling plays a key role in ACC tumorigenesis. $Notch^{mut}$ are found in ~20% of ACC tumors, which are aggressive with a poor prognosis. Approved or standard therapies for relapsed/metastatic ACC are lacking, regardless of Notch status. Investigational drug AL101, a γ-secretase inhibitor, blocks Notch signaling and inhibits tumor growth in $Notch^{mut}$ patient-derived ACC xenografts. AL101 has clinical activity at 4 mg once weekly (QW) with a disease control rate (DCR) of 68% (15% partial response, (PR)) and appears to be well tolerated. An additional cohort of 42 patients was enrolled at 6 mg QW, and here we update the final results of the trial. **Methods:** ACCURACY is an open-label, multicenter phase 2 study of AL101 (4 and 6 mg intravenous QW) in subjects with R/M ACC with $Notch1\text{-}4^{mut}$ (ASCO '19, Abstr TPS6098). Subjects required evidence of disease progression within 6 months of entry or newly diagnosed metastatic disease and an ECOG performance status of 0-1. The primary endpoint was overall response rate (ORR) by RECIST v1.1 (or modified MD Anderson bone criteria), as assessed by investigators. Secondary endpoints were ORR by central review, duration of response, and safety. The study provided ≥80% power to detect an increase of the ORR from 8% to 25% using a type I error of 5%. **Results:** A total of 82 subjects were enrolled in the study. The data cutoff date used was Oct 25, 2021. Most common (≥20%) treatment-related adverse events of all grades in the study were diarrhea (78%; grade 3 (gr3) 10%), fatigue (67%; gr3 6%), nausea (60%; gr3 7%). Pharmacokinetics (PK) and blood pharmacodynamics (PD) both displayed a dose dependent change in AL101 plasma concentration and modulation of Notch target gene expression (Hes1 and Hes4), respectively. Of the 77 evaluable subjects, there were 9 PRs (12%) and 44 SDs (57%) for a disease control rate of 69%. **Conclusions:** Investigational drug AL101 at both 4 and 6 mg QW appears to be well tolerable in $Notch^{mut}$ R/M ACC. Additional efficacy and PK/PD data will be presented Clinical trial information: NCT03691207. Research Sponsor: Ayala Pharmaceuticals.

Disposition and baseline characteristics of subjects treated with AL101[a].

	4 mg QW	6 mg QW
Treated, n	45	37
Gender, n (%)		
Male	20 (44)	24 (57)
Female	25 (56)	18 (43)
Median age, years	50	59
Race, n (%)		
White	31 (69)	33(79)
Black	4 (9)	2 (5)
Asian	2 (4)	1 (2)
Other/not reported	8 (18)	6 (14)
Prior systemic therapy, n (%)	27 (60)	19 (51)
Disease status at screening, n (%)[b]		
Metastatic	42 (93)	36 (86)
Local recurrence	15 (33)	11 (28)
Treatment naïve and metastatic	4 (9)	6 (14)
Most common sites of metastases, n (%)[b]		
Lung	22 (49)	22 (52)
Bone	13 (29)	15 (36)
Liver	8 (18)	13 (31)

QW=once weekly.
[a]Data cutoff Oct 25, 2021.
[b]Subjects may select more than 1 category.

6047 **Poster Session**

Imaging biomarkers of collagen architecture on baseline biopsies in association with response in patients with head and neck squamous cell carcinoma treated with immunotherapy. *First Author: Reetoja Nag, Case Western Reserve University, Cleveland, OH*

Background: Though immunotherapy (IO) has robust clinical efficacy, only a subset of head and neck squamous cell carcinoma (HNSCC) patients have shown to benefit from it. Collagen, a major component of the Tumor Microenvironment (TME), is involved in cancer fibrosis and collagen fiber organization has been shown to be associated with patient outcome for different cancers. In this work, we evaluated whether computationally extracted collagen fiber orientation disorder (CFOD) features from tumor related stroma regions (TS) in digitized H&E-stained slides can help in distinguishing between responders and non-responders to immunotherapy in HNSCC patients. **Methods:** Whole slide images (WSIs) from 43 HNSCC patients treated with immunotherapy (23 non-responders and 20 responders) were obtained from University Hospitals, Cleveland; response was defined as per RECIST v1.1. A derivative-of-Gaussian model was used to identify collagen fiber orientations in TS of the digitized WSIs. Different statistics (e.g. mean, standard deviation, skewness) of the various disorder descriptors (e.g., contrast and entropy) were calculated across all the neighborhood windows in the tumor region to generate the final CFOD feature set. Minimum Redundance Maximum Relevance algorithm was employed to identify the top 3 features, which were combined with a Naive Bayes classifier to differentiate between responders and non-responders. Cross-validation was used to validate the classifier over 100 iterations via the area under the receiver operating characteristics curve (AUC). Multivariable analysis was done using a logistic regression method to see how different parameters (gender, age, smoking status) will affect IO response. **Results:** WSIs of responders to immunotherapy showed more disorganized collagen fiber structure as compared to non-responders WSIs. The selected top 3 features were related to the contrast feature descriptor from the orientation co-occurrence matrix. The average AUC for the model based on CFOD was 0.77±0.24. The results for multivariable analysis are shown in Table 1. **Conclusions:** We demonstrated an association between the architectural organization of collagen fiber from baseline biopsies of HNSCC patients with response to immunotherapy. Furthermore, we demonstrate a classifier based on computationally derived CFOD features able to derive detailed assessments of collagen orientation. None of the parameters analyzed were significantly associated with change in IO response ($p<0.05$). Further validation on a larger independent cohort is warranted. Research Sponsor: U.S. National Institutes of Health, Other Foundation, Other Government Agency.

Multivariable analysis for IO response.

Parameter	p value
Gender (Male/Female)	p=0.14
Age (<60 years/≥60years)	p=0.19
Smoking status (Yes/No)	p=0.54

6048 **Poster Session**

Outcomes and adverse events of low-dose nivolumab in platinum refractory head and neck cancers. *First Author: Hemanth Kumar, Tata Memorial Hospital, Mumbai, India*

Background: Nivolumab is one of the recommended regimens for platinum refractory and second line treatment in head and neck cancers as per NCCN guidelines. However, accessibility of nivolumab in low- and middle-income countries is less than 1-3%. There is data suggesting that low doses of nivolumab can also be effective. Hence in this analysis we explore the outcomes and adverse events with low doses of nivolumab. **Methods:** The head and neck medical oncology unit of Tata memorial hospital maintains a prospective database of all patients undergoing immunotherapy. A query was raised in this database to identify head and neck cancer patients who were treated with low doses of nivolumab. We identified 42 patients. The baseline characteristics, compliance to nivolumab, the reason for administration of low dose and the outcomes (progression free survival, date of progression, date of death) were recorded. The dose of nivolumab used in this study was 40mg flat dose every 2 weeks. Descriptive statistics were performed. Kaplan Meier estimates were used to see overall survival (OS) and progression free survival (PFS). **Results:** The median age of the patients was 48.8 (IQR: 43 - 56.4) Male to female ratio was 13:1. The site of the disease was oral cavity in 29 (69%) patients, oropharynx in 3 (7%) patients, larynx in 4 (9.5%) patients, and others in 7(17%) patients. All patients were platinum refractory and had progressive disease within last 6 months of last dose of platinum. The ECOG performance status was 1 in 37 (88.1%) patients and 2 in 5 (11.9%) patients. All patients received low dose nivolumab in view of financial constraints to access full dose. The response was recorded in 32 patients. Out of them 6 had a partial response (14.3%). The median PFS was 4.9 months (95% Confidence interval: 3.4 - 6.4) and OS was 8 months (95% confidence interval: 5.9-10.1). The details regarding PD L-1 expression and effectiveness of nivolumab will be presented at the conference. **Conclusions:** Low doses of nivolumab can be an option which is efficacious in patients who do not have access to standard dose nivolumab. There is need for testing this regimen in large randomized studies as full dose of nivolumab is not accessible in low- and middle-income countries. Research Sponsor: None.

6049 **Poster Session**

Racial disparity in receipt of immunotherapy treatment among elderly patients with head and neck cancer. *First Author: Nosayaba Osazuwa-Peters, Duke University School of Medicine, Department of Head and Neck Surgery & Communication Sciences, Durham, NC*

Background: The United States Food and Drug Administration in 2016 approved immune checkpoint inhibitors (immunotherapy) as a treatment option for head and neck squamous cell carcinoma. However, it is unclear if there are clinical or sociodemographic differences among patients receiving immunotherapy as part of their care. We aimed at characterizing the clinical and non-clinical factors associated with receipt of immunotherapy among elderly patients with head and neck cancer. **Methods:** We utilized data from *Navigating Cancer*, which included information on systemic therapy for elderly patients (≥ 65 years), diagnosed with head and neck cancer in a community oncology setting between 2017 and 2021. We estimated clinical (tumor stage [grouped as early, or stage I and II vs. advanced stage, or stage III and IV] and anatomic subsite [oropharyngeal vs. non-oropharyngeal]) and non-clinical (age, smoking history, race, sex, and marital status) factors associated with immunotherapy use based on multivariable logistic regression analysis. **Results:** There were 4,619 patients in our study cohort, 74.3% male and 87.1% white. Among these patients, 11.1% had received immunotherapy. We found an association between race and receipt of immunotherapy. After adjusting for covariates, white patients with head and neck cancer had 74% increased odds of receiving immunotherapy as part of their treatment (aOR: 1.74; 95% CI 1.25, 2.42), compared to non-whites. There were no statistically significant differences in the odds of immunotherapy use based on age, sex, or smoking history. Patients with non-oropharyngeal disease were significantly more likely to receive immunotherapy than those with oropharyngeal cancer (aOR: 1.26; 95% CI 1.01, 1.56), as were those with advanced stage disease (aOR: 2.72; 95% CI 1.90, 3.91) compared with those early-stage. **Conclusions:** We identified clinical and non-clinical factors associated with receipt of immunotherapy in this cohort of elderly patients with head and neck cancer, and white patients were significantly more likely to receive immunotherapy as part of their care. Equitable access to immunotherapy and other treatment options will reduce cancer-related health disparities and improve survival of patients with head and neck cancer. Research Sponsor: None.

6050 **Poster Session**

Digital spatial profiling to uncover biomarkers of immunotherapy outcomes in head and neck squamous cell carcinoma. *First Author: Niki Gavrielatou, Department of Pathology, Yale School of Medicine, New Haven, CT*

Background: Immunotherapy (ITx) has become the standard of care in the treatment of recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC). However, response rate is limited to 13-18% of patients, underlining the need to identify mechanisms implicated in response or resistance. This study aims to uncover novel biomarkers of ITx outcomes in R/M HNSCC using digital spatial profiling (DSP) technology. **Methods:** Pre-treatment biopsy samples of 50 ITx-treated R/M HNSCC patients, constructed in the form of tissue microarray (YTMA496), were included in our discovery cohort. Cases underwent DSP with the Human Immuno-Oncology protein panel (NanoString Technologies), comprising 71 photocleavable oligonucleotide-labeled primary antibodies, used for target-protein quantification in 4 distinct molecularly defined compartments: tumor (CK+), leukocyte (CD45+), macrophage (CD68+) and immune stroma (CD45+/CD68+). All markers were explored for associations with progression-free (PFS) and overall survival (OS) using a univariate Cox regression model. Significant markers were validated using an alternative quantitative immunofluorescence method as well as in an independent validation cohort of 29 ITx-treated R/M HNSCC cases (YTMA523). **Results:** Univariate DSP data analysis revealed high beta2-microglobulin (B2M), LAG-3, CD25 and 4-1BB in tumor, high B2M, CD45 and CD4 in stroma, and low fibronectin in the macrophage compartment, as markers associated with improved PFS. Increased levels of B2M and CD25 in tumor and CD11c in stroma were also correlated with prolonged OS. Focusing on B2M, cases at the top tertile of tumor B2M expression were associated with improved PFS and OS [HR, 0.43; 95% confidence interval (CI), 0.21-0.9; p = 0.034 and HR, 0.41; 95% CI, 0.18-0.90; p = 0.047, respectively], by an orthogonal QIF method. Findings were replicated in our validation cohort for PFS [HR, 0.41; 95% CI, 0.19-0.93; p = 0.034] and showed a similar trend for OS [HR, 0.44; 95% CI, 0.19-1.0; p = 0.074]. B2M-high tumors also had significant enrichment with immune-cell markers (CD3, CD4, CD8, CD11c, CD68 and CD163) and increased immune checkpoint expression (PD-L1, ICOS, TIM-3, LAG-3, IDO1, B7-H3), predominantly in the tumor compartment. **Conclusions:** Our study indicates that intact, highly functional antigen presentation, sustained by high B2M expression in tumor, confers survival benefit in ITx treated R/M HNSCC patients, an effect driven by increased intra-tumoral immunogenicity. Research Sponsor: U.S. National Institutes of Health.

6051 **Poster Session**

Immune-related gene expression signature in patients with recurrent/metastatic head and neck cancer treated with immunotherapy. *First Author: Lisa F. Licitra, Fondazione IRCCS Istituto Nazionale dei Tumori, University of Milan, Milan, Italy*

Background: In platinum-resistant recurrent-metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) patients (pts), survival improvements have been achieved with immune checkpoint inhibitors (ICI), however this benefit is limited to a relatively small subgroup of pts. Predictive biomarkers are still under investigation and their contribution to the clinic has been limited. An immune-related cluster (CI6) has been defined by means of a metanalysis in locally advanced HNSCC. **Methods:** Gene expression profiling was performed on two cohorts of platinum resistant R/M HNSCC pts treated with ICI alone: i) 20 patients as training set, divided in long-term (OS >18 months; n=12) and short-term (OS < 6 months; n=8) survivors matched according to site of recurrence (distant metastases only, or locoregional recurrence with/out metastases); ii) 80 patients enrolled in a phase II trial (EudraCT number: 2017-000562-30; NIVACTOR study) as testing set. The molecular subtyping stratification (De Cecco, Oncotarget 2015) was applied. Subsequently, a score was determined between each sample and the centroids for the 6 clusters previously identified. The threshold point was imputed in the training set as the closest value to the observed prevalence. A Cox multivariable analysis including TMB, CPS and TPS PD-L1 status, age, tumoral subsite and performance status (PS) was performed. **Results:** Among all the clusters, CI6 turned out to be significant and applied to training set it provided evidence to discriminate pts' survivals (AUC=0.86, 95%CI=0.7-1.0; p=2E-05). The stratification based on CI-6 along with the cut-off point defined in the training set were challenged in the testing set: samples were divided in 28 (35%) having high CI-6 scores and 52 (65%) with low scores, reaching HR=0.46 (95% CI= 0.27-0.76; p=0.0024). Multivariate analysis showed that only CI6 (high vs low, HR=0.44; p=0.00443) and PS (1,2 vs 0, HR 1.85; p=0.02686) resulted to be significant on pts' OS. **Conclusions:** By analysing two series of pts receiving immunotherapy alone, we identified an immune-related gene expression signature, able to discriminate the prognosis of platinum-resistant R/M HNSCC pts. The multivariate analysis confirmed the immune-related CI6 as factor linked to outcome in pts treated with immunotherapy, as well as it confirmed the importance of PS. An analysis of the signature on pts receiving first line treatment with immunotherapy is currently ongoing. Research Sponsor: AIRC (IG 21740 to PB), Pharmaceutical/Biotech Company.

Clinical-pathological characteristics		Nivactor cohort N=80	Low CI-6 N=52	High CI-6 N=28	p value
Age, years	median (range)	65.5 (33-84)	65 (33-77)	67 (39-84)	0.4827***
Gender	male	65	42	23	1 *
	female	15	10	5	
Response	CR+PR	12	3	9	0.004252**
	SD+PD	67	48	19	
	NA	1	1	0	
Performance status (PS)	0	9	5	4	0.7124**
	1	71	47	24	
PD-L1 status	Positive	30	19	11	0.06379**
	Negative	39	29	10	
	NA	11	4	7	

Chi-squared test (X^2) in * cases. Fisher's exact test in ** cases. Wilcoxon test in *** case.

6052 **Poster Session**

Personalized circulating tumor DNA (ctDNA) analysis in patients with recurrent/metastatic head and neck squamous cell cancer (R/M HNSCC). *First Author: Kirsty Taylor, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Immuno-oncology agents (IO) have become standard-of-care in the treatment of R/M HNSCC, but only a subset of patients (pts) benefit. Highly sensitive quantification of plasma circulating tumor DNA (ctDNA) may permit real time assessment of disease under selective pressures of treatment. **Methods:** R/M HNSCC pts treated with platinum-based chemotherapy (CT) or IO (anti-PD1/L1 +/- second IO) underwent serial ctDNA collection pre-cycles 1/2/3 and at disease progression, corresponding to timepoints (T) 1-4. T1 was considered baseline. Whole exome sequencing of pt tumor tissue identified patient specific somatic variants which were used as targets for RaDaR, a personalized multiplexed PCR-based NGS assay. Matched buffy coat DNA was sequenced to filter germline mutations and identify confounding CHIP. RaDaR was applied at each available T, an estimated variant allele frequency (eVAF) was calculated and correlated with progression free- (PFS) and overall- survival (OS). Findings were compared against prior (ESMO 2021) data generated using a fixed 580 gene CAPP-seq (CAncer Personalized Profiling by deep Sequencing) panel designed specifically against squamous cell carcinoma. **Results:** A total 114 plasma samples from 38 pts were analyzed. Of 35 pts with ctDNA detected at T1 and/or T2, 26 received IO and 9 CT. Median age was 62 (20-84), 77% were male, 69% prior smokers and 26% HPV positive. Median PFS and OS, for all 35 pts, was 2.57 mo (95% CI 0.48-4.66) and 8.37 mo (95% CI 5.42-11.32) respectively. For IO treated pts, median PFS was 2.45 mo (95% CI 0-5.18) and median OS 7.38 mo (95% CI 3.84-10.93). RaDaR panels targeted a median 48 variants (17-50). ctDNA was detected in 35/38 (92%) patients at baseline, with median eVAF 0.345% (range 0.0004% - 43.37%). ctDNA abundance at baseline did not correlate with PFS or OS. A decrease in Δ eVAF from T1 to T2, by > 30%, or > 50% identified pts with improved PFS, with HR 0.45 (0.21, 0.96) $p = 0.04$, 0.31 (0.14, 0.70) $p < 0.01$, and 0.23 (0.10, 0.56) $p < 0.01$, respectively. Similar results were observed for the 26 IO pts, with HR 0.40 (0.16, 1.03) $p = 0.06$, 0.19 (0.05, 0.66) $p < 0.01$, and 0.06 (0.01, 0.47) $p < 0.01$, respectively. A similar, but non-significant, trend was seen in median OS for pts with a decrease vs. increase in Δ eVAF (T1 to 2), 8.8 mo vs 7.3 mo (HR = 0.87 (0.42, 1.79)). For 31 pts, a comparison of Δ ctDNA levels, based on personalized RaDaR vs. CAPP-seq assays, from T1 to T2 demonstrated a correlation coefficient of $R = 0.57$, $P < 0.01$. **Conclusions:** In pts with R/M HNSCC, a decrease in ctDNA eVAF after first treatment correlated with improved PFS. There was a significant correlation between fixed CAPP-seq and personalized RaDaR assays when comparing Δ in ctDNA levels. Clinical Trial: NCT03712566. Research Sponsor: BMO Financial Group Chair in Precision Cancer Genomics, University Health Network, Pharmaceutical/Biotech Company.

6053 **Poster Session**

Tumor cell budding as a prognostic and potentially therapeutically targetable biomarker in head and neck cancer. *First Author: Jan Budczies, Institute of Pathology, University of Heidelberg, Heidelberg, Germany*

Background: Several studies have demonstrated a negative prognostic impact of tumor cell budding (TCB) in HPV- head and neck squamous cell carcinoma (HNSCC), but analyses of its prognostic impact in HPV+ HNSCC and of the underlying molecular alterations are lacking. **Methods:** The study cohort included 331 HPV- and HPV+ HNSCC from TCGA with digitalized H&E-stained slides available. Corresponding mutation, methylation, and gene expression data were obtained from the pan-cancer atlas web page. Tumor buds were defined as clusters of up to four tumor cells separated from the tumor mass. The numbers of tumor buds were evaluated in ten digital high-power fields by a senior pathologist. A two-tier cellular dissociation grading system was introduced by separating tumors with six or more tumor buds (TCB-high) from tumors with fewer tumor buds (TCB-low). The impact of TCB on overall survival (OS) was analyzed using Cox proportional hazard models. Results with $p < 0.05$ were considered significant. Association of TCB with mutations was analyzed using the Wilcoxon test. Association of TCB with gene expression and methylation was analyzed using Spearman correlations. Lists of altered genes were compiled correcting the p-values with the Benjamin-Hochberg method and controlling the FDR at 5%. **Results:** In a univariate analysis, OS was significantly shorter in TCB-high tumors compared to TCB-low tumors in HPV- HNSCC (HR = 1.4, 95% CI 1.0-2.3) and HPV+ HNSCC (HR = 5.0, 95% CI 1.9-13.7). Shorter OS in TCB-high HNSCC was confirmed in a multivariate analysis including age, sex, HPV status, tumor site, tumors stage, and tumor margin status (HR = 1.7, 95% CI 1.2-2.4). Significant association of TCB with mutations was detected for two genes: NSD1 mutations correlated negatively with TCB in HPV- HNSCC, while TP53 mutations correlated positively with TCB in HPV+ HNSCC. Methylation of 126 (1%) genes was associated with TCB in HPV- HNSCC, while methylation of 511 (3%) genes was associated with TCB in HPV+ HNSCC. Expression of 422 (2%) genes was associated with TCB in HPV- HNSCC, while expression of 786 (4%) genes was associated with TCB in HPV+ HNSCC. Among these genes, those annotated to the epithelial mesenchymal transition were highly significantly enriched in both HPV- HNSCC (5.5-fold enrichment) and HPV+ HNSCC (2.7-fold enrichment). **Conclusions:** Evaluation of TCB based on digital HE slides was conducted in a large clinically and molecularly characterized HNSCC cohort. The prognostic impact of TCB could be validated in HPV- HNSCC, while a prognostic impact of TCB could be demonstrated for the first time in HPV+ HNSCC. TCB correlated with mutations of only two genes and theses correlations were imperfect. A plethora of genes correlated with TCB on the level of methylation and gene expression level. These genes should be further analyzed and prioritized for the evaluation of therapeutic targeting. Research Sponsor: German Cancer Aid.

6054 **Poster Session**

The mutational landscape of medullary thyroid carcinoma using whole-exome sequencing in China. *First Author: Chen Huang, China-Japan Friendship Hospital, Beijing, China*

Background: Medullary thyroid carcinoma (MTC) is a rare malignancy, and its molecular pathogenesis is far from being understood. Therefore, a relatively comprehensive and accurate genomic profiling is needed for the future molecular diagnosis, treatment and early prevention of MTC patients. **Methods:** In this study, we investigated both the somatic and germline mutational spectrum of MTC, whole-exome sequencing (WES) was performed on tumor samples and matched noncancerous tissues from 30 MTC patients. Genetic alterations were defined and analyzed using MutSigCV and novel germline mutations were identified using MutationTaster and cross-referenced in PubMed. **Results:** In somatic mutational spectrum we found the top three significantly mutated genes (SMGs) in our MTC samples were RET, FAM186A and PRG4 genes (33%, 33% and 27%, respectively). For the germline mutations, FAT4 was detected as the most common mutated genes, following by RET and FAT1. Besides, we identified 30 novel germline mutations such as IGF1R, PDK1, NOTCH1, RPTOR, MPL, SETD2 and ARID2. Those mutated genes have been previously associated with neurofibromatosis, Lynch syndrome and other diseases respectively and now predicted potential functional pathogenicity in the patients with MTC. **Conclusions:** The study elucidated a relatively more comprehensive genomic landscape of MTC. In addition to the RET gene, which has been studied extensively, other SMGs may also be of interest including novel germline mutations. These findings may indicate the potential basis of molecular diagnosis, early prevention and targeted therapeutic options for patients with MTC in the future. Research Sponsor: None.

6055 **Poster Session**

Gut microbiome/metabolome predicts response to immune checkpoint blockers (ICB) in patients with recurrent metastatic head and neck squamous cell cancer (RM HNSCC). *First Author: Shahla Bari, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: Gut microbiome has emerged as an important predictor of response to ICB therapy in various cancers, most notably in melanoma. Due to functional redundancy of microbiota, there has been lack of consistency in gut microbial signature associated with ICB response. Microbial metabolites in addition to taxonomy may play a superior role in predicting response to ICB. Gut microbiome/metabolome signatures of ICB response is unknown in RM HNSCC patients. **Methods:** Two cohorts of patients were included (stool and plasma samples were collected)- cohort 1, newly diagnosed RM HNSCC patients starting first line ICB, for whom samples were collected before ICB initiation (baseline) and post-treatment at 3, 6, and 12 months. Cohort 2 with durable response (disease control lasting $\geq$ 6 months), with single sample collected at study entry. 16s rRNA sequencing was performed on stool samples while plasma metabolites were quantitated using Q Exactive plus Orbitrap mass spectrometer. Response was defined as partial response (PR) or complete response (CR) as per RECIST 1.1 **Results:** The 16-S sequence was carried on 31 samples (cohort 1- 16 baseline, 7 post treatment; cohort 2- 8 durable responders). Targeted metabolomics was completed on 92 plasma samples [cohort 1-27 baseline and 50 post-treatment, cohort 2- 15]. Responders had a significantly higher Shannon's diversity index, lower Fermicutes to Bacteroidetes ratio, and were enriched with genus Bacteroides and Lachnospiracea incerate sedis at baseline and post treatment, compared to non-responders ($p < 0.05$). At species level, baseline and post treatment microbiome of responders was enriched with Eubacterium oxidoreducens and Bacteroides uniformis. Ruminococcus was preferentially enriched in durable responders. Targeted analysis of plasma metabolites (associated with gut microbial metabolism) showed that responders had a significantly lower baseline adenosine, Inosine and xanthine level as compared to non responders. Further, Inosine levels decreased with response, while levels increased in non-responders ($p < 0.05$), suggestive of consumption by re-activated T cells Further, ICB responders had significantly lower Kynurenine to tryptophan ratio compared to non responders **Conclusions:** This is the first study evaluating association of gut microbiome and metabolome on response to first line ICB, in RM HNSCC patients. We found higher diversity and specific gut microbial signatures associated with ICB response. Interestingly, we found that inosine and kynurenine/tryptophan pathways, both which play a crucial role in host as well as gut microbial metabolism were differentially expressed in ICB responders. Our results if validated in larger cohort, lays groundwork for gut microbiome and importantly microbial metabolite modulation to improve response to ICB in RM HNSCC. Research Sponsor: Circle of Hope For Cancer Research, Moffitt cancer center internal funding.

6056 **Poster Session**

Cataloging targetable dependencies of head and neck cancer cell lines in the DepMap CRISPR screens. *First Author: Devraj Basu, The University of Pennsylvania, Philadelphia, PA*

Background: The DepMap genome-wide loss of function CRISPR screens offer new insight into gene dependencies in HPV(-) head and neck squamous cell carcinoma (HNSCC) cell lines. We aimed to leverage this data to guide preclinical studies by cataloging targetable dependencies and identifying ones predicted to offer a therapeutic window. We also aimed to identify targets representing potential synthetic lethalities by testing for associations between genetic alterations and dependency profile. **Methods:** DepMap was queried for gene probability and effect scores in cell lines from 77 tumors, including 62 HPV(-) HNSCCs plus 15 ESCCs, which have comparable etiology, genetic features, and tissue of origin. A probability score of ≥ 0.5 was used as the threshold for essentiality. Essential genes were selected for analysis by 3 criteria: (1) presence in ≥10% cell lines, (2) lack of dependency in CRISPR screens of normal human cell lineages, and (3) designation as druggable by the Drug-Gene Interaction Database. Gene set enrichment analysis was performed using the Hallmark Gene Sets. DepMap gene effect scores were used to prioritize targets likely to have a useful therapeutic window based on median scores greater than for *EGFR* (0.676), a target with established albeit modest utility for HNSCC. The Open Targets platform was used to identify targets with inhibitors used in trials for other cancers and/or nonmalignant diseases. Associations between dependencies and genetic alterations were defined using two-sample t-tests, with filter conditions of $p < 0.05$ and effect size ≥1. **Results:** The 231 genes meeting selection criteria had a median gene effect score of 0.56. The criteria captured targets of standard therapeutic agents including *TYMS* (5-FU), tubulin genes (paclitaxel), *EGFR* (cetuximab), plus known oncogenes like *PIK3CA*. GSEA showed enrichment of known oncogenic signaling pathways including PI3K/AKT and JAK/STAT, as well as hallmark cancer processes like DNA repair and apoptosis. 90% were not known oncogenes cataloged in the OncoKB Database. 45 genes had a median gene effect score between that of *EGFR* and the median for common essential genes, including 7 without known cancer-promoting roles: *OTOP1, DHRSX*, *UTP11*, *MBTPS1*, *SLC25A3, PPIAL4G*, and *RBM10*. 17% had inhibitors that reached a non-HNSCC phase II trial, including 10 targets not previously tested in cancer. Novel associations between dependencies and genetic alterations included *DDX3X* with *NOTCH1-mut*, *ITGB1* with *CDKN2Amut*, and *ATP1A1* with *HRASmut*. **Conclusions:** We catalog targetable dependencies in cell line models of HNSCC. While well-studied targets were captured, many genes lacked known roles in malignancy. Targets of inhibitors tested in other diseases provide new tools to guide preclinical studies. Association of some dependencies with known molecular subgroups in HNSCC may enhance use of cell line models to personalize therapy. Research Sponsor: U.S. National Institutes of Health.

6057 **Poster Session**

Association between up-front surgery and risk of stroke in U.S. veterans with oropharyngeal squamous cell carcinoma. *First Author: Lova Sun, University of Pennsylvania, Philadelphia, PA*

Background: Cardiovascular disease and stroke are important causes of long-term morbidity and mortality in patients with oropharyngeal squamous cell carcinoma (OPSCC). Cancer treatments including radiotherapy to the neck and chemotherapy have been associated with increased risk of stroke. In the era of treatment de-intensification for OPSCC, up-front surgical treatment has been proposed as one strategy that allows for de-escalation or avoidance of (chemo)radiotherapy. We sought to quantify the cumulative incidence of stroke in patients treated for non-metastatic OPSCC, and then evaluate whether patients receiving up-front surgery for OPSCC have decreased risk of stroke compared to those undergoing non-surgical treatment. **Methods:** We identified a cohort of 10,436 United States veterans diagnosed with non-metastatic OPSCC from 2000-2020, of whom 2,717 received up-front surgery (with or without perioperative radiotherapy or chemoradiotherapy) and 7,719 received non-surgical therapy (definitive radiotherapy or chemoradiotherapy). We estimated the cumulative incidence of stroke in this population, accounting for death as a competing risk. To assess the association between up-front surgery and risk of stroke, we generated a propensity score for the probability of receiving surgical treatment and used inverse probability weighting to construct pseudo-populations balanced on all potential confounders. Cox regression models of the inverse probability weighted population were used to estimate the cause-specific hazard ratio of stroke associated with surgical vs non-surgical treatment. **Results:** The 10-year cumulative incidence of stroke was 12.5% (95% CI 11.8-13.23) and death was 57.3% (95% CI 56.2-58.4). Up-front surgical patients who underwent perioperative (chemo)radiotherapy had shorter radiation and chemotherapy courses compared to non-surgical patients, suggestive of lower treatment intensity. Propensity score generation and inverse probability weighting yielded good overlap and covariate balance between surgical and non-surgical treatment groups. The inverse probability weighted cause-specific hazard ratio of stroke associated with up-front surgical treatment was 0.77 (95% CI 0.66-0.91, p = 0.002). This association was consistent across subgroups defined by age (> /≤65 years) and baseline cardiovascular risk factors (hypertension, hyperlipidemia, diabetes). **Conclusions:** In over 10,000 US veterans with OPSCC, cumulative incidence of stroke was 12.5% at 10 years. Up-front surgical treatment was associated with a 23% reduced risk of stroke compared to definitive (chemo)radiotherapy. These findings present an important additional risk-benefit consideration to factor into treatment decisions and patient counseling, and should motivate future studies to examine cardiovascular events in this high-risk population. Research Sponsor: University of Pennsylvania ENT Faculty Pilot Grant.

6058 **Poster Session**

Intraoperative radiation therapy for locally advanced and recurrent head and neck cancer. *First Author: Celina Chiodo, Loyola University Chicago, Arlington Heights, IL*

Background: Intraoperative Radiation Therapy (IORT) allows precise delivery of radiation therapy (RT) to a limited target area at high risk of cancer recurrence while minimizing RT to nearby organs at risk. IORT may be particularly beneficial for patients with locally recurrent head and neck cancer (HNC) in a previously irradiated field and for locally advanced HNC cases, in which obtaining negative surgical margins may be difficult. This study aims to present a single institution experience with IORT for HNC patients. **Methods:** This study included HNC patients treated consecutively with IORT at our institution between 2014 and 2018. Charts were reviewed for patients' and tumors' characteristics, IORT technical details, IORT-induced adverse events, and treatment outcomes. **Results:** The study included 23 eligible patients. Median patient age was 66 (range 33-91). Tumor sites included parotid gland (43%), lymph nodes (43%), oral tongue (9%), and ear (4%). 52% of patients received IORT upfront with or without postoperative adjuvant external beam radiation therapy (EBRT), while 48% received salvage IORT after local tumor recurrence. The median prescribed IORT dose was 7.5 Gy (range 5-14 Gy) in a single fraction prescribed to 5 mm depth with Flat applicators (median diameter of 5 cm). 92% of patients did not experience wound healing complications. One patient (4%) developed postoperative acute thromboembolic stroke, a second patient (4%) experienced protracted wound healing. At a median follow-up of 36 months (range 2-81), 42% of patients presented with no evidence of disease (NED), overall survival was 54%, 13% of patients were alive with disease, and 46% died with disease. Local-regional recurrence rate was 39% (median time to local recurrence was 18 months, range 2-60), rate of distant metastasis was 43% (median time to distant metastasis was 23 months, range 5-60), and 30% of patients had both local-regional recurrence and distant metastases. The percent of local-regional recurrence and distant metastases among patients receiving salvage IORT was 64% and 73% respectively, compared to 23%, and 15% respectively in those receiving upfront IORT with or without adjuvant EBRT. **Conclusions:** In this single institution chart review study, IORT to locally advanced and recurrent HN cancer patients was a safe treatment modality, with tumor control comparable to historical EBRT data. Larger prospective studies are needed to further assess the utility of IORT in the management of locally advanced and recurrent HN cancer. Research Sponsor: None.

6059 **Poster Session**

Impact on xerostomia for patients with nasopharyngeal carcinoma treated with superficial parotid lobe-sparing intensity-modulated radiation therapy (SPLS-IMRT): A prospective phase II randomized controlled study. *First Author: Huageng Huang, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: In the intensity-modulated radiation therapy (IMRT) era, xerostomia remains one of the most common radiation-induced toxicities in nasopharyngeal carcinoma (NPC) patients. We first proposed the superficial parotid lobe–sparing IMRT (SPLS-IMRT) technique in NPC, which has been proved to significantly reduce the mean doses of bilateral entire parotid glands and superficial parotid lobes. To further validate its clinical benefits, we conducted a prospective phase II randomized controlled study to compare the incidence of xerostomia in NPC patients treated with SPLS-IMRT and conventional IMRT (C-IMRT). **Methods:** Patients with histologically confirmed NPC who met the eligibility criteria were randomly assigned in a 1:1 ratio to receive either SPLS-IMRT or C-IMRT. The V36 (the percentage volume receiving a dose of 36 Gy) of the entire parotid gland was constrained to be less than 40% in both groups. Additionally, V26 (the percentage volume receiving a dose of 26 Gy) of the superficial parotid lobe was constrained to be less than 30% in the SPLS-IMRT group. The primary endpoint was the incidence of xerostomia at 12 months post-IMRT. The secondary endpoints included the xerostomia questionnaire (XQ) score, unstimulated salivary flow rate (USFR), stimulated salivary flow rate (SSFR), and survival outcomes. **Results:** From January 2018 to September 2018, 90 patients were enrolled (45 per group). Eighty-two patients were included for xerostomia analysis (42 in the SPLS-IMRT group and 40 in the C-IMRT group). At 12 months post-IMRT, the incidence of xerostomia in the SPLS-IMRT group was significantly lower than that in the C-IMRT group (83.4% vs. 95.0%; $P = 0.007$), especially the grade 3 xerostomia (0% vs. 12.5%; $P < 0.001$). However, the median change in XQ score (XQ_{change}) was similar between the two groups (11.9 points vs. 14.1 points; $P = 0.194$). Moreover, there was a significantly higher median fractional USFR (0.67 vs. 0.35; $P = 0.024$) and SSFR (0.66 vs. 0.32; $P = 0.021$) in the SPLS-IMRT group than the C-IMRT group. All 90 patients were included for survival analysis. With a median follow-up time of 37.8 months (IQR, 33.9–38.5 months), the 3-year locoregional relapse-free survival, distant metastasis-free survival, and overall survival in the SPLS-IMRT and C-IMRT groups were 92.5% vs. 90.9% (hazard ratio [HR], 1.84; $P = 0.477$), 83.8% vs. 81.7% (HR, 1.13; $P = 0.816$), and 88.9% vs. 88.2% (HR, 0.96; $P = 0.949$), respectively. **Conclusions:** SPLS-IMRT significantly reduced the incidence of xerostomia at 12 months post-IMRT in NPC by recovering parotid gland function earlier than C-IMRT, without compromising survivals. Phase III clinical trials are needed to confirm this result. Clinical trial information: NCT05020067. Research Sponsor: the National Natural Science Foundation of China (No. 82003081).

6060 **Poster Session**

Camrelizumab plus apatinib as induction therapy for locally advanced head and neck squamous cell carcinoma (IMplus): A single-arm phase II study. *First Author: Lulu Ye, Department of Oral and Maxillofacial-Head Neck Oncology, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine; College of Stomatology, Shanghai Jiao Tong University; National Center for Stomatology, Shanghai, China*

Background: Immune checkpoint inhibitor combined with antiangiogenic agent has been investigated in many solid tumors, including advanced head and neck squamous cell carcinoma (HNSCC; NCT02501096), but the evidence is limited. This study was conducted to investigate the efficacy and safety of anti-programmed cell death-1 antibody camrelizumab plus antiangiogenic agent apatinib as induction therapy in patients with locally advanced HNSCC. **Methods:** In this single-center phase II trial (NCT04440917), patients with untreated locally advanced HNSCC who had inoperable lesions, could not tolerate surgery, or refused surgery were enrolled. Patients received camrelizumab 200 mg once every 2 weeks and apatinib 250 mg once daily for two 28-day cycles, followed by local treatment based on the re-examination results. The primary endpoint was objective response rate (ORR) after induction therapy, as assessed according to the Response Evaluation Criteria In Solid Tumors version 1.1. Simon's two-stage design was adopted for this study. **Results:** Between December 2019 and July 2021, 18 patients were enrolled in the first stage. Eight (44%) patients had oropharyngeal carcinoma, nine (50%) had oral carcinoma, and one (6%) had hypopharyngeal carcinoma. There were six (33%), three (17%), and nine (50%) patients with stage III, IVA, and IVB disease, respectively. After induction therapy, six patients achieved complete response, nine achieved partial response, and three had stable disease, with an ORR of 83%. The study proceeded to the second stage and the enrollment for another 14 patients is ongoing. Two (11%) patients with partial response received surgery and adjuvant radiotherapy, and 16 (89%) received radical radiotherapy. With a median follow-up duration of 18 months (range, 9-26), only one disease recurrence and no deaths occurred. The most common adverse events during induction therapy were hypertension (ten [56%]), oral pain (nine [50%]), and increased aspartate aminotransferase (five [28%]). Only one [6%] grade 3 hypertension and one [6%] grade 3 proteinuria were observed, and no grade 4 or 5 adverse events occurred. **Conclusions:** Camrelizumab plus apatinib showed promising antitumor activity as induction therapy in patients with locally advanced HNSCC, with acceptable safety profile. Clinical trial information: NCT04440917. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

6061 **Poster Session**

Recombinant human endostatin combined with intensity-modulated radiotherapy in low-risk locoregionally advanced nasopharyngeal carcinoma: A phase II, randomized, multicenter clinical trial. *First Author: Min Kang, Department of Radiation Oncology, The First Affiliated Hospital of Guangxi Medical University, Nanning, China*

Background: Concurrent chemoradiotherapy (CCRT) is currently considered to be the standard treatment for locoregionally advanced nasopharyngeal carcinoma (LA-NPC), accompanied with non-neglectable toxicity and unsatisfactory compliance. Therefore, it is highly warranted to explore an alternative regimen for LA-NPC. This trial aimed to assess and investigate the efficacy and safety of recombinant human endostatin (Rh-endostatin) with intensity-modulated radiotherapy (IMRT) for low-risk LA-NPC. **Methods:** Patients with low-risk LA-NPC were randomly assigned into ERT group (n=60, receiving Rh-endostatin plus radiotherapy) and CCRT group (n=60, receiving cisplatin plus radiotherapy). The primary endpoint was the 5-year overall survival (OS). Non-inferiority was shown if the upper limit of the 95% CI for the difference in 5-year OS between the ERT group and CCRT group did not exceed 15%. The secondary endpoint was 3-year progression-free survival (PFS). **Results:** A total of 120 patients were included in the trial. After a median follow-up of 71 months (IQR 62-75), the 5-year OS rate was 88.1% in the ERT group and 77.6% in the CCRT group, with a difference of 10.5% (95% CI: -0.03 to 0.24; $P_{non\text{-}inferiority} = 0.002$). Patients in the ERT group had better 3-year PFS than that in the CCRT group (89.8% vs 70.6%; HR = 0.362; 95% CI: 0.150-0.873; $P_{log\text{-}rank} = 0.018$). The overall all-grade toxicity burdens were heavier in CCRT group. No patients died of treatment-related causes. **Conclusions:** Rh-endostatin combined with IMRT had favorable efficacy, fewer toxic effects and more improved quality of life, which might be a promising alternative regimen to CCRT for low-risk LA-NPC in clinic. Clinical trial information: NCT02237924. Research Sponsor: National Natural Science Foundation of China (No. 81760542 and No. 82160467), the Projects for Research and Development of Medical and Health Appropriate Technology of Guangxi Zhuang Autonomous Region (No. S2018087), the Key Research and Development Prog.

Survival outcomes for intention-to-treat analysis.

	Rh-endostatin + radiotherapy (n = 60)	Chemoradiotherapy (n = 60)	Hazard ratio (95% CI)	p value
5-year rate (95%CI)				
5-year OS	88.1% (79.9-96.3)	77.6% (66.8-88.4)	0.495 (0.208-1.180)	$P_{non\text{-}inferiority} = 0.002$
5-year PFS	81.4% (71.4-91.4)	70.6% (58.8-82.4)	0.561 (0.263-1.198)	$P_{log\text{-}rank} = 0.129$
5-year LRRFS	94.8% (89.1-99.9)	92.0% (84.4-99.6)	0.641 (0.143-2.865)	$P_{log\text{-}rank} = 0.557$
5-year DMFS	84.6% (75.4-93.8)	80.7% (70.5-90.9)	0.718 (0.297-1.734)	$P_{log\text{-}rank} = 0.458$
3-year rate (95%CI)				
3-year OS	93.2% (86.8-99.6)	79.3% (68.9-89.7)	0.342 (0.122-0.960)	$P_{log\text{-}rank} = 0.032$
3-year PFS	89.8% (82.2-97.4)	70.6% (58.8-82.4)	0.362 (0.150-0.873)	$P_{log\text{-}rank} = 0.018$
3-year LRRFS	96.6% (91.9-99.9)	92.0% (84.4-99.6)	0.651 (0.146-2.911)	$P_{log\text{-}rank} = 0.572$
3-year DMFS	93.2% (86.7-99.7)	80.7% (70.5-90.9)	0.325 (0.103-1.021)	$P_{log\text{-}rank} = 0.042$

Data are % (95% CI). OS, overall survival; PFS, progression-free survival; LRRFS, locoregional recurrence-free survival; DMFS, distance metastasis-free survival (DMFS) rate.

6062 **Poster Session**

Dynamic cell free HPV DNA is an early measure of treatment responsiveness in patients receiving induction chemotherapy for HPV-related head and neck cancer. *First Author: Linda (Yilin) Cao, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*

Background: Induction chemotherapy (IC) is being studied as a chemoradiation (CRT) de-intensification strategy in HPV-related head and neck cancer (HNC), but using imaging response for eligibility selection is distinctly limited by delayed correlation with biological response and difficulty in distinguishing active tumor from treatment effect. We report serial cell free HPV DNA (cfHPV DNA) dynamics as a quantitative measure of early treatment responsiveness for HPV-related HNC patients receiving IC followed by CRT. **Methods:** Patients with high-risk HPV-positive (by in situ hybridization), locally advanced HNC who received IC followed by definitive CRT were enrolled starting on Sept 26, 2021. Patients received 1-2 cycles of platinum/taxane IC prior to initiating standard-dose CRT. Peripheral blood cfHPV DNA levels were measured biweekly during IC and weekly during CRT with the SafeSEQ HPV test from Sysmex Inostics, an NGS-based, CLIA-certified assay designed to sensitively detect and quantify HPV16 and HPV18 DNA in plasma. Tumor volumes were assessed on the pre- and post-IC planning CT scans by the treating radiation oncologist. **Results:** To date, 72 plasma samples have been processed across 11 enrolled patients with median age 66 years (range: 35-79). The primary disease sites included 7 oropharynx (OPX), 1 sinonasal, 2 nasopharyngeal, and 1 larynx. All patients had at least cT3 disease or cN3 disease (AJCC 8), with 6 patients having cT4 disease. Five (45.5%) have a smoking history, each > 10 pack-years. We report cfHPV DNA and tumor volume measurements at key timepoints for the 8 patients who have completed IC below. **Conclusions:** Serial cfHPV DNA identifies a group of locally advanced HPV-related HNC patients who have complete/near-complete cfDNA clearance during IC. This may provide an earlier readout of individualized treatment responsiveness compared to radiologic assessment, and may therefore be a preferred metric for CRT de-intensification eligibility. Clearance velocity will be evaluated with our granular biweekly IC and weekly CRT cfHPV DNA dataset to help further elucidate tumor response kinetics with this paradigm. Research Sponsor: Sysmex Inostics.

		Baseline cfHPV DNA Copies/mL plasma	Mid-IC cfHPV DNA Primary (cc)	End of IC cfHPV DNA Nodal (cc)	cfHPV DNA Change Primary	Baseline Tumor Volume		Tumor Volume Change	
						Nodal			
T4aN1 OPX	HPV16	375.6	Not detected	Not detected	-100%	17.7	2.9	-84%	-80%
T2N3 OPX	HPV16	788.4	< 1	< 1	-99%	17.6	69.5	-67%	-61%
T3N0 sinonasal	HPV18	11.6	3.1	6.6	-43%	16.6	–	-58%	–
T2N3 OPX	HPV16	5567.3	225.4	77.7	-99%	43.9	145.4	-35%	-46%
T4aN1 OPX	HPV16	160.4	Not detected	Not detected	-100%	67.2	3.0	-54%	-91%
T3N2 OPX	HPV16	138.8	299.2	1170.6	+743%	48.3	26.0	-46%	+21%
T4aN0 OPX	HPV16	2253.9	1628.5	1490.5	-34%	259.8	–	+31%	–
T4aN2 OPX	HPV16	2374.9	5.6	8.4	-99%	57.8	56.8	-60%	-78%

6063 **Poster Session**

Camrelizumab in combination with concurrent chemoradiotherapy as first-line treatment for nonoperative head and neck cancer: A comparative study. *First Author: Feng Liu, Hunan Cancer Hospital and The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, China*

Background: We hypothesized that concurrent chemoradiotherapy (CCRT) plus concurrent and adjuvant camrelizumab as first-line treatmentwas associated with improved survival compared with concurrent chemoradiotherapy alone for nonoperative locoregionally advanced head and neck squamous cell carcinoma (HNSCC). The purpose of this comparative study was to compare the efficacy and toxicity of CCRT plus concurrent and adjuvant camrelizumab versus CCRT alone in nonoperative locoregionally advanced HNSCC. **Methods:** One hundred and eighty patients with nonoperative locoregionally advanced HNSCC (cancer of the oral cavity, oropharyngeal cancer, hypopharyngeal cancer and laryngeal cancer) received either CCRT plus concurrent and adjuvant camrelizumab (camrelizumab + CCRT group, n = 90) or CCRT alone (CCRT alone group, n = 90). Patients in both groups received curative cisplatin-based concurrent chemoradiotherapy. The radiation dose was 70 Gy (2.0 Gy/fraction). In camrelizumab + CCRT group, concurrent camrelizumab (200mg/day on days 1, 22, 43) was added to CCRT, followed by adjuvant camrelizumab (200mg, every 3 weeks for 6 months or until disease progression, unacceptable adverse events or withdrawal of consent). **Results:** Compared with CCRT alone, the addition of concurrent and adjuvant camrelizumab significantly improved complete response (CR) rates (92.2% vs. 80.0%; P = 0.018), 3-year disease free survival (DFS, 72.2% vs. 56.7%; P = 0.029), locoregional recurrence-free survival (LRRFS, 76.7% vs. 61.1%; P = 0.024), and overall survival (OS, 78.9% vs. 63.3%; P = 0.033). Reactive cutaneous capillary endothelial proliferation was higher in the camrelizumab + CCRT group (6.7% vs. 0.0%; P = 0.013). No statistically significant differences in other acute (mucositis, leukopenia, thrombocytopenia, anemia, etc.) and late toxic effects (mucosal necrosis, trismus, cranial nerve palsy, etc.) were observed between the two groups. The addition of camrelizumab (CCRT plus camrelizumab vs. CCRT alone) was a significant independent prognostic factor for 3-year DFS, LRRFS and OS (P = 0.038, P = 0.032, and P = 0.048, respectively). **Conclusions:** Concurrent chemoradiotherapy plus concurrent and adjuvant camrelizumab as first-line treatment is associated with a considerable survival benefit, with acceptable adverse events, as compared with concurrent chemoradiotherapy alone, among patients with nonoperative locoregionally advanced head and neck squamous cell carcinoma. Our ongoing prospective clinical trial (registered with chictr.org.cn, number ChiCTR2200056298) will further investigate the efficacy of camrelizumab in combination with chemoradiotherapy for HNSCC. Research Sponsor: Hunan Provincial Science and Technology Department (NO. 2021JJ30426) (China), Other Foundation.

6064 **Poster Session**

Pathologic response after induction chemo-immunotherapy with single or double immune checkpoint inhibition in locally advanced head and neck squamous cell carcinoma (HNSCC): Expansion cohorts of the CheckRad-CD8 trial. *First Author: Markus Hecht, Department of Radiation Oncology, Universitatsklinikum Erlangen, Friedrich-Alexander-Universitat Erlangen-Nürnberg, Erlangen, Germany*

Background: Targeting the immune checkpoint CTLA-4 in addition to PD-1/PD-L1 alone did not increase efficacy in HNSCC, whereas this has not been studied in combination with chemotherapy. Induction chemo-immunotherapy followed by pathologic response-based patient selection for chemotherapy-free radioimmunotherapy was efficient in locally advanced HNSCC (J Immunother Cancer. 2022 Jan;10(1):e003747). The expansion cohorts of the CheckRad-CD8 trial studied safety and efficacy of induction chemo-immunotherapy with increased dose or without CTLA-4 inhibition. **Methods:** Patients with previously untreated stage III-IVB (AJCC 8th edition) HNSCC were eligible for this multicenter phase II trial. Induction chemo-immunotherapy of the main cohort (MC) consisted of a single cycle of cisplatin 30mg/m^2 d1-3, docetaxel 75mg/m^2 d1, durvalumab 1500mg fix dose d5 and tremelimumab 75mg fix dose d5. Patients in expansion cohort 1 (EC1) received this combination with high dose tremelimumab 300mg fix dose d5 and patients in expansion cohort 2 (EC2) received no tremelimumab. In EC1 and EC2 prophylactic G-CSF was recommended. Patients with at least 20% increase of intratumoral CD8+ immune cell density or pathological complete response (pCR) in the re-biopsy entered chemotherapy-free radioimmunotherapy up to a total dose of 70Gy. The current analysis focuses on toxicity and pathologic response after induction chemo-immunotherapy. **Results:** Between Sep 2018 and Sep 2021, 80 patients were enrolled in the MC (one excluded), 20 in EC1 and 20 in EC2 (one excluded) subsequently. In the MC, EC1 and EC2 a total of 56%, 50%, 58% were stage IV and 29%, 30%, 26% had p16 positive oropharyngeal tumors. Baseline median intratumoral CD8+ immune cell density was 395/mm^2, 505/mm^2 and 763/mm^2 in MC, EC1 and EC2. After induction chemo-immunotherapy 41 (52%), 12 (60%) and 11 (58%) of the patients had pCR in the re-biopsy in MC, EC1 and EC2. Patients with residual tumor after induction therapy had a median intratumoral CD8+ immune cell density of 670/mm^2, 781/mm^2 and 1605/mm^2, which was a median increase by factor 3.0, 2.1 and 4.8 in the corresponding patients' tissue samples. In the cohorts MC, EC1 and EC2 the overall rate of grade 3-4 adverse events per patient was 1.38, 1.35 and 0.58. The corresponding rate of non-hematologic adverse events per patient was 0.84, 0.95 and 0.37, respectively. **Conclusions:** Neither increase of tremelimumab dosage nor its omission did significantly affect pathologic response to induction chemo-immunotherapy with cisplatin/ docetaxel/ durvalumab. Non-hematologic toxicity was slightly increased for high dose tremelimumab and clearly decreased without tremelimumab. The role of concomitant administration of tremelimumab with radiotherapy cannot be assessed until the final study analysis. Clinical trial information: NCT03426657. Research Sponsor: AstraZeneca.

6065 **Poster Session**

Quality of life and two-year results of a randomized phase III study of dysphagia-optimized intensity modulated radiotherapy (DO-IMRT) versus standard IMRT (S-IMRT) in head and neck cancer. *First Author: Christopher Nutting, Royal Marsden NHS Foundation Trust, London, United Kingdom*

Background: Most newly diagnosed oro- & hypopharngeal cancers (OPC, HPC) are treated with (chemo)RT with curative intent but at the consequence of adverse effects on quality of life. We investigated if using DO-IMRT to reduce RT dose to the dysphagia/ aspiration related structures (DARS) improved swallowing function compared to S-IMRT. **Methods:** Patients with T1-4, N0-3, M0 OPC/HPC were randomised 1:1 to S-IMRT (65 Gray (Gy)/30 fractions (f) to primary & nodal tumour; 54Gy/30f to remaining pharyngeal subsite & nodal areas at risk of microscopic disease) or DO-IMRT. The volume of the superior & middle pharyngeal constrictor muscle (PCM) (OPC) or inferior PCM (HPC) lying outside the high-dose target volume was set a mandatory mean dose constraint in DO-IMRT. Treatment allocation was by minimisation balanced by centre, use of induction/concomitant chemotherapy, tumour site & AJCC stage. Primary endpoint was mean MD Anderson Dysphagia Inventory (MDADI) composite score 12 months after RT. Secondary endpoints included University of Washington (UW)-QoL, Performance Status Scale Head & Neck (PSS-HN) domain scores (range: 0-100), swallow volume, swallow capacity and local control. **Results:** 112 patients (56 S-IMRT, 56 DO-IMRT) were randomised from 22 UK & Ireland centres from 06/2016 - 04/2018. 111/112 had RT doses as prescribed (1 patient died before RT). Outcome measures at 12 and 24 months are summarised below. DO-IMRT had higher MDADI scores at 12 (p = 0.04) and 24 (p = 0.07) months. Clinically important improvements in swallowing function were seen in patients receiving DO-IMRT using PSS-HN domains and the UW-QoL tool. **Conclusions:** DO-IMRT improved patient reported swallowing function compared with S-IMRT. Improvements were seen in overall MDADI as well as functional scores in both PSS-HN and UW-QoL. Clinical trial information: 25458988. Research Sponsor: Cancer Research UK and National Institute for Health Research.

	12 months			24 months		
	S-IMRT (n = 54)	DO-IMRT (n = 55)	p-value	S-IMRT (n = 51)	DO-IMRT (n = 54)	p-value
MDADI Mean score (SD)	70.6 (17.3)	77.7 (16.1)	0.04	73 (17.4)	79.6 (16.5)	0.07
PSS-HN Normalcy of diet score > 50	58% (25/43)	71% (36/51)	0.50	73% (30/41)	81% (38/47)	0.55
PSS-HN Eating in public score > 50	74% (32/43)	84% (43/51)	0.35	85% (35/41)	92% (43/47)	0.57
UW-QoL "Able to swallow as well as ever"	15% (7/46)	40% (21/52)	0.01	20% (8/41)	40% (19/47)	0.04
UW-QoL "Saliva of normal consistency"	7% (2/29)	8% (3/39)	0.67	4% (1/26)	6% (2/36)	0.61
UW-QoL "Can taste food normally"	11% (5/45)	23% (12/52)	0.04	24% (10/41)	33% (16/48)	0.02
Median UW-QoL Physical subscale score (IQR)	74 (66-85)	83 (76-88)	0.02	78 (70-85)	85 (77-90)	0.02
Median UW-QoL Social-Emotional subscale score (IQR)	83 (70-92)	83 (74-92)	0.82	87 (78-95)	88 (80-96)	0.33

6066 **Poster Session**

Feasibility and quality of life of postoperative concurrent radiotherapy and toripalimab in elderly patients with head and neck squamous cell carcinoma (IMPORT trial). *First Author: Ximei Zhang, Department of Radiotherapy, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China*

Background: For elderly patients with locally advanced head and neck squamous cell carcinoma (HNSCC), the role of postoperative concurrent chemotherapy was controversial since the intolerable toxicities and increased acute mortality, thus, radiotherapy alone was recommended. Aimed to seek out a feasible regimen for concurrent treatment, we evaluated the feasibility and quality of life of postoperative concurrent radiotherapy and toripalimab (anti-PD-1 antibody) in elderly HNSCC patients. **Methods:** The IMPORT trial was an investigator-initiated, multicentre, open-label, parallel-group, phase 2, randomized study. Patients were enrolled at 3 hospitals in China. We randomly assigned (1:1) patients aged > 65 years, with ECOG Performance Status(PS) of 0–2, and with postoperative Stage III-IV (AJCC 8th Staging system) HNSCC to concurrent radiotherapy (60-66Gy) and toripalimab (240mg on D0, D21 and D42)(RT+PD-1 group) or radiotherapy alone(RT group). Following stratification by PS(0-1 vs 2) and pathological adverse features (extranodal extension or positive margin vs others), patients were randomly assigned using a computer-generated randomization list. Acute toxicities were reported. Quality of life were evaluated by EORTC QLQ-C30 and QLQ-H&N35 at baseline, week3, week6 and 1 month after radiotherapy, and the standard scores were compared between groups by linear mixed-effects models. **Results:** Between September 2020 and December 2021, 38 patients randomly assigned(19 per group). The median age were 70 years (range 66-81) for the RT+PD-1 group and 73 years (range 67-78 years) for RT group. 16 (84.2%) patients in the RT+PD-1 group and 15 (78.9%) patients in the RT group complete the planed radiation dose. In the RT+PD-1 group, 13 (68.4%) patients completed 3 cycles of toripalimab, 3 (15.8%) patients completed 2 cycles due to adverse events and 3 (15.8%) patients declined toripalimab; The most common adverse events of grade 3-5 was oral mucositis (55.6% vs 58.8%) and lymphocyte count decreased(61.1% and 41.2%) in RT+PD-1 group and RT group. In the RT+PD-1 group, only 1 patients experienced grade 3 immune-related enteritis. As to the quality of life scores evaluated by QLQ-C30, no difference was found in standard score of global health status, as well as in most functional scales including: physical, emotion, cognitive and social, except for role functioning (p = 0.045). As to the symptom scale scores evaluated by QLQ-H&N35, no difference was found in standard score of pain, swallowing, dry mouth, opening mouth, and stick saliva, except for speech problem (p = 0.032). **Conclusions:** For elderly patients with locally advanced HNSCC, postoperative concurrent radiotherapy and toripalimab was safe and feasible. Concurrent toripalimab did not worsen quality of life scores in the majority of cases. Clinical trial information: NCT04523883. Research Sponsor: Shanghai Hospital Development Center, WU JIEPING MEDICAL FOUNDATION and Shanghai Anti-Cancer Research Foundation.

6067 **Poster Session**

Transoral robotic surgery (TORS)-guided radiotherapy (RT) volume de-intensification in p16-positive unknown primary squamous cell carcinoma (SCC) of the neck: A phase 2 trial (FIND). *First Author: John R de Almeida, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: TORS has improved the likelihood of identifying an oropharyngeal cancer for patients presenting with unknown primary. We evaluate the oncologic and functional outcomes after reduction of RT volumes based on TORS findings. **Methods:** Patients with p16-positive, neck SCC (cN1-N3) with no primary on examination and CT/MRI were included between 08/2017 and 12/2019. All patients underwent PET-CT, surgical evaluation with either therapeutic intent including neck dissection for cN1 without extranodal extension (Group 1, n=9) or diagnostic intent (Group 2, n=13). Patients underwent excision of palatine tonsil (PT) followed by lingual tonsil (LT), if the PT was negative, or excision of PET-CT avid regions. Pharyngeal-sparing radiotherapy (PSRT) was given when no primary was found (pT0) and for primaries completely excised (margins >= 3mm). Unilateral neck radiotherapy (UNRT) was given for lateralized (>1 cm from midline) primaries or pT0 with unilateral disease. The primary outcome was 2-year out-of-treated volume failures (OTVF). Swallowing-related quality of life (SR-QOL) was measured using MD Anderson Dysphagia Inventory (MDADI) composite score. A sample size of 22 was required assuming OTVF cannot exceed 15% (vs. 1% historical), power of 0.8, alpha of 0.05 (one-sided), and loss to follow-up of 10%. **Results:** All 22 patients [median age 60 (46-68); 86% male; 86% N1, 9% N2, 5% N3] underwent surgical evaluation. PET-CT showed suspicious findings in 12 (55%) [sensitivity = 0.44, specificity = 0.29]. Excision of PT and LT were performed in 14 (64%) and 14 (64%) patients respectively; and 8 (36%) had previous PT. Oropharyngeal primaries were found in 17 patients (77%) [14 (64%) single primary, 3 (13%) two primaries]. RT volume de-intensification was achieved in 11 patients (50%) who had PSRT and 10 (45%) who had UNRT. In Group 1, adjuvant RT was given to 6 (67%) and CRT to 1 (11%). In group 2, 8 (62%) had RT and 5 (38%) had CRT. There were no OTVF, local, or regional failures [median follow-up 29 months]. Two-year OS, DFS, and LRC were 100%, 95%, and 100%. SR-QOL showed good recovery (Table). Grade III/IV surgical as well as acute and late toxicities occurred in 2 (9%), 5 (23%), and 1 (5%) respectively. **Conclusions:** TORS evaluation for p16-positive unknown primary SCC allowed RT volume de-intensification with excellent disease control and quality of life. Future randomized trials can compare transoral surgery versus existing diagnostic approaches. MDADI composite scores. Clinical trial information: NCT03281499. Research Sponsor: Surgical Oncology Innovation Fund - Princess Margaret Cancer Center.

mean (SD)	Baseline	Post-Op	End of Treatment	12 month
Cohort (n=22)	93.8 (9.9)	76.8 (16.6)	64.3 (19.6)	85.0 (14.4)
Primary RT (n=11)	97.1 (3.4)	72.8 (19.3)	55.9 (17.8)	86.8 (12.8)
PSRT (n=11)	90.5 (13.0)	80.9 (13.1)	74.5 (17.3)	82.9 (16.4)
UNRT (n=10)	92.7 (12.0)	71.4 (18.8)	62.0 (22.0)	84.7 (15.3)
BNRT (n=10)	97.1 (3.4)	82.5 (12.8)	66.5 (17.7)	86.0 (13.1)

6068 **Poster Session**

Neoadjuvant chemotherapy plus tislelizumab followed by concurrent chemoradiotherapy in patients with locoregionally advanced nasopharyngeal carcinoma: A single-arm, phase II trial. *First Author: Qiu-Yan Chen, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Neoadjuvant treatment with gemcitabine plus cisplatin (GP) prior to concurrent chemoradiotherapy (CCRT) has favorable survival outcomes with acceptable toxicity in patients with locoregionally advanced nasopharyngeal carcinoma (LANPC), 10% of whom achieved complete response (CR) after neoadjuvant treatment. Immune checkpoint blockade therapy plus GP regimen has been shown to improve the survival in recurrent or metastatic NPC. We investigated the efficacy and safety of neoadjuvant treatment with GP plus tislelizumab, an anti-PD-1 monoclonal antibody, in previously untreated LANPC. **Methods:** In this phase II, single-armed Simon two-stage study, eligible patients are of age 18-70, with adequate haematological, renal, and hepatic function, diagnosed with staged III-IVa (AJCC 8th) non-keratinizing LANPC. Enrolled patients received intravenous gemcitabine (1000 mg/m2) on days 1 and 8, cisplatin (80 mg/m2) on day 1, and tislelizumab (200mg) on day 1 every 3 weeks for 3 cycles followed by standard CCRT. The primary endpoint was CR rate after neoadjuvant treatment, using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 by investigator. The secondary endpoints included pathology complete response (pCR) rate, 2-year progress-free survival (PFS), overall survival (OS), locoregional failure-free survival (LRRFS), distant metastasis-free survival (DMFS), and toxicity. This study is registered with ClinicalTrials.gov, NCT04833257, all enrolled patients have finished their treatment and the follow-up is ongoing. **Results:** From April 14th 2021 to August 5th, 2021, a total of 63 patients (median age 46y, 74.6% male) were enrolled at Sun Yat-sen University Cancer Center. As of January 31st, 2022, the median follow-up is 7.37 months, no patients had disease progression. The CR rate after neoadjuvant treatment was 41.3% (95% CI, 28.8% to 53.8%). The ORR and pCR rate were 88.9% (95% CI, 80.9% to 96.9%) and 75.8% (95% CI, 64.8% to 86.8%), respectively. The incidence of acute treatment-related AEs (trAEs) and immune-related adverse events (irAEs) of grade 3 or 4 was 69.8% and 3.2%, respectively. All of irAEs for grade 3 or 4 were hepatotoxicity and skin rash. Long-term efficacy is awaited. **Conclusions:** Neoadjuvant treatment with GP plus tislelizumab achieved impressive CR rate and pCR rate with manageable toxicities. Further follow-up is needed to confirm the long-term efficacy. Clinical trial information: NCT04833257. Research Sponsor: None.

6069 **Poster Session**

TPF induction chemotherapy versus PF adjuvant chemotherapy plus concurrent chemoradiotherapy for locoregionally advanced nasopharyngeal carcinoma: A multicenter, randomized controlled, III trial. *First Author: He Qianyong, Affiliated Hospital of Guizhou Medical University, Guiyang, China*

Background: To investigate the efficacy and safety of the two modes of concurrent chemoradiotherapy combined with induction or adjuvant chronotherapy for the treatment of locoregionally advanced nasopharyngeal carcinoma. **Methods:** A total of 266 patients with locoregionally advanced NPC were enrolled from May 2018 to July 2021 and randomly divided into a test (n = 133) and a control (n = 133) group. In the test group, the docetaxel and cisplatin plus fluorouracil (TPF) regimen was used to induce chronological chemotherapy for 3 cycles (docetaxel 75mg / m2, D1, cisplatin 75mg / m2, d1-d5, fluorouracil 750mg / m2 / D, d1-d5) + 3 cycles of concurrent chemoradiotherapy (cisplatin 100mg / m2; The control group was treated with three cycles of concurrent chemoradiotherapy (cisplatin 100mg / m2) + cisplatin plus fluorouracil (PF) regimen with adjuvant schedule chemotherapy for three cycles (cisplatin 80mg / m2 on days d1-d5, fluorouracil 800mg / m2 / d on days d1-d5). In both groups, intensity-modulated radiation therapy was used with a total dose of 69.96 Gy to the primary tumor at T1 and T2, 72.6 Gy to the primary tumor at T3 and T4, and 69.96 Gy to the positive lymph nodes. Acute adverse effects and survival were compared between the two groups. **Results:** A median follow-up of 19 months, 129 patients in the test group and 124 in the control group were evaluable for efficacy and adverse effects.Compliance was 96.99% and 90.22%, respectively. The 2-year overall survival rates were 91.7% and 90.5%, and the 2-year progression free survival rates were 92.4% and 90.4% in the test and control groups, respectively, with no significant difference ($P > 0.05$). The test group had a lower incidence of radiation mucositis, dry mouth, and dysphagia than the control group ($P < 0.05$), whereas the test group had a higher incidence of leukopenia, neutropenia, hemoglobin loss, vomiting ($P < 0.05$), decreased radiation dermatitis, platelets There were no significant differences in the categories of creatinine elevation and transaminase elevation ($P > 0.05$). **Conclusions:** The patients' compliance was good and the toxic effects such as radiation mucositis, dry mouth and dysphagia were reduced under the treatment mode in which the TPF induced chemotherapy combined with concurrent chemoradiotherapy.Although the toxic effects such as leukopenia, neutropenia, hemoglobin reduction and vomiting were increased, the efficacy was comparable with that of the PF in which the adjuvant schedule chemotherapy combined with concurrent chemoradiotherapy. Clinical trial information: NCT-03574324. Research Sponsor: None.

6070 **Poster Session**

Neoadjuvant nivolumab with or without IDO inhibitor in head and neck squamous cell carcinoma (HNSCC): Final pathologic and clinical outcomes. *First Author: Adam Luginbuhl, Department of Otolaryngology, Thomas Jefferson University, Philadelphia, PA*

Background: Indoleamine 2,3-dioxygenase (IDO) catalyzes the degradation of tryptophan to kynurenine. In order to improve the clinical efficacy of PD-1 inhibition, we designed a novel neoadjuvant trial to test the immunological and therapeutic effects of nivolumab (nivo) and the IDO inhibitor BMS986205 in combination in previously untreated HNSCC utilizing an interim radiographic assessment to determine response treatment prior to surgery. **Methods:** We conducted an investigator-initiated, multi-institutional, two-arm, 3:1 randomized neoadjuvant trial in patients with previously untreated HNSCC of any stage who were candidates for complete surgical resection. Patients were stratified by HPV status. Patients in arm A received 480 mg of nivolumab alone. Subjects in arm B received BMS986205 100 mg po qday beginning 1 week prior to nivolumab 480 mg. Both groups were evaluated at week 5 with CT scans. Radiographic response was evaluated at both the primary site and any involved lymph nodes. Patients with at least a 10% reduction in volume at either the primary or lymph nodes with no evidence of progression continued on to a second cycle of the assigned treatment. Patients with stable disease or progression proceeded to surgery at week 5 without additional study treatment. Imaging, blood and tumor were obtained pretreatment and post treatment and used for immunological correlatives. 2 blinded independent pathologist provided pathologic treatment effect (pTE) scores for primary tumor and lymph nodes. The primary endpoint was radiographic response leading to additional study treatment. **Results:** 42 patients were randomized and completed treatment to the primary endpoint evaluation including 22 HPV+ oropharyngeal HNSCC. Four patients did not proceed with planned surgery: 2 progression, 1 patient preference, and 1 toxicity. 3 patients in Arm B developed hepatitis with 2 subjects having a delay in surgery. 36% of patients (n=4) in Arm A (nivo alone) and 42% of patients (n= 13) in Arm B (nivo+IDO) were considered radiographic responders and continued to a second cycle of therapy (p= 1.0). Pathologic treatment effect (pTE) was significantly higher in subjects who were treated with a second cycle: median of 85% pTE (responders) compared to median of 5% pTE (nonresponders) at the primary site (p=0.018) with 6/16 (38%) subjects in the radiographic responders and 1/20 (5%) in radiographic non-responders demonstrating a CR at the primary site. In the lymph node compartment, the median pTE was 73% compared to 23% in radiographic responders vs non-responders (p=0.04). **Conclusions:** In previously untreated HNSCC, nivolumab +/- IDO inhibitor demonstrated a significantly greater pTE after a second dose in radiographic responders. The addition of IDO-inhibitor to anti-PD1 did not result in a significant increase in radiographic or pathologic response over nivolumab alone. NCT03854032. Clinical trial information: NCT03854032. Research Sponsor: Bristol Myers Squibb.

6071 **Poster Session**

Six-year follow-up from the weekly-three-weekly study comparing cisplatin once-a-week to once-every-three-weeks as concurrent chemoradiation for locally advanced head and neck squamous cell carcinoma. *First Author: Vanita Noronha, Tata Memorial Centre, Mumbai, India*

Background: In the weekly-3-weekly (W3W) study, cisplatin at 100 mg/m^2 once-every-3-weeks led to superior locoregional control compared to cisplatin 30 mg/m^2 once-a-week in combination with radical radiation for locally advanced head and neck squamous cell carcinoma (LAHNSCC). We report the updated analysis of the study. **Methods:** In this phase III open label non-inferiority study conducted between 2013 and 2017, 300 patients with LAHNSCC were randomly assigned to receive cisplatin 100 mg/m^2 once-in-3-weeks or cisplatin 30 mg/m^2 once-a-week, concurrently with radiation. The primary endpoint was locoregional control. Secondary outcomes included progression free survival (PFS), overall survival (OS), toxicity, and quality of life. **Results:** As of February 5, 2022 (median follow-up, 77.3 months), 132 patients (44%) have had an event for locoregional recurrence; 75 (50%) in the once-a-week cisplatin arm and 57 (38%) in the once-every-3-weeks cisplatin arm. The updated estimated cumulative 2-year locoregional control rates were 59.3% and 75.3% in the once-a-week and once-every-3-weeks cisplatin arms, respectively; absolute difference, 16% (95% CI, 7.19 to 24.81). The estimated 5-year locoregional control rates were 48.2% and 55.2% in the once-a-week and once-every-3-weeks cisplatin arms respectively; absolute difference, 7% (95% CI, -2.5 to 16.5). The median time to locoregional failure was 46.1 months (95% CI, 31.63 to 60.56) in the once-a-week cisplatin arm, and 57.9 months (95% CI, 47.1 to 68.6) in the once-every-3-weeks cisplatin arm; HR, 1.43 (95% CI, 1.01 to 2.02); P = 0.042. The estimated median PFS was 17.5 months (95% CI, 0 to 38.31) in the once-a-week cisplatin arm, versus 37.5 months (95% CI, 28.45 to 46.45) in the once-every-3-weeks cisplatin arm; HR, 1.13 (95% CI, 0.85 to 1.5); P = 0.41. Events for OS included 173 (57.7%) deaths; 109 (36.3%) patients are alive, and 18 (6%) are lost to follow-up. The 5-year OS in the once-a-week and once-every-3-weeks cisplatin arms were 43.1% and 48.6%, respectively. Estimated median OS was 38.5 months (95% CI, 16.3 to 60.7) in the once-a-week cisplatin arm, versus 57.3 months (95% CI, 38.6 to 75.9) in the once-every-3-weeks cisplatin arm; HR, 1.19 (95% CI, 0.89 to 1.6); P = 0.238. Details regarding chronic toxicities and second primaries will be presented. **Conclusions:** Long term follow-up confirms that cisplatin at 100 mg/m^2 administered once-every-3-weeks concurrently with radical radiation for LAHNSCC leads to superior locoregional control and should remain the standard of care. The study was not powered to test for a difference in OS; OS was numerically higher in the once-every-3-weeks cisplatin arm, but the difference did not attain statistical significance. Clinical trial information: CTRI/2012/10/003062. Research Sponsor: Tata Memorial Center Research Administration Council.

6072 **Poster Session**

Preoperative durvalumab (D) with or without tremelimumab (T) for resectable head and neck squamous cell carcinoma (HNSCC): Updated results with high dimensional profiling of circulating immune cells. *First Author: Chang Gon Kim, Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea*

Background: Although PD-1 blockade has improved survival in patients with recurrent and/or metastatic HNSCC, safety and efficacy of neoadjuvant immunotherapy with PD-L1 inhibitor with or without CTLA-4 inhibitor has not been investigated. Here, we report the updated results of the safety and efficacy of a preoperative D with or without T (D+/-T) in patients with resectable HNSCC, accompanied with high dimensional profiling of circulating immune cells. **Methods:** Patients with locally advanced but resectable HNSCC were eligible. Enrolled patients were randomized into D or D+T, stratified by primary site and human papilloma virus (HPV) infection status. A single dose of preoperative D (1500mg) or D+T (1500mg+75mg) was administered, with surgery planned 2 to 8 weeks later for curative resection. Postoperative (chemo) radiation was prescribed based on standard guidelines, followed by maintenance with D every 4 weeks for 1 year. Dynamic changes in circulating immune cells were tracked with mass cytometry. The primary objective was to determine the local recurrence rate. Secondary endpoints included pathologic response, safety, survival outcome, and exploration of immune dynamics. **Results:** As of January 25th 2022 for the interim analysis, a total of 45 patients were completely enrolled and received surgical resection (D: 21 patients, D+T: 24 patients). Oropharyngeal cancer was most common (n = 23; 51.1%) and HPV-mediated cancer was observed in 20 patients (44.4%). Neoadjuvant D+/-T had acceptable safety profiles and was not associated with delays in surgery or unexpected adverse events. Tumor shrinkage was observed in 31 patients (68.9%), with 15.6% of average tumor shrinkage (range; 100.0% to -80.0%). Major pathologic response (no more than 10% of viable tumor cells) was achieved in 3 patients (6.7%), including 2 cases with pathologic complete response (4.4%). During median follow-up duration of 407 days after surgery, local recurrence and systemic recurrence were documented in 9 patients (20.0%) and 7 patients (15.6%), respectively. Median disease-free survival and overall survival was 910 days and not reached, respectively. High dimensional immune profiling with mass cytometry revealed that D+T disproportionally increased the frequency of regulatory T cells accompanied with the upregulation of their functional markers, which was absent in patients treated with D monotherapy. **Conclusions:** These updated data suggested that preoperative D+/-T was safe and feasible and had the potential to provide clinical benefits for patients with resectable HNSCC. Distinct immunologic changes in circulating immune cells were induced by each treatment regimen, warranting further investigation. The trial is ongoing and the updated outcomes with immune correlates will be presented in this ASCO. Clinical trial information: NCT03737968. Research Sponsor: None.

6073 **Poster Session**

Phase III randomized control study evaluating adjuvant metronomic chemotherapy in locally advanced head and neck cancers post-radical chemoradiation (MACE-CTRT). *First Author: Sunil Chopade, Tata Memorial, Mumbai, India*

Background: Locally advanced head and neck cancer treated with radical chemoradiation have unsatisfactory outcomes. Oral metronomic chemotherapy improves outcomes in comparison to maximum tolerated dose chemotherapy in the palliative setting. There is also limited evidence that it may do so in an adjuvant setting. Hence this randomised study was conducted. **Methods:** Patients of HN cancer with primary in oropharynx, larynx or hypopharynx, with PS 0-2 post radical chemoradiation with documented complete response were 1:1 randomised to either observation or oral metronomic adjuvant chemotherapy (MAC) for 18 months. MAC consisted of weekly oral methotrexate (15 mg/m2) and celecoxib (200 mg PO BD). The primary endpoint was OS and the overall sample size was 1038. The study had 3 planned interim analyses for efficacy and futility. **Results:** 137 patients were recruited and an interim analysis was done. The 3 year PFS in the observation arm was 67.1% (95% CI 53.8-77.3) and the same in the MAC arm was 62.5%(95%CI 49.4-73.1). The corresponding hazard ratio was 1.402 (95% CI 0.7393-2.66, P-value = 0.3). The 3 year OS in the observation arm was 77.3% (95% CI 64.4-86) and the same in the MAC arm was 64.1% (95%CI 51-74.5). The corresponding hazard ratio was 1.588 (95% CI 0.8734-2.886, P-value = 0.1). Any grade mucositis was seen in 30 patients (45.5%) in the MAC arm and 20 patients (28.2%) in the observation arm (P-value = 0.05). The rate of grade 3 or above mucositis was 7.6%(n = 5) in the MAC arm and 1.4%(n = 1) in the observation arm (P-value = 0.106). **Conclusions:** Both arms had similar OS. Hence observation post complete response post radical chemoradiation remains the standard of care. Clinical trial information: CTRI/2016/09/007315. Research Sponsor: Tata Memorial Center Research Administration Council.

6074 **Poster Session**

Recurrence pattern after chemoradiotherapy for HPV-associated oropharyngeal squamous cell carcinoma with respect to induction chemotherapy and escalated radiation dose-results from a prospective randomized phase II study. *First Author: Signe Friesland, Dep. of Oncology, Karolinska Institute, Stockholm, Sweden*

Background: Patients with HPV associated squamous cell carcinoma of the oropharynx have a favorable outcome with respect to tumor control and overall survival (OS) after treatment with chemoradiotherapy (CRT). The leading cause of death in these patients is reported to be peripheral metastases. Because of the favorable outcome for these patients, the medical community tries to find methods to ameliorate treatment intensity, mainly in order to reduce long term morbidity. However, between 10 and 15 % of patients relapse locally in the primary tumor as first site of disease failure. **Methods:** In this multicentre, randomized, controlled, phase II trial 152 patients with locoregionally advanced oropharyngeal cancer were randomized in a 1:1 ratio to either radiotherapy with cetuximab (arm B) versus the same regimen preceded by 2 cycles of induction chemotherapy (IC) with taxotere/cisplatin/5-FU (arm A). To decrease risk of local failure, an escalated radiation (RT) dose of 74.8 Gy was delivered to T3/T4 tumors and to T2 tumors > 3 cm in the base of tongue. Eligibility criteria included patients 18-75 years, ECOG performance status 0-1 and adequate organ functions. Primary endpoint of the study was to compare PFS between the treatment arms, secondary objectives were recurrence pattern, locoregional control, OS and toxicity. **Results:** PFS at 2 years was 84.2% (95%CI 76.4-92.8) in arm A and 78.4 (95%CI 69.5-88.3) in arm B (p = 0.20). At the time of analysis there were 26 disease failures, 9 in arm A and 17 in arm B. In arm A there were 3 local, 2 regional and 4 distant relapses as first site of recurrence, and in arm B 4, 4 and 9 relapses in corresponding sites. Local relapse rate as first site of failure was low, i.e. in 4.7%. Local failures constituted 7 relapses out of all 26 (27%), and in 4 of these local failures (57%), the escalated dose was given. In arm B, patients who had no IC, there were more than twice as many patients who had distant metastases as first site of relapse compared to arm A (n.s.). No patient who had a response to IC in the primary tumor or in regional lymph nodes, respectively, measured with CT or MRI, of either CR+CR or CR+PR, had any recurrence, local, regional or distant. So, IC could identify 22 out of 73 evaluable patients (30%) in arm A, who never had any recurrence during follow up. **Conclusions:** A high incidence of distant metastases as first site of failure is recognized while local failure rate is low. However, despite a high RT dose of 74.8 Gy, delivered to the primary tumor, relapses can appear in this site. Radiological response of tumor to IC could identify patients with no tumor relapse, at least within the first years of follow up, possible candidates for de-escalation treatment protocols. Clinical trial information: 2009-013438-26. Research Sponsor: None.

6075 **Poster Session**

Nivolumab-based induction chemoimmunotherapy and PD-L1 expression in locoregionally advanced HPV-associated oropharyngeal squamous cell carcinoma. *First Author: Ari Rosenberg, University of Chicago, Department of Medicine, Chicago, IL*

Background: Blockade of the PD-1/PD-L1 immune checkpoint improves survival in recurrent/metastatic head and neck cancer. PD-L1 expression is a biomarker that enriches for clinical benefit with anti-PD-1 therapy alone or in combination with chemotherapy in this setting. The role of PD-L1 expression as a predictive biomarker in locoregional human papillomavirus associated (HPV+) head and neck cancer (HNC) treated with induction nivolumab-based chemoimmunotherapy is unknown. We evaluate PD-L1 expression and response to induction chemoimmunotherapy in the context of an investigator initiated trial, OPTIMA II. **Methods:** Patients with locoregionally advanced HPV+ HNC were enrolled to the prospective OPTIMA II study evaluating induction chemoimmunotherapy followed by response adaptive de-escalated locoregional therapy. Induction therapy consisted of nivolumab, nab-paclitaxel, and carboplatin, for three cycles. Anatomic imaging of the head and neck with either CT or MRI was obtained at baseline and following induction therapy. Expression of PD-L1 was assessed by immunohistochemistry on baseline biopsies and calculation of tumor proportion score (TPS) and combined positive score (CPS) was performed. Response is defined as percentage of tumor shrinkage per RECIST 1.1 criteria. Deep response rate is defined as the proportion of patients with > = 50% tumor shrinkage. Kruskal-Wallis and Mann-Whitney tests were used for analysis. **Results:** Twenty-nine patients (pts) underwent evaluation of PD-L1 expression and started treatment with induction chemoimmunotherapy. Median age 61 (range 37-81), smoker > 20 pack years in 24%, tonsil primary in 79%, and HPV16 subtype in 97%. The median response following induction was 63% (range 29% to 100%). PD-L1 TPS scores were < 1, 1-19, and > = 20 in 28%, 34%, and 38% respectively. PD-L1 CPS scores were < 20 and > = 20 in 55% and 45% respectively. Median response among PD-L1 TPS of < 1, 1-19, and > = 20 was 49%, 59%, and 66% respectively (p = 0.16). Among PD-L1 CPS of < 20 and > = 20, median response was 57% and 69% respectively (p = 0.11). The deep response rate among PD-L1 CPS < 20 and > = 20 was 69% and 77% respectively. **Conclusions:** Deep responses were observed following induction chemoimmunotherapy in locoregionally advanced HPV+ HNC. There was a non-significant increase in median response and deep response rate with higher expression of PD-L1. Evaluation of PD-L1 expression as a biomarker for response with induction chemoimmunotherapy is worthy of further investigation in locoregional HPV+ disease. Clinical trial information: NCT03107182. Research Sponsor: Bristol Myers Squibb.

6076 **Poster Session**

Factors associated with adherence to remote patient monitoring for early detection of dehydration risk during radiation treatment for head and neck cancer. *First Author: Sarah Phillips, Eastern Virginia Medical School, Norfolk, VA*

Background: Remote patient monitoring (RPM) may improve the early detection and mitigation of cancer treatment-related complications, health-related outcomes and quality of life. RPM's success may depend, in part, on patients' adherence to remote monitoring protocols. However, factors that influence adherence to RPM are largely unknown. Daily blood pressure/pulse (BP/P), weight, and electronic patient-reported outcomes (ePROs) were monitored remotely in head and neck cancer (HNC) patients undergoing radiation treatment (RT) to identify dehydration risk. We evaluated potential factors associated with RPM adherence. **Methods:** During RT (average 6 to 7 weeks), participants were asked to take daily (Monday-Friday) measures of BP/P and weight using Bluetooth-enabled devices and to complete daily ePROs using a mobile tablet application (app). Data were provided to their physicians for daily review. The MD Anderson Symptom Inventory-Head and Neck (MDASI-HN) was completed at baseline and end of RT, and 6-8 weeks post-RT completion. The Patient Activation Measure (PAM) was completed at baseline and 6-8 weeks post-RT completion. A device usability survey measuring perceived usefulness of RPM was completed at the end of RT. Adherence to daily monitoring was recorded objectively. Longitudinal analyses compared the relationship between demographic, clinical, and PRO data and monitoring adherence. **Results:** Participants (n = 169) were 80% male, 87% White, and 91% married. Overall adherence to monitoring BP/P, weight, and ePROs was 83%, 82% and 74%, respectively. Greater HN-specific symptom severity and interference was associated with decreased adherence to daily monitoring of BP/P, weight, and ePROs (P< 0.021). Higher PAM scores were associated with higher adherence to daily monitoring of BP/P only (p = 0.006). Participants reported modest levels of perceived usefulness of RPM across four categories: symptom management, early problem detection, illness monitoring by healthcare provider, and feeling of security during RT. Only a single item indicating perceived feeling of security was associated with greater adherence to daily monitoring of blood pressure/pulse (p = 0.032) and weight (p = 0.007). **Conclusions:** A benefit of frequent RPM may be early detection and mitigation of symptoms during RT for HNC, however, increasing symptom burden experienced during treatment may interfere with adherence to daily monitoring. Better adherence may be attributed to patients perceiving a sense of security from daily monitoring and may suggest a potentially important value that patients gain from RPM. Understanding factors that impact patient adherence to RPM may help improve acceptability and clinical utility of RPM in oncology. Clinical trial information: NCT02253238. Research Sponsor: U.S. National Institutes of Health.

6077 **Poster Session**

Outcomes by tobacco history in E3311, a phase II trial of transoral surgery (TOS) followed by pathology-based adjuvant treatment in HPV-associated (HPV+) oropharynx cancer (OPC): A trial of the ECOG-ACRIN Cancer Research Group. *First Author: Ranee Mehra, Greenebaum Comprehensive Cancer Center, University of Maryland, Baltimore, MD*

Background: E3311 is a phase II randomized study which showed favorable outcomes among intermediate (INT) risk HPV+ OPC patients (pts) who underwent TOS followed by pathology-guided or adapted, deintensified adjuvant treatment. Among HPV+ pts treated with definitive chemoradiation, survival outcomes are worse among those who smoked > 10 pack years (pk-yrs). **Methods:** We retrospectively analyzed demographics, pathologic results, and efficacy outcomes from E3311 by smoking group (current (C) vs. former (F) and > 10 vs. ≤10 pk-yrs the latter a pre-specified stratification factor for INT patients). Binary and categorical variables were compared using a chi-square test (or Fisher s exact test for small sample sizes). Ordinal variables were compared using a Wilcoxon rank sum test. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method and compared using a log-rank test. **Results:** Among 359 evaluable pts, performance status (PS) was significantly worse for pts with > 10 pk-yrs vs. ≤10 pk-yrs (15.4% vs. 7.9% with PS of 1, p = 0.034). Primary site, margin status, histologic grade, stage, and extranodal extension were not significantly different between the groups of > 10 vs. ≤10 pk-yrs. Smoking status (F vs. C) was available for 182 pts with a history of smoking. Slightly more C vs. F smokers had tonsil as primary site (79.5% vs. 65.0%, p = 0.09). Positive margins were significantly more frequent among C smokers (10.3% vs. 2.1%; p = 0.029). Overall, there were no significant differences in PFS (p = 0.55) or OS (p = 0.94), comparing those with > 10 vs. ≤10 pk-yrs, or comparing C vs. F smokers (p = 0.76, p = 0.82, respectively). Similarly, no significant differences were observed within the treatment arms. (Table 1) **Conclusions:** In this analysis of smoking status in E3311, INT risk HPV+ OPC pts who are C smokers or have a history of > 10 pk-yrs had favorable 3-yr PFS and OS rates that were not significantly worse than those with < 10 pk-yrs history. This data represents the first treatment approach for HPV+ OPC in which outcomes were not influenced by smoking status. Clinical trial information: NCT01898494. Research Sponsor: U.S. National Institutes of Health.

	Smoking History (pk-yrs)	N (pts)	3-yr PFS (%), 90% CI	3-yr OS (%), 90% CI
All evaluable pts, N = 356*	> 10	104	95.5, (91.9%, 99.2%)	96.8, (93.8%, 99.8%)
	< 10	252	92.5, (89.7%, 95.3%)	95.4, (93.1%, 97.6%)
Arm A	> 10	7	100%	100%
	≤ 10	30	96, (90%, 100%)	96, (91%, 100%)
Arm B	> 10	33	97 (92%, 100%)	100
	≤ 10	67	94 (89%, 99%)	99, (96%, 100%)
Arm C	> 10	30	95, (88%, 100%)	96, (90%, 100%)
	≤ 10	78	93, (88%, 98%)	95, (90%, 99%)
Arm D	> 10	34	93, (86%, 100%)	93, (85%, 100%)
	≤ 10	77	90, (84%, 96%)	93, (89%, 98%)
Known Smoking status, N = 182	Current (C)	39	93.8, (87.2%, 100%)	94.3, (88.0%, 100%)
	Former (F)	143	94.7, (91.6%, 98.0%)	95.6, (92.7%, 98.5%)

*3 pts missing smoking history data.

6078 **Poster Session**

Phase 2 pilot trial of RRx-001 as an anti-mucositis agent in patients with head and neck cancer treated with chemoradiation (PREVLAR). *First Author: Marcelo Raul Bonomi, James Cancer Hospital Solove Research Institute, The Ohio State University, Columbus, OH*

Background: Severe oral mucositis (SOM) is a dose limiting toxicity during radiotherapy and cisplatin for head and neck cancers. The aim of this 4-arm randomized controlled pilot trial was to evaluate the efficacy of different schedules of a novel radioprotectant, RRx-001 versus standard-of-care (SOC), to reduce duration, time to onset and incidence of SOM in patients received cisplatin-based chemoradiotherapy (CRT) for oral cavity or oropharyngeal cancer (OCC). **Methods:** Patients with locally advanced OCC treated with definitive or postoperative CRT were randomized to receive RRx-001 by 15-minute intravenous infusion in one of three different schedules versus none. The days and severity of mucositis were prospectively evaluated. Oral mucositis was assessed weekly during and after CRT as well as 28 days after completion. The pre-specified efficacy endpoints were duration of grade 3-4 SOM, resolution of SOM, time to onset of SOM and incidence of SOM. **Results:** A total of 53 patients were enrolled between June 2018 and July 2019 across 11 institutions. Forty-five (out of 53) patients received study drug and were efficacy evaluable. RRx-001 were well tolerated with no associated serious adverse events. All RRx-001 arms numerically outperformed SOC on the pre-specified efficacy measures, and the greatest effect estimate was observed on Arm 1 (RRx-001 pretreatment only + CRT). The following endpoints favored treatment with RRx-001. Median SOM duration by treatment was 22 and 40 days for Arm 1 and SOC respectively. Time to onset of SOM was by 38 days (Arm 1) vs. 26 days (SOC). On Arm 1, 83% of patients had SOM resolution vs 60% on SOC). Gastrostomy requirement was reduced by 45%. No patients on Arm 1 developed grade 4 mucositis vs 30% developed grade 4 mucositis on the SOC arm. Furthermore, the incidence of oropharyngeal dysphagia, which can substantially impair nutrition, was reduced by treatment with RRx-001, occurring at 50% vs 70% for Arm 1 vs SOC respectively. Treatment with RRx-001 resulted in highly significant decrease in the duration of SOM through 60 Gy with a median SOM of 1 day vs 17 days for Arm 1 vs SOC respectively (Wilcoxon rank-sum test p < 0.001). Median cumulative cisplatin dose was significantly greater for RRx-001 Arm 1 than SOC (557.4 mg vs. 438 mg, Wilcoxon p = 0.025). **Conclusions:** Compared with SOC, SOM among RRx-001-treated patients given 3 different treatment schedules was less severe, of shorter duration, demonstrated delayed time to onset and resolved earlier. Overall, the incidence, duration and severity of SOM and dysphagia was reduced. The safety profile of RRx-001 was similar to SOC. These results will inform the design of a Phase 3 pivotal study of RRx-001 in the prevention of SOM in at-risk cancer patients. Clinical trial information: NCT03515538. Research Sponsor: EpicentRx Inc.

6079 **Poster Session**

Yatagarasu: A single-arm, open-label, phase 2 study of apalutamide (APA) plus goserelin (GOS) for patients (pts) with far locally advanced or recurrent/metastatic (fLA/RM) and androgen receptor (AR)-expressing salivary gland carcinoma (SGC). *First Author: Yoshitaka Honma, Department of Head and Neck, Esophageal Medical Oncology, National Cancer Center Hospital, Tokyo, Japan*

Background: Overexpression of AR is identified as a potential molecular target of SGC treatment. Combined androgen blockade (CAB) with bicalutamide has been evaluated previously, but the clinical usefulness of CAB with a next generation AR inhibitor has been unclear in SGC. We prospectively assessed the efficacy and safety of APA+GOS for pts with AR-expressing SGC. **Methods:** Eligible pts had fLA/RM SGC, and AR expression with at least 1% of cell nuclei immunohistochemistry staining positive. Pts were treated with APA 240 mg orally once daily and GOS 3.6 mg subcutaneously once 28 days. Primary endpoint was overall response rate (ORR) by central review according to RECIST v1.1, and a response (complete response [CR] or partial response [PR]) was confirmed by repeat assessments at least 4 weeks after the initial evaluation showing a response. Primary analysis was performed based on first 24 response evaluable (RE) pts who had been observed at least 24 weeks (Primary RE pts). The ORR was tested using exact test based on the binominal distribution, the null hypothesis for ORR of 14% was rejected when at least 8 of the 24 Primary RE pts were responders, and the efficacy was to be declared. Key secondary endpoints included clinical benefit rate (CBR), disease control rate (DCR), duration of response (DOR), and time to response (TTR) in the Primary RE pts, and overall survival (OS), progression free survival (PFS), and safety in the treated pts. **Results:** Twenty-six of the 31 pts treated with APA+-GOS were regarded as RE by central review. For the 24 Primary RE pts, ORR was 25.0% (6/24), while 37.5% (9/24) including unconfirmed PR. Clinical benefit rate and DCR in the Primary RE pts were 50.0% and 70.8%, respectively. At the data cut-off (Apr 28, 2021), 5 of 6 pts with confirmed response were still on protocol treatment. Median PFS and OS in the treated pts were 7.43 months (mos) and not reached, respectively, with the median follow-up period of 8.57 mos. Grade 3 or higher treatment-related adverse events were reported in 4/31 (12.9%) pts, and the events were rash maculo-papular (n=2), anemia (n=1), and leukopenia (n=1). **Conclusions:** This is the first prospective trial evaluating CAB with APA for AR-expressing SGC. Although this study did not meet the predefined criteria of efficacy, clinically meaningful activity with well-tolerated safety profile of APA+GOS was shown. Clinical trial information: NCT04325828. Research Sponsor: Janssen Pharmaceutical K.K.

	Primary RE pts (N=24)
CR, n (%)	0
PR, n (%)	6 (25.0)
SD, n (%)	11 (45.8)
PD, n (%)	7 (29.2)
ORR, n (%), (95% CI)	6 (25.0) (9.8, 46.7)
CBR (CR, PR, and SD ≥24 weeks), n (%), (95% CI)	12 (50.0) (29.1, 70.9)
DCR (CR, PR, and SD), n (%), (95% CI)	17 (70.8) (48.9, 87.4)
DOR, median mos (95% CI)	NE (6.64, NE)
TTR, median mos (range)	1.87 (1.7, 3.7)

NE = not estimable, SD = stable disease.

6080 **Poster Session**

Pralsetinib in patients (pts) with advanced or metastatic *RET*-altered thyroid cancer (TC): Updated data from the ARROW trial. *First Author: Aaron Scott Mansfield, Mayo Clinic, Rochester, MN*

Background: Alterations in *RET* are targetable oncogenic drivers in TC. Pralsetinib is a highly potent, selective RET inhibitor, with demonstrated efficacy in pts with *RET*-altered TC. In a previous analysis of the Phase I/II ARROW trial (NCT03037385; data cutoff: 22 May 2020), overall response rates [ORR; measurable-disease population] with pralsetinib at 400 mg once daily (QD) were 60% (33/55) and 71% (15/21) in pts with *RET*-mutant medullary TC (*RET*-mutant MTC) who had received prior multikinase inhibitors cabozantinib and/or vandetanib (C/V), and those who were treatment naïve, respectively, and 89% (8/9) in pts with previously treated *RET* fusion-positive TC (*RET*-fp TC). Here we report an updated analysis of these cohorts in the intention-to-treat (ITT) population. **Methods:** Adult pts with *RET*-altered locally advanced/metastatic TC who had enrolled in ARROW and initiated pralsetinib at 400 mg QD, were included. Phase II primary endpoints: ORR (by blinded independent central review, per RECIST v1.1) and safety. Efficacy endpoints for this analysis were assessed in the ITT population. Safety was assessed in all pts with *RET*-altered TC who initiated pralsetinib at 400 mg QD. Enrolment cutoff: 23 August 2020 for the ITT population; data cutoff: 12 April 2021. **Results:** The ITT population comprised 145 pts with *RET*-mutant MTC (with or without prior systemic therapy, including C/V) and 22 pts with *RET*-fp TC, 21 of whom had received prior systemic therapy (including multikinase inhibitor[s] and/or radioactive iodine). In pts with *RET*-mutant MTC who had received prior C/V (n = 67), ORR was 51% (34/67; 95% CI 38–63; 2 complete responses [CR]; 32 partial responses [PR]), median duration of response (DoR) was 25.8 months (95% CI 18.0–not reached [NR]) and median progression-free survival (PFS) was 24.9 months (95% CI 19.7–31.2). In treatment-naïve pts with *RET*-mutant MTC, ORR was 72% (48/67; 95% CI 59–82; 4 CR; 44 PR), and median DoR and median PFS were not reached. In pts with previously treated *RET*-fp TC, ORR was 86% (18/21; 95% CI 64–97; 3 CR; 15 PR), median DoR was 17.5 months (95% CI 16.0–NR) and median PFS was 19.4 months (95% CI 13.0–NR). Median overall survival (OS) was not reached in any of the cohorts. The safety population comprised 172 pts with *RET*-altered TC treated at 400 mg QD. The most common treatment-related adverse events (TRAEs) were increased aspartate aminotransferase (n = 67; 39%), anemia (n = 60; 35%), hypertension (n = 57; 33%) and decreased white blood cell count (n = 52; 30%). Serious TRAEs were reported in 27 pts (16%); the most frequent was pneumonitis (n = 5; 3%). Nine pts (5%) discontinued pralsetinib due to a TRAE and one patient (< 1%) died due to a TRAE (*pneumocystis jirovecii* pneumonia) following 44 days (< 3 cycles) on pralsetinib. **Conclusions:** In this updated analysis including more pts, pralsetinib continues to be efficacious with a manageable safety profile in pts with *RET*-altered TC. Clinical trial information: NCT03037385. Research Sponsor: F. Hoffmann-La Roche Ltd and Blueprint Medicines.

6081 **Poster Session**

Cabozantinib versus placebo in patients (pts) with radioiodine-refractory (RAIR) differentiated thyroid cancer (DTC) who progressed after prior VEGFR-targeted therapy: Outcomes in prespecified subgroups based on histology subtypes. *First Author: Jaume Capdevila, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Universitat Autònoma de Barcelona, Barcelona, Spain*

Background: DTC comprises multiple histology subtypes, the most common being papillary and follicular. Based on results of the phase 3 COSMIC-311 trial, the multikinase inhibitor cabozantinib was recently approved by FDA for the treatment of pts with RAIR DTC who progressed after prior VEGFR-targeted therapy (Brose et al. 2021). In an extended follow-up, median (m) progression-free survival (PFS) was 11 months (mo) for cabozantinib vs 1.9 mo for placebo (HR 0.22, 96% CI 0.15–0.32, *P*< .0001) in the intent-to-treat (ITT) population (Capdevila et al. ESMO 2021. Abstr LBA67). Here we present outcomes for prespecified subgroups based on the baseline histology subtypes of papillary and follicular thyroid cancers. **Methods:** Pts were randomized 2:1 to cabozantinib (60 mg QD) or placebo. Placebo pts could cross over to open-label cabozantinib upon disease progression per blinded independent radiology committee (BIRC). Primary endpoints were PFS (ITT) and objective response rate (ORR, first 100 randomized pts), per RECIST v1.1 assessed by BIRC. **Results:** After a median follow-up of 10.1 mo, 258 pts (170 cabozantinib, 88 placebo) had been randomized (data cutoff 8 Feb 2021); 150 pts (96 cabozantinib, 54 placebo) had papillary thyroid cancer (PTC) and 113 pts (78 cabozantinib, 35 placebo) had follicular thyroid cancer (FTC), with the PTC and FTC subgroups each including 5 pts with both PTC and FTC. Sixty-three pts (~56%) within the FTC subgroup had Hurthle cell and poorly differentiated variants. mPFS was 9.2 mo for cabozantinib vs 1.9 mo for placebo in the PTC subgroup (HR 0.27, 95% CI 0.17–0.43) and 11.2 mo vs 2.6 mo in the FTC subgroup (HR 0.18, 95% CI 0.10–0.31). The mPFS was 11.1 mo for cabozantinib and 1.9 mo for placebo for pts with Hurthle cell and poorly differentiated variants (HR 0.12, 95% CI 0.05–0.27). The ORR was 15% for cabozantinib vs 0% for placebo in the PTC subgroup and 8% vs 0% in the FTC subgroup. Median duration of cabozantinib exposure was 5.5 mo for the PTC subgroup and 7.3 mo for FTC. Grade 3/4 treatment-emergent adverse events (TEAE) in the cabozantinib arm occurred in 59% of pts in the PTC subgroup and 68% of pts in the FTC subgroup; discontinuations due to TEAE occurred in 17% and 15% of pts, respectively. **Conclusions:** In the extended follow-up, cabozantinib maintained superior efficacy vs placebo irrespective of histology subtype, including the aggressive Hurthle cell and poorly differentiated variants. The moderately higher rates of grade 3/4 TEAE in the FTC vs the PTC subgroup could be attributed to the longer median duration of exposure of cabozantinib in the FTC subgroup. Clinical trial information: NCT03690388. Research Sponsor: Exelixis, Inc.

6082 **Poster Session**

Impact of intensive multimodal treatment on the outcomes of patients with anaplastic thyroid cancer. *First Author: Firas Baidoun, Department of Hospital Medicine, Cleveland Clinic, Cleveland, OH*

Background: Anaplastic thyroid cancer (ATC) is a rare and aggressive type of thyroid malignancy with very poor prognosis and outcome despite therapy. The rarity of this disease and the poor functional status of ATC patients limit the ability to conduct clinical trials, thus there is a lack of large, controlled trials to guide treatment and evaluate the benefit of combined modality therapy. **Methods:** The National Cancer Database (NCDB) was queried for patients diagnosed with ATC at age 18 or older between 2004 and 2018. After excluding patients with unknown number of treatment modalities, Charlson-Deyo score of 3 or more and patients lost follow-up, we split the cohort into three groups according to the number of treatment modalities they received. Treatment modalities include surgery, radiation, and systemic therapy. Then, we evaluated the overall survival (OS) between the three groups. We studied the OS using Kaplan-Meier estimates and multivariate cox regression analyses to evaluate factors associated with OS. Additionally, propensity score matching (accounting for age, gender, race, Charlson-Deyo score, and clinical M stage) was used for more robust results. **Results:** A total of 3,460 patients with ATC were included in the analysis, of which 1,472 (42.5%) either received one type of therapy or did not receive any therapy (group1), 1,092 (31.6%) received bimodal therapy (group 2), and 896 (25.9%) received trimodal therapy (group 3). We found that group 3 had better OS compared to group 1 and group 2 (median OS 9.1 months vs 1.7 months and 4.9 months, respectively with P < 0.001 for all). Propensity score matching yielded 896 patients in each group. We found that group 3 had better OS compared to group 1 and group 2 (median OS 9.1 months vs 1.9 months and 5.2 months, respectively with P < 0.001 for all). Same trend was found in subgroup analysis when we split the cohort according to the metastatic status; in M0 group (median OS was 10.4 months vs 1.9 months and 6.1 months, respectively with P < 0.001 for all), in M1 group (median OS was 5.9 months vs 1.4 months and 3.7 months, respectively with P < 0.001 for all). On multivariate analysis, group 1 and group 2 were associated with worse OS compared to trimodal treatment (HR 2.721; 95% CI: 2.466 - 3.002 and HR 1.434; 95% CI: 1.299 - 1.582, P < 0.001 for all). **Conclusions:** Patients with ATC who were treated with intensive trimodal therapy had statistically significant improvement in OS compared to patients who received less intense therapy. This survival benefit was observed in both metastatic and non-metastatic groups. While we acknowledge the limitations of this retrospective analysis, our results showed the critical role of intensive therapy approach in this aggressive malignancy. Research Sponsor: None.

6083 **Poster Session**

Cabozantinib (C) versus placebo (P) in patients (pts) with radioiodine-refractory (RAIR) differentiated thyroid cancer (DTC) who have progressed after prior VEGFR-targeted therapy: Outcomes in prespecified subgroups based on prior VEGFR-targeted therapy. *First Author: Jorge Hernando, Medical Oncology Department. Vall Hebron University Hospital, Vall Hebron Institute of Oncology (VHIO), Barcelona, Spain*

Background: Based on the results of the phase 3 COSMIC-311 trial, the multikinase inhibitor C was recently approved by the FDA for the treatment of RAIR DTC pts who progress after prior VEGFR-targeted therapies, such as lenvatinib (L) or sorafenib (S), and for whom there was no standard of care (Brose et al. *Lancet Oncol.* 2021). In an extended follow-up of the intent-to-treat (ITT) population, C-treated pts achieved a median (m) progression-free survival (PFS) of 11 months (mo) vs 1.9 mo with P (HR 0.22, 96% CI 0.15–0.32, *P* < .0001); here we present outcomes for prespecified subgroups who received prior L, S, or both. **Methods:** Pts were randomized 2:1 to C (60 mg QD) or P. P pts could cross over to open-label C upon disease progression per confirmation by blinded independent radiology committee (BIRC). The primary endpoints were PFS (ITT) and objective response rate (first 100 randomized pts), per RECIST v1.1 by BIRC. Pts must have received L or S and progressed during or after 1–2 prior VEGFR inhibitors. **Results:** After a median follow-up of 10.1 mo, 258 pts (170 C, 88 P) had been randomized (data cutoff 8 Feb 2021); 96 (~37%) had received prior S (no L), 102 (~40%) prior L (no S), and 60 (~23%) prior S and L. Median PFS was 16.6 for C vs 3.2 mo for P in prior S (no L) (HR 0.13, 95% CI 0.06–0.26); 5.8 vs 1.9 mo in prior L (no S) (HR 0.28, 95% CI 0.16–0.48), and 7.6 vs 1.9 mo in prior S and L (HR 0.27, 95% CI 0.13–0.54). In the C arm, 21% of pts in prior S (no L), 3% in prior L (no S), and 8% in S and L subgroups had confirmed partial response, and 1 pt had a confirmed complete response in prior L (no S); there were no responses with P. Stable disease as best response was 67% for C vs 45% for P in prior S (no L), 68% vs 32% in prior L (no S), and 74% vs 38% in prior S and L. Median duration of C-exposure was 7.0 mo in prior S (no L), 5.6 mo in prior L (no S) and 5.9 mo in prior S and L. Grade 3/4 treatment-emergent adverse events (TEAE) occurred in 63% pts in prior S (no L), 57% in prior L (no S), and 69% in prior S and L. Discontinuations of C due to TEAE occurred in 16% of pts in prior S (no L), 13% in prior L (no S), and 23% in prior S and L. There were no treatment-related deaths. **Conclusions:** In the extended follow-up, C maintained its superior PFS vs P irrespective of prior L and/or S. AEs in each subgroup were consistent with that of the overall population. This is also the first phase 3 study demonstrating a clinical benefit with C after prior L in RAIR DTC pts. Clinical trial information: NCT03690388. Research Sponsor: Exelixis, Inc.

6084 **Poster Session**

The efficacy and safety of anti–PD-1 antibody toripalimab combined with surufatinib in neoadjuvant treatment of locally advanced thyroid cancer: A phase II study. *First Author: Jiaying Chen, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: Surgery is the primary treatment for locally advanced thyroid cancer. However, some locally advanced patients are not candidates for R0/1 resection. There is limited evidence of neoadjuvant treatment in locally advanced thyroid cancer. Surufatinib targets multiple kinases (VEGFR1-3, FGFR1 and CSF-1R) involved in tumor angiogenesis and tumor immune evasion. It is efficient, tolerable and safe for patients with radioiodine-refractory differentiated thyroid cancer to receive surufatinib. In addition, surufatinib plus toripalimab (an anti-PD-1 antibody) showed encouraging antitumor activity and an acceptable safety profile in advanced solid tumors. This study aimed to evaluate the efficacy and safety of surufatinib plus toripalimab in locally advanced thyroid cancer in the neoadjuvant setting. **Methods:** In this single-arm phase II study, patients with pathologically confirmed diagnosis of unresectable or borderline resectable differentiated thyroid cancer were eligible and received a combination of 250 mg surufatinib (oral, qd) with 240 mg toripalimab (IV, q3w). Treatment was continued until satisfied for curative surgery, disease progression, withdrawal of consent, unacceptable toxicity or investigator decision. Primary endpoint was objective response rate (ORR) by RECIST 1.1. Secondary endpoints included R0/1 resection rate, disease control rate (DCR), time to remission (TTR), adverse events (AEs), etc. **Results:** This study is ongoing. 10/10 patients were enrolled. 6 patients received ≥4 cycles of surufatinib plus toripalimab treatment and were also evaluated for efficacy. The ORR was 66.7% with 4 partial response (PR) and 2 stable disease (SD). 4 PR and 1 SD patients received R0 resections after neoadjuvant treatment. The safety was consistent with previously reported. No grade ≥3 AEs were observed. Specific AEs data are still being counted. **Conclusions:** Surufatinib in combination with toripalimab as neoadjuvant therapy for locally advanced thyroid cancer was feasible and majority of patients achieved R0 resection. AEs were mainly grade 1-2, and this combination was well-tolerated. The combination of these two agents should be further investigated for neoadjuvant treatment of locally advanced thyroid cancer based on good results. Clinical trial information: NCT04524884. Research Sponsor: Fudan University.

6085 **Poster Session**

A phase II study to evaluate the efficacy and safety of camrelizumab plus famitinib in advanced or metastatic thyroid cancer. *First Author: Dongmei Ji, Department of Head & Neck tumors and Neuroendocrine tumors, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: Many studies have confirmed that the combination with anti-vascular drugs can significantly improve the efficacy of anti-PD-1/PD-L1 inhibitor in a variety of tumors. Camrelizumab is a humanized anti-programmed cell death receptor 1 (PD-1) antibody. Famitinib is a tyrosine kinase inhibitor which exhibits anti-angiogenesis and antiproliferative effects via targeting VEGFR-2, c-Kit and PDGFR-β. Herein, we aimed to evaluate the efficacy and safety of camrelizumab plus famitinib in the treatment of advanced or metastatic thyroid cancer. **Methods:** A single-arm, open-label phase II study was conducted, patients (pts) with advanced or metastatic thyroid cancer were recruited, including radioiodine-refractory differentiated thyroid cancer (group 1), differentiated thyroid cancer ineligible for 131I treatment (group 2), medullary thyroid cancer (group 3) and anaplastic thyroid cancer (group 4). Pts received camrelizumab 200mg i.v. on day 1 of each 21-day cycle and oral famitinib 20mg po qd in 21-day cycles until progressive disease or drug intolerance. The primary endpoint was objective response rate (ORR). The secondary endpoints were safety, adverse events (AEs), duration of response (DoR), disease control rate (DCR), progression-free survival (PFS) and overall survival (OS). **Results:** Between Jan 14, 2020 and Feb 9, 2022, 74 pts were enrolled. There were 12/26/5/31 pts in group 1/2/3/4 respectively. Median follow-up time was 11.4 months. In group 1, of 12 evaluable pts, confirmed ORR, ORR and DCR accounted for 33.3%, 41.7% and 100.0%, respectively. In group 2, of 25 evaluable pts, the confirmed ORR and DCR were 44.0% and 96.0%, respectively. In group 3, of 5 evaluable pts, the confirmed ORR and DCR were 40.0% and 100.0%, respectively. In group 4, of 24 evaluable pts, the confirmed ORR, ORR and DCR were 62.5%, 75% and 95.8%, respectively. PFS and OS were not yet mature for group 1-3, and in group 4, of all enrolled pts, estimated median PFS was 8.4 months and estimated median OS was 13.6 months. 73 pts were included in safety set. The most common treatment related AEs were diarrhea (37.0%), palmoplantiplanar swelling syndrome (34.2%), hypertension (31.5%) and fatigue (31.5%). **Conclusions:** Camrelizumab plus famitinib demonstrated promising anti-tumor efficacy with acceptable toxicity in pts with advcanced or metastatic thyroid cancer. Clinical trial information: NCT04521348. Research Sponsor: None.

6087 **Poster Session**

The prevalence and prognostic impact of mutations promoting chromatin remodelling dysregulation in non-resectable or recurrent/metastatic adenoid cystic carcinoma. *First Author: Samuel Rack, Christie Hospital NHS Foundation Trust, Manchester, United Kingdom*

Background: Few effective drug therapies exist for patients with recurrent/metastatic (R/M) adenoid cystic carcinoma (ACC). Mutations in genes encoding chromatin remodelling proteins are described in almost 50% of ACC patients (pts). Novel drug therapies are being developed to target these pathways, and may have clinical utility in this subgroup. We sought to classify mutations in chromatin remodelling genes in ACC based on predicted pathogenicity and to determine the impact of chromatin remodelling dysregulation (CRD) on clinical outcomes. **Methods:** Matched clinical-genomic data from 269 pts with non-resectable or R/M ACC were included in this study. 130 pts were prospectively recruited to an ethically approved study. For these pts, DNA extracted from FFPE tissue was sequenced on a commercially available platform to detect point mutations, indels and copy number variation in 324 genes. In addition, clinical-genomic data from 139 ACC pts were collected from cBioPortal (MetTropism, Cell 2021) for analysis. Mutations were classified as pathogenic using COSMIC, ClinVar and OncoKB. Univariate survival analysis was performed to determine the impact of one or more mutations in chromatin remodelling genes on survival from first recurrence or metastasis. p values determined using Kaplan-Meier and log-rank. **Results:** In 269 pts with non-resectable or R/M ACC, mutations promoting CRD were identified in ARID1A (11%), CREBBP (5%), EP300 (5%), KMT2C (1%), KMT2D (5%), KDM6A (13%), and SETD2 (3%). CRD mutations were identified in 94/269 (35%) pts, with 27/269 (10%) having 2 or more CRD mutations. For patients in whom CRD mutations were present survival from recurrence was decreased (median OS 4.6 v 8.2 years, HR 1.65 (95% confidence interval (CI) 1.13-2.40), p = 0.01). Analysis of each individual CRD gene identified that association with decreased survival from recurrence was significant for mutations in KDM6A (n = 35; median OS 4.2 vs 6.5 years; HR 2.01 (95% CI 1.25-3.22); p = 0.004), CREBBP (n = 11; median OS 4.2 vs 5.9 years; HR 2.97 (95% CI 1.20-7.38); p = 0.019) and SETD2 (n = 7; median OS 3.7 vs 5.9; HR 2.47 (95% CI 1.002-6.09); p = 0.042). Previous studies have identified NOTCH pathway activation and TP53 loss-of-function as prognostic. In a secondary analysis of pts without NOTCH activation and/or TP53 mutations (n = 202), OS from recurrence was decreased in those with CRD mutations (n = 58 median OS 5.7 vs 9.2 years, HR 1.5 (CI 95% 0.95-2.55), p = 0.07). **Conclusions:** We have identified a novel prognostic group of ACC pts characterised by mutations promoting CRD, which may have potential therapeutic options. Alterations in EP300/CREBBP/ARID1A may provide a rationale for treatment with CREBBP/EP300 inhibitors currently in clinical development. Significant co-occurrence with NOTCH gain of function may provide a rationale for future combination studies. Research Sponsor: Syncona Foundation, The Christie NHS Foundation Trust Charity, The Harriet Bowman Foundation, The Infrastructure Industry Foundation.

6088 **Poster Session**

A pilot study of trametinib in combination with paclitaxel in the treatment of anaplastic thyroid cancer. *First Author: Eric Jeffrey Sherman, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Anaplastic Thyroid Cancer (ATC) is a rare and highly aggressive tumor with extremely poor prognosis. Outside of the recent approval of dabrafenib/trametinib for BRAF mutant tumors, there are no other standard treatment available for metastatic ATC. The majority of ATC is driven through the MAPK pathway. Data in lung cancer suggested synergy with trametinib, a MEK inhibitor, and taxanes. **Methods:** In this pilot study we used Trametinib (2 mg) daily with Paclitaxel (80 mg/m^2) administered weekly for the first 3 weeks out the 4 week-cycle. Restaging imaging was performed every 6-8 weeks (1.5-2 cycles). Eligible patients had ATC with baseline ECOG performance status ≤ 1 and were enrolled at Memorial Sloan Kettering Cancer Center. Prior treatment allowed. Prior brain metastases were allowed if treated and stable off of steroids. Primary objective was PFS at 6 months with the target of > 2 subjects out of 12 at the time point. **Results:** 12 patients (6 men and 6 women) were enrolled between 11/2017 and 10/2021. Seven (58%) had prior radiation to the neck; 4 (33%) had prior treatment (not including with radiation) for ATC; 1 (8%) had prior brain metastases. Three (25%) partial responses were reported, and five (41.67%) reported stable disease. Subjects with partial responses had a BRAF V600E mutation (1), BRAF fusion gene (1), and a RAS mutation (1). Median time on treatment was 10.5 weeks (3-47+ weeks). Median overall survival was 26 weeks (3-59+). Six-month progression free survival (PFS) was achieved in 3 patient (25%), one of whom remains on study. 2 patients discontinued treatment due to unacceptable toxicity. The most frequent adverse events observed (all grades) were anemia (75%), increased AST, diarrhea and leukopenia (all 50%). Grade 3/4 AEs included neutropenia (25%), with anemia, AST increased, febrile neutropenia, and lymphopenia, all 16.67%. Grade 4 reactions included lymphopenia (n = 2) and leukopenia (n = 1). **Conclusions:** Our target progression-free survival (PFS) at 6 months was observed on this study. The combination of trametinib and paclitaxel should be evaluated in a larger cohort of patients in the future. Clinical trial information: NCT03085056. Research Sponsor: Novartis, Philanthropy.

6089 **Poster Session**

Phase 2 of trametinib plus radioiodine in *RAS*-mutant and wild-type, radioiodine-refractory thyroid cancer (ETCTN9446). *First Author: Bharat Burman, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: A pilot study showed MEK inhibition could enhance radioiodine (RAI) avidity/efficacy in 5 *RAS* mutant (MUT), RAI-refractory (RAIR) thyroid cancer (TC) patients (pts). This phase 2 trial with the MEK 1/2 inhibitor trametinib (tram) was conducted to define the efficacy of this "redifferentiation" strategy in *RAS* MUT RAIR pts and separately in a *RAS* wild-type (WT) cohort. **Methods:** Recurrent and/or metastatic, RAIR TC pts w/ *RAS* MUT (Cohort A) or *RAS* WT (excluding $BRAF^{V600E}$) (Cohort B) tumors were treated w/ tram (2 mg orally daily). Progressive disease or new/worsening disease-related symptoms was required for Cohort A pts. ^{124}I PET was performed at baseline and the fourth week of tram. If the second ^{124}I PET showed increased RAI avidity allowing > 2000 cGy to be delivered to a tumor w/ < 300 mCi ^{131}I, pts were treated w/ ^{131}I, guided by whole body and blood dosimetry. Tram was continued through 2 days s/p ^{131}I. Pts who did not qualify for ^{131}I from A/B were taken off study or continued tram alone (Cohort C). For Cohort A (n = 25), the two co-primary endpoints were objective response rate (ORR) and progression-free survival (PFS) 6 months (mos) s/p ^{131}I. Observing either >4 pts w/ confirmed complete or partial response (cCR or cPR) or > 9 progression-free at 6 mos would be considered promising. Secondary endpoints were the proportion of pts w/ increased ^{124}I, safety/tolerability of tram and thyroglobulin changes s/p RAI. The Cohort B primary endpoint was the proportion of pts whose tumors exceeded the lesional dosimetry threshold for ^{131}I w/ tram. An exploratory endpoint for Cohort C was best objective response (BOR) w/ tram. **Results:** 25 *RAS* MUT pts enrolled in Cohort A. 23 had at least one (> 1) ^{124}I (-) lesion, 21 had >1 ^{124}I (+) lesions and 4 pts had tumors lacking any ^{124}I uptake. After tram treatment, 22/25 had increased ^{124}I uptake; 17/23 had ^{124}I (-) tumors convert positive. Importantly, 15/25 (60%) pts had increased ^{124}I uptake and met lesional dosimetry criteria for ^{131}I on tram. Of 14 pts treated w/ ^{131}I, 8 (57%) achieved cPR, 3 (21%) stable disease (SD) and 3 (21%) progression of disease (PD) 6 mos s/p RAI, translating to 32% ORR and 44% 6-month PFS among all 25 pts. Cohort B had 9 pts (4 Class II *BRAF* alterations, 4 *RET* rearrangements, 1 *STK11* mutation). 3/4 pts w/ Class II *BRAF* altered tumors qualified for ^{131}I, leading to 1 cPR, 2 SD 6 mos s/p ^{131}I. 1/4 pts w/ *RET* rearranged tumors qualified for ^{131}I, producing SD at 6 mos. The *STK11* MUT pt did not have increased ^{124}I uptake w/ tram. 7 ^{131}I-ineligible pts enrolled to continue tram (Cohort C). Two serious adverse events (grade 3 anemia [Cohort A], grade 3 ejection fraction decrease [Cohort C]) and 3 grade 1 blurred vision/decreased visual acuity AEs were related to tram. **Conclusions:** Trametinib enhanced RAI uptake/efficacy in a subset of *RAS* MUT and Class II *BRAF* altered tumors. Further study to define the efficacy and optimal application of this therapeutic strategy is warranted. Clinical trial information: NCT02152995. Research Sponsor: U.S. National Institutes of Health.

6090 **Poster Session**

Single-cell immune mapping of adenoid cystic carcinoma (ACC) reveals potential therapeutic targets for the aggressive solid subtype. *First Author: Luana Guimaraes de Sousa, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: ACC is a common salivary gland malignancy for which there is no FDA approved therapies. Despite a quiet genome, ACC has significant tumoral heterogeneity, which may facilitate the metastatic relapse. Studies focusing on the deep profile of ACC tumor microenvironment (TME) are lacking. Here we explored the TME of ACC using imaging mass cytometry (IMC) and assessed TME attributes and its association with histology and clinical outcomes. **Methods:** Two tissue microarrays from 62 ACC patients (pts) were built and stained with 37 metal-tagged markers. IMC was performed with the Fluidigm Helios CyTOF instrument utilizing the Hyperion Imaging System Laser ablation. Tissue and cell segmentation and multiplex imaging analysis were performed with Visiopharm software using pre-trained artificial intelligence algorithms. Comparison of cell types and markers densities among histology sub-groups were analyzed with Wilcoxon signed-rank test and its association with overall survival (OS) with log-rank and Cox Proportional Hazards. **Results:** Of 62 pts, 37% (23/62) had solid histology, 19% (12/62) were metastatic at diagnosis, and 55% (30/54) had disease recurrence during follow-up. With a median follow-up of 7.9 y, the median OS was 9.3y (CI 95%, 7.8-NR). Pts with solid subtype had poorer OS than non-solid histology (5.2 vs 14.6 y, p = 0.004). The IMC final dataset comprised 507,524 single-cells. No significant differences were found in cell subpopulations density between solid and non-solid histology. The most represented cell population in the stroma were macrophages, followed by CD8+ T cells, and fibroblasts. A higher percentage of M2-macrophage was associated with poor survival (p = 0.001), whereas, a higher percentage of M1-macrophage (M1:M2 ratio) was associated with better prognosis. No other immune cell type, fibroblasts or immune cell functional markers (TIGIT, TIM3, granzyme B, and PD-L1) correlated with survival. Regarding tumor markers, a higher expression of BCL-2, B7-H4, and Ki67 in the tumor cells were associated with worst survival; and remained statistically associated after adjustment for histology and staging (all p < 0.001). Solid histology had a significantly higher density of tumor cells expressing B7-H4, BCL-2, and Ki67 compared to cribriform and tubular histology. A higher expression of myoepithelial marker (p63+) were associated with a better survival when compared with tumors with low p63 expression. **Conclusions:** ACC's TME is composed mainly of macrophages. Despite having no significant differences in cellular composition, a higher density of tumor cells expressing BCL-2, B7-H4 and Ki67 were found in the solid histology and these markers were independent predictors of poor prognosis. The overexpression of BCL-2 and B7-H4 in the solid histology provides a scientific rationale for BCL-2 and/or B7-H4 targeting for the most aggressive ACC. Research Sponsor: U.S. National Institutes of Health.

6091 **Poster Session**

Efficacy and safety of selpercatinib in RET-altered tumors: A systematic review and meta-analysis. *First Author: Mina Choudhry, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA*

Background: RET proto-oncogene encodes receptor tyrosine kinase. Selpercatinib was the first RET-specific tyrosine kinase inhibitor approved by FDA in RET-altered tumors (pralsetinib was approved afterward). This systematic review and meta-analysis will assess the efficacy and safety of selpercatinib in RET-altered tumors. **Methods:** A search was performed on PubMed, Embase, Cochrane, WOS, and clinicaltrials.gov. We used the following mesh and Emtree terms, "selpercatinib" AND "proto oncogene proteins c ret," from the inception of literature till 10/15/2021. We screened 187 articles and included 2 phase I/II clinical trials (N = 309) in this meta-analysis. We excluded preclinical trials, case reports, case series, review articles, observational studies, meta-analysis, and clinical trials not providing any information about the efficacy of selpercatinib in RET-altered tumors. The quantitative analysis was performed using the R programming language. **Results:** In 2 clinical studies (N = 309), 144 patients had RET-altered advanced non-small cell lung cancer (NSCLC) and 162 had thyroid cancer. RET mutations were reported in 143 patients and RET-fusion in 163 tumors. 179 patients were previously treated with systemic therapy while 127 patients were treatment naïve. Pooled overall response (OR), complete response (CR), partial response (PR), progressive disease (PD), and stable disease (SD) were 72% (95% CI = 0.64-0.78, I^2= 40%), 6% (95% CI = 0.03-0.13, I^2= 49%), 66% (95% CI = 0.57-0.74, I^2= 50%), 3% (95% CI = 0.01-0.06, I^2= 0), and 24% (95% CI = 0.18-0.30, I^2= 22%), respectively, in RET-altered thyroid/NSCLC patients. Pooled OR was 67% (95% CI = 0.60-0.73, I^2= 0), 78% (95% CI = 0.64-0.87, I^2= 51%), 75% (95% CI = 0.58-0.87, I^2= 68%), and 71% (95% CI = 0.63-0.78, I^2= 0%) in previously treated, treatment naïve, RET-fusion tumor, and RET-mutation tumor patients, respectively. Pooled incidence of ≥grade 3 any adverse event, rise in ALT, rise in AST, diarrhea, hypertension, and QT abnormalities were reported in 58% (95% CI = 0.43-0.72, I^2= 85%), 10% (95% CI = 0.08-0.14, I^2= 0), 11% (95% CI = 0.07-0.15, I^2= 17), 5% (95% CI = 0.03-0.08, I^2= 0), 17% (95% CI = 0.11-0.26, I^2= 62%), and 4% (95% CI = 0.02-0.07, I^2= 18%) of the participants, respectively. **Conclusions:** Selpercatinib was safe and effective in patients with RET-altered NSCLC and thyroid cancer regardless of prior treatment status and type of RET alteration. On indirect comparison, the safety profile with selpercatinib was better than previously used non-specific RET-inhibitors. Randomized clinical trials (RCTs) NCT04211337 and NCT04194944 are in progress to compare selpercatinib with non-specific RET inhibitors and chemotherapy/PD-1 inhibitor. More RCTs are needed to assess the combinations of selpercatinib with other drugs. Research Sponsor: None.

6092 **Poster Session**

Prognostic factors in sinonasal cancers: A multicenter pooled analysis. *First Author: Alberto Hernando-Calvo, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Sinonasal cancers (SC) are heterogeneous diseases. Despite multimodality treatment, overall survival (OS) remains unsatisfactory. We aimed to identify prognostic factors (PFs) associated with patterns of failure and OS in non-metastatic SC (nmSC). **Methods:** We retrospectively reviewed a pooled dataset of nmSC from Princess Margaret (Canada) and Catalan Institute of Oncology (Spain) treated with definitive surgery ± postop radiotherapy (RT) or RT ± chemo according to institutional protocols between 2010-2019. In squamous cell carcinoma (SCC), HPV status was tested by p16 staining, and HPV DNA (ISH or PCR) if equivocal. The primary goal was to assess the association of tumor histology, stage (by 7th edition TNM), and other clinicopathological variables on locoregional control (LRC), distant control (DC) and OS. Actuarial rates were calculated with Kaplan–Meier (KM) method. Multivariable analysis (MVA) calculated hazard ratios (aHR) adjusted for histology type, T-/N-categories, and primary treatment. **Results:** Out of 342 pts, median age was 62 years (y) (range 21-96), Male:Female = 212:130, 95% had ECOG 0-1. Tumor histology types were: 192 (56%) SCC (p16+: 35; p16-/untested: 157), 40 (12%) adenocarcinoma (AD), 33 (10%) sinonasal undifferentiated carcinoma or sinonasal neuroendocrine tumors (SNUC/SNEC), 28 (8%) malignant melanoma (MM), 27 (8%) esthesioneuroblastoma (ES) and 22 (6%) adenoid cystic carcinoma (ACC). Median follow up was 3.6 y (range 0.1-11.3). Three-year actuarial rates for each endpoint are included in table. The PFs for LRC by MVA were: SNUC/SNEC (vs SCC) histology, T3-4 (vs T1-2: aHR 2.4, p = < 0.01) and N+ (vs N-: aHR 1.7, p = 0.02) diseases. The PFs for DC were: MM (vs SCC) and SNUC/SNEC (vs SCC) histology, and T3-4 (vs T1-2: aHR 6.0, p = 0.01) disease. The PFs for OS were: MM (vs SCC) histology, older age (aHR 1.0, p < 0.01), T3-4 (vs T1-2: aHR 5.6, p < 0.01), and N+ (vs N-: aHR 2.5, p < 0.01) disease. There was no difference in primary surgery vs RT in any outcome endpoint (all p > 0.05). p16+ SCC had a marginally higher LRC but similar DC and OS vs p16-/untested SCC (table). **Conclusions:** This large multicentre cohort of nmSC shows different patterns of relapse and survival with different tumor histologies. Our results suggest that individualization of treatment and follow-up strategies by histologic type is recommended to optimize outcomes in these orphan diseases. Research Sponsor: None.

3y Outcome	LRC	aHR	p	DC	aHR	p	OS	aHR	p
SCC	67% (59-73)	REF		94% (89-97)	REF		68% (61-76)	REF	
AD	69% (48-81)	1.1	0.72	89% (72-96)	1.9	0.27	74% (60-91)	1.2	0.52
ACC	82% (55-93)	0.6	0.21	91% (64-98)	2.6	0.06	67% (50-90)	1.0	0.89
ES	83% (58-93)	0.7	0.43	96% (69-99)	0.6	0.64	82% (67-100)	0.6	0.29
MM	64% (39-78)	1.0	0.85	42% (19-58)	10.0	< 0.01	31% (17-56)	2.0	0.01
SNUC/SNEC	83% (61-93)	0.4	0.03	54% (30-69)	8.0	< 0.01	59% (43-80)	1.5	0.20
SCC									
HPV-/untested	64% (55-71)	REF		93% (88-96)	REF		66% (59-75)	REF	
HPV+	79% (58-89)	0.6	0.16	97% (78-100)	0.4 (univariable analysis)	0.40	75% (62-92)	0.7	0.40

6093 **Poster Session**

Phase I study of AIC100 in relapsed and/or refractory advanced thyroid cancer and anaplastic thyroid cancer. *First Author: Jing Mei Hsu, Weill Cornell Medicine, New York, NY*

Background: ICAM-1 is a cell surface glycoprotein that is typically expressed on endothelial cells and immune cells and a ligand for LFA-1 integrin. It is also overexpressed in several malignancies, in particular anaplastic and advanced thyroid cancer. We designed an affinity tuned ICAM-1-directed CAR T cell (micromolar affinity) that preferentially binds overexpressed ICAM-1 on tumor cells and spares normal cells. The CAR T cells also express somatostatin receptor 2 (SSTR2), which allows tracking of CAR T cells in vivo via DOTATATE PET/CT scan. Murine studies showed excellent responses in ICAM-1 expressing thyroid cancer without significant toxicities. We are conducting a first-in-human phase 1 clinical trial to evaluate the feasibility, safety and preliminary efficacy of ICAM-1 in patients with relapsed/refractory thyroid cancer or anaplastic thyroid cancer who are BRAF wild-type, or BRAF mutated after failure of BRAF specific therapy (NCT04420754). **Methods:** This is a dose-escalation study with modified toxicity probability interval design and cohorts of 3 Patients. Patients receive a single dose of 1x 10^7 (Cohort 1), 1 x 10^8 (Cohort 2) or 5 x 10^8 (Cohort 3) ICAM-1 CAR T cells after FLU/CY lymphodepleting (LD) chemotherapy. Additional CAR T infusion is allowed if patients achieve partial response or stable disease. Whole-body Fluorodeoxyglucose (FDG) and DOTATATE PET/CT is used to stage tumor and track CAR T cells in vivo, respectively. **Results:** All ICAM-1 CAR T infusion products met target transduction efficiency. Two patients with progressive anaplastic thyroid cancer received ICAM-1 CAR T therapy at dose-level I. Evaluation of CAR T cellular kinetics demonstrated transient peripheral blood CAR T cell expansion. One patient developed grade 1 cytokine release syndrome (CRS) with fever. Several tumor lesions from this patient showed DOTATATE avidity, indicating CAR T homing to the tumor, concomitant with decrease in FDG avidity, suggesting biological activity at ~2 weeks post CAR T infusion. DOTATATE avidity at 2 weeks post CAR T infusion also appeared to match that of CAR T abundance in the blood. Updated results on additional patients and cohorts will be presented. **Conclusions:** Adoptive cellular therapy with ICAM-1 directed CAR T is safe and feasible at dose level 1 in patients with anaplastic thyroid cancer. DOTATATE PET allows visualization of expansion and homing of SSTR2 expressing CAR T cells, while concomitant FDG PET permits correlation with biological activity. Clinical trial information: NCT04420754. Research Sponsor: Affyimmune Therapeutics.

6094 **Poster Session**

Self-care for head and neck cancer survivors with lymphedema and fibrosis: A pilot randomized clinical trial. *First Author: Jie Deng, University of Pennsylvania School of Nursing, Philadelphia, PA*

Background: Lymphedema and fibrosis (LEF) are debilitating late effects in head and neck cancer survivors (HNCS). Initial therapy is usually directed by therapists following which patients undertake a LEF self-care program (SCP). No evidence based LEF-SCP are available. We report on the feasibility and preliminary efficacy data of a multifaceted LEF-SCP. **Methods:** 59 HNCS with LEF were randomized to: Usual care (n = 20), usual care + LEF-SCP (n = 20), and usual care + LEF-SCP + routine follow-up with a lymphedema therapist (n = 19). Assessments were conducted at baseline, 3-, 6-, 9-, and 12-months. Outcome measures include feasibility and preliminary efficacy (LEF progression, symptom burden, and jaw range of motion [ROM]). Multivariate covariance pattern model analysis was used to test for difference between arms. **Results:** 1) Feasibility: LEF-SCP training sessions - 80% completion rate; 90% satisfaction with the LEF-SCP; self-care adherence was similar between arms; no adverse event. 2) Preliminary Efficacy: Compared to usual care, participants randomized to LEF-SCP (+/- follow-up) showed a decrease in LEF severity ($p < 0.05$), reduction in symptom burden ($p < 0.05$), without significant improvement in jaw ROM. No significant differences were noted between the patients +/- follow-up with a lymphedema therapist. There was a trend to improved self-efficacy in patients participating in the LEF-SCP. **Conclusions:** The LEF-SCP is feasible and potentially efficacious for HNCS. Further testing is warranted. Clinical trial information: NCT03030859. Research Sponsor: American Cancer Society.

6095 **Poster Session**

Apatinib versus placebo in patients with locally advanced or metastatic, radioactive iodine-refractory, differentiated thyroid cancer: Post hoc analyses from the REALITY randomized clinical trial. *First Author: Yansong Lin, Department of Nuclear Medicine, Peking Union Medical College Hospital, Beijing, China*

Background: In the multicenter, double-blind, randomized, phase 3 REALITY study, apatinib significantly improved clinical benefits in terms of progression-free survival (PFS), overall survival (OS) and objective response rate (ORR) compared to placebo with a tolerable safety profile in patients with progressive locally advanced or metastatic radioactive iodine-refractory, differentiated thyroid cancer (RAIR-DTC). Here, we investigate the association between baseline characteristics and survival endpoints. **Methods:** Post-hoc analyses of PFS and OS were done in patients treated with apatinib according to the following subgroups: ECOG performance status (PS) (0 vs 1-2), thyroglobulin (Tg) (< 223 vs ≥ 223 ng/mL), and tumor target lesions diameter (< 33.2 vs ≥ 33.2 cm). **Results:** Among 92 patients with RAIR-DTC included in the study, 46 patients received apatinib. As of December 3, 2021, median PFS was 25.77 (95% CI 11.14-not reached [NR]) vs 11.08 months (95% CI 7.17-NR) for ECOG PS 0 / 1-2, though no statistical significance (HR 0.454, 95% CI 0.161-1.285, p = 0.1373). The median OS was significant prolonged in patients with ECOG PS of 0 compared with those ECOG 1-2 (not reached vs 29.42 months, 95% CI 18.87-NR; HR 0.199, 95% CI 0.054-0.733, p = 0.0152). In subgroups by Tg, median PFS was 25.77 (95% CI 9.11-NR) vs 11.08 (95% CI 5.65-NR) months for Tg < 223 / ≥ 223 ng/mL. A trend towards improved PFS was observed (HR 0.444, 95% CI 0.145-1.361, p = 0.1556). The median OS was significantly improved in patients with Tg < 223 in contrast to those Tg ≥ 223 ng/mL (NR vs 25.87 months, 95% CI 13.58-NR; HR 0.151, 95% CI 0.033-0.689, p = 0.0147). The median PFS for tumor target lesions diameter < 33.2 cm was significantly improved relative to those ≥ 33.2 cm (25.77, 95% CI 11.14-NR vs 9.11 months, 95% CI 5.65-NR) with a significant difference (HR 0.289, 95% CI 0.097-0.859, p = 0.0255); OS data in two subgroups were not mature (NR, 95% CI 29.42-NR vs NR, 95% CI 17.95-NR; HR 0.364, 95% CI 0.112-1.184, p = 0.0932). **Conclusions:** Post-hoc analysis indicated that among patients receiving apatinib, longer OS benefits were associated with better ECOG PS, lower Tg levels; longer PFS benefits were associated with smaller tumor diameter. These results suggest a better prognosis for early initiation of apatinib treatment in patients with RAIR-DTC. Clinical trial information: NCT03048877. Research Sponsor: This study was funded by the National Natural Science Foundation of China (grant 81771875) and the Project on Inter-Governmental International Scientific and Technological Innovation Cooperation in the National Key Projects of Research and Development Pla, Pharmaceutical/Biotech Company.

6096 **Poster Session**

The effect of anlotinib on unresectable differentiated thyroid cancer (T4): A retrospective study. *First Author: Xin Wu, West China Hospital, Chengdu, China*

Background: Though the majority of differentiated thyroid cancer (DTC) patients obtained a good prognosis after standardized therapy, approximately 15% of DTC patients will progress to unresectable disease. Part of locally advanced (T4) thyroid cancer patients with progressive invasion into vasculature/windpipe/esophagus lost the surgery opportunity because of difficult in achieving R0/R1 resection. The study aimed to evaluate the efficacy and safety of anlotinib in T4 PTC. **Methods:** Retrospectively included T4 papillary thyroid cancer (PTC) patients from West China Hospital of Sichuan University between Sep. 2020 and Feb. 2022. The patients were prescribed with Anlotinib (12 mg orally daily, two weeks on/one week off) at least two courses. The tumor response was defined by RECIST v. 1.1. The primary endpoint was objective response rate (ORR). **Results:** The study included 22 T4 PTC patients, including 8 patients with lung metastasis. The median age of patients was 59.2 years, 8/22 patients were male. The median follow-up was 5.5 months (2-13 months). Totally, the ORR was 68.2% (CR: 9.1%; PR: 59.1%), disease control rate (DCR) was 95.5% (SD: 27.3%), one patient progressed (PD). 8 patients with lung metastasis, the ORR was 75% (6/8). The average tumor shrinkage rate was 42.1%. And two female patients (T4aN1M1 and T4bN1M0 respectively) obtained CR. Additionally, one juvenile patient (14 y) also response to Anlotinib treatment with 55.2% tumor shrinkage, and no obvious AE was observed in this patient. Most adverse events (AEs) were grade 1 or 2. Common AEs of all grades were hypertension (68.2%), hypertriglyceridemia (36.4%), proteinuria (31.8%), and tended to discontinue when treatment ceased. **Conclusions:** Anlotinib demonstrated antitumor activity in the treatment of unresectable T4 PTC; Juvenile PTC patients also response to Anlotinib treatment; Anlotinib treatment was tolerable in T4 PTC patients. Research Sponsor: None.

6097 **Poster Session**

Circulating tumor DNA profiling and serial analysis in salivary gland carcinomas reveal unique mutational subsets and actionable alterations. *First Author: Jeffery Scott Russell, Huntsman Cancer Institute, Salt Lake City, UT*

Background: Salivary gland carcinoma is a rare head and neck malignancy without any FDA approved treatment options. ctDNA profiling has been shown to be a valuable tool in identifying novel targets and expanding potential therapeutic options. Here, we report the landscape of ctDNA in a large dataset of salivary gland carcinomas. **Methods:** Analysis of genomic results from blood samples with a diagnosis of salivary gland carcinoma that were prospectively collected between January 2017 to December 2021 for clinical Guardant360 testing. Histologic subtype was documented by ordering providers as available. Serial tests were defined as having Guardant360 analysis performed on more than one sample collected at more than one timepoint. **Results:** Among 222 patients tested with Guardant360, 59.5% were male and the median age was 64 years (range 22-93 years). Of reported diagnoses, 137 (61.7%) patients had salivary gland carcinoma NOS. The remaining samples were designated by specific salivary histology: 13 (5.9%) salivary gland mucoepidermoid carcinoma (SGMC), 19 (8.6%) salivary gland adenocarcinoma (SGA), 37 (16.7%) salivary gland adenoid cystic carcinoma (SGACC), and 16 (72%) salivary duct carcinoma (SDC). ctDNA genomic alterations (GAs) were identified in 205 (81.3%) of 252 samples. The median variant allele fraction was 0.6% (range 0.01%-46.4%). TMB was evaluated in 45 samples of which 33 were evaluable and the median and 80th percentile of TMB was 8.44 and 11.81 mut/Mb. MSI-H was not detected in any of the 181 samples tested for MSI. The most commonly altered genes were TP53, PIK3CA, ERBB2, ATM, EGFR and HRAS across all collected salivary samples. Further analysis stratified genetic alterations by tissue subtype. Other than TP53, common mutations by salivary gland carcinoma subtype included: PI3KCA (SGACC/SDC), ERBB2 (SGA), and EGFR (SGMC). In regards to serial analysis, 16 patients had at least 2 serial tests. When comparing the subsequent testing within the same patient, 3 patients had potentially new actionable GAs (including *BRAF*, *KRAS* mutations and *EGFR* amplification) on the subsequent test that were not identified on the original test. **Conclusions:** Blood-based liquid biopsy can be applied in salivary gland tumors to detect genomic alterations in ctDNA which may provide opportunities for therapeutic intervention in a cancer with limited treatment options. Additionally, ctDNA testing may be used to identify resistant alterations to potential therapy. Finally, longitudinal assessment of ctDNA may shed light on tumor evolution and additional therapeutic targets may be found. Further assessment of serial ctDNA analysis and the potential impact on patient clinical outcomes needs to be elucidated. Research Sponsor: None.

TPS6098 **Poster Session**

A phase II/III trial of chemotherapy plus cetuximab versus chemotherapy plus bevacizumab versus atezolizumab plus bevacizumab following progression on immune checkpoint inhibition in recurrent/metastatic head and neck cancers: ECOG-ACRIN EA3202. *First Author: Aarti K. Bhatia, Yale School of Medicine & Yale Cancer Center, New Haven, CT*

Background: There is no standard treatment beyond progression on first-line pembrolizumab (P) in patients with R/M HNSCC. Vascular endothelial growth factor (VEGF) modulates anti-tumor immunity via proliferation of inhibitory T regulatory and myeloid-derived suppressor cells, inhibition of dendritic cell maturation and suppression of effector T cell responses. Efficacy data from other disease sites and from early-phase trials done in HNSCC suggests promising clinical activity of VEGF and PD-1 inhibitor combination therapy. We have thus designed a Phase II/III, randomized, multi-arm trial to evaluate the efficacy of atezolizumab (A) and bevacizumab (B) beyond progression on P in patients with R/M HNSCC. **Methods:** EA3202 is enrolling patients with CPS ≥1% R/M HNSCC previously treated with P either alone or in combination with other checkpoint inhibitors without progression for at least 12 weeks. In phase II, patients will be randomized to one of three treatment arms: platinum doublet chemotherapy (C) plus cetuximab (E) for six cycles followed by E maintenance (control arm), C + B for six cycles followed by B maintenance, or A + B. Therapy in each arm will continue until progression, toxicity, or for a total period of two years. Patients will be stratified by p16 status, CPS score (≥ 20 vs. < 20), distant metastases (M0 vs M1), and disease progression pattern with first-line P (while on P vs. after discontinuation). 216 patients will be enrolled. The primary endpoint for phase II is progression-free survival (PFS). Each experimental arm will be compared to the control arm at a one-sided alpha level of 0.10. Pre-specified rules will be used to pick a winner among the two experimental arms, which will then advance to phase III against the control arm. 214 patients will be enrolled in phase III for a total sample size of 430 patients. The primary endpoint for phase III is overall survival (OS) which will be compared using a stratified log-rank test. Secondary endpoints include OS in the two phase III arms among the CPS ≥ 20 cohort and comparison of grade 3 or higher treatment-related adverse events between the two arms. A total of 277 OS events will be required for full information for phase III evaluation to give a nominal ~90% power at one-sided alpha level 0.0125. 144 patients enrolled in phase II (from the control and selected experimental arms) will be included in the phase III analysis. With this design the overall study power is at least 80% under a true 40% hazard reduction for PFS and 35% hazard reduction for OS. Blood and tumor tissue will be banked. EA3202 was activated in December 2021. It is the first randomized study to compare systemic treatments for R/M HNSCC in the immunotherapy era and will define the best second-line treatment approach beyond P. Clinical trial information: NCT05063552. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

TPS6099 **Poster Session**

TACTI-003: A randomized phase IIb study of eftilagimod alpha (soluble LAG-3 protein) and pembrolizumab as first-line treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma. *First Author: Douglas Adkins, Washington University School of Medicine, St. Louis, MO*

Background: Eftilagimod alpha (efti) is a soluble LAG-3 protein targeting a subset of MHC class II molecules that mediate antigen presenting cell (APC) and CD8 T-cell activation. Data from a non-randomized, phase II trial of efti plus pembrolizumab (TACTI-002) showed encouraging antitumor activity and manageable safety when given as second-line treatment of patients with recurrent or metastatic head and neck squamous-cell carcinoma (RM-HNSCC). TACTI-003 (NCT04811027) is a multicenter, open label, randomized phase IIb trial to investigate efti plus pembrolizumab in the first-line setting for RM-HNSCC. **Methods:** A total of 154 patients (pts) are currently being recruited into two cohorts (A+B). In cohort A, pts with tumors that are CPS≥1 will be randomly assigned 1:1 to receive either efti (30 mg subcutaneously Q2W for initial 6 months, thereafter Q3W) plus pembrolizumab (400 mg intravenously Q6W) for up to two years or pembrolizumab alone. Randomization will be stratified by CPS (1-19 vs. ≥ 20) and ECOG PS (0 vs. 1). Pts with tumors that are CPS < 1 will receive efti plus pembrolizumab (cohort B). Imaging will be performed every 9 weeks. The primary endpoint (EP) is objective response rate (ORR) by RECIST1.1. Secondary EPs include overall survival, ORR according to iRECIST, time to and duration of response, disease control rate, progression-free survival, occurrence of anti-efti -specific antibodies, safety, and quality of life. Exploratory endpoints comprise biomarkers. The study has been approved by relevant competent authorities, ethic committees and IRBs. Clinical trial information: NCT04811027. Research Sponsor: Immutep S.A.

TPS6100 **Poster Session**

innovaTV 207: New combination dosing cohorts in the open label phase 2 study of tisotumab vedotin in solid tumors. *First Author: Xiuning Le, Department of Thoracic Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Tisotumab vedotin (TV; TIVDAK) is a tissue factor (TF)-directed antibody-drug conjugate that has been granted accelerated approval in the US for treatment of adults with recurrent/metastatic (r/m) cervical cancer with disease progression on or after chemotherapy. TV remains investigational in other tumor types including squamous cell carcinoma of the head and neck (HNSCC) and squamous non-small cell lung cancer (sqNSCLC). This abstract presents the addition of Part D to innovaTV 207 (NCT03485209), a global, open label, multicenter phase 2 trial investigating the safety, tolerability, and activity of TV in solid tumors. Untreated patients (pts) with r/m HNSCC or sqNSCLC enrolled in Part D will receive either TV in combination with pembrolizumab (pembro) or TV + pembro and a platinum agent. Based on encouraging preliminary safety and efficacy results with 2.0 mg/kg TV once every 3 weeks (Q3W) in combination with pembro or carboplatin (carbo) in innovaTV 205 cervical cancer study cohorts, TV is being evaluated at 2.0 mg/kg Q3W in combination with pembro or pembro + carbo (or cisplatin). **Methods:** Up to 140 treatment-naive pts with r/m HNSCC or sqNSCLC will be enrolled in Part D of innovaTV 207. First, the All-Comers cohorts for HNSCC and sqNSCLC will each enroll up to 30 pts, regardless of PD-L1 expression, for Q3W dosing with 2.0 mg/kg TV in combination with 200 mg pembro and AUC 5 carbo. After enrollment in the HNSCC All-Comers Cohort is complete, up to 20 pts with HNSCC will be enrolled into a Cisplatin Safety Cohort for dosing with 2.0 mg/kg TV in combination with 200 mg pembro and 100 mg/m^2 cisplatin. Completion of enrollment in the All-Comers Cohort for each tumor type will also be followed by enrollment of up to 30 pts with HNSCC (CPS ≥1) and 30 pts with sqNSCLC (TPS ≥1%) into PD-L1 Selected cohorts for dosing with TV in combination with 200 mg pembro. Response will be assessed every 6 weeks for the first 6 months, every 12 weeks for the next 6 months, and then every 6 months after that. Pts with HNSCC must have had no previous systemic therapy for metastatic disease (exception is systemic therapy given as part of multimodal treatment for locally advanced disease completed > 6 months prior). Pts with NSCLC must have histologically or cytologically documented squamous cell NSCLC and must not have had any previous systemic therapy for metastatic disease or radiation therapy to the lung that is > 30 Gy within 6 months of the first dose of study drug. The primary endpoint is investigator-determined confirmed ORR per RECIST v1.1. Secondary endpoints include confirmed and unconfirmed ORR per RECIST v1.1, disease control rate, duration of response, time to response, PFS, OS, safety and tolerability, pharmacokinetics, and immunogenicity. The trial opened in June 2018 and was amended to add Part D in November 2021. Part D enrollment will begin in early 2022; updates will be provided at the meeting. Clinical trial information: NCT03485209. Research Sponsor: Seagen Inc., Pharmaceutical/Biotech Company.

TPS6101 **Poster Session**

TIRA study: A phase III, multicenter, randomized controlled study of toripalimab plus radical chemoradiotherapy with or without concurrent cisplatin in patients with high-risk locoregionally advanced nasopharyngeal carcinoma. *First Author: Cheng Xu, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Patients with locoregionally advanced nasopharyngeal carcinoma (LA-NPC) suffer a high risk of distant metastasis and require guideline-recommended multimodality therapy. However, cisplatin-based concurrent chemotherapy leads to a high incidence of severe toxicities and low patient compliance, consequently limiting survival improvement. Toripalimab, an immune checkpoint inhibitor targeting programmed cell death 1 (PD-1), has a novel anti-cancer mechanism and mild toxicity spectrum. Robust evidence showed that given toripalimab + gemcitabine-cisplatin (GP) chemotherapy regimen, the median progression-free survival could be markedly improved in patients with recurrent and metastatic NPC. Besides, PD-1 antibody + radiotherapy is also regarded as a promising therapeutic strategy due to the synergistic effect. Therefore, we hypothesized that the de-intensification strategy using toripalimab + induction chemotherapy (IC) followed by radiotherapy alone would obtain equivalent survival and low toxicity in patients with LA-NPC compared with toripalimab + IC followed by concurrent chemoradiotherapy. **Methods:** TheTIRA study is a multicenter, randomized, controlled, open-label, phase III study. Since August 2021, we have been recruiting high-risk LA-NPC patients (stage III-IVa, except $T_{3\text{-}4}N_0M_0$ & $T_3N_1M_0$) from 12 Chinese centers. Our target sample size is temporarily set at 494 patients with 247 for each arm. Patients will be 1:1 ratio randomized to the experimental or control arm. Patients in the experimental arm will receive induction-concurrent toripalimab (240 mg, d1, Q3W $\times$ 6 cycle) with IC (gemcitabine 1000 mg/m^2, d1 & d8 + cisplatin 80 mg/m^2, d1, Q3W $\times$ 3 cycle) + intensity-modulated radiotherapy (IMRT, 70 Gy in 33 fractions), and thereafter adjuvant toripalimab (240 mg, d1, Q3W $\times$ 11 cycle). Patients in the controlled arm will receive an additional concurrent cisplatin (100 mg/m^2, d1, Q3W $\times$ 2 cycle). The primary endpoint is the 3-year failure-free survival. Secondary endpoints include 3-year overall survival, 3-year distant metastasis-free survival, 3-year locoregional recurrence-free survival, quality-of-life assessment according to the systems of the European Organization for Research and Treatment of Cancer and the Functional Assessment of Cancer Therapy, and safety profile. Exploratory analysis will be performed for potential biomarkers of survival prediction including PD-L1 expression and tumor-infiltrating lymphocytes. Clinical trial information: NCT04907370. Research Sponsor: None.

TPS6102 **Poster Session**

Phase 2 trial of enoblituzumab plus retifanlimab or tebotelimab in first-line treatment of patients (pts) with recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN). *First Author: Grzegorz Obara, Comprehensive Cancer Centers of Nevada, Las Vegas, NV*

Background: Head and neck cancer accounts for ~900,000 cases and over 400,000 annual deaths worldwide as of 2021. Pts with R/M SCCHN have a poor prognosis with median overall survival <1 year. Programmed death (PD)-protein 1 (PD-1) and PD-ligand 1 (PD-L1) blockade has shown antitumor activity in advanced SCCHN. Enoblituzumab (MGA271) is an investigational monoclonal antibody (mAb) that binds B7-homolog 3 (B7-H3) with enhanced binding to the activating Fc gamma receptor CD16A, particularly the low-affinity allele CD16A-158. B7-H3 is overexpressed in many cancers, including SCCHN, but not in most normal tissues. Retifanlimab (MGA012, INCMGA00012) is an investigational anti-PD-1 mAb, blocking binding of PD-L1 or PD-ligand 2 (PD-L2) to PD-1. Tebotelimab (MGD013) is an investigational, Fc-bearing bispecific, tetravalent DART® molecule designed to bind PD-1 and lymphocyte activation gene 3, inhibiting their interaction with PD-L1 or PD-L2 and major histocompatibility complex class II. In vitro data suggest that both retifanlimab and tebotelimab have potential to sustain enoblituzumab-mediated immune activation and antitumor activity (Obara G, et al. *Ann Oncol.* 2021;32[suppl 5]:S814). Combination of enoblituzumab with retifanlimab or tebotelimab sustained the ability of natural killer cells and CD8+ T cells to produce interferon gamma upon restimulation. Both retifanlimab and tebotelimab enhanced enoblituzumab-dependent cytotoxicity targeting B7-H3–expressing tumor cells. In a phase 1/2 study, the combination of enoblituzumab with pembrolizumab was well tolerated (Aggarwal C, et al. *J Immunother Cancer.* 2022 [under review]). The overall response rate in anti-PD-1/PD-L1–naïve pts with SCCHN (post platinum) was 33% (6/18), including 1 confirmed complete and 5 confirmed partial responses, warranting further development of this combination in R/M SCCHN. **Methods:** This is an open-label, nonrandomized study in first-line treatment of pts with R/M SCCHN. Approximately 50 pts with PD-L1 combined positive score (CPS) ≥1 will receive enoblituzumab 15 mg/kg plus retifanlimab 375 mg and 30 pts with CPS <1 will receive enoblituzumab 15 mg/kg plus tebotelimab 600 mg. Dosing is once every 3 weeks with tumor assessment at the end of Cycle 2 and every 3 cycles thereafter. Pts with no prior systemic therapy for R/M SCCHN are eligible. Pts who completed systemic therapy >6 months before the study, if given as part of multimodal treatment for locally advanced disease, are eligible. In the tebotelimab cohort, safety data will be reviewed for dose-limiting toxicities through Cycle 2 Day 7 on the first 12 pts (2 mini cohorts of 6 pts each). All pts will be followed for survival after the last dose of study drug. The first pt was enrolled in March 2021, and 28 pts are on treatment as of January 19, 2022. Clinical trial information: NCT04634825. Research Sponsor: MacroGenics, Inc.

TPS6103 **Poster Session**

A phase 1, first-in-human, drug dose-escalation study of RM-1995 photoimmunotherapy, as monotherapy or combined with pembrolizumab, in patients with advanced cutaneous squamous cell carcinoma or with head and neck squamous cell carcinoma. *First Author: David M. Cognetti, Thomas Jefferson University, Philadelphia, PA*

Background: RM-1995 comprises an antibody against CD25, conjugated with a light-activatable dye (IRDye 700DX), which can subsequently be activated by illumination with 690 nm non-thermal red light for precise, targeted cell killing. Administration of the antibody-dye conjugate followed by local illumination results in target cell membrane disruption, while limiting damage to surrounding tissue. CD25 (IL-2Rα) is highly expressed by regulatory T cells (Tregs), thereby providing an opportunity to specifically target intratumoral Tregs for depletion via photoimmunotherapy. Tregs are critical in promoting immune homeostasis; however, in the context of solid tumors, Treg-mediated suppression detrimentally constrains anticancer T-cell responses, and a low ratio of CD8+ T cells:Tregs in the tumor is negatively correlated with clinical outcomes. Preclinical data suggest that RM-1995 photoimmunotherapy treatment alleviates local Treg-mediated restraint within the tumor microenvironment. Anticancer responses were further improved when combined with anti-PD-1 checkpoint inhibition. **Methods:** A phase 1 first-in-human dose-escalation study of RM-1995 photoimmunotherapy as monotherapy, or in combination with pembrolizumab, in patients with advanced cutaneous squamous cell carcinoma (cuSCC) and head and neck squamous cell carcinoma (HNSCC) is now enrolling (NCT05220748). The phase 1a portion will evaluate safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy of single-agent RM-1995 photoimmunotherapy and determine the maximum tolerated dose or maximum administered dose of RM-1995 with a fixed light dose for tumor illumination. The phase 1b portion will include combination therapy with pembrolizumab. Enrolled patients will receive RM-1995 IV, followed 24±4 hours later by local tumor illumination. Pembrolizumab (200 mg) will be administered 5–7 days prior to RM-1995 infusion, then again 3 weeks later. Patients may be eligible to receive repeated photoimmunotherapy cycles for up to 12 months. Primary outcomes include safety and tolerability, and dose finding. The study will include cuSCC or HNSCC patients with locally advanced or locoregional disease with or without metastases that has recurred or progressed on or after platinum-based chemotherapy, and who are not eligible for further locoregional treatment. Other criteria include ECOG 0–2 and having ≥1 tumor accessible for illumination. Key exclusion criteria are: tumor sites located in sensitive or vital anatomic structures or invading a major blood vessel (unless treated to prevent hemorrhage); and other clinically significant or uncontrolled disease processes. An estimated 18 patients will be enrolled into each portion of the study. Clinical trial information: NCT05220748. Research Sponsor: Rakuten Medical Inc.

TPS6104 **Poster Session**

A phase 1/2 trial to evaluate the safety and antitumor activity of tipifarnib and alpelisib for patients with PIK3CA-mutated/amplified and/or HRAS-overexpressing recurrent/metastatic head and neck squamous cell carcinoma. *First Author: Glenn J. Hanna, Dana-Farber Cancer Institute, Boston, MA*

Background: Understanding connections between key cellular pathways is particularly important when selecting combinatorial cancer therapies. HRAS preferentially activates PI3K 5-fold more efficiently than KRAS, while KRAS is a more efficient activator of RAF (Yan et al. 1998). Further, mutant HRAS is insufficient for oncogenic transformation if it is unable to recruit PI3K in preclinical models (Gupta et al. 2007). Conversely, mutant PI3K requires RAS to drive tumor growth (Zhao and Vogt 2008). HRAS mutation/overexpression and *PIK3CA* mutations/amplifications account for up to 50% of head and neck squamous cell carcinoma (HNSCC). Recognition of these interdependencies was the basis for the evaluation of HNSCC PDX models which demonstrated additive or synergistic anti-tumor effects that confirmed the codependency of these pathways, thus providing robust rationale for investigating combined pathway inhibition in the clinic. The KURRENT trial is enrolling patients with HRAS and/or *PIK3CA*-dependent tumors who will receive combination treatment with tipifarnib (a potent and selective inhibitor of farnesyltransferase, a critical enzyme for HRAS activity) and alpelisib, a PI3K inhibitor. **Methods:** The KURRENT trial (KO-TIP-013, NCT04809233) is an ongoing multicenter, open-label, 2-cohort, phase 1/2 trial designed to evaluate the safety of the combination of tipifarnib and alpelisib, determine the recommended combination dose(s) regimen, and evaluate preliminary anti-tumor activity in patients with recurrent/metastatic (R/M) HNSCC whose tumors are dependent upon HRAS and/or *PIK3CA* signaling. The trial will enroll 40 HNSCC patients; 20 each into two biomarker defined cohorts (Cohort 1; *PIK3CA*; Cohort 2; HRAS). Participants must have documented treatment failure from at least one prior therapy in the R/M setting and have measurable disease by RECIST v1.1. At the starting dose level, participants will receive tipifarnib at 300 mg twice daily on days 1-7 and 15-21 and alpelisib 200 mg each morning continuously during a 28-day cycle. The trial will use an adaptive dose escalation design (based on a Bayesian logistic regression model) to characterize safety, tolerability, and clinical activity of the combination to identify the Optimal Biologically Active Dose (OBAD) while maintaining a dose limiting toxicity (DLT) rate < 33%. No formal interim analysis is planned as the model-based dose escalation process requires decisions based on real-time evaluation of aggregate toxicity and efficacy data. All observed/available data among each cohort will be evaluated before choosing the combination dose for a subsequent cohort. Enrollment into the *PIK3CA* cohort began in October 2021. Clinical trial information: NCT04809233. Research Sponsor: Kura Oncology, Novartis.

TPS6105 **Poster Session**

A phase II study evaluating the efficacy of niraparib and dostarlimab (TSR-042) in recurrent/metastatic head and neck squamous cell carcinoma. *First Author: Vidhya Karivedu, Division of Medical Oncology, Ohio State University, Columbus, OH*

Background: Despite improvement in outcomes with checkpoint (PD-1) inhibitors in some patients (pts) with recurrent and metastatic head and neck squamous cell carcinoma (RM HNSCC), overall survival (OS) remains poor, necessitating novel therapy combinations. Fanconi Anemia (FA) and FA-related DNA repair pathways alterations have been associated with cumulative tumor mutational burden (TMB) due to genomic instability. High TMB is associated with improved response to PD-1 inhibitors. DNA pathway repair mutations have been reported in 17% of sporadic HNSCC. Ataxia-Telangiesctasia Mutated (ATM) loss has been reported in 60% of human HNSCC biopsies and FA-related defects were reported in 15-21% of human HNSCC biopsies and cell lines. Poly (ADP-ribose) polymerase (PARP) inhibition has already demonstrated efficacy as a single agent in multiple cancers which harbor a DNA repair defect. Preclinical data also showed PARP inhibitor (PARPi) upregulates PD-L1 expression in cancer lines and animal models via inactivation of glycogen synthase kinase 3 (GSK3β). Importantly, blockade of PD-1 re-sensitized PARPi treated cells to induce T-cell mediated cytotoxicity. Combination of PARPi and anti-PD-1 therapy significantly increased therapeutic efficacy in vivo compared to single agent. Therefore, we hypothesized that the combination of a PARPi (niraparib) and PD-1 blockade (dostarlimab) in our ongoing phase II study would enhance overall response (OR) and survival in R/M HNSCC pts (NCT04313504). **Methods:** Eligible pts must have a confirmed histopathology of non-cutaneous RM HNSCC not amenable to local therapy, progressive disease (PD) after at least one line of platinum-based chemotherapy and/or immunotherapy, age>18, ECOG <2, no prior therapy with PARPi and adequate bone marrow, liver, and renal function. Seven of 14 pts have been enrolled in the first stage of the study. If 8 or more pts develop either stable disease (SD), partial (PR) or complete response (CR), 9 additional patients will be accrued for a total of 23 patients. Pts will receive 200 mg PO niraparib daily in 28-day cycles along with dostarlimab 500mg (Q3W) for 4 doses followed by 1000mg (Q6W) until PD or unacceptable toxicity. An interim analysis will be performed to assess efficacy and safety after 14 patients become evaluable. Tumor response will be assessed per RECIST v1.1. Primary endpoint is best OR including SD, PR, and CR; Secondary endpoints include adverse events determined by CTCAE v5.0, progression free survival and OS. Integrated tissue analysis includes DNA pathway repair defects and TMB. Additional exploratory analyses including peripheral and immune cell activation will be performed on tissue and plasma samples. Clinical trial information: NCT04313504. Research Sponsor: GSK is providing both funding and drug for this study.

TPS6106 **Poster Session**

Phase 3 randomized study for evaluation of physician's choice treatment and triple metronomic as second-line therapy in head and neck cancer. *First Author: Ashay Karpe, Cardinal Gracias Memorial Hospital, Vasai, India*

Background: Around 85% of head and neck cancer patients in India are seen in locally advanced stage which either relapse or fail after the first line treatment. The options of systemic therapy treatment in second line (after first line palliative chemotherapy or failure within 6 months of chemotherapy as part of multimodality treatment) are limited. The median progression free survival (PFS) of 1-3 months and median overall survival (OS) of 4-6 months are reported across various studies. There is need for having effective medical treatment option. Rationale- Triple metronomic is oral, cheap and requires minimum resources. We will be comparing physician choice of standard systemic therapies with ASCO recommended triple metronomic therapy. **Methods:** Design- Open label randomized, superiority. Study Period- 4 years. Inclusion- Head and Neck cancer patients (Age > 18 years) either platinum refractory or planned for second line (ECOG PS ≤2 and adequate organ function). Exclusion- Uncontrolled comorbidities, Pregnancy & lactating women. Baseline - blood parameters, EORTC QOL & HN module and baseline axial imaging. Central stratified randomization (Computer generated randomization sheet) will be done- ; the stratification will be for site of tumor (oral cavity versus others) and ECOG PS (0-1/2). Arm A: Triple metronomic (Per Oral)- Erlotinib 150 mg once daily, Celecoxib 200 mg twice daily & Weekly Methotrexate 9 mg/m^2. Arm B: Physician choice therapy- Docetaxel, Paclitaxel, Cetuximab, Nivolumab, Afatinib, Pembrolizumab, 5-Flurouracil, Capecitabine Therapy will be continued till progression or intolerable side effects. Adverse events monitoring as per the NCI CTCAE 5 criteria. The response will be monitored in accordance with institutional standards. Quality of life (EORTC) would be collected at baseline, at 2 months and at 6 months. The 6 month OS assumed on the basis of previous data of docetaxel was 55, we assume that it would increase with a target hazard ratio 0.561 with type 1 error of 5%, type 2 error of 20% and 10% lost to follow up rate. The sample size is 114. Events required for analysis-93. Outcome measures & Statistical analysis:OS- from date of randomization to date of death. Patients alive at their last follow ups would be censored. PFS from date of randomization to date of progression or death whichever is earlier. Patients who have not progressed at their last follow ups would be censored. OS and PFS will be estimated by Kaplan meier analysis and would be compared between the arms by the log rank test. Cox proportional hazard model would be constructed for calculation of hazard ratio. The model would also be used to see the impact of chemotherapy regimen on overall survival in accordance with known prognostic factors. Age (below or above 60 years), gender, site, hemoglobin level (equal to or below 12 g/dl or above it) and PS (0-1 versus 2). To compare the QOL scores between the 2 arms. Clinical trial information: CTRI/2021/08/036002. Research Sponsor: None.

TPS6107 **Poster Session**

A phase 1b/2 study of nanatinostat and valganciclovir in patients with advanced Epstein-Barr virus positive (EBV$^+$) solid tumors and in combination with pembrolizumab in patients with recurrent/metastatic nasopharyngeal carcinoma (RM-NPC). *First Author: A. Dimitrios Colevas, Stanford Cancer Institute, Stanford, CA*

Background: Epstein-Barr virus (EBV) is linked to the development and pathogenesis of nasopharyngeal carcinoma (NPC). Most patients present with advanced stage disease at diagnosis (Li 2014); first-line chemoradiation is commonly followed by recurrence and poor prognosis emphasizing the need for new treatment options. Targeting EBV in NPC represents a novel therapeutic approach. EBV is predominantly latent in NPC; pre-clinical studies demonstrated that induction of the viral lytic phase by histone deacetylase inhibitors (HDACi) renders EBV$^+$ tumor cells susceptible to the cytotoxic activity of ganciclovir (GCV) (Hui 2016). Nanatinostat (Nstat), a potent Class-I HDACi, induces the expression of the lytic BGLF4 protein kinase in EBV$^+$ tumor cells, which activates the nucleoside analog GCV via phosphorylation. Phosphorylated GCV becomes incorporated into the cellular DNA causing chain termination and apoptosis. The all-oral combination of Nstat and valganciclovir (VGCV), a pro-drug of GCV, has demonstrated favorable safety and preliminary efficacy in a phase 1/2 study in patients with recurrent EBV$^+$ lymphoma (NCT03397706). This phase 1b/2, open-label, multicenter study will evaluate the safety, tolerability, pharmacokinetics, and preliminary activity of Nstat + VGCV in patients with advanced EBV$^+$ solid tumors. Additionally, the combination of pembrolizumab together with Nstat + VGCV will be evaluated in recurrent/metastatic NPC (RM-NPC) patients. NPC frequently exhibits high PD-L1 expression levels; however, PD-1 inhibitors resulted in limited response rates ranging from 20-30% in the RM-NPC setting. **Methods:** Phase 1b utilizes a 3+3 dose escalation design to determine the recommended Phase 2 dose (RP2D) of Nstat + VGCV in patients with EBV$^+$ RM-NPC. In Phase 2, up to 60 patients with EBV$^+$ RM-NPC will be randomized 1:1 to receive Nstat + VGCV at the RP2D with or without pembrolizumab to evaluate safety, tolerability, overall response rate, and potential pharmacodynamic markers of drug activity, including plasma EBV DNA levels. Additionally, patients with EBV$^+$ solid tumors other than RM-NPC will receive Nstat + VGCV at the RP2D in a separate Phase 1b dose expansion cohort. Patients eligible for the phase 1b dose escalation and phase 2 will have EBV$^+$ RM-NPC with 1-3 prior lines of platinum-based chemotherapy and no available curative therapies. Patients with advanced EBV$^+$ non-NPC solid tumors (gastric cancer, lymphoepithelioma-like carcinoma, leiomyosarcoma) and no curative therapies are eligible for the phase 1b expansion cohort. All patients must have measurable disease per RECIST v1.1 and adequate bone marrow, liver, and renal function. Enrollment began in January 2022. Clinical trial information: NCT05166577. Research Sponsor: Viracta Therapeutics.

TPS6108 **Poster Session**

Phase I trial of the ATR inhibitor BAY 1895344 combined with stereotactic body radiation therapy and pembrolizumab for recurrent head and neck squamous cell carcinoma. *First Author: Yvonne Marie Mowery, Duke University Medical Center, Department of Radiation Oncology, Durham, NC*

Background: Despite aggressive multimodal treatment that typically includes radiation therapy (RT), recurrence rates approach 50% for patients with non-HPV-related locally advanced HNSCC. Treatment options for unresectable recurrent or metastatic HNSCC are limited, though PD-1 inhibitors improve survival for a subset of patients. Radiation resistance contributes to locoregional recurrence—a major driver for HNSCC morbidity and mortality. In preclinical studies, we observed significant HNSCC radiosensitization by targeting ataxia telangiectasia and Rad 3-related (ATR) kinase with small molecule inhibitor BAY 1895344. ATR inhibition with RT has also been shown preclinically to increase antigen presentation and anti-tumor T cell activity. Similarly, preclinical data suggest synergy between BAY 1895344 and anti-PD-1 therapy. We hypothesize that treating recurrent HNSCC with concurrent anti-PD-1 therapy, ATR inhibition and RT will improve tumor control through radiosensitization and stimulating a host anti-tumor immune response. An ongoing clinical trial (NCT04095273) is assessing concurrent BAY 1895344 and pembrolizumab, but BAY 1895344 with concurrent RT has not been evaluated in patients. To determine the safety and optimal dosing of concurrent RT and BAY 1895344, we opened a multi-institutional, CTEP-sponsored phase I trial (NCT04576091) evaluating reirradiation with stereotactic body radiation therapy (SBRT) combined with BAY 1895344 and pembrolizumab for patients with recurrent HNSCC. **Methods:** Eligible patients for this single-arm trial are adults with recurrent, unresectable HNSCC who received prior head and neck RT and cisplatin. Exclusion criteria include gross skin or mandible involvement, disease encasing >180° of the carotid artery, and prior RT < 6 months before enrollment. Patients with oligometastatic disease (<5 metastases) are eligible. The initial dose escalation phase utilizes a Bayesian Optimal Interval design to determine the MTD for concurrent SBRT and BAY 1895344. In cycle 1, patients receive 200 mg pembrolizumab, followed by 2 weeks of BAY1895344 (30 mg PO Q12h, 3 days on/4 days off). In cycle 2, patients receive pembrolizumab followed by SBRT with concurrent BAY1895344. SBRT dose levels are 21 Gy or 24 Gy delivered in 3 fractions every 2-3 days. Three doses of BAY 1895344 (dose levels: 10 mg, 20 mg, or 30 mg) are given Q12h with each RT fraction. Up to 8 patients will be treated at the starting dose level (24 Gy; 10 mg BAY 1895344). The target DLT rate is 0.33 and the dose elimination rate is 0.75. DLT is defined as any grade >4 AE within 90 days of RT completion. An 18-patient expansion cohort will be enrolled at the MTD. Pre-treatment tissue and serial blood samples will be collected for correlative studies. This trial opened to accrual in November 2021, with no patients enrolled as of February 2022. Clinical trial information: NCT04576091. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

TPS6109 **Poster Session**

A pilot study of neoadjuvant cemiplimab with platinum-doublet chemotherapy and cetuximab in patients with resectable, locally advanced head and neck squamous cell carcinoma (HNSCC). *First Author: Lara Dunn, Memorial Sloan-Kettering Cancer Center, New York, NY*

Background: Definitive treatment of locally advanced HNSCC can require radical surgery and reconstruction often resulting in unacceptable functional consequences. Radiotherapy, often with concurrent chemotherapy, is administered postoperatively to achieve the best chance for cure. Induction chemotherapy has previously been shown to reduce the extent of surgical resection and need for adjuvant radiation (RT). The purpose of this trial is to evaluate if an induction regimen combining cytotoxic chemotherapy, EGFR targeting, and immune checkpoint blockade can pathologically downstage resectable HNSCC sufficiently to decrease surgical morbidity and justify omission of adjuvant RT-based therapy. Compared to standard docetaxel, cisplatin, and 5-FU (TPF), docetaxel, cisplatin, and cetuximab (TPC) has been shown to be a therapeutic alternative with a more favorable toxicity profile. Targeting PD-1 alone can induce significant pathologic responses in resectable HNSCC patients. Combining PD-1 inhibitors with cetuximab has shown promising activity in incurable HNSCC; cetuximab may optimize the tumor immune microenvionment for PD-1 therapy by stimulating IFN-gamma secretion to increase dendritic cell maturation and CD8 T cell expression of PD1. Based on this rationale, we are evaluating the novel induction regimen of platinum, docetaxel, cetuximab plus cemiplimab (anti-PD1 antibody). **Methods:** This is a 10-patient pilot study for locally advanced, resectable HNSCC patients for whom standard management requires adjuvant RT +/- chemotherapy. Patients will receive neoadjuvant treatment with a loading dose of cetuximab and cemiplimab followed by 3 cycles of cisplatin or carboplatin, docetaxel, cetuximab and cemiplimab followed by definitive surgical resection of the primary site +/- neck dissection(s). Post-operative RT +/- radiosensitizing agent(s) will be administered per standard of care (SOC) based on pathologic staging (rather than clinical staging at presentation). If the pathologic stage following induction and surgery is ypT0-2N0 without adverse features, adjuvant RT will not be administered and 6 months of adjuvant cemiplimab will be given. Otherwise, patients will receive SOC adjuvant RT-based treatment. The primary endpoint is safety and tolerability. Secondary endpoints include feasibility assessed by the number of patients whose definitive surgery was delayed due to toxicity and quantifying the number in whom clinical to pathologic downstaging is achieved and the planned surgery and/or need for adjuvant-RT based therapy is modified. Exploratory endpoints include evaluating the association between biomarkers in the tumor microenvironment and peripheral blood with pathologic response. 8 of 10 patients have been enrolled. Clinical trial information: NCT04722523. Research Sponsor: Regeneron Pharmaceuticals, Internal Grants: Serra Initiative on the Management of Head and Neck Cancer Side Effects and Department of Medicine Investigator Initiated Trial RFA.

TPS6110 **Poster Session**

NANORAY-312: A phase III pivotal study of NBTXR3 activated by investigator's choice of radiotherapy alone or radiotherapy in combination with cetuximab for platinum-based chemotherapy-ineligible elderly patients with locally advanced head and neck squamous cell carcinoma. *First Author: Christophe Le Tourneau, Institut Curie, Paris, France*

Background: Elderly patients with locally advanced head and neck squamous cell carcinoma (LA-HNSCC) are largely underrepresented in clinical trials (CT). Broad access to CTs in this population is challenging due to an increased prevalence of comorbidities and ageing-related conditions. However, as population-age increases, more and more elderly patients are diagnosed with LA-HNSCC although many are not eligible to receive standard cisplatin-based concurrent chemoradiation (CRT). CRT-related toxicities, treatment burden and compliance are a concern. NBTXR3, a first-in-class radioenhancer, composed of functionalized hafnium oxide nanoparticles, is administered by one-time intratumoral injection and activated by radiotherapy (RT). NBTXR3 is designed to locally amplify the tumor-killing effect of radiotherapy without additional toxicity to surrounding healthy tissue. NBTXR3 has been shown to prime the adaptive immune response in cancer models. NBTXR3 obtained EU marketing approval in preoperative treatment of locally advanced soft tissue sarcomas. In a Phase I trial of NBTXR3 + RT alone in elderly LA-HNSCC patients, the combination was shown to be safe and an Objective Response Rate (ORR) of 85.4% and CRR of 51.2% was reported at ASTRO 2021. A pivotal randomized phase III study was initiated and is now recruiting. **Methods:** NANORAY-312 [NCT04892173] is a global, open-label, randomized (1:1), 2-arm, Investigator's choice Phase III (Pivotal Stage) study to investigate the efficacy and safety of NBTXR3/RT±cetuximab versus RT±cetuximab in treatment-naïve, platinum-ineligible, elderly patients with LA-HNSCC. 500 patients will be enrolled. Eligible patients are ≥65 years with at least one measurable (RECIST 1.1) biopsy-confirmed T3-4 (AJCC v8) SCC of the oral cavity, oropharynx, hypopharynx, or supraglottic larynx which is amenable for intratumoral injection. For patients with oropharyngeal cancer, human papilloma virus (HPV) status must be known. In addition to the primary tumor, a single accessible LN in the neck is eligible for intranodal injection. The primary objective is PFS. The key secondary endpoint is OS. Other secondary endpoints include ORR, safety and tolerability and quality of life. Enrollment began in January 2022 and is ongoing. Clinical trial information: NCT04892173. Research Sponsor: Nanobiotix.

TPS6111 **Poster Session**

A phase II study of pemetrexed and pembrolizumab in recurrent and/or metastatic salivary gland malignancies. *First Author: Katharine Andress Rowe Price, Department of Oncology, Mayo Clinic, Rochester, MN*

Background: Treatment options for recurrent and/or metastatic (R/M) salivary gland cancer (SGC) are limited with response rates to standard cytotoxic chemotherapy (CT) low at 10-30%, and responses to single-agent immune checkpoint inhibition (ICI) <10%. Current therapeutic agents used to treat R/M SGC have an unfavorable toxicity profile including cytotoxic CTs such as cisplatin and doxorubicin and the targeted therapy lenvatinib. Treatments with general applicability and acceptable side effect profile are urgently needed. Pemetrexed (PTX) is a multi-targeted anti-folate CT with an excellent safety and toxicity profile with promising responses reported in a case series of patients (pts) with R/M SGC (Viscuse P and Price K. Marked responses to pemetrexed chemotherapy for metastatic adenocarcinoma of the parotid gland: case series. *Head Neck* 2019;41(6):E99-103.). As the combination of PTX and pembrolizumab (PMB) showed enhanced responses and survival in pts with lung cancer, we hypothesize that PTX and PMB will have efficacy in pts with R/M SGC and that the combination will have improved anti-cancer activity compared with historical controls. Correlative studies on archived tissues include methylthioadenosine phosphorylase loss, PDL1 expression, and thymidylate synthase expression as potential biomarkers of response. **Methods:** MC200708 is a single institution (3-site), open-label, single arm phase II study of PTX and PMB in patients with R/M SGC. Pts will be treated in two cohorts: one for pts with adenoid cystic carcinoma (ACC) and the other for pts with all other types of SGC (non-ACC cohort). Eligible pts must be ≥18 years old, have a pathologically confirmed SGC that is not amenable to curative-intent therapy, ECOG 0-2, adequate organ function, and at least 1 measurable lesion by RECIST 1.1. Any number of lines of prior therapy is allowed; prior treatment with checkpoint inhibitors and/or PTX is allowed. Key exclusion criteria: serious medical co-morbidity or autoimmune disease, prior grade 3-4 adverse event (AE) or grade 2-4 lung AE with ICI, and uncontrolled brain metastases. Simon's two-stage design will be used for each cohort separately given the expected difference in responses in pts with ACC and non-ACC. Primary endpoint is overall response rate. Secondary endpoints are progression free and overall survival and toxicity. All patients will receive the same treatment of PTX 500 mg/m2 IV + PMB 200 mg IV every 3 weeks until disease progression or treatment intolerance. Response assessments will occur every 3 cycles. Enrollment began July 2021 and 16 of the planned 45 patients (ACC cohort 9 of 20 pts, non-ACC 7 of 25) have been accrued. Clinical trial information: NCT04895735. Research Sponsor: Merck.

TPS6112 **Poster Session**

Abemaciclib in metastatic or locally advanced anaplastic thyroid cancer. *First Author: Vishesh Khanna, Stanford Cancer Center, Palo Alto, CA*

Background: Anaplastic thyroid cancer (ATC) is a rare and lethal tumor of thyroid epithelium, with disease-specific mortality approaching 100%. ATC accounts for > 50% of the 1200 annual deaths attributable to thyroid cancer. In the pre-molecular era, treatment options were largely ineffective, reflected in a median overall survival of 3-4 months following diagnosis. Outcomes have improved in *BRAF V600E*-mutated ATC with the FDA approval of dabrafenib and trametinib (Subbiah et al. *JCO*, 2018). However, a significant need exists for patients with BRAF wild-type tumors and patients with BRAF-mutated tumors who progress following treatment with BRAF-directed therapies. Abemaciclib is a CDK4/6 inhibitor currently FDA-approved in combination with endocrine therapy for hormone-positive breast cancer. Genomic analyses of ATC have indicated the presence of an intact Rb (Retinoblastoma) expression as well as the existence of *CDKN2A* (the gene encoding human p16) mutations in up to 32% of patients with ATC (Khan et al., *Head Neck*, 2019). Moreover, Lee et al. in 2008 reported undetectable p16 levels in 24 out of 27 (89%) patients with ATC. Low p16 levels would be expected to result in accelerated S phase entry, leading to uncontrolled ATC growth. Finally, studies in mouse xenograft models have demonstrated that ribociclib (a CDK4/6 inhibitor) slows proliferation and induces apoptosis of ATC cells (Lee et al., *Cancer Letters,* 2018). These molecular alterations and pre-clinical data provide a mechanistic rationale by which to evaluate CDK4/6 inhibitors in ATC and, to date, no CDK4/6 inhibitors have been evaluated in thyroid cancer. **Methods:** This multicenter, single-arm Phase 2 study will evaluate the safety and efficacy of treatment with abemaciclib in patients with histologically confirmed unresectable or metastatic ATC, using an optimal Simon two-stage design. Patients with BRAF V600E+ ATC must have progressed on or have an intolerance to dabrafenib and trametinib. The study intervention is abemaciclib 200 mg orally twice daily. The primary endpoint is overall response rate at eight weeks from the start of treatment. Secondary endpoints include progression-free survival and overall survival. Currently, 6 patients have been enrolled. Planned genomic analysis will be conducted to identify potential predictive biomarkers. Clinical trial information: NCT04552769. Research Sponsor: None.

6500 **Oral Abstract Session**

The effect of a multilevel community health worker-led intervention on health-related quality of life, patient activation, acute care use, and total costs of care: A randomized controlled trial. *First Author: Manali I. Patel, Stanford University School of Medicine, Stanford, CA*

Background: Low-income and minority populations have less activation in their cancer care, lower health-related quality of life, greater acute care use and total costs of care than affluent and white populations. Community-based interventions are needed to improve patient experiences and quality of cancer care equitably among these populations. We used community-based participatory methods to refine a previously tested intervention for use in urban communities. The intervention, LEAPS, uses community health workers trained to activate patients in discussions with their cancer clinicians regarding advance care planning and symptom-burden and to connect patients with community-based resources to overcome social determinants of health. We conducted a randomized controlled trial of LEAPS in collaboration with an employer-union health plan in Atlantic City, NJ and Chicago, IL. Members of the employer-union health plan with newly diagnosed with hematologic and solid tumor cancers were randomized to the 6-month LEAPS intervention. The objective of the study was to determine whether LEAPS improved quality of life (primary). Secondarily, we evaluated the effect of LEAPS on patient activation, acute care use, and total costs of care. **Methods:** We used generalized linear regression models to evaluate differences in quality of life and patient activation scores between groups from baseline to 4- and 12-months post-enrollment and regression models offset for length of follow-up to compare emergency department use, hospitalizations, and total costs of care. **Results:** A total of 160 patients were consented and randomized into the study (80 intervention; 80 control). There were no differences in demographic or clinical factors across groups. The majority were non-White (74%), female (53%), mean age 57 years with breast (31%) or lung cancer (21%) and Stage 3 or 4 (63%) disease. At 4- and 12-months follow-up, the intervention group had greater improvements in quality of life overtime as compared to the control group (difference in difference: 11.5 $p < 0.001$) and greater change in patient activation overtime (difference in difference: 11.9 ($p < 0.001$)). At 12-months follow-up there were no differences in emergency department use (0.44 (0.71) versus 0.73 (0.22) $p = 0.22$) however intervention group participants had fewer hospitalizations (1.55 (0.86) vs. 2.29 (1.31), $p = 0.002$) and lower median total costs of care ($72,585 vs. $153,980, $p = 0.04$). **Conclusions:** Integrating community-based interventions into clinical cancer care delivery for low-income and minority populations can significantly improve patient activation, reduce hospitalizations and total costs of care. These interventions may represent a sustainable resource to facilitate equitable, value-based cancer care. Clinical trial information: NCT03699748. Research Sponsor: U.S. National Institutes of Health.

6501 **Oral Abstract Session**

The PACES Study: A controlled before and after pragmatic trial of a cancer clinic–based intervention to increase early referral to specialist palliative care. *First Author: Aynharan Sinnarajah, Queen's University, Kingston, ON, Canada*

Background: Early referral to specialist palliative care (SPC) can improve symptom and quality of life outcomes that matter most to cancer patients during the late stage of their illness. We tested a multifaceted oncologist-facing intervention (Palliative Care Early and Systematic) in the real-world setting of a busy cancer clinic for its ability to increase the proportion of patients who receive early SPC (defined as SPC ≥90 days before death). **Methods:** This is a pragmatic controlled before-and-after study performed in 18 outpatient cancer clinics in two tertiary cancer centers in neighboring metropolitan cities. The control city was chosen to match as closely as possible the intervention city for population size, characteristics, and health services availability. Adults deceased from colorectal cancer (CRC) between April 2017 to December 2020 residing in either the intervention or control city. Decedents who did not visit an oncologist in the year prior to death were excluded as they were unlikely to have received the intervention. Patients who died ≤120 days after diagnosis with CRC were excluded as providers would have had insufficient time to implement the intervention. In the baseline phase (April 2017 to December 2018) patients received usual care. In the intervention phase (April 2019 to December 2020), new clinical practice guidelines and resources were implemented to increase early SPC referrals by oncologists. These changes included: a) systematically screening patients attending treatment clinics for unmet PC needs and alerting the primary oncologist, b) addition of a community-based palliative clinical nurse specialist to handle increased referrals and enhance communication and co-management of patient needs among providers, and c) implementation of templated 'shared care' letters (all providers and patient) to improve awareness of patients' needs. The primary outcome was the proportion of CRC decedents who received early SPC. **Results:** 695 decedents were included: 341 in the baseline phase (153 control, 188 intervention) and 354 in the intervention phase (145 control, 209 intervention). From baseline to intervention, in the intervention arm, the proportion of decedents who received early SPC increased from 45% to 57%; in the control arm the proportion decreased from 48% to 44% (17% difference in differences; 95%CI -2% to 32%; P=0.03). **Conclusions:** A multifaceted intervention aimed at increasing oncologists' awareness of their patients' appropriateness for early SPC increased by 17% the proportion of patients receiving early SPC as compared to controls. Additional research is needed to determine if in a real-world clinical setting further increasing the proportion of patients receiving early PC beyond 57% is feasible, and to understand the role of screening and alerting for oncologists. Research Sponsor: Canadian Institute for Health Research (CIHR), Other Government Agency.

6502 **Oral Abstract Session**

Impact of an interdisciplinary goals of care program on hospital outcomes at a comprehensive cancer center during the COVID-19 pandemic: A propensity score analysis. *First Author: David Hui, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Many hospitals have established goals-of-care (GOC) programs in response to the COVID-19 pandemic; however, few have reported their outcomes. MD Anderson Cancer Center launched a multicomponent interdisciplinary GOC (myGOC) program in March 2020 that involved risk stratification, team huddles to discuss care planning, oncologist-initiated GOC discussions, communication training, palliative care involvement, rapid-response GOC team deployment, and daily monitoring with immediate feedback. We examined the impact of this myGOC program among medical inpatients. **Methods:** This single-center study with a quasi-experimental design included consecutive adult patients with cancer admitted to medical units at MD Anderson Cancer Center, Texas during an 8-month pre-implementation (May 1, 2019 to December 31, 2019) and post-implementation period (May 1, 2020 to December 31, 2020). The primary outcome was intensive care unit (ICU) mortality. Secondary outcomes included ICU length of stay, hospital mortality, and proportion/timing of patients with in-hospital do-not-resuscitate (DNR) orders, medical power of attorney (MPOA), living will (LW) and out-of-hospital DNR (OOHDNR). Propensity score weighting was used to adjust for differences in potential covariates, including age, sex, cancer diagnosis, race/ethnicity, and Sequential Organ Failure Assessment (SOFA) Score. With a sample size of 600 ICU patients over each time period and a baseline ICU mortality of 28%, we had 80% power to detect a 5% reduction in mortality using a two-tailed test at 5% significance level. **Results:** This study involved 12,941 hospitalized patients with cancer (Pre n = 6,977; Post n = 5,964) including 1365 ICU admissions (Pre n = 727; Post n = 638). After myGOC initiation, we observed a significant reduction in ICU mortality (28.2% vs. 21.9%; change -6.3%, 95% CI -9.6, -3.1; $P = 0.0001$). We also observed significant decreases in length of ICU stay (mean change -1.4 days, 95% CI -2.0, -0.7 days; $P < 0.0001$) and in-hospital mortality (7% vs. 6.1%, mean change -0.9%, 95% CI -1.5%, -0.3%; $P = 0.004$). The proportion of hospitalized patients with an in-hospital DNR order increased significantly from 14.7% to 19.6% after implementation (odds ratio [OR] 1.4, 95% CI 1.3, 1.5; $P < 0.0001$) and DNR was established earlier (mean difference -3.0 d, 95% CI -3.9 d, -2.1 d; $P < 0.0001$). OOHDNR (OR 1.3, 95% CI 1.1, 1.6, $P < 0.0007$) also increased post-implementation but not MPOA and LW. MPOA, LW and OOHDNR were documented significantly earlier relative to the index hospitalization in the post-implementation period ($P < 0.005$ for all). **Conclusions:** This study showed improvement in hospital outcomes and care plan documentation after implementation of a system-wide, multicomponent GOC intervention. Our findings may have implications for GOC programs during the pandemic and beyond. Research Sponsor: None.

6503 **Oral Abstract Session**

Impact of high-deductible health plans on delays in metastatic cancer diagnosis. *First Author: Nicolas Trad, Harvard Medical School, Boston, MA*

Background: High-deductible health plans (HDHPs) have grown rapidly in recent years, and now cover over one-half of U.S. workers. Patients in HDHPs are liable for the costs of all cancer-related care until their annual deductible is met, with the exception of screening tests such as colonoscopy and mammography. Due to increased out-of-pocket obligations, patients may postpone presenting for concerning symptoms or diagnostic testing, leading to delayed diagnosis. We therefore assessed the impacts of HDHPs on the timing of metastatic cancer detection. **Methods:** Using a nationally representative cohort of privately insured members in a national commercial and Medicare Advantage database (2003-2017), we studied 345,401 individuals age 18-64 years whose employers mandated a switch from a low-deductible (≤$500) plan to a high-deductible (≥$1,000) plan. Our control group consisted of 1,654,775 contemporaneous individuals whose employers offered only low-deductible plans. Both groups had a 1-year baseline period when all members were enrolled in low-deductible plans, and we followed members for a maximum of 13.5 years. Participants were matched with respect to age, gender, race/ethnicity, morbidity (ACG) score, poverty level, geographic region, employer size, baseline primary cancer, baseline medical and pharmacy costs, and follow-up duration. We used a validated claims-based algorithm to detect incident metastatic cancer diagnoses. We assessed time to metastatic cancer diagnosis in the baseline period (pre-HDHP switch) and follow-up period (post-HDHP switch) using a weighted Cox proportional hazards model. **Results:** After matching, there were no systematic differences between the HDHP and control groups with regard to observable baseline characteristics (standardized differences < 0.1). The mean age of participants was 42 years and the mean ACG score was 0.75. 49% were female, 48% lived in low-income neighborhoods, and 62% were White. We detected 1,668 metastatic events over a mean follow-up period of 38 months. There were no differences in time to metastatic diagnosis in the baseline year, prior to the HDHP switch (HR 0.96, $p = 0.67$). After employer-mandated HDHP switch, HDHP participants had lower odds of metastatic cancer diagnosis (HR 0.88, $p = 0.01$), indicative of delayed detection relative to the control group. **Conclusions:** Compared with conventional health plans, HDHPs are associated with delayed detection of metastatic cancer. These findings imply that patients postpone seeking care for concerning symptoms or defer diagnostic testing when exposed to high cost-sharing. Given recent advances that have improved survival of patients with advanced-stage cancers, future research efforts should investigate the impacts of HDHPs on quality of life, engagement in palliative care, and use of treatments in this patient population. Research Sponsor: Thomas O. Pyle Fellowship (Harvard Medical School - Department of Population Medicine).

6504 **Oral Abstract Session**

Growing financial burden from targeted oral anticancer medicines among Medicare beneficiaries with cancer. *First Author: Meng Li, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The rapidly rising costs of targeted oral anticancer medicines (TOAMs) raise concerns over their affordability. Our goal was to examine recent trends in the uptake of TOAMs among cancer patients with Medicare Part D, the share of TOAM users who reached catastrophic coverage, and the annual spending on TOAMs in the catastrophic phase. **Methods:** Using the 5% SEER-Medicare, we included patients aged 65 and older who had one primary cancer diagnosis between 2011 and 2016. We included person-years where patients were enrolled in a Part D plan for the entire year, did not receive the Low-Income Subsidy (LIS) at any time of the year, and received anticancer systemic therapies. We estimated the trends in the share of patients who used TOAMs, the percentage of TOAM users reaching catastrophic coverage, and the total and patient out-of-pocket spending on TOAMs in the catastrophic phase in a year. **Results:** From 2011 to 2016, the uptake of TOAMs among our study population increased from 3.6% to 8.9%. The percentage of non-LIS TOAM users who reached catastrophic coverage increased from 54.6% to 60.3%. Among those who reached the catastrophic phase, mean total gross spending on TOAMs in the catastrophic phase increased from $16,074 to $64,233 and mean patient out-of-pocket spending from $596 to $2,549. The mean 30-day total spending increased from $4,011 to $8,857, and the mean 30-day out-of-pocket spending from $154 to $328. **Conclusions:** The high and growing burden from TOAMs highlighted the need for reining in drug prices and capping out-of-pocket spending. Research Sponsor: None.

6505 **Oral Abstract Session**

The Medicaid expansion of the Affordable Care Act and participation of patients with Medicaid in cancer clinical trials. *First Author: Joseph M. Unger, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: The Affordable Care Act (ACA) Medicaid Expansion (ME) resulted in increased use of Medicaid insurance nationwide. However, the impact of the ACA ME on access to clinical trials has not been examined. **Methods:** We examined the number and proportion of patients insured by Medicaid at enrollment over time using data from the SWOG Cancer Research Network. We examined all patients 18-64 years old enrolled to treatment trials between April 1, 1992 to February 28, 2020 using Medicaid vs. private insurance. Interrupted time-series analysis was used; first implementation of the ACA ME (in 2014) was the independent exposure variable. Segmented logistic regression was used to estimate the difference between actual enrollment of patients using Medicaid to the expected rate had the ACA ME not been implemented. To account for secular trends related to economic conditions, we adjusted for the monthly unemployment rate using data from the Bureau of Labor Statistics. Indicator variables to reflect administrative differences in Medicaid by presidential administration were included. **Results:** In total, 47,042 patients age < 65 years were analyzed, including 31,565 (67.1%) females, 18,987 (40.4%) age < 50 years, and 4,709 (10.0%) with Medicaid coverage. Overall, a 20% (OR = 1.20, 95% CI, 1.11-1.30, p < .001) increase per year in the odds of patients using Medicaid was detected following the ACA ME. Based on pre-ACA patterns, the proportion of patients using Medicaid decreased during periods of economic growth and low unemployment; thus, the model-based estimate of the proportion of patients with Medicaid insurance had the ACA ME not occurred was only 7.4% (95% CI, 4.8%-9.5%) at the end of the study period (February 2020), when national unemployment was low (3.5%). In contrast, the actual rate was 20.8% (95% CI, 17.1%-25.0%). Patterns were consistent by age but not by sex, with a stronger 29% (OR = 1.29, 95% CI, 1.17-1.42, p < .001) annual increase in the proportion of Medicaid use for female patients compared to only 7% (OR = 1.07, 95% CI, 0.94-1.23, p = .26) for males. The increase per year of Medicaid use for patients from states that implemented the ME in 2014 or 2015 was 27% (OR = 1.27, 95% CI, 1.16-1.41, p < .001) compared to 7% for patients from other states (OR = 1.07, 95% CI, 0.94-1.22, p = .28). **Conclusions:** The implementation of the ACA ME was associated with nearly a threefold increase (20.8% vs. 7.4%) in the proportion of patients using Medicaid in cancer clinical trials by early 2020. Improved access to clinical trials for more vulnerable patients is critical for improving confidence that trial findings apply to the general cancer population. These findings suggest that the recently enacted Cancer Treatment Act – which mandates that state Medicaid programs cover the routine care costs of clinical trial participation – may continue to improve access to clinical trials for those with Medicaid insurance. Research Sponsor: American Cancer Society, Other Foundation, U.S. National Institutes of Health.

6506 **Oral Abstract Session**

Changes in opioid prescription, potential misuse, and substance use disorder in pediatric cancer survivors following the 2016 CDC opioid prescribing guideline. *First Author: Xu Ji, Emory University and Children's Healthcare of Atlanta, Atlanta, GA*

Background: The 2016 Centers for Disease Control and Prevention (CDC) guideline for prescribing opioids, despite not being intended for cancer-related pain, has been shown to be associated with declines in opioid prescriptions among adults with cancer. We examine the changes in opioid prescription, potential misuse, and substance use disorder (SUD) following the guideline release among pediatric cancer survivors, a population at high risk for chronic pain. **Methods:** Using nationwide private insurance claims data, we identified survivors (aged ≤21 years at cancer diagnosis) who completed treatment for leukemia, lymphoma, central nervous system, bone, or gonadal cancers in 2009-2018 (N=8,969). We also identified enrollees without cancer who were matched based on age, gender, and region as a control group (N=44,845). Outcomes included (1) any opioid prescription and (2) any indicator for potential misuse or SUD within 1-year post-therapy. We conducted interrupted time series analysis, where time period was assessed by quarters based on the quarter-year of patients' therapy completion. Segmented linear regression was conducted to estimate the immediate change ("level" change) and the change in the time trend ("slope" change) in each outcome after the guideline release in March 2016, accounting for autocorrelation. **Results:** Before the guideline release, opioid prescription rate (21.1% vs. 7.2%) and rate of potential misuse or SUD (5.6% vs. 1.9%) were higher among survivors than controls (p<0.05). Post guideline release, we found a declining trend in opioid prescription rate among survivors (slope change = -1.0 percentage point [ppt]; p<0.001). Survivors also experienced an immediate level decrease (-2.0 ppt; p=0.040) and a decreasing trend (slope change = -0.4 ppt; p=0.004) in the rate of potential misuse or SUD. Among controls, there were decreasing trends in opioid prescription rate (slope change = -0.3 ppt; p<0.001) and rate of potential misuse or SUD (slope change = -0.1 ppt; p=0.042). By three years post guideline release, relative reductions in opioid prescription rate and rate of potential misuse or SUD were 51.8% and 76.0%, respectively, among survivors (p<0.05), with controls experiencing smaller relative reductions (29.4% and 36.5%; p<0.05). **Conclusions:** Following the release of the CDC opioid prescribing guideline in March 2016, there were reductions in opioid prescription rate and rate of potential opioid misuse or SUD among both pediatric cancer survivors and controls, with survivors experiencing greater reductions. Research Sponsor: This work was supported by a Pediatric Research Alliance Pilot Grant and Children's Healthcare of Atlanta.

6507 **Oral Abstract Session**

Association of Medicaid expansion under the Affordable Care Act and overall survival among children with cancer. *First Author: Justin Michael Barnes, Washington University School of Medicine, St. Louis, MO*

Background: State Medicaid expansions under the Affordable Care Act are associated with increased Medicaid coverage among children, including those with cancer. Since the expansions did not directly affect Medicaid eligibility criteria for children, these changes suggest "welcome mat" effects, where previously uninsured children become enrolled in Medicaid after their parents gain coverage. Insurance improvements from the expansions have been associated with improved cancer outcomes for non-elderly adults. However, it is unclear whether the expansions also impacted childhood cancer outcomes. **Methods:** Data for children ages 0-14 years diagnosed with cancer from 2011-2017 were queried from central cancer registries covering cancer diagnoses from 43 states as part of the Centers for Disease Control's National Program of Cancer Registries. The primary outcome was 2-year overall survival. We utilized difference-in-differences analyses to compare changes in 2-year survival from 2011-2013 to 2014-2017 between children who resided in states expanding Medicaid by 2014 vs. states not expanding Medicaid within the study period. Analyses were adjusted for covariates including age, race/ethnicity, sex, metropolitan residence, cancer type, and stage at diagnosis. **Results:** A total of 42,970 children with cancer were included. Overall, there were increases in 2-year survival among children in expansion states (90.5% in 2011-2013 to 91.4% in 2014-2017) but no change among children in non-expansion states (90.0% in 2011-2013 to 90.0% in 2014-2017). In adjusted difference-in-differences analyses, there was no significant change in survival after Medicaid expansion for children in expansion vs. non-expansion states (1.01 percentage points, 95% CI = -0.23 to 2.25, p = 0.11). In difference-in-differences analyses by race/ethnicity, there was a significant expansion-associated improvement in survival in Black children (3.97 percentage points, 95% CI = 0.02 to 7.93, p = 0.049) but not in White children (0.4 percentage points, 95% CI = -1.07 to 2.04, p = 0.54). There were also expansion-associated improvements in survival among children residing in counties with the lowest quartile of county income (5.88 percentage points, 95% CI = 0.38 to 11.38, p = 0.036) but not for those in higher income counties (1.15, 1.23, and 0.12 percentage points for 2nd, 3rd, and 4th quartiles, respectively). **Conclusions:** Medicaid expansion, through presumed increases in Medicaid coverage via welcome mat effects, was associated with increased 2-year survival for Black children and children residing in low-income counties. However, the concentration of Black children in states that have not expanded Medicaid highlights the need for further advocacy to more fully achieve improved outcomes. Future data are needed to clarify potential long-term impacts of Medicaid expansion on childhood cancer outcomes. Research Sponsor: None.

6508 **Oral Abstract Session**

A health insurance navigation intervention tool (HINT) for survivors of childhood cancer: Randomized pilot trial results from the Childhood Cancer Survivor Study.

First Author: Elyse R. Park, Department of Psychiatry and Medicine, Massachusetts General Hospital, Boston, MA

Background: Childhood cancer survivors are vulnerable to being underinsured and health insurance-related financial burden. Low health insurance literacy reduces survivors' ability to utilize health insurance. We conducted a pilot randomized controlled trial (RCT) to assess a virtually delivered health insurance navigation tool (HINT) intervention to improve health insurance literacy (HIL) and decrease financial burden. **Methods:** Using a multiphase, mixed methods design, we developed and tested a theoretically-driven 4-session intervention that included: 1) Learning About Survivorship Healthcare Needs, 2) Learning About Your Plan in Relation to Policy, 3) Navigating Your Plan and Obstacles, and 4) Managing Care Costs. Eligible CCSS participants were insured and had wireless device access. We assessed feasibility and preliminary efficacy of HINT versus enhanced usual care (EUC; health insurance booklet) on HIL (16-item instrument assessing knowledge and confidence with health insurance terms and activity, ACA provisions knowledge (8-items), psychological financial burden (7-items assessing worry due to medical costs), and satisfaction with health insurance coverage (1 item) using multivariable linear regression. **Results:** From 8/20 to 5/2021, 82 participants enrolled (39.7% participation rate); 53.7% female; 82% white, 7% Hispanic, and 7% black; 52.4% <40 years of age; and 57.3% from a Medicaid expansion state. 25.6% reported previously being uninsured. 57.3% were diagnosed <10 years of age, and 40.1% had ≥1 severe chronic health condition. There were gaps in health insurance literacy (HIL mean 28.5, sd=9.0; 16-60 (high-low); 39.0% were not familiar with the Affordable Care Act (ACA), and many lacked ACA provisions knowledge (e.g., appeals for coverage denials (56.1%). 82% completed 4 sessions; 92.6% completed the 5-month follow-up survey. Compared to EUC, HINT significantly improved HIL, ACA provisions knowledge, psychological financial hardship, and health insurance satisfaction (p's ≤ 0.03). **Conclusions:** Findings affirm health insurance literacy gaps among a national sample of insured long-term survivors. Results support the feasibility and preliminary efficacy of HINT on improving health insurance literacy, satisfaction, and psychological financial burden. HINT is the first intervention to demonstrate improvements in long-term survivors' health insurance literacy and psychological financial burden. Clinical trial information: NCT04520061. Research Sponsor: ACS.

	HINT		EUC		
	BL M(SD)	FU M(SD)	BL M(SD)	FU M(SD)	Multivariable Coeff (95% CI)*
HIL	29.2 (9.7)	19.8 (5.1)	27.8 (8.3)	26.1 (7.7)	-7.6 (-4.11, -11.1) p<0.001
Financial Burden	1.7 (2.17)	1.2 (1.9)	1.0 (1.6)	1.2 (1.9)	-0.9 (-1.6, -0.3) p<0.006
ACA Knowledge	3.2 (1.7)	5.1 (1.2)	3.6 (1.41)	4.0 (1.6)	1.2 (0.4, 2.0) p<0.003
Insurance Satisfaction	2.9 (1.1)	2.2 (1.1)	2.4 (1.1)	2.3 (1.0)	-0.57 (-0.5, -1.1) p=0.03

6509 **Poster Discussion Session**

State public welfare spending and racial/ethnic disparities in overall survival among adults with cancer.

First Author: Justin Michael Barnes, Washington University School of Medicine, St. Louis, MO

Background: State public welfare spending may partially address social determinants of health and mitigate structural racism. However, its association with racial and ethnic disparities and overall survival for newly diagnosed patients with cancer is unknown. **Methods:** Adults ages 18 and older with a new cancer diagnosis from 2007-2016 were queried from the Surveillance, Epidemiology, and End Results program. Annual state spending data were obtained from the US Census Bureau. We evaluated the association of 5-year overall survival (OS) and public welfare spending using cluster-robust regression. Analyses were conducted overall, by race and ethnicity, and by cancer site. To determine whether public welfare spending was associated with changes in racial and ethnic disparities in survival, we additionally assessed for interaction effects between public welfare spending and race and ethnicity. Analyses were adjusted for covariates including age, sex, metropolitan residence, state, county-level income and education, insurance status, cancer site, stage at diagnosis, and year of diagnosis. Sensitivity analyses were conducted also accounting for state Medicaid expansion effects and state spending on health care and hospitals. **Results:** A total of 2,925,550 individuals were identified in our cohort. 5-year OS was 10.6% lower in non-Hispanic Black vs. White patients. Public welfare spending was not associated with 5-year OS overall (0.25 % per 10% increase in spending, -1.47 to 1.96, p = .78) or for non-Hispanic White patients (0.52% per 10% increase in spending, 95% CI -1.30 to 2.33, p = .58). However, increased public welfare spending was associated with increased 5-year OS among non-Hispanic Black patients (2.02% per 10% increase in spending, 95% CI = 0.01 to 4.03, p = .049). There was a 4.46% (95% CI = 2.63 to 6.30, $p_{interaction}$< .001) narrowing of the 5-year OS disparity in non-Hispanic Black relative to White patients per 10% increase in spending, or a 42% closure of the 10.6% OS disparity. Specifically, increased public welfare spending was associated with a narrowed Black vs. White 5-year OS disparity for patients with breast (7.50% increase in 5-yr OS for non-Hispanic Black relative to White per 10% increasing in spending, corresponding to closing 42.1% of the disparity), cervical (12.2%, 45.9%), colorectal (3.37%, 44.9%), head and neck (8.23%, 35.7%), liver (4.54%, 44.8%), lung (1.76%, 63.3%), ovarian (6.43%, 35.9%), prostate (2.89%, 41.9%), bladder (7.62%, 42.9%), and uterine cancers (14.9%, 40.9%). Results were similar after accounting for state health care and hospital spending and state Medicaid expansion effects. **Conclusions:** State investment in public welfare was associated with improved 5-year OS for non-Hispanic Black individuals with cancer, decreasing racial disparities in cancer outcomes overall and for many cancer sites. Research Sponsor: None.

6510 **Poster Discussion Session**

Racial and ethnic disparities in adherence and reported symptoms during routine collection of patient-reported outcomes (PROs).

First Author: Samuel U Takvorian, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Background: Routine collection of PROs for patients with cancer is an evidence-based practice and critical component of high-quality cancer care, but real-world adherence and reporting patterns are poorly understood. We examined differences in PRO adherence and reported symptoms by race and ethnicity. **Methods:** We conducted a retrospective cross-sectional study using de-identified electronic health record data from a National Cancer Institute Comprehensive Cancer Center. Participants included adults seen in follow-up at one of two medical oncology practices (1 academic, 1 community) from June 2019 to February 2020, during which two validated PRO instruments (NCI PRO-CTCAE and PROMIS Global v1.2) were routinely administered electronically via portal or tablet at return visits. Adherence was defined for each participant as the proportion of visits in which a PRO questionnaire was completed within 30 days. Using ordinary least squares regression, we modeled patient adherence as a function of race/ethnicity and adjusted for age, sex, insurance, median area income, ECOG performance status, cancer type, cancer stage, visit site, and number of visits during the study. Among study participants completing at least one PRO questionnaire, we modeled reported symptoms from the first questionnaire using a similar approach. **Results:** From June 2019 to February 2020, there were 29,726 patients (mean [SD] age 60.8 [15.1] years; 18,045 [60.7%] female) seen across 111,262 medical oncology visits. Of these patients, 19,971 (67.2%) completed at least one PRO questionnaire. Adjusted mean PRO adherence and reported symptoms varied by race/ethnicity, with Black and Hispanic patients reporting significantly higher symptom burden than White patients (Table). **Conclusions:** In this large cohort reflecting real-world PRO collection patterns, Black and Hispanic patients were less likely than White patients to complete PRO questionnaires, but more likely to report more severe symptoms. There is urgent need to ensure equitable PRO access and implementation and to address greater reported symptom burden among minority patients. Research Sponsor: None.

	White (referent)[a]	Black[b]	Hispanic[b]	Other[b]
PRO adherence	0.49 (0.43, 0.54)	-0.09 (-0.12, -0.06)	-0.04 (-0.11, 0.03)	-0.11 (-0.15, -0.07)
PRO symptoms[c]				
Fatigue	1.78 (1.72,1.83)	+0.17 (0.12,0.21)	+0.21 (0.11,0.31)	+0.03 (-0.03,0.09)
Decreased appetite	1.16 (1.12,1.19)	+0.17 (0.14,0.20)	+0.08 (0.01,0.15)	+0.08 (0.04,0.12)
Nausea	1.27 (1.23,1.30)	+0.05 (0.02,0.08)	+0.09 (0.02,0.16)	+0.01 (-0.03,0.06)
Sadness	1.36 (1.32,1.40)	+0.11 (0.07,0.14)	+0.22 (0.15,0.30)	+0.08 (0.03,0.12)
Anxiety	1.48 (1.44,1.53)	+0.04 (0.02,0.07)	+0.15 (0.07,0.23)	0 (-0.05,0.05)
Quality of life	1.99 (1.94,2.04)	+0.22 (0.17,0.26)	+0.14 (0.05,0.23)	+0.10 (0.05,0.15)

[a]Mean (95% CI) [b]Mean difference (95% CI) [c]Standardized scale, 1=lowest to 5=highest symptom burden.

6511 **Poster Discussion Session**

Racial and socioeconomic disparities in telemedicine use among US patients initiating cancer treatment during the COVID-19 pandemic.

First Author: Jenny S Guadamuz, University of Southern California, Los Angeles, CA

Background: The COVID-19 pandemic was associated with declines in in-person clinical visits. While telemedicine visits have increased, uptake has varied. Here we assess demographic and socioeconomic factors associated with telemedicine use among patients initiating treatment for 21 common cancers at community oncology clinics. **Methods:** This retrospective study uses the nationwide Flatiron Health electronic health record-derived de-identified database of patients with cancer. Patient characteristics were determined using structured and unstructured data curated via technology-enabled abstraction. We included patients (≥ 18 years) who initiated first-line cancer treatment between March 2020 and September 2021 (follow-up through December 2021). We focused on differences in telemedicine use (≥ 1 telemedicine visit within 90 days after treatment initiation) across race/ethnicity, insurance coverage, rurality (per Rural-Urban Commuting Areas), and socioeconomic status (SES). SES was defined using census block group data from the American Community Survey (2015-2019) (quintiles representing least to most affluent areas) based on patient addresses and measured using the Yost Index (incorporating income, home values, rental costs, poverty, blue-collar employment, unemployment, and education information). We used logistic regression models adjusted for clinical characteristics (*i.e.*, age, sex, performance status, and stage) to examine differences in telemedicine use. **Results:** This study included 24,164 patients (48.1% women, median age: 69 [interquartile range: 61-77] years), of whom 15.9% used telemedicine services. Black patients were less likely to use telemedicine services than White patients (11.4% vs. 15.6%, odds ratio [OR] 0.69 [95% confidence interval [CI]: 0.59-0.79], p<0.01). Telemedicine use was also lower among patients without documented insurance than well-insured (commercial and Medicare payers) patients (10.7% vs. 15.9%, OR 0.62 [95% CI: 0.54-0.72], p<0.01). Those in rural (9.8%, OR 0.51 [95% CI: 0.45-0.58], p<0.01) and suburban areas (13.1%, OR 0.71 [95%: 0.64-0.79], p<0.01) were less likely to use telemedicine services than patients in urban areas (17.6%). Finally, patients in the least affluent areas had lower telemedicine use than those in the most affluent areas (10.2% vs. 24.3%, OR 0.35 [95% CI: 0.31-0.40], p<0.01). **Conclusions:** During the COVID-19 pandemic, nearly one-fifth of patients initiating cancer treatment used telemedicine services. However, there were substantial disparities: Black, uninsured, non-urban, and less affluent patients are less likely to use telemedicine services. While telemedicine may expand access to specialty care, the proliferation of these services may widen cancer care disparities if vulnerable populations do not have equitable access. Research Sponsor: Flatiron Health.

6512 **Poster Discussion Session**

Parental informed consent comprehension in childhood cancer clinical trials: Associations with social determinants of health. *First Author: Paula Aristizabal, University of California San Diego Moores Cancer Center, Population Sciences, Disparities and Community Engagament, La Jolla, CA*

Background: Adequate informed consent (IC) comprehension is an ethical right prior to participation in clinical trials. Research investigating IC comprehension and associations with social determinants of health (SDoH) is lacking. We assessed whether SDoH and related contextual factors were associated with parental IC comprehension in therapeutic childhood cancer clinical trials. **Methods:** We prospectively enrolled parents of children with newly-diagnosed cancer. Univariable and multivariable regression were used to assess whether objective IC comprehension and related domains (*Purpose/Procedures/Randomization, Risks/Benefits, Alternatives*, and *Voluntariness*) were associated with SDoH (ethnicity, marital status, language, education attainment, employment, insurance, socio-economic status, health literacy [HL]) and contextual factors (cancer type, voluntariness, satisfaction with IC). **Results:** Of 223 parents included, 112 (50%) were Hispanic and 38% of Hispanics were monolingual Spanish-speaking. In adjusted multivariable analyses, limited HL was significantly associated with lower overall IC comprehension (β = -7.22; 95% CI, -10.9 to -3.59; P < 0.001) and lower comprehension of *Purpose/Procedures/Randomization* (β = -7.53; 95% CI, -11.3 to -3.73; P < 0.001), *Risks/Benefits* (β = -8.14; 95% CI, -15.5 to -0.772; P = 0.031), and *Alternatives* (β = -17.0; 95% CI, -30.5 to -3.57; P = 0.013). Preferred Spanish language of written/verbal medical information was significantly associated with lower comprehension of *Purpose/Procedures/Randomization* (β = -8.50; 95% CI, -15.1 to -1.89; P = 0.012) and *Voluntariness* (β = -20.1; 95% CI, -34.9 to -5.33; P = 0.008). Lower satisfaction with informed consent (β = 0.988; 95% CI, 0.460 to 1.52; P < 0.001) and single marital status (β = -4.42; 95% CI, -7.81 to -1.02; P = 0.011) were significantly associated with lower IC comprehension. **Conclusions:** Among parents of children with newly diagnosed cancer who provided consent for their child's participation in a therapeutic clinical trial, limited HL was consistently associated with lower IC comprehension in all domains analyzed, except for *Voluntariness*. Spanish language preference for medical information was associated with lower comprehension of two domains; and lower satisfaction was associated with lower overall IC comprehension. These findings suggests that parents with limited HL, limited English-proficiency, and lower satisfaction may not fully comprehend the IC and thereby not truly make informed decisions. Our findings highlight the potential role of language-concordant interventions tailored to the participant's HL level in order to ultimately improve IC comprehension and contribute to a reduction of disparities in clinical trial participation and promote equitable translation of discoveries and treatments to underserved groups. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

6513 **Poster Discussion Session**

Analysis of patient (pt) withdrawal of consent using 11,993 pts from 58 alliance for clinical trials in oncology trials. *First Author: Sumithra J. Mandrekar, Alliance Statistics and Data Management Center, Mayo Clinic, Rochester, MN*

Background: Pt recruitment receives well-deserved attention, but pt retention is also important for trial interpretability and generalizability. We report on trends and predictive factors for withdrawal of pt consent, defined as pt cessation from trial participation for reasons not mandated in the protocol. **Methods:** Alliance phase II/III trials that enrolled pts during 2013 – 2019 were included. All pts had ≥2 years (yrs) of follow-up. Primary outcome was withdrawn consent (yes; no) within 2 yrs of enrollment. Pt factors included year of enrollment, age, race, ethnicity, and gender. Trial factors included randomization, use of placebo, and use of radiation. Univariable (Uni) and full multivariable (MV) logistic regression models (including all factors from Uni setting) with a Bonferroni p-value correction (p < .004 considered significant) were used. **Results:** Median age was 62 yrs, with 67% female, 82% White, 9% Black or African American, and 7% Hispanic. 52% of trials were phase II, 5% II/III and 43% III. Common (> 10%) trial categories included 22% experimental therapeutics or rare tumors, 12% gastrointestinal, 12% genitourinary, 12% neuro-oncology and 10% symptom intervention. 78% of trials were randomized, 22% placebo-controlled and 14% used radiation. 1060 (9%) pts withdrew consent within 2 yr of enrollment (range,5.7% -9.8%) during 2013-2019. In Uni models, all trial and pt factors significantly predicted pt withdrawal except age, race, and gender (See table). In MV models, pts of Hispanic origin, and >75 yrs were more likely to withdraw. Trials using radiation had less likelihood of pt withdrawal. Placebo-controlled randomized trials had higher likelihood of withdrawal. **Conclusions:** Both trial and pt factors contribute to higher rates of pt withdrawal from clinical trials. Understanding these factors will enable investigators to focus on pt education and optimization of trial design to improve pt retention and the overall clinical trial plan. Support: U10CA180821, U10CA180882 Research Sponsor: U.S. National Institutes of Health.

Factor*	2 yr Withdrawal N (%)	Uni OR (95% CI)**	Uni P value	MV OR (95% CI)**	MV P value
Year Enrolled (continuous)	1060 (8.8)	1.07 (1.03–1.11)	0.0009	1.02 (0.97–1.06)	0.47
Age, yr ref: < 65	669 (9.1)		0.012 (overall)		0.003 (overall)
65-75	250 (7.7)	0.84 (0.71–0.98)	0.024	0.94 (0.80–1.11)	0.48
75+	141 (10.2)	1.15 (0.94–1.40)	0.17	1.39 (1.12–1.72)	0.003
Ethnicity Hispanic ref: nonHispanic	97 (11.3)	1.55 (1.21–1.98)	0.0005	1.67 (1.30–2.15)	0.0001
Trial type ref: randomized no placebo	554 (7.3)		< .0001 (overall)		< .0001 (overall)
Not randomized	40 (6.1)	0.84 (0.60–1.18)	0.32	0.79 (0.56–1.11)	0.18
Randomized placebo	466 (12.4)	1.81 (1.58–2.07)	< .0001	1.64 (1.38–1.94)	< .0001
Radiation ref: radiation not used	133 (5.9)	0.57 (0.47–0.70)	< .0001	0.68 (0.54–0.86)	0.001

*Only included statistically significant in Uni or MV **OR < 1 denotes lower likelihood of withdrawal

6514 **Poster Discussion Session**

Neighborhood socioeconomic disadvantage, tobacco use, and cessation indicators among adults with cancer in the United States: Results from 10 ECOG-ACRIN trials. *First Author: Angela Wangari Walter, University of Massachusetts Lowell, Lowell, MA*

Background: Tobacco use is a modifiable risk factor for adverse outcomes among patients diagnosed with cancer. Despite ASCO's recommendation for assessment and treatment of tobacco use, integration into cancer care is suboptimal. Socioeconomic contexts influence access and utilization of tobacco treatment, but little is known about the relationship between neighborhood socioeconomic disadvantage (NSD) and tobacco assessment, assistance, and cessation among cancer patients enrolled in clinical trials. **Methods:** The NCI Cancer Patient Tobacco Use Questionnaire (C-TUQ) was centrally administered to participants enrolled in 10 ECOG ACRIN clinical trials (9 therapeutic, 1 imaging). We examined associations of NSD with patient-reported rates of receiving brief tobacco cessation support (i.e., Ask, Assist (counseling)) and cessation (past 30d quit attempts and duration). NSD was measured using the national Area Deprivation Index (ADI) based on participant's zip code. Associations between ADI (low, intermediate, and high) and tobacco variables were evaluated using logistic regression and ANOVA. **Results:** 740 patients, completing the C-TUQ between June 2017-October 2021, can be classified as 402 (54%) never smokers, 81 (11%) current smokers, and 257 (35%) former smokers. Patients were 70% male; 94% white; 3% Hispanic; mean age 58.8 (SD 9.0). Cancer diagnoses were 36% leukemia; 19% lymphoma, 18% prostate, 11% breast; 9% melanoma, 7% myeloma, and 0.5% head and neck. Patients were categorized into high (33%), intermediate (34%) and low (33%) disadvantaged neighborhoods. Patients in high (vs. low) disadvantaged neighborhoods were more likely to report being asked about smoking (OR = 3.90; 95% CI (confidence interval), 1.61 to 9.46; p = 0.0062) but less likely to report receiving counseling to help quit smoking (OR = 0.20; 95% CI, 0.06 to 0.73; p = 0.0234). Patients from high disadvantaged neighborhoods had the shortest quit duration, followed by patients from intermediate and low disadvantaged neighborhoods (mean = 145.78, 187.66, and 210.98 months, respectively, p = 0.0372). **Conclusions:** Greater socioeconomic neighborhood disadvantage was associated with increased assessment of tobacco use but decreased tobacco treatment referral, and the shortest quit duration. More research is needed to promote increased referral to tobacco treatment for individuals with cancer from disadvantaged neighborhoods to promote and sustain cessation. Research Sponsor: U.S. National Institutes of Health.

6515 **Poster Discussion Session**

Breast cancer screening in persons experiencing homelessness. *First Author: Sarah S Kilic, Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic Foundation, Cleveland, OH*

Background: Persons experiencing homelessness (PEH) suffer from poor health outcomes, including worse cancer mortality, compared to persons not experiencing homelessness. A portion of the disparity in cancer outcomes is attributable to reduced access to cancer screening, leading to more advanced-stage disease and a higher risk of death compared to the general population. Data regarding cancer screening rates in PEH are scarce. We therefore sought to evaluate baseline rates of breast cancer screening in PEH. **Methods:** All patients presenting for care from January 1, 2014 onward at a hospital system spanning five counties in a populous Midwestern state were screened for homelessness. Homelessness was identified by two criteria: presence of the Z-code for homelessness (Z59) in the patient's electronic medical record, and/or patient's address on record listed as an address matching that of a regional homeless shelter, transitional housing, or "homeless." Identified PEH were maintained in a prospective registry. For each female PEH in the screening age range, billing data for completed breast cancer screening mammography performed in the previous five years (1/1/17-12/31/21) were extracted (CPT codes 77063, 77067). Data were also extracted for a cohort of non-PEH patients eligible for screening. Demographic and clinical data were extracted for all patients. This study was approved by the hospital system's IRB. **Results:** A total of 3,474 female (biological sex) PEH were identified, with 1,320 eligible for screening mammography (alive and between the ages of 40 and 79) in the study timeframe. The median age was 53.5 years old; 44% were Black, 48% White, 8.5% unknown/other race, and 3% Hispanic ethnicity. 28% of PEH were uninsured, and 67% had government insurance; 66% had an assigned primary care physician (PCP). Of PEH eligible for screening mammography, 237 (18%) had at least one screening mammogram during this five-year interval (2017, 2.2%; 2018, 4.3%; 2019, 3.6%; 2020, 3.7%; 2021, 4.3%). In a cohort of 6,240 non-PEH eligible for screening over the same timeframe, the screening mammography rate was 32%, which was significantly higher than the screening rate for PEH (p < 0.00001). Compared to PEH who did not undergo screening mammography, PEH who underwent screening mammography were more likely to have an assigned PCP (90% vs 38%, p < 0.00001), to be a non-current tobacco user (56% vs 35%, p < 0.00001), and to be a non-current illicit drug user (84 % vs 68%, p = 0.0015). PEH who underwent screening mammography were significantly less likely to be uninsured (12% vs 31%, p < 0.00001). **Conclusions:** In the largest study of its kind to date, we identified low rates of breast cancer screening in female PEH. Interventions to increase breast cancer screening in this vulnerable population are urgently needed and may include increased access to PCPs, tobacco and drug cessation programs, and provision of health insurance. Research Sponsor: None.

6516 **Poster Discussion Session**

Associations between interpersonal violence and cancer risk factors for transgender and cisgender people. *First Author: Ash B. Alpert, Brown University School of Public Health, Providence, RI*

Background: Cancer risk factors for transgender people are largely unexplored. Extreme rates of interpersonal violence experienced by transgender people may increase the risk of cancer. The associations between exposure to interpersonal violence and cancer risk factors have not been investigated. **Methods:** We searched for experiences of violence in cohorts of 923 transgender and 1846 cisgender people matched by age, follow-up time, and year of the first encounter and measured the association between these experiences and smoking as well as BMI ≥ 40. We then estimated the prevalence ratios for these risk factors using robust Poisson regression models including gender identity, violence, and their interaction, adjusted for age and follow-up time. **Results:** Transgender people experienced more violence than cisgender people. Among transgender people, there were significantly higher rates of smoking among those who had experienced any type of violence (50% vs 35%, p<.0001) and borderline significantly higher rates of BMI ≥ 40 (23% vs 18%, p=.05). Among cisgender people, significantly higher rates of smoking in those who had experienced violence (52% vs 31%, p<.0001) and significantly higher rates of BMI ≥ 40 (23% vs 11%, p<0.001) were also demonstrated. No statistically significant difference was demonstrated in the association between violence and smoking in transgender compared with cisgender people (prevalence ratio (PR) .87, p=.17). A statistically significant difference was demonstrated in the association between violence and BMI ≥ 40 in transgender compared to cisgender people (PR .65, p=.02). **Conclusions:** Given the association between violence and cancer risk factors, eliminating violence is of profound concern to the oncology community. Violence across the life course is markedly higher in transgender versus cisgender people. Interventions are urgently needed to eliminate violence. Cancer prevention research should investigate the efficacy of methodologies known to impact interpersonal violence, including those modifying structural factors to decrease socioeconomic disparities, stigma, and oppression. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

Violence experienced by transgender and cisgender people.

Description	Total N=2769 (%)	Transgender cohort N=923 (%)	Cisgendercohort N=1846 (%)	Chi-square p-value
Any violence	718 (25.93)	438 (47.45)	280 (15.17)	<0.0001
Any childhood violence	396 (14.3)	278 (30.12)	118 (6.39)	<0.0001
Any childhood sexual violence	184 (6.64)	126 (13.65)	58 (3.14)	<0.0001
Any adult violence	557 (20.12)	338 (36.62)	219 (11.86)	<0.0001
Any adult sexual violence	126 (4.55)	95 (10.29)	31 (1.68)	<0.0001
Familial violence	345 (12.46)	244 (26.44)	101 (5.47)	<0.0001
School-based violence	115 (4.15)	99 (10.73)	16 (0.87)	<0.0001
Intimate partner violence	199 (7.19)	107 (11.59)	92 (4.98)	<0.0001

6517 **Poster Discussion Session**

A case-control study of healthcare disparities in sex and gender minority patients with breast cancer. *First Author: Erik Eckhert, Stanford University School of Medicine, Stanford, CA*

Background: Disparities in the quality of diagnosis and treatment of breast cancer in sex and gender minority (SGM) populations are largely undefined. Only 24% of studies funded by the National Cancer Institute capture data on sexual orientation, while only 10% capture data on gender identity. To address this gap, the National Academies 2020 Report calls for adding sexual orientation and gender identity (SOGI) to ongoing data collection efforts. This case-control study matching SGM patients with breast cancer to cisgender heterosexual controls is the result of linking SOGI data to the Stanford University Healthcare (SHC) Oncoshare breast cancer database, which integrates data from the electronic medical record (EMR) and California Cancer Registry. **Methods:** An initial database query across the SHC EMR was performed for charts containing SOGI terms in patients with breast cancer seen in SHC Oncology. 686 charts were identified for manual review and after eliminating false positives, the sample was reduced to 92 SGM patients, who were then matched by year of diagnosis, age, stage, ER-status, and HER-2 status to cisgender heterosexual controls within Oncoshare. Additional data on demographics, diagnosis, treatment, and relapse were then manually abstracted from the EMR. **Results:** The SGM cohort was comprised of 80% lesbians, 13% bisexuals and 6% transgender men. The median age at diagnosis across both groups was 49. SGM patients were 72% white, 4% Asian, 12% Black or Latinx 6% other compared to 63% white, 24% Asian, 6% Black or Latinx, 6% other in the controls (p = 0.0006). Thirteen percent and 32% of SGM patients engaged in risky alcohol and illicit drug use respectively, compared to 3% and 6% of controls (p = 0.028; p < 0.0001). Estrogen exposure risk factors including median age of menarche, first delivery, menopause, and use of exogenous estrogens were balanced between the two groups, but SGM patients had fewer children (median 0 vs 2, p < 0.0001). There was a delay in time to diagnosis from symptom onset in SGM patients versus controls (median 64 days vs 37 days, p = 0.043). There was no difference in surgical approach, use of post-lumpectomy radiation, or use of neoadjuvant chemotherapy for stage III disease. However, SGM patients were less likely to undergo chest reconstruction (55% vs 82%, p = 0.0098) and if ER+, to complete ≥5 years of ER-directed therapy (53% vs 72%, p = 0.048). SGM patients used more alternative medicine (46% vs 29%, p = 0.033) and had a higher rate of documented refusal of recommended oncologic treatments (38% vs 21%, p = 0.0088). Correspondingly, SGM patients experienced a higher recurrence rate (31% vs 14%, p = 0.0124). **Conclusions:** To our knowledge, this is the first study to examine quality of diagnosis and treatment of breast cancer in SGM patients. Several novel potential healthcare disparities are identified, which should be further evaluated in population-based studies to inform interventions. Research Sponsor: Breast Cancer Research Foundation.

6518 **Poster Discussion Session**

Validity and efficiency of progression-free survival (PFS)-2 as a surrogate endpoint for overall survival (OS) in advanced cancer. *First Author: Rachel Woodford, NHMRC Clinical Trials Centre, Camperdown, Australia*

Background: PFS is used widely as a primary endpoint in oncology trials and as a surrogate for OS. PFS-2, defined as time from randomization to progression on second line therapy, is potentially a more reliable surrogate than PFS but requires additional follow-up time. We evaluated the validity and efficiency of PFS-2 as a surrogate endpoint for OS and compared its performance with PFS. **Methods:** We performed an electronic search to identify randomized trials of advanced solid tumors reporting on PFS, PFS-2 and OS as pre-specified endpoints. We compared the correlations in the relative treatment effect for OS with PFS and PFS-2. We extracted data from Kaplan-Meier survival curves to create individual patient data to estimate time to statistical significance (TSS), defined as logrank P < 0.05. We further computed the samples size (person-year follow-up) required to reach statistical significance and assessed for the effect of survival post-progression (SPP). If trials failed to reach statistical significance for a particular endpoint, the maximal follow-up time was used. **Results:** Our study consisted of 39 analysis units with 20714 patients. Correlations of the OS treatment effect with the PFS and PFS-2 treatment effects were r= 0.12 (95% CI 0.00-0.13) and r= 0.67 (95% CI 0.08-0.69) respectively. The median differences in TSS between OS with PFS, OS with PFS-2, and PFS2 with PFS were 8.7, 8.4, and 3.2 months respectively. For trials with a SPP < 12 months, smaller differences in the median TSS as compared to SPP ≥12 months were seen. The median differences in follow-up required to reach statistical significance were 329, 151 and 122 person-years (PY) respectively. These differences were equivalent to a median 18.3% increase in sample size required for PFS-2 over PFS. The median increase in sample sizes were 18.2% and 22.3% for trials with SPP < 12 and ≥12 months respectively. **Conclusions:** PFS-2 has a stronger correlation with OS benefit than PFS. When PFS-2 is used as primary endpoint, trials will require an additional median 3.2 months to achieve statistical significance, and an additional 18.3% increase of sample size over PFS. PFS-2 balances between improved correlation with OS but modest increase in follow-up time and sample size. PFS-2 should therefore be considered as a primary endpoint in future trials of advanced cancers. Research Sponsor: None.

	N	OS-PFS	OS-PFS-2	PFS2-PFS
Difference in TSS (months) [95% CI]	39	8.7 [8.5-9.0]	8.4 [8.2-8.6]	3.2 [2.3-3.4]
SPP < 12 months, difference in TSS	15	3.2 [2.9-3.5]	1.0 [0.7-1.3]	1.8 [1.4-2.2]
SPP≥12 months, difference in TSS	20	18.2 [17.9-18.6]	13.0 [12.6-13.3]	3.2 [2.9-3.5]
Difference in PY follow-up [95% CI]	39	329 [315-342]	151 [140-162]	122 [113-130]
SPP < 12 months, difference in PY follow-up	16	63 [49-76]	38 [24-52]	18 [16-20]
SPP≥12 months, difference in PY follow-up	20	593 [574-613]	320 [303-336]	156 [148-165]

6519 **Poster Discussion Session**

Is health-related quality of life (HRQoL) reporting keeping pace with new drug approvals in hematology and oncology: A five-year analysis of 245 drug approvals. *First Author: Medhavi Gupta, Women & Infants Hospital, Brown Alpert School of Medicine, Providence, RI*

Background: HRQoL data in cancer clinical trials can inform tolerability of new drugs, facilitate informed decision-making, and influence health care and policy decisions, but are frequently underreported. We reviewed all registration trials that informed Food and Drug Administration (FDA) approval between 2015-2020 for latency and quality of HRQoL reporting. **Methods:** HRQoL data for each clinical trial associated with FDA drug approval between 7/2015-5/2020 was collected retrospectively from multiple sources including the FDA and clinicaltrials.gov website, conference abstracts, and journal manuscripts. The aim of the study was to analyze the proportion of trials reporting HRQoL, quality of HRQoL data, latency between FDA approval and first reporting of HRQoL data, and association between changes in HRQOL and overall survival (OS) and progression-free survival (PFS) outcomes. **Results:** Of the 259 trials involving 245 drug approvals, majority involved solid tumors (61.4%), were phase III (59.1%), and led to approval based on a non-PFS/OS endpoint (52.9%). HRQoL was a pre-specified endpoint in 55.2% and reported in 49.8% trials. HRQoL data was published by the time of FDA approval in only 41.8% cases, 24.8% reported HRQoL data > 12 mo after approval. Further, among trials reporting HRQoL (n = 129), HRQoL data was first reported in the primary paper in only 34.1%, and either in an ancillary paper in 41.9% or an ancillary abstract in 24% trials. Of the 129 trials with HRQoL data, an improvement in HRQoL was seen in 44.2%, no significant change in 41.9%, mixed results in 11.6%, and worsening in 2.3% of trials. Overall, by the time of FDA approval, OS and PFS data were reported in 59% (152/259) and 65% (168/259) trials respectively with an OS benefit seen in 23.9% (62/259) trials, and PFS benefit in 38.6% (100/259) trials. Of the 84 trials that led to FDA approvals based solely on response rate, HRQoL was reported in only 23.8% (n = 24) with a HRQoL benefit seen in only 9.5% (n = 8) trials. Trials reporting either no significant impact on HRQoL or a mixed impact on HRQoL reported median OS benefit of 4.6 months and 4.2 months respectively. In trials reporting HRQoL data > 6 mo from FDA approval, OS benefit of < 3 mo was seen in 17.8% (8/45) trials. No significant time trends were noted during the study period. **Conclusions:** There was significant underreporting of HRQoL outcomes in trials (< 50%) associated with FDA drug approvals between 2015-2020 with majority of trials reporting HRQoL data in an ancillary paper/abstract, and at a much later time than the FDA approval. While it is widely accepted that timely dissemination of HRQoL data from cancer drug trials are vital for clinical and regulatory decisions, no improvement in reporting rates were noted over past 5 years. Only 10% of drugs approved on the basis of response rates showed improvement in HRQoL in the registration trials. Research Sponsor: This work was supported by Roswell Park Cancer Institute and National Cancer Institute grants P30CA016056.

6520 **Poster Discussion Session**

Real-world progression-free survival (rwPFS) and time to next line of therapy (TTNT) as intermediate endpoints for survival in metastatic breast cancer: A real-world experience. *First Author: Chris Labaki, Dana Farber Cancer Institute, Boston, MA*

Background: Real-world progression-free survival (rwPFS) and time to next line of therapy (TTNT) are two endpoints of clinical interest in patients with metastatic breast cancer (MBC). Their validation as intermediate endpoints for overall survival (OS), in a real-world setting, remains not fully established. **Methods:** We conducted a retrospective cohort study using the nationwide US Electronic Health Record-derived de-identified Flatiron Health database. The study population included pts diagnosed with MBC from Jan 1, 2011 to Feb 30, 2021. rwPFS was defined as the time from start of first-line systemic therapy for MBC to disease progression or death. TTNT was defined as the time from start of first-line systemic therapy until start of next line of therapy. The nonparametric Kendall tau correlation between each surrogate endpoint (rwPFS and TTNT) and OS was evaluated using the Hougaard copula model in the Weibull margin distribution. Kendall's tau (τ) with its 95%CI was calculated across the entire dataset, and within each disease subgroup defined by receptor (ER and/or PR status defined as hormone receptor [HR], and HER2) status. This work was conducted on behalf of the imCORE network and the Dana-Farber Cancer Institute. **Results:** Overall, 9,770 patients with MBC were included. Median age was 63 years (IQR: 54-72 years). HR+/HER2- disease represented the most frequent MBC subtype (n=6,287; 64.4%), followed by HER2+ (n=2,096; 21.5%) and triple negative (n=1,387; 14.2%) disease. Median f/u was 41.5 months (95%CI: 40.4 to 42.8). Median OS in the overall population was 32.4 months (95%CI: 31.2 to 33.3). Median rwPFS was 11.5 months (95%CI: 11.1 to 11.9), and median TTNT was 11.1 months (95%CI: 10.7 to 11.5). Across the entire population, the correlation of rwPFS with OS was 0.54 (95%CI: 0.53-0.56), while the correlation of TTNT with OS was 0.47 (95%CI: 0.46-0.48) (Table). **Conclusions:** rwPFS and TTNT may represent meaningful intermediate endpoints for OS in patients with MBC overall, and within the different disease subgroups. Research Sponsor: Roche/ Genentech.

Median OS, rwPFS and TTNT and correlation of each pair of evaluated endpoints in all subgroups.

	Overall Population (n=9,770)	HR+/HER2- MBC (n=6,287)	HER2+ MBC (n=2,096)	Triple-negative MBC (n=1,387)
Median OS, months (95%CI)	32.4 (31.2-33.3)	35.4 (34.2-36.6)	41.7 (38.9-44.0)	13.5 (12.6-14.6)
Median rwPFS, months (95%CI)	11.5 (11.1-11.9)	13.3 (12.7-14.0)	13.4 (12.6-14.4)	5.44 (5.11-5.83)
Median TTNT, months (95%CI)	11.1 (10.7-11.5)	11.8 (11.3-12.4)	14.4 (13.6-15.4)	6.6 (6.2-7.0)
rwPFS-OS Correlation: τ (95%CI)	0.54 (0.53-0.56)	0.51 (0.49-0.52)	0.54 (0.52-0.56)	0.60 (0.57-0.62)
TTNT-OS Correlation: τ (95%CI)	0.47 (0.46-0.48)	0.43 (0.41-0.44)	0.45 (0.43-0.49)	0.57 (0.54-0.59)
rwPFS-TTNT Correlation: τ (95%CI)	0.55 (0.54-0.56)	0.51 (0.48-0.52)	0.52 (0.49-0.54)	0.66 (0.64-0.69)

6521 **Poster Session**

Representation of women in clinical trials supporting the FDA-approval of contemporary anticancer therapies. *First Author: Melissa A. Babcook, The Ohio State University James Cancer Center, Columbus, OH*

Background: Contemporary anticancer drugs frequently have different efficacy and side effects in men and women. Yet, whether women are well-represented in pivotal trials supporting contemporary anticancer drugs is unknown. The objective of this study was to characterize the representation of women in trials supporting the use of contemporary anticancer drugs. **Methods:** We retrospectively evaluated all pivotal (phase II and III) trials supporting FDA-approval of anticancer drugs from 1998 to 2018, derived from Drugs@FDA, clinicaltrials.gov, MEDLINE, and publicly available FDA-drug reviews. Expected population rates were derived from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program, and US Census databases. The primary outcome was the report of any gender-specific analysis of efficacy and/or safety, irrespective of treatment-arm. The secondary outcome was the proportional representation of women across trials, evaluated by a participation-to-prevalence ratio (PPR) of 0.85, according to cancer-type. Female representation was also assessed as change across time. Differences in pooled binary endpoint hazard ratios, by the presence or absence of adequate female representation, were also assessed. **Results:** In total, there were 97,566 participants, enrolled in 189 clinical trials, evaluating 123 anticancer therapies. Gender was reported in 182 (96.3%) clinical trials, of which 43.4% (42,299) were women, compared to 55.6% (55,267) men ($P < 0.01$). Overall, women were under-represented in clinical trials of anticancer therapies by a mean of 16.5% compared to the proportional incidence of all cancers in women. Women were the most under-represented in gastric (PPR = 0.821) and liver (PPR = 0.619) cancer trials. Sex-based drug efficacy analysis was only published in 36.8% of trials. Over time, the trend of percentage women recruited into clinical trials increased, but not at a rate comparable to prevalence (-5.0 to -5.5% of prevalence), and the gap in under-representation of women in anticancer therapy clinical trials is widening. **Conclusions:** Among pivotal clinical trials supporting contemporary FDA-approved cancer drugs, women were frequently under-represented. Additional studies are needed to understand the impact of under-representation on contemporary anticancer therapy outcomes. Research Sponsor: None.

6522 **Poster Session**

Impact of travel burden on overall survival in patients with lung cancer. *First Author: Dragomir Stoyanov, Medical University of Varna, Varna, Bulgaria*

Background: High-volume specialized centers are more efficient at managing patients with lung cancer than low-volume centers. Centralization of cancer treatment has the potential to improve patient outcomes and quality of treatment. However, the growing centralization also increases patient's travel burden (measured as travel distance or travel time) and may negatively impact access to specialist services. The aim of our study was to evaluate the potential impact of travel burden on clinical outcomes in patients with lung cancer. **Methods:** A retrospective analysis of a single Bulgarian center was performed. A total of 9240 lung cancer patients treated between 2005-2020 were included in the study. Travel distance between patients' city of residence and the treating facility was calculated with an online tool to determine the shortest route for travel using the existing road network. The mean of travel time values for every workday of the week was calculated to control for daily changes in typical traffic. The probability of survival was estimated using the Kaplan-Meier method and differences in survival in each subgroup were evaluated with a log-rank test. **Results:** About one third of all included patients were living in the same city as the treating facility (n = 2746, 29.7%). The medians for travel distance and travel time were used to stratify patients into subgroups. According to travel distance the patients were grouped into three strata – same city, < 50 km and ≥ 50 km. A cut-off of 60 min was used to stratify patients into three groups by travel time – same city, < 60 min and ≥ 60 min. Overall survival in our patient population was significantly lower with increasing travel distance ($p < 0.001$, Mantel-Cox log rank) and travel time ($p < 0.001$, Mantel-Cox log rank). The 1-year OS rate according to travel distance was 27.1% in the same city group, 22.4% in < 50 km group and 20.5% in ≥ 50 km group ($p < 0.001$). The corresponding values for the 5-year OS rate were: 2.9%, 2.6% and 1.4% ($p < 0.001$). **Conclusions:** In this retrospective study we discovered significant differences in overall survival of patients with lung cancer depending on travel distance and travel time to the treating oncological facility. Despite having similar clinical and pathological characteristics (age, sex, stage at initial diagnosis, histologic subtype), the median overall survival was significantly lower in those subgroups of patients with a higher travel burden. Research Sponsor: None.

Overall survival in travel burden subgroups.

Parameter	Subgroup	Median OS (months)	95% Confidence Interval
Travel distance			
	Same city	6.000	5.662 – 6.338
	< 50 km	5.300	5.049 – 5.551
	≥ 50 km	5.100	4.819 – 5.381
Travel time			
	Same city	6.000	5.662 – 6.338
	< 60 min	5.267	5.038 – 5.495
	≥ 60 min	5.133	4.806 – 5.461

6523 **Poster Session**

Disparities in speed to BMT consult and allograft in 279 adults with AML. *First Author: Warren Benjamin Fingrut, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Whether patient (pt) ancestry impacts the time to BMT is not established. **Methods:** We hypothesized that non-European (non-EURO) ancestry AML pts are at increased risk of delayed time to transplant. Thus, we analyzed time to allograft (Allo) by ancestry defining delayed (late) times as: Allo Indication to BMT Consult (Ind. – Consult) > 90 days, Consult – BMT > 120 days & Allo Indication to BMT (Ind. - BMT) > 180 days. We studied pts < 70 yrs transplanted 1/2016-7/2021. **Results:** In 279 AML pts (median 56 yrs, range 19-69), BMT indication was date of diagnosis if ELN 2017 intermediate/ high risk &/or high risk mutations &/or sAML in 261 (94%) pts, or date of refractory/ relapsed disease in 18 (6%) pts. European (EURO) pts (n = 195, 70%; median 60 yrs) were older than non-EURO pts (n = 84, 30%; median 49 yrs), p < .001. Most HLA-matched sibling (SIB) (27/33, 82%) & 8/8 HLA-matched unrelated donor (mURD, 113/138, 82%) recipients were EURO; more non-EURO pts received HLA-disparate grafts [cord blood (CB)/ haplo/ mmURD]: 48/84 (57%) vs 55/195 (28%), p < .001. Overall, median (range) times for BMT Ind. - Consult, Consult - BMT, & Ind. - BMT were 45 (1-1127), 86 (13-1628), & 135 (23-1683) days. 15% of pts had late BMT Ind. - Consult, 27% late Consult – BMT, & 28% late Ind. - BMT. In multivariate analysis (significant variables in Table), more older pts had late Consult - BMT & Ind. - BMT; more non-EURO pts had late Ind. - Consult, Consult - BMT & Ind. – BMT; & despite mostly being non-EURO (35/67, 52%), fewer CB recipients had late Consult - BMT. In mURD pts, BMT Ind. - BMT time was delayed in non-EURO (median 182 days) vs EURO (median 128 days) pts (p = 0.04); there was no difference in CB pts (BMT Ind. - BMT EURO pt median 118 vs non-EURO pt median 108 days, p = 0.42). During the pandemic, as compared with EURO pts BMT delays were further exacerbated in non-EURO pts (Ind. - Consult median 13 & Ind. - BMT median 33 days). **Conclusions:** Few older non-EURO pts are allografted. Matched SIB & 8/8 mURD transplants predominantly serve EURO pts; the majority of non-EURO pts receive HLA-disparate grafts. Older age & non-EURO ancestry are associated with delayed BMT. CB transplants (CBT) are the fastest regardless of ancestry. Finally, the pandemic further exacerbated delays for non-EURO pts. Strategies to mitigate referral barriers (esp. for older non-EURO pts), prompt adult donor evaluations, efficient URD searches, & utilization of all alternative donors are critical to ensure timely BMT for all. Given the rapid availability, CBT should have high priority in high-risk or urgent pts & speedy graft procurement can compensate for late referral. Research Sponsor: None.

Endpoint	Variable	Group	% Late	OR	95% CI
Late Ind. - Consult	Ancestry	EURO	*11*	-	
		Non-EURO	*23*	*2.24*	1.09, 4.59
Late Consult - BMT	Age	≤ 55	*21*	-	
		> 55	*32*	*1.92*	1.05, 3.60
	Ancestry	EURO	23	-	
		Non-EURO	*36*	*2.99*	1.59, 5.72
	Donor	CB	16	-	
		Adult	31	2.39	1.10, 5.54
Late Ind. - BMT	Age	≤ 55	20	-	
		> 55	*32*	*2.26*	1.24, 4.24
	Ancestry	EURO	*24*	-	
		Non-EURO	*37*	*2.60*	*1.40, 4.87*

6524 **Poster Session**

Survival among patients with multiple myeloma in the U.S. military health system compared to the Surveillance, Epidemiology, and End Results (SEER) program.

First Author: Alexander Dew, Walter Reed National Military Medical Center, Bethesda, MD

Background: Multiple myeloma (MM) is the second most common hematologic malignancy and remains incurable despite therapeutic advances. The US Military Health System (MHS) provides universal healthcare to beneficiaries and has been associated with improved survival across multiple malignancies. It is unknown whether access to universal healthcare via the MHS translates to improved survival for MM patients. We sought to answer this question by comparing survival data from the Department of Defense's Automated Central Tumor Registry (ACTUR) and the NCI's SEER database. **Methods:** Patients 18 years and older diagnosed with histologically confirmed MM between 1987-2013 were identified in ACTUR (N=1,488) and SEER (N=2,976) databases. Two SEER patients were matched to an ACTUR patient by age group, sex, race, and diagnosis year group. Five and 10-year survival was compared between ACTUR and SEER patients using Kaplan-Meier curves and log-rank tests. Cox proportional hazard model was used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) adjusted for potential confounders of age at diagnosis, sex, race and diagnosis year. The proportional hazards assumption for the analysis was assessed with log-log survival curves. **Results:** Median survival in the ACTUR patients was 47.1 months (95% CI: 43.9-50.4) compared to 33.0 months (95% CI: 32.0-35.0) in the SEER group. Five and 10-year survival was superior in patients from the ACTUR group compared to the SEER group with an aHR of 0.74 (95% CI: 0.68-0.81) and 0.79 (95% CI: 0.74-0.85) after adjustment for potential confounders, respectively. The survival advantage of ACTUR patients was preserved when stratified by age, sex, race, and diagnosis year. **Conclusions:** Patients treated with MM in the MHS had superior 5 and 10-year overall survival when compared to the general population. This benefit remained despite age, sex, race, and diagnosis year. Our study findings suggest the benefits of universal healthcare provided by the MHS improve survival among MM patients. Further research is warranted to delineate factors which improve survival and reduce disparity in the treatment of MM patients. Research Sponsor: Henry M. Jackson Foundation for the Advancement of Military Medicine.

Five and 10-year survival stratified for age, sex and race.

		Database	N	5-year survival aHR (95%CI)	10-year survival aHR(95%CI)
Dataset		SEER	2976	Reference	Reference
		ACTUR	1488	0.74 (0.68-0.81)	0.79 (0.74-0.85)
By Age	Age < 65	SEER	1655	Reference	Reference
		ACTUR	865	0.71 (0.63, 0.80)	0.78 (0.71, 0.87)
	Age >= 65	SEER	1321	Reference	Reference
		ACTUR	623	0.83 (0.74, 0.93)	0.86 (0.78, 0.96)
By Sex	Male	SEER	1888	Reference	Reference
		ACTUR	944	0.80 (0.72, 0.89)	0.84 (0.77, 0.92)
	Female	SEER	1088	Reference	Reference
		ACTUR	544	0.70 (0.61, 0.80)	0.78 (0.69, 0.88)
By Race	White	SEER	1962	Reference	Reference
		ACTUR	981	0.79 (0.72, 0.87)	0.83 (0.76, 0.91)
	Black	SEER	726	Reference	Reference
		ACTUR	363	0.72 (0.60, 0.86)	0.80 (0.68, 0.93)

6525 **Poster Session**

Overall cancer survival inequalities in the state of São Paulo: A comparison between public and private systems.

First Author: Bruno Casaes Teixeira, Adelphi Real World, Bollington, United Kingdom

Background: Brazilian cancer patients under the public healthcare system receive diagnoses and treatment at a later disease stage on average than private patients, likely due to the public system having less access than the private system to treatment and diagnostic technologies. The impact of the different healthcare systems on survival is unknown. We aimed to evaluate the difference in overall survival (OS) in cancer patients under public vs. private healthcare systems in São Paulo, Brazil. **Methods:** Data were drawn from the hospital-based cancer registry of the Fundação Oncocentro de São Paulo capturing clinical and demographic data including clinical setting (private/public), date of diagnosis, and disease stage. All patients had complete medical records and malignant, well classified tumors. Analyses used Cox proportional hazards regressions. For multivariate (MTV) and propensity score matched (PSM) analyses; tumor topology and morphology, patient demographics and diagnostic care setting were used as covariates. Analyses were performed for overall cancers and for 20 separate tumor types as recommended by the National Institute of Cancer. **Results:** Data from 189,850 patients were analyzed. For all cancers, the hazard ratio (HR) for OS for public vs. private healthcare was 2.30 (CI 95% 2.20 - 2.39) in univariate (UNV), 1.59 (CI 95% 1.52 - 1.66) in MTV and 1.69 (CI 95% 1.61 - 1.77) in PSM, indicating that patients under the public system were between 2.30 and 1.69 times less likely to survive their cancer (Table 1). The cancer type with the biggest HR using PSM was multiple myeloma (HR 2.37 CI95% 1.82 - 3.08). **Conclusions:** Our results show Brazilian cancer patients under the public healthcare system were in some cases more than twice as likely to die from cancer than private patients. Despite possible differences between these populations in lifestyle and other potential influencing factors, our results most likely reflect differences between the two systems in access to treatment and diagnostic technologies. Our findings highlight the inequality of care in public vs. private healthcare in Brazil. Focus should be on closing the gap between the two systems in cancer diagnosis and treatment. Research Sponsor: None.

Overall survival hazard ratio in all cancer patients by demographic characteristics.

Method	Comparator	Hazard ratio	95% Confidence interval	p-value
Univariate	Healthcare: Public vs. private	2.30	2.20, 2.39	<0.001
	Tumor grade: IV vs. I	27.37	26.31, 28.48	<0.001
	Education: Illiterate vs. college	1.76	1.68, 1.85	<0.001
	Year of diagnosis: 2011-2015 vs. 1999-2003	1.34	1.29, 1.40	<0.001
Multivariate	Healthcare: Public vs. private	1.59	1.52, 1.66	<0.001
	Tumour grade: IV vs. I	26.92	25.86, 28.02	<0.001
	Education: Illiterate vs. college	1.40	1.33, 1.47	<0.001
	Year of diagnosis: 2011-2015 vs. 1999-2003	1.21	1.16, 1.26	<0.001
Propensity Score Matching	Healthcare: Public vs. private	1.69	1.61, 1.77	<0.001

6526 **Poster Session**

Impact of equal access by race and ethnicity on patients in the Veterans Health Administration (VHA) treated for diffuse large B-cell lymphoma (DLBCL).

First Author: Snegha Ananth, University of Texas Health at San Antonio, San Antonio, TX

Background: Racial and ethnic disparities in access to care and outcomes are well-established and are critical issues across several malignancies, including DLBCL. Previous studies from national registry datasets have shown racial disparities in DLBCL disease characteristics, treatment and outcomes. The VHA is an equal access system providing a unique environment to investigate cancer disparities across the disease continuum. **Methods:** This is a retrospective chart review of 4033 randomly selected patients with an ICD code for lymphoma treated within the VHA between 01/01/2011 and 12/31/2017. Data abstractors collected baseline patient and disease characteristics and treatment responses for those with an initial diagnosis of DLBCL in that time frame. Survival time was determined via electronic health record query on 11/30/2021. Chi-square tests were used to analyze relationship between race and variables of interest. Cox proportional hazards model was used to estimate hazard ratios (HR) for race and controlling factors. **Results:** 2141 DLBCL patients met our inclusion criteria. 97% were male. Majority were Non-Hispanic Whites (NHW 75%) followed by Non-Hispanic Blacks (NHB 12.5%), Hispanics (H 5.7%) and others (O 6.8%). NHB were diagnosed at younger median age (63 years) when compared to the NHW, H and O (68 years). There was no statistically significant difference in stage at diagnosis, IPI score, cell of origin (COO) and hit status amongst racial subgroups. Outcomes analysis (Table) revealed similar treatment and response rates, median OS, 1- and 2- year survival across all racial subgroups. However, after adjusting for age, IPI, COO, and exposure to agent orange, and including up to 10-years of survival data, H had 36% lower risk of death (HR=0.64, 95% CI 0.44-0.93) than NHW, while NHB and O had similar outcomes to NHW. **Conclusions:** This large retrospective study is a continuation of our group's work (Williams et al, 2020) that doubles the cohort size and confirms that when standard of care therapy is given with equal access to care, short-term treatment and survival outcomes are same for all races. Further studies are needed to analyze risk factors associated with differences in long term outcomes. Research Sponsor: None.

Outcomes analysis.

Characteristic	NHW, N (%)	NHB, N (%)	H, N (%)	O, N (%)	P value: NHW vs.		
Total population	1607 (75)	268 (12.5)	123 (5.7)	143 (6.8)	NHB	H	O
Treatment received							
No	96 (6)	13 (5)	4 (3)	5 (4)	0.47	0.21	0.22
Yes	1511 (94)	255 (95)	119 (97)	138 (96)			
Response to 1st line of treatment							
CR	997 (73)	173 (74)	81 (76)	92 (74)	0.58	0.81	0.41
PR	174 (13)	23 (10)	14 (13)	20 (16)			
SD	45 (3)	9 (4)	2 (1)	2 (2)			
PD	149 (11)	29 (12)	10 (10)	10 (8)			
(Evaluable N = 1830)							
Survival Rate							
1 year	1241 (77)	205 (77)	92 (75)	109 (76)	0.79	0.54	0.78
2 years	1102 (69)	185 (69)	85 (69)	93 (65)	0.88	0.90	0.76
Median OS (months)	54 (14-80)	57 (14-81)	57 (11-86)	51 (13-74)	0.41	0.32	0.24

6527 **Poster Session**

Saving TIME: Accuracy of a text intervention to minimize the time burden of cancer care.

First Author: Erin Mary Bange, Abramson Cancer Center, Philadelphia, PA

Background: Patients with cancer spend substantial time receiving cancer care. There is a need for innovative strategies to decrease the time burden of cancer therapy. The current care model consists largely of in-person visits to assess treatment toxicity. Most patients treated with immunotherapy, however, do not experience substantial toxicity. We designed and evaluated a text-based instrument to identify patients without symptoms of immunotherapy toxicity. This instrument has the potential to be combined with lab assessment to identify individuals who can safely proceed directly to treatment, lessening the need for in-person office visits. **Methods:** This cross-sectional study evaluated the performance characteristics of a text-based instrument to identify patient-reported immunotherapy toxicity, against the gold standard in-person provider assessment documented in the electronic medical record (EMR). Those eligible for inclusion spoke English, were receiving single agent immune checkpoint blockade for a solid tumor, and had access to a mobile device with text messaging capabilities. The instrument contained 16 questions adapted from the NCI Pro-CTCAE and was administered via text-message 96 hours prior to the patient's scheduled infusion visit. Patient perspectives were quantified via a 13-item questionnaire. **Results:** Between October 1 and November 25, 2021, 50 patients enrolled in the study, and 45 patients completed the instrument (90% response). The median age was 68 (IQR 60-72), 31 (62%) were male, and 44 (88%) were white. Most patients received either pembrolizumab (n=27, 54%) or nivolumab (n=17, 34%) in the palliative setting (n=37, 74%) for genitourinary (n=15, 30%), lung (n=13, 26%), or skin (n=11, 22%) cancer. Patients who completed the instrument were younger (median age 67 vs 76) than those who did not complete the instrument. The prevalence of immune related toxicity documented in the EMR was 57.8%. The sensitivity and negative predictive value of the instrument was 100% (95% CI 0.87-1.00) and 100% (95% CI 0.664-1.00), respectively; other accuracy parameters are presented in the Table. The patient user questionnaire revealed that visual impairment, lack of access to a smart phone, and lack of recognition of the instrument were barriers to completion. **Conclusions:** A text-based platform is both feasible and effective at identifying patients who are not experiencing symptoms of immune toxicity, and when combined with lab assessment, can eliminate office visits for up to 47% of patients. A prospective clinical trial to assess this is underway (NCT05134636). Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

Accuracy parameters of E-triage tool.

	Estimate	95% CI
Positive Predictive Value	0.722	[0.548, 0.858]
Negative Predictive Value	1	[0.664, 1.00]
Sensitivity	1	[0.868, 1.00]
Specificity	0.474	[0.244, 0.711]
Accuracy*	0.778	[0.629, 0.888]

*Proportion of correct e-triage screens (true positives + true negatives).

6528 **Poster Session**

Financial toxicity in Hispanic cancer survivors: A nationally representative pancancer analysis. *First Author: Nishwant Swami, University of Massachusetts Medical School, Worcester, MA*

Background: A cancer diagnosis can pose a significant financial burden to patients and their families, both during and after treatment. Financial toxicity has long-term consequences, with cancer being the most commonly cited reason for medical cost-associated bankruptcy in the United States. We used nationally representative survey data to assess financial toxicity in cancer survivors, with a focus on Hispanic patients given known disparities in socioeconomic and cancer outcomes. **Methods:** 2013-2018 data from the National Health Interview Survey (NHIS) was used to select individuals aged 18 years old and older who reported any previous diagnosis of cancer. Financial toxicity was defined as unmet healthcare need, health care unaffordability, and/or general financial stress. Individuals were disaggregated by race/ethnicity, and patients who self-identified as Hispanic were further classified by country of origin. Survey-adjusted percentages characterize the cohort. Multivariable logistic regression generated adjusted odds ratios (aORs) with 95% CI for each category of financial toxicity, with non-Hispanic White (NHW) used as reference. **Results:** Hispanic patients in aggregate had the highest prevalence of all 3 categories of financial toxicity when compared to other racial/ethnicity groups (35% unmet healthcare need, 61% healthcare unaffordability, 61% financial stress). Mexican (aOR: 2.53 95%CI: 1.82–3.52), Cuban/Cuban-American (aOR: 1.97 95%CI: 1.17–3.34), and patients of Central/South American heritage (aOR: 2.61 95%CI: 1.67–4.10) were more likely to have healthcare unaffordability. Unmet healthcare needs were higher in Mexican patients (aOR: 1.43 95%CI: 1.03-1.99) and patients of Cuban descent (aOR: 1.96 95%CI: 1.07-3.58). Financial stress was highest among patients of Central/South American heritage (aOR: 4.20 95%CI: 2.50-7.05) and Mexican patients (aOR: 1.84 95%CI: 1.27-2.66). Mediator analyses further revealed that disparities persisted even after adjusting for socioeconomic status in Mexican patients (healthcare unaffordability - aOR: 1.65 95%CI: 1.14-2.40) and patients of Central/South American heritage (healthcare unaffordability – aOR: 1.99 95%CI: 1.23-3.21; general financial stress – aOR: 2.97 95%CI: 1.71 – 5.17). **Conclusions:** Our study highlights significant disparities in the financial impact of cancer treatments on Hispanic patients. Disaggregation by Hispanic country of origin illustrates differences within the Hispanic and Hispanic-American population and reveals specific groups that may be at particular risk of financial harm. Targeted interventions to improve health care access and affordability are needed to increase equity and improve outcomes. Research Sponsor: None.

6529 **Poster Session**

Analysis of demographic characteristics and disparities of enrollment in cancer clinical research at the U.S. National Cancer Institute (NCI): A 15-year experience. *First Author: Nirmal Choradia, National Cancer Institute, Bethesda, MD*

Background: Racial, gender, and socioeconomic disparities in cancer clinical trials participation have been well documented. The intramural program of the NCI in the National Institutes of Health (NIH) Bethesda campus conducts clinical research where participants are referred by their physician or self-referred, treated without charge and receive aid in travel expenses. We sought to describe the demographics of participants and identify potential disparities. **Methods:** We used the clinical research data repository of the NIH, Biomedical Translational Research Information System (BTRIS), to extract self-reported demographic data of enrollees in NCI protocols from 2005-2020. Comparisons were made with the U.S. population of patients with cancer as captured in the Surveillance, Epidemiology, and End Results (SEER) Program (2005-2018). The average household income per zip code was derived from the American Community Survey at five-year increments from 2011, 2015, and 2019. **Results:** We obtained data on 40,007 participants; 38,531 (95%) came from the U.S., of which 18,606 (48%) from DC, Maryland, or Virginia (DMV). Median age at consent was 54 years (range 2 – 89). Proportions of basic demographic attributes and corresponding values from SEER data were presented. Notably, Hispanic male, non-Hispanic female, and white female participants were under-represented in NCI clinical research compared to SEER data. African Americans were under-represented in the non-DMV population (5%) vs. the DMV (19%). Also, for patients from the DMV area, median income was consistently less for African American participants compared to White and Asian participants. **Conclusions:** The identified disparities may be partially due to the specific research activities available at the NCI, but strategies aiming at increasing the participation and representation of under-represented groups are required. Research Sponsor: None.

	NCI U.S. (2005-2020) (N = 38,527)		SEER (2005-2018) (N = 9,121,230)	
Ethnic Group	**Male**	**Female**	**Male**	**Female**
Non-Hispanic	20,544 (53%)	14,361 (37%)	4,036,498 (44%)	4,203,238 (46%)
Hispanic	1,396 (4%)	1,323 (3%)	881,494 (10%)	399,241 (4%)
Unknown	513 (1%)	390 (1%)	0 (0%)	0 (0%)
Race				
White	17,243 (45%)	12,092 (31%)	3,645,518 (40%)	3,807,537 (42%)
African American	2,790 (7%)	1,844 (5%)	467,916 (5%)	493,007 (5%)
Asian/Pac. Islander	933 (2%)	845 (2%)	226,814 (3%)	304,547 (3%)
Am. Indian/Alaska Native	63 (0%)	56 (0%)	19,496 (0%)	23,599 (0%)
Unknown	1,424 (4%)	1237 (4%)	75,995 (1%)	56,801 (1%)

6530 **Poster Session**

Availability of data for screening, offering, and consenting patients to cancer clinical trials: Report from an ASCO-ACCC collaboration. *First Author: Alice R. Pressman, Sutter Health, Walnut Creek, CA*

Background: Only a small fraction of patients with cancer participate in treatment trials. Patients identifying as members of racial and ethnic minority groups are consistently underrepresented in these trials. A recent systematic review reported that patients, regardless of race and ethnicity, are willing to enroll in trials if asked to participate by their treating clinician. Prospective and longitudinal data and metrics at the site- and clinician-level are necessary to understand whether patients are equitably considered for clinical trials. **Methods:** ASCO and Association of Community Cancer Centers (ACCC) developed a self-assessment for trial sites to record and gauge the number of patients across races and ethnicities screened, offered, and enrolled into clinical trials. Research sites, from across the US, were recruited through an open call to apply to participate in the ASCO-ACCC Pilot Project. There were 65 sites assigned to this pilot study, which tested the feasibility and utility of the site assessment. Sites were asked to enter 2019 and 2020 aggregate data for each step along the clinical trial enrollment continuum by select races and ethnicities (Black, Hispanic/Latinx, White) and overall. **Results:** 62 of 65 sites completed the study and represented a range of settings and practice types (61% academic, 26% hospital/health system, 13% independent). Only 2 sites (3%) were able to provide the data requested at each enrollment step in the assessment (table). Sites that collected the data did not do so routinely (table) and most had to compile data through multiple sources and/or manual extraction (40-100% across enrollment steps). Sites with missing data reported they did not collect data at all (36-64% across enrollment steps), did not collect data in a systematic way (0-29% across enrollment steps), or stated it would be too burdensome to manually review charts to extract data (12-29% across enrollment steps). **Conclusions:** Data collection and routine evaluation of participation metrics, by race and ethnicity, are necessary to assess and monitor equity and diversity in clinical trials. Most sites in this study did not collect, or routinely collect, data for screening, offering, and consenting patients to clinical trials. Without these data, sites are unable to evaluate and monitor whether their patients have equitable access to clinical trials or establish strategies to address any inequities. ASCO and ACCC will continue to partner with sites to better understand their processes and the feasibility of collecting such data in a systematic and automated way, such as through electronic health record systems. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

Enrollment Step	% Sites with Data	% Sites Routinely Collecting Data*
Screening		
Initial Screen	18	0
Eligibility Screen	31	6
Eligibility Confirmation	42	14
Offered Trials Onsite	18	5
Offered Trials Offsite	6	0
Patient Consented	64	39

*Among 62 participating sites.

6531 **Poster Session**

Are pivotal clinical trials for lymphomas that led to drug approval representative of the population affected by these diseases? *First Author: Mycal Casey, Medical College of Georgia, Augusta, GA*

Background: There are significant inequities in cancer care and outcomes in the United States (US) and worldwide. Race, ethnicity, and sex all define sub-groups affected by these inequities. Randomized controlled trials (RCTs) provide new therapies in cancer care. Many new drugs have been recently approved for the management of lymphoma. We examined whether pivotal clinical trials included populations representative of those affected. **Methods:** Lymphoma clinical trials were collected from the US Food and Drug Administration (FDA) Databases 'Oncology (cancer)/Hematologic Malignancies approval notifications' and 'Novel Drug Approvals' between 2011 and 2021. Trials were also reviewed for demographic data on ClinicalTrials.gov (CT.gov) and Primary Literature related to the drug approval. Only studies for adult patients were included; one study was excluded due to inconsistencies in the total patients enrolled and the totals by race. Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) RCTs were not included. The burden of diseases based on Surveillance, Epidemiology, and End Results (SEER) data was used as a comparison for US participants. **Results:** Thirty-three pivotal trials were identified from the FDA databases (2011-2021); 18 (54.5%) had available race data on CT.gov or in Primary Literature. Three trials focused on classical Hodgkin's Lymphoma (cHL) and 15 on Non-Hodgkin's Lymphoma (NHL). Two of the three trials for cHL with available data for race reported ethnicity data. Only 10 of 15 NHL trials that reported race demographics had available ethnicity data. Table 1 shows trials that had available data for race and ethnicity along with proportions from the SEER data. There was underrepresentation of Blacks and to some extent Hispanics in both cHL and NHL trials. Females were also underrepresented, particularly in NHL trials. **Conclusions:** There is racial, ethnic, and sex misrepresentation within clinical trials that led to approval of drugs for lymphomas in the US between 2011 and 2021. In addition, there was significant underreporting of racial and ethnic subgroups noted in the clinical trials. Research Sponsor: None.

Demographic distribution.

	Hispanic	AI-AN	Asian-PI	Black	White	Other/Not Reported	Female	Male	Total
cHL RCTs	109 (7.2%)	2 (0.1%)	129 (6.6%)	71 (3.6%)	1679 (85.8%)	76 (3.9%)	835 (42.7%)	1122 (57.3%)	1957
cHL SEER%	11.0%	0.2%	2.4%	11.9%	84.0%	1.4%	47.5%	52.5%	-
NHL RCTs	106 (5.7%)	9 (0.3%)	175 (6.1%)	81 (2.8%)	2353 (81.4%)	274 (9.5%)	1130 (39.1%)	1762 (60.9%)	2892
NHL SEER%	8.4%	0.3%	3.2%	8.1%	86.4%	2.1%	46.8%	53.2%	-

Abbreviations: AI-American Indian, AN-Alaskan Native, PI-Pacific Islander, cHL-classical Hodgkin's Lymphoma, NHL-Non-Hodgkin's Lymphoma, SEER-Surveillance, Epidemiology, and End Results, RCTs-Randomized Controlled Trials.

6532 **Poster Session**

Overcoming barriers to tumor genomic profiling through direct patient social media outreach. *First Author: Seyram A Doe-Tetteh, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Tumor genomic profiling is increasingly used to identify actionable genomic alterations as a guide to therapy selection. To overcome barriers to genomic testing for patients with rare cancers, we initiated a program to offer free clinical tumor genomic testing worldwide to patients with select rare cancer subtypes. **Methods:** Patients were recruited through social media outreach, engagement with disease advocacy groups, or via physician referral, with a focus on recruiting patients with histiocytosis, germ cell tumors and rare pediatric cancers. Tumor and patient-matched germline DNA were analyzed using the MSK-IMPACT targeted sequencing next generation sequencing panel with return of results to patients and their local physicians. Whole exome recapture of MSK-IMPACT DNA sequencing libraries was performed for patients with female germ cell tumors to define the genomic landscape of this rare cancer subtype. **Results:** 359 cancer patients expressed interest in the Make-an-IMPACT program, of whom 333 were enrolled. Tumor tissue was received for 288 (86.4%), with 250 (86.8%) having tumor DNA of sufficient quantity and quality for MSK-IMPACT testing. 14 histiocytosis patients have received genomically guided therapy to date, of whom 13 (93%) have had clinical benefit based on local MD response assessment with a mean treatment duration of 16.7 months (range 3-32+). Whole exome sequencing of ovarian GCTs identified a subset with fully haploid genotypes, a phenotype rarely observed in other cancer types. Actionable genomic alterations were rare in ovarian GCT (28%), however, 2 ovarian GCTs and squamous transformation had high tumor mutational burden, one of whom had a complete response to pembrolizumab. **Conclusions:** Social media outreach can facilitate the assembly of cohorts of rare cancers of sufficient size to define their genomic landscape. By profiling tumors in a clinical laboratory, results could be reported to patients and their local physicians where they could be used to guide treatment selection. This can also open the door to diversifying and being able to study the genomic landscape in a diverse cohort. Research Sponsor: Cycle for Survival, the Marie-Josee and Henry R. Kravis Center for Molecular Oncology.

6533 **Poster Session**

Cost of consent document (CD) translation is a potential barrier to consenting limited English-proficient participants (LEPPs) in non-industry–sponsored studies (NISS). *First Author: Maria A Velez, Department of Medicine, Division of Hematology/Oncology, UCLA, Los Angeles, CA*

Background: Racial/ethnic minority patients (pts) are underrepresented in cancer clinical trials. Challenges specific to LEPPs include the need for translated CDs, which can cause research delays and add cost. While most enrollment barriers are similar between industry sponsored studies (ISS) and NISS, costs of CD translation are typically covered by the sponsor in ISS. NISS often have limited, or no funds allocated for CD translation. Although it is required that LEPPs sign translated CDs, we hypothesized that investigators on NISS would find ways to avoid incurring the cost of CD translation. **Methods:** All pts who consented to studies at the UCLA Jonsson Comprehensive Cancer Center from 2013-2018 were included. Electronic health record data was reviewed. Adult LEPPs had a primary language other than English and their chart either flagged them as needing an interpreter or the pt used an interpreter in their care 6 months before or after the consent date. For pediatric patients, regardless of the pt s primary language, LEPPs had a guardian who needed an interpreter within 6 months of the consent date. CD language was documented when available by chart review, but when not, we evaluated all IRB-approved CDs for the corresponding study and assumed that the pt signed appropriately translated CDs if available at the time of consent or within the following month. Chi square tests were used to compare the proportion of LEPPs who consented to NISS vs ISS and the proportion of LEPPs who consented with CDs not in their primary language. All analyses were performed using JMP, Version 16. SAS Institute Inc., Cary, NC, 19892021. **Results:** Although we do not have access to data on to whom consents were offered, of the 12202 consenting events during the study period, the proportion of consenting events for LEPPs was 2.7% in NISS vs 5.4% for ISS ($p < 0.01$). This difference did not appear to be driven by study type, as results were similar when only consenting events for interventional studies ($n = 9886$) were considered, with LEPPs representing 2.4% in NISS vs 5.5% in ISS ($p < 0.01$). Among LEPPs, 67.2% of participants who consented to NISS consented with CDs in a language other than their primary language vs 32.2% in ISS ($p < 0.01$). LEPPs who consented with language appropriate CDs represented 0.9% of those consenting to NISS vs 3.7% for ISS ($p < 0.01$). **Conclusions:** LEPPs consented less frequently to NISS compared to ISS, and when they did consent to NISS, the CDs were usually not translated into the pt s primary language. We posit that the cost of translating CD discourages investigators from consenting LEPPs to NISS. Approaches that reduce or eliminate translation costs should increase the availability of translated CDs, potentially increasing enrollment of LEPPs to NISS while ensuring that they are fully informed about the purpose, procedures, and risks involved in these trials. Research Sponsor: UCLA Jonsson Comprehensive Cancer Center Seed Grant.

6534 **Poster Session**

Association of U.S. county social vulnerability with cancer mortality. *First Author: Akhil Mehta, Loma Linda University Department of Internal Medicine, Loma Linda, CA*

Background: Social determinants of health (SDOH) can predispose underserved communities to poor cancer outcomes. The CDC has created a Social Vulnerability Index (SVI) score for US counties that integrates four SDOH: socioeconomic status, household composition & disability, minority status & language, and housing type & transportation. Scores range from 0 to 1, with higher values signifying more vulnerability. SVI is a significant determinant of overall mortality, but its association with cancer mortality is unclear. This study aimed to investigate if there is a relationship between SVI and cancer mortality. **Methods:** CDC WONDER (Wide-Ranging Online Data for Epidemiological Research) was used to estimate age-adjusted mortality rates per 100,000 person-years with 95% CIs for adults > 18 years of age from 3,030 (96%) US counties between 2014-2018 for a composite of three cancers (lung, breast, and colon cancer), individual cancer subtypes, and demographic groups (sex, ethnicity/race, urban/rural classification). Age-adjusted mortality rates were compared across SVI quartiles: 1st (least vulnerable) to 4th (most vulnerable). Linear regression was used to identify the association between the 4th vs. 1st SVI quartile and the odds of being above the median mortality rate for composite cancers, individual cancer subtypes, and demographic groups. **Results:** Overall, age-adjusted composite cancer mortality rate per 100,000 person-years was 122.9 (lung cancer 82.8, breast cancer 38.1, colon cancer 21.9). The largest concentration of most vulnerable US counties and composite cancer mortality was in the southeastern US. Age-adjusted composite cancer mortality rates increased from 1st to 4th SVI quartiles. Counties in the 4th SVI quartile vs. 1st SVI quartile were significantly more likely to be above the median mortality rate for composite cancer (OR 6.46 [95% CI, 5.16 - 8.08]), lung cancer (6.88 [5.46 - 8.66]), breast cancer (2.77 [2.17 - 3.54]), and colon cancer (6.20 [4.82 - 7.97]). Among all races, non-Hispanic Black adults in the 4th SVI quartile vs. 1st SVI quartile were significantly more likely to be above the median mortality rate for composite cancer (OR 9.46 [95% CI, 6.19 - 14.4]), lung cancer (13.8 [7.87 - 24.1]), breast cancer (5.53 [3.16 - 9.68]), and colon cancer (6.34 [3.69 - 10.9]). Moreover, rural counties in the 4th SVI quartile vs. 1st SVI quartile were between 2- to 8-times more likely to be above the median mortality rate for composite cancer and individual cancer subtypes. **Conclusions:** This study highlights the most socially vulnerable US counties have higher cancer mortality rates than the least vulnerable US counties. Furthermore, non-Hispanic Black adults and rural counties in the most socially vulnerable category have higher cancer mortality rates than those in the least socially vulnerable category. Additional work is needed to understand how SVI can be used for better resource allocation to help mitigate cancer mortality. Research Sponsor: None.

6535 **Poster Session**

Feasibility of systematic screening for unmet social determinants of health (SDoH) needs and associated resource utilization in ambulatory oncology. *First Author: Ashley Odai-Afotey, Brigham and Women's Hospital, Boston, MA*

Background: Addressing unmet SDoH needs may reduce interruptions to cancer care caused by ED visits and hospitalizations (EDH). We aimed to determine feasibility of systematic screening for unmet patient-reported SDoH needs within a large tertiary academic comprehensive cancer center and association of unmet needs with EDH. **Methods:** We conducted a cross-sectional analysis of SDoH needs among new oncology patient (pts) consults from 5/15-9/21 at Dana-Farber Cancer Institute (DCFI). Pts completed an intake questionnaire including demographics, disease, and SDoH needs of financial distress, health literacy/numeracy, social isolation on a dichotomous or 5-point Likert scale. We ran bivariate and multivariable models on the association between demographics, SDoH and EDH within 30 days of consult using robust generalized estimating equations controlling for clustering by consult provider. **Results:** 125,997 unique new consults were seen from 5/15 – 9/21 of which 20,913 completed the intake questionnaire and were alive at 30 days after consult. Respondents were age 40-64 (50%), female (60%), non-Hispanic (84%), White (90%) and English speaking (97%), and 7% had an EDH within 30 days of consult. The most reported SDoH need was limited health numeracy (26%). In bivariate analysis, factors associated with ED visits were: non-English language, lung or GU/GYN cancer, living > 25 mi from DFCI and limited health literacy and numeracy (all $p < 0.05$). Demographics associated with hospitalizations included: White race and English as a primary language (EPL) (both $p < 0.05$). Multivariable analysis showed female gender (OR 1.53, $p < 0.01$), lung (OR 3.22*) and GU/GYN (OR 2.21*) ($p < 0.05$ for both) cancer, and living > 25 mi from DFCI (OR 2.50, $p < 0.0001$) were associated with increased likelihood of ED visit while EPL (OR 1.80, $p < 0.05$) and GU/GYN (OR 1.65, $p < 0.01$*) cancer were associated with increased likelihood of hospitalization. **Conclusions:** It is feasible to systematically screen for unmet SDoH which are associated with increased frequency of ED visits. Differences in characteristics associated with ED vs. hospitalization could indicate possible bias or suggest SDoH needs as a reason for avoidance of costly medical care. Further study will expand SDoH screening and measure impact of resource matching to reduce disruptions to cancer care. Research Sponsor: Brigham and Women's Leadership for Health Equity Grant.

SDoH	ED visit, n (%)	p	Hospitalization, n (%)	p	Adjusted† OR for ED, (p)	Adjusted† OR for Hospitalization, (p)
Limited Health Literacy	54 (2)	< 0.01	208 (6)	0.93	1.21 (0.44)	0.93 (0.57)
Limited Health Numeracy	74 (1)	0.03	367 (7)	0.32	1.34 (0.19)	1.11 (0.24)
Financial Distress	33 (1)	0.41	226 (6)	0.92	0.68 (0.10)	0.98 (0.81)
Social Isolation	29 (1)	0.75	166 (6)	0.16	0.81 (0.46)	0.97 (0.74)

*Compared to breast cancer †Model covariates: age, gender, distance, primary language, SDoH & disease

6536 **Poster Session**

Incidental pulmonary nodules, lung cancer screening, and lung cancer in the Medicare population. *First Author: Raymond U. Osarogiagbon, Multidisciplinary Thoracic Oncology Department, Baptist Cancer Center, Memphis, TN*

Background: Low-dose CT lung cancer screening (LDCT) saves lives, but only 5%-10% of eligible persons in the US have participated. Management of indeterminate pulmonary nodules (IPNs) identified on CT scans may also reduce lung cancer mortality. We assessed the frequency of IPNs, estimated cumulative lung cancer rates following IPNs, and compared characteristics of lung cancers diagnosed following IPNs versus LDCT screens. **Methods:** We defined 2 cohorts in the SEER-Medicare database: persons with 12+ months of Medicare Part A&B coverage during 2014-2019 comprised the 5% sample cohort; persons in SEER-Medicare diagnosed with lung cancer during 2015-2017 with Part A&B coverage for the prior 18-month period comprised the lung cancer cohort. We defined IPNs as chest CTs with ICD-10 codes of R91.1 (solitary pulmonary nodule) or R91.8 (other nonspecific abnormal finding of lung field) on the same date as the CT; we used corresponding ICD-9 codes through September 2015. We classified lung cancer cohort cases by whether they had an LDCT (LDCT group), an IPN without an LDCT screen (IPN-only), or neither (Referent) within 18 months before diagnosis. We compared cancer stage and survival between these groups. **Results:** Of 627,547 subjects in the 5% sample cohort, 58.6% were women; 85.6% were non-Hispanic White (NH-Whites) and 7.7% non-Hispanic Black (NH-Blacks). Over median 5.0 years follow-up, 26.3% had chest CTs and 12.0% had IPNs. The IPN rate was similar by sex but significantly higher in NH-Whites (12.7%) than NH-Blacks (9.7%). The cumulative lung cancer rate following initial IPNs was 2.27% at two years. Of the 44,194 lung cancer cohort cases (85.8% NH-White, 8.2% NH-Black), 26.9%, 2.9% and 70.2% were in the IPN-only, LDCT, and Referent groups, respectively. NH-Whites comprised a higher proportion of LDCT than of IPN-only cases (90.1% vs. 88.4%), while for NH-Blacks, the reverse was true (5.4% vs. 6.5%). The ratio of LDCT:IPN lung cancer cases was 1:9. Among IPN-only and LDCT group cases, 52.0% and 50.3%, respectively, were localized stage, compared to 21.5% for the Referent group. Among all localized cases, 45.4% and 4.9% were in the IPN-only and LDCT groups, respectively. Comparing 3-year survival between IPN vs LDCT vs Referent groups, respectively: aggregate overall survival rates were 53.5% v 59.2% v 29.2%; aggregate lung cancer-specific survival, 71.1% v 75.3% v 46.6%; overall survival for localized cases, 73.2% v 80.7% v 62.9%; lung cancer-specific survival rates for localized cases, 88.2%, 91.8% and 81.4%. **Conclusions:** Subjects with IPNs had similar stage distribution and survival as LDCT-screened subjects. Almost half of localized cases had prior IPNs, compared to a < 5% of LDCT-screened cases. IPN programs, by circumventing implementation barriers to LDCT, may expand access to early lung cancer detection, including to African American patients and in places where LDCT coverage is not available. Research Sponsor: None.

6537 **Poster Session**

Population-based impact of rurality and neighborhood-level socioeconomic disadvantage on pediatric cancer mortality in Washington State. *First Author: Timothy James Daeeun Ohlsen, Pediatric Hematology/Oncology, Department of Pediatrics, University of Washington, Seattle, WA*

Background: Emerging evidence suggests mortality among children with cancer differs based on socioeconomic factors. The effects of residential location in relation to these factors are not well-characterized. We examined associations of rurality and neighborhood-level socioeconomic (SE) disadvantage with mortality in pediatric patients with cancer. **Methods:** We conducted a retrospective cohort study using Washington State (WA) Cancer Registry data (1992-2013) linked to state birth (1974-2013) and death records (1992-2013) to identify all children born in WA diagnosed with cancer < 20 years. We defined rural residence as patient addresses within 2010 census tract level rural-urban commuting area (RUCA) codes of ≥4.0 at diagnosis. Neighborhood-level socioeconomic disadvantage was determined using 2010 census block-group level Area Deprivation Index (ADI) quintiles normalized to WA. Patient addresses within the highest ADI quintile were categorized as having SE disadvantage. children in four mutually exclusive groups was compared using Kaplan-Meier analysis, pairwise log rank testing, and Cox proportional hazard ratios (HR): non-rural with SE disadvantage, rural without SE disadvantage, rural with SE disadvantage, and non-rural without SE disadvantage (). Models were adjusted for sex, race and ethnicity, age at diagnosis, birth year, and cancer type. **Results:** We identified 4,417 children for analysis. Median length of follow up among survivors was 5.0 years (interquartile range: 1.0-11.5). SE disadvantaged and 13% were rural. Pairwise log rank tests showed mortality differences among children living in rural, SE disadvantaged, or rural and SE disadvantaged neighborhoods when compared with children without either factor (individual p-values all < 0.005); no other differences were noted. Relative to children in non-rural areas without SE disadvantage, the mortality HR for those in non-rural areas with SE disadvantage was 1.68 (95% confidence intervals [CI] 1.37-2.07). The HR for children in rural areas without SE disadvantage was 1.59 (95% CI 1.19-2.12). The HR for children in rural areas with SE disadvantage was 1.56 (95% CI 1.20-2.03). In sub-analyses, associations for rurality and SE disadvantage remained significant for leukemia mortality, but CNS and solid tumor mortality was only associated with SE disadvantage (but not rural) status. Acute lymphoblastic leukemia mortality was associated with rural (but not SE disadvantage) status. **Conclusions:** Children with cancer living in socioeconomically disadvantaged and/or rural neighborhoods at diagnosis had higher mortality relative to those in non-rural areas with lower neighborhood deprivation. Associations varied by disease type. The individual effects of SE disadvantage and rurality suggest that interventions should be designed to target both factors. Research Sponsor: Alex's Lemonade Stand Foundation for Childhood Cancer grant, Other Government Agency.

6538 **Poster Session**

Cancer risk factors and cancer in transgender versus cisgender people: Real-world data from a tertiary health care institution. *First Author: Ash B. Alpert, Brown University School of Public Health, Providence, RI*

Background: Data are sparse regarding the prevalence of cancer and cancer risk factors among transgender people. Transgender people experience structural stigma and extreme rates of violence that may contribute to cancer through multiple mechanisms. The purpose of this study was to assess cancer risk factors and cancer in transgender people in a single institutional electronic health record (EHR) and compare the rates to those among cisgender, or non-transgender, people. **Methods:** Using a combination of structured gender identity data, diagnosis codes, and keyword searches, we identified a cohort of transgender people seen at our institution, a large tertiary care center. We next identified a cohort of cisgender people matched by age, year of first encounter in our EHR, and years of follow-up. Among these cohorts, we searched for cancer, premalignant lesions, human immunodeficiency virus (HIV), human papilloma virus (HPV), and hepatitis and assessed body mass index (BMI) and smoking status through structured EHR fields. Lastly, we compared the prevalence of cancer, premalignant lesions, and cancer risk factors between the two cohorts using chi-square tests. If expected cell sizes were <5, exact tests were used. **Results:** We identified cohorts of 923 transgender and 1846 cisgender people matched by age, follow-up time, and year of the first encounter. Rates of smoking (42 versus 34%, p < 0.0001), BMI ≥ 40 (21% versus 13%, p < 0.0001), and HIV (3 versus 0%, p < 0.0001) were significantly higher among transgender compared with cisgender people. Rates of premalignant lesions and cancer did not significantly differ between cohorts. **Conclusions:** In this large sample of patients seen at our institution, rates of several cancer risk factors were higher for transgender than cisgender people. No differences were demonstrated in prevalence of premalignant lesions and cancer between groups. These data require confirmation in larger national datasets. Interventions that decrease structural oppression and provide support for tobacco cessation, decreased transmission of HIV, and access to high-quality food and exercise are also called for. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

Cancer risk factors and cancer in transgender and cisgender people.

	Cisgender N = 1846 (%)	Transgender N = 923 (%)	Chi-square p-value
Maximum BMI ≥40 kg/m2	239 (13.0)	189 (20.5)	<0.0001
Ever smoked tobacco	629 (34.1)	389 (42.2)	<0.0001
Any cancer-associated virus	90 (4.9)	68 (7.4)	0.008
Hepatitis B	11 (0.6)	12 (1.3)	0.05
Hepatitis C	28 (1.5)	18 (2.0)	0.40
HIV	7 (0.40)	31 (3.4)	<0.0001
HPV	55 (3.0)	20 (2.2)	0.21
Diagnosis of Cancer or Premalignancy	119 (6.5)	49 (5.3)	0.23

6539 **Poster Session**

Theory-guided assessment of barriers and facilitators to adequate informed consent for childhood cancer clinical trials: Using the Exploration, Preparation, Implementation, Sustainment (EPIS) framework. *First Author: Paula Aristizabal, University of California San Diego Moores Cancer Center, Population Sciences, Disparities and Community Engagament, La Jolla, CA*

Background: To participate in childhood cancer clinical trials, parents/legal guardians must provide informed consent (IC), which is a fundamental ethical right. However, barriers to achieving valid IC include: use of medical jargon, misunderstanding about clinical trials procedures, tremendous emotional distress surrounding the initial cancer diagnosis, and the complexity and length of the IC forms. There are scarce data on using theory to assess perspectives of parents of children with cancer on barriers and facilitators for adequate IC in diverse populations. **Methods:** Using implementation science theory and methods, we assessed parent-reported barriers and facilitators to adequate IC, in a convenience sample that included a significant number of Hispanics. Twelve qualitative semi-structured interviews and 224 open-ended surveys were conducted with 236 parents of children with newly-diagnosed cancer at Rady Children's Hospital-San Diego, a large quaternary children's hospital in California. Fifty-three percent of participants were Hispanic and 38% were monolingual Spanish-speakers. We utilized the Exploration, Preparation, Implementation, Sustainment (EPIS) Framework, specifically domains of outer context, inner context, bridging and innovation factors. Four main codes (IC concepts and delivery; desired clinical trial information; motivations and emotions related to clinical trial enrollment; and potential areas for interventions) were used as a coding guide for analysis. Interviews and surveys were transcribed and coded for thematic analysis by three independent coders to identify key barriers and facilitators. **Results:** Four main themes were identified as barriers: 1) Complexity of the IC forms and discussion (lengthy, confusing, not available in Spanish, and use of medical jargon); 2) parents feeling emotionally overwhelmed, anxious and pressured around the IC; 3) parents viewing the clinical trial as the only treatment option; and 4) mistrust and fear of clinical trial procedures. Four IC facilitators were identified: 1) simpler explanations of study procedures; 2) provider flexibility for accommodations when delivering the IC, including psychosocial support; 3) active promotion of voluntariness and trust; and 4) supplemental education in lay language, including request for peer-education, decision aids, and navigation to "bridge the provider-patient gap." **Conclusions:** Our implementation science approach identified multiple barriers and facilitators to adequate IC in a diverse sample of parents. Findings can inform potential interventions to enhance IC for childhood cancer clinical trials, including the use of decision aids, peer-navigation, and interventions tailored to the language and culture of the individual. Research Sponsor: U.S. National Institutes of Health.

6540 **Poster Session**

Racial/ethnic disparities in serious illness communication for patients with cancer. *First Author: Julia L. Frydman, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: Racial/ethnic disparities in serious illness communication exist between patients with cancer and their oncologists. Our prior work has shown that goals of care discussions are three minutes shorter with racial/ethnic minority patients. In this study, we sought to compare oncologist's use of serious illness communication skills, patient participatory behavior, and overall communication quality during encounters with patients with advanced cancer of different self-reported races/ethnicities. **Methods:** We analyzed baseline recordings from a two-arm multisite randomized controlled trial to test a coaching model of communication skills training for solid tumor oncologists and their newly diagnosed advanced cancer patients. We audio recorded post-imaging patient-oncologist encounters for patients receiving systemic cancer treatment and coded transcripts for oncologist's use of serious illness communication skills (coded as count/encounter): open-ended questions, reflections, empathic responses to patient empathic opportunities, empathic statements, "sorry" statements, and elicitation of questions. We also assessed global codes of oncologist communication (assessed on 5-point Likert scales): flow, concerns addressed, attention, warmth, and respect. Finally, we coded patient participatory behavior (coded as count/encounter): asking questions and assertive responses. We compared the skills and behaviors by race/ethnicity of the patient using the non-parametric Kruskal-Wallis test. **Results:** We included the 56 (38%) recordings with oncologists who did not receive the intervention. The patients in these encounters were 25 (45%) female; 32 (57%) over the age of 65; 23 (41%) White Non-Hispanic, 20 (36%) Black Non-Hispanic, and 11 (20%) Hispanic. Overall, oncologists responded empathically to patients' emotions only 19% of the time. Oncologists used fewer reflective statements with Black Non-Hispanic patients (mean 0.3 statements/encounter) as compared to White Non-Hispanic patients (1.1) and Hispanic patients (1.1), $p = 0.02$. Furthermore, coders rated oncologists as being less likely to address concerns of Black Non-Hispanic patients (mean Likert scale 3.1) as compared to White Non-Hispanic (3.8) and Hispanic (3.4) patients, $p = 0.04$. Finally, coders rated oncologists as having less warmth with Black Non-Hispanic patients (mean Likert scale 2.9) as compared to White Non-Hispanic (3.8) and Hispanic (3.3) patients, $p = 0.04$. **Conclusions:** In this diverse sample of patients with advanced cancer, oncologists used fewer reflective statements, were less attentive to concerns, and expressed less warmth with Black Non-Hispanic patients. Interventions are needed to overcome these striking racial/ethnic disparities in serious illness communication for patients with cancer. Research Sponsor: PCORI.

6541 **Poster Session**

Health literacy in patients with cancer: A multicenter national study. *First Author: Elena Paillaud, AP-HP, Hôpital Européen Georges Pompidou, Department of Geriatrics, Paris, France*

Background: Health literacy (HL) is defined as the motivation and skills to access, understand, evaluate, and use information to make appropriate health decisions. The level of LS is low in Europe, including in France. For chronic patients, a low literacy is associated with limited skills in the self-management of the disease, the monitoring of treatments and is an obstacle in therapeutic education. In France, there is no study on patients with cancer. However, our pilot study with older adults with cancer showed that 72% had a low level of LS, a level defined by a questionnaire validated in French (Functional, Communicative and Critical Health Literacy-FCCHL, a score ≤ 4 = low level). The objective of this multicenter study is to evaluate HL in 2 cohorts of cancer patients: adults aged 65 and over (OLD) and adults aged 18 to 64 (Y). **Methods:** This multicenter cross-sectional study enrolled 1,518 patients aged 18 and over from 27/09/21 to 29/10/21 in 26 centers. Patients were either admitted in outpatient unit, or seen in oncology/geriatric oncology consultation, and with a treatment plan. They completed the FCCHL and 11 questions on the use of digital. Demographic and health data were also collected. The FCCHL consists of 3 subscales evaluating functional (access to information – 5 items), interactive (understanding of information – 5 items) and critical (use of information – 4 items) HL. The score for each subscale is calculated by taking the sum obtained for each item divided by the number of items and varies from 1 (low) to 5 (high). The overall score is calculated from the subscale scores. The primary endpoint was the rate of patients with an overall score of HL $\leq$ 4 (no. of subjects estimated at 420 per cohort, considering non-evaluable patients and an expected rate of HL ≤ 4 from 70% to 80%). Patients' characteristics and their use of digital have been described. In addition, a multivariate exploratory analysis of the factors associated with an LS≤ 4 in the OLD cohort was performed. **Results:** Most patients (1,327(87%)) had completed all the FFCHL items (658 (84%) OLD cohort; 669 (91%) Y cohort). The proportion of men was higher in the OLD cohort (48% vs 34% Y cohort). Many of the patients lived at home in the 2 cohorts (98%) and half in urban area (56% cohort OLD vs 52% cohort Y). The patients had an advanced stage of cancer (70% OLD cohort vs 61% Y cohort). A low level of HL was reported in 70% of the Y cohort and in 78.7% of the OLD cohort. The use of digital tools was lower in the OLD cohort: 41% had never used the internet for their health vs. 14% in cohort Y; this use was very low for online consultations (respectively 83 and 64% never used them). For the OLD cohort, only advanced and/or metastatic cancer stage was associated with HL≤ 4 (after center adjustment). **Conclusions:** These results show a low level of HL in older as in the younger population. Actions need to be implemented for the detection of moderate or weak HL in the way to reduce barriers in the management of cancer treatments. Research Sponsor: PACan platform / French National Cancer Institute.

6542 **Poster Session**

Bringing experimental therapeutics clinical trials network (ETCTN) to underrepresented population. *First Author: Joaquina Celebre Baranda, University of Kansas Cancer Center-Clinical Research Center, Fairway, KS*

Background: Access to health care including clinical trials (CT) leading to paradigm-changing cancer treatments are critical for high quality cancer care and equity in society. In this report, we highlight methods in accruing to ETCTN wherein underrepresented rural, low-income, and racial minorities comprise >50% of enrollment. **Methods:** University of Kansas Cancer Center (KUCC) is one of eight National Cancer Institute (NCI) designated cancer centers awarded CATCH-UP.2020 (CATCH-UP), a congressionally mandated P30 supplement to enhance access for minority/underserved populations to ETCTN precision medicine CT. KUCC catchment area is 23% rural by Rural Urban Continuum Codes (RUCC); almost 90 % of counties are designated primary care HPSA's (Health Professional Shortage Areas). KUCC Early Phase and Masonic Cancer Alliance (rural outreach network) partnered to operationalize CATCH-UP. We engaged disease-focused champion investigators in disease working groups and MCA physicians who selected scientifically sound CT that fit catchment area needs. Patient and Investigator Voices Organizing Together, a patient research advocacy group provided practical feedback. MCA navigator coordinated recruitment. Telehealth was used for rural patients that would have a significant distance to travel just to be screened. **Results:** CATCH-UP was initiated in September 2020. Twenty-eight CT were activated, many in community sites. Average activation time was 81 days. Delays were mainly from CT amendments. KUCC enrolled the first patient in the CATCH-UP program. In 6 months, we met accrual requirements (24/year, 50% minorities). During first year, we enrolled 47 (>50% minorities), an increase of 680% from our average accrual of 6/year (>50% minorities) in ETCTN through Early Drug Development Opportunity Program (2016-2020). To date, we have enrolled 61, 54% from rural, HPSA, race and other minorities. Although the proportion of minorities did not change but remained high, this funding allowed us to substantially increase the number of patients from a catchment area with high proportion of geographically and socioeconomically underserved minorities given access to early phase CT through ETCTN. **Conclusions:** Amid COVID-19 pandemic, the NCI CATCH-UP program and methods we used allowed access to novel therapies for rural, medically underserved, and other minority groups. Funded by NIH: 3P30CA168524-09S2. Research Sponsor: U.S. National Institutes of Health.

6543 **Poster Session**

Representativeness of patients enrolled in the Lung Cancer Master Protocol (Lung-MAP). *First Author: Riha Vaidya, SWOG Statistics and Data Management Center, Seattle, WA*

Background: A major goal of Lung-MAP, a biomarker-driven master protocol conducted within the National Clinical Trials Network of the NCI using a public-private partnership, was to improve access to novel therapeutics. Representative enrollment of patient sub-groups in clinical trials is essential for improving confidence that trial findings are valid and applicable to all patients. We examined the representativeness of patients enrolled in Lung-MAP by demographic and area-level measures compared to patients in other advanced non-small cell lung cancer (NSCLC) trials and with the US NSCLC population. **Methods:** We analyzed data on patients enrolled to Lung-MAP between 2014-2020 according to sex, age (< 65 years v. ≥ 65 years), race (White v. Black v. Asian), ethnicity (Hispanic v. not Hispanic), residence (rural v. urban), insurance type (Medicaid or no insurance v. private), and neighborhood socioeconomic deprivation (quintiles of Area Deprivation Index score). Rates were compared to SWOG-led NSCLC trials conducted between 2001-2020 (date range to provide sufficient power) and, where possible, to US NSCLC population rates using Surveillance, Epidemiology, and End Results (SEER) registry data (2014-2018). Two-sided tests of proportions at the 5% level were used for all comparisons. **Results:** 3,556 patients enrolled to Lung-MAP were compared to 2,267 patients enrolled to SWOG-led NSCLC studies. Lung-MAP patients were more likely to be ≥ 65 years old (57.2% v. 46.7%; $p < .001$) and from rural areas (17.3% v. 14.3%; $p = .002$) but less likely to be female (38.6% v. 47.2%; $p < .001$), Asian (2.7% v. 5.1%; $p < 0.0001$), or Hispanic (2.4% v. 3.7%; $p = .003$). Compared to the US NSCLC population, Lung-MAP patients were less likely to be ≥ 65 years (57.2% v. 73.5%; $p < .001$), female (38.6% v. 47.8%; $p < .001$), or a racial or ethnic minority (15.5% v. 19.3%; $p < .001$). Lung-MAP patients were more likely to be from socioeconomically deprived neighborhoods (42.2% vs. 36.5%, $p < .001$). Among patients aged < 65 years, Lung-MAP enrolled more patients reporting Medicaid/no insurance as their primary insurance (27.6% v. 17.9%; $p < .001$). **Conclusions:** Lung-MAP improved access to novel therapeutics for older patients, rural patients, those with Medicaid/no insurance, and patients from socioeconomically deprived areas compared to other NSCLC trials. Lung-MAP enrolled exclusively squamous cell lung cancers from 2014-2018, which explains decreased representation of females. Consistent with prior research, Lung-MAP patients were younger and less diverse compared to the US NSCLC population. Further examination of the underrepresentation of Asian and Hispanic patients in Lung-MAP is required to identify barriers to access and potential solutions. The conduct of a master protocol across multiple locations may improve trial participation for patients with limited access due to area-level (rural, socioeconomic deprivation) or insurance barriers. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

6544 **Poster Session**

Racial disparities in receipt of guideline-concordant care for early-onset colorectal cancer in the U.S. *First Author: Leticia M Nogueira, American Cancer Society, Atlanta, GA*

Background: Early-onset colorectal cancer patients who are Black are less likely to survive than white patients, even for early-stage disease, possibly due to differences in receipt of guideline-concordant care. This study evaluated racial disparities in receipt of timely and guideline-concordant colon and rectal cancer care in a large nationwide sample. **Methods:** Non-Hispanic Black and white individuals aged 20-49 years newly diagnosed with colorectal cancer during 2004-2019 were selected from the National Cancer Database. Patients who received all care recommended by the National Comprehensive Cancer Network (staging, surgery, lymph node evaluation, chemotherapy, and radiotherapy) for which they were eligible according to cancer subsite and clinical and pathological TNM stage were considered guideline concordant. Demographic characteristics (age and sex), comorbidities, and health insurance coverage type were added sequentially to a series of multivariable models to estimate contribution to racial disparities in receipt of guideline-concordant care. Racial disparities in time from diagnosis date (among rectal cancer patients eligible for neoadjuvant chemotherapy) and surgery date (among colon cancer patients eligible for adjuvant chemotherapy) to date of chemotherapy initiation was evaluated using restricted mean survival time. **Results:** Of the 84,728 colon and 62,483 rectal cancer patients, 20.8% and 14.5% were Black, respectively. Black patients were less likely to receive guideline concordant care than white patients diagnosed with colon and rectal cancer, respectively (Table). Demographic characteristics and comorbidities combined explained less than 5% of the disparity, while health insurance coverage type explained 28.6% and 19.4% of the disparity among colon and rectal cancer patients, respectively. Restricted mean time to chemotherapy was statistically significantly longer among Black than white patients for colon (54.0 vs 48.7 days, p < .001) and rectal cancers (49.6 vs 40.9 days, p < .001), respectively. **Conclusions:** Black patients diagnosed with early-onset colorectal cancer receive worse and less timely care than their white counterparts. Differences in health insurance coverage type, a modifiable factor, were the largest identified contributor to the racial disparities in receipt of guideline-concordant care, suggesting that improved access to care could help mitigate disparities in cancer outcomes. Research Sponsor: None.

	Guideline Concordant N (%)	Non-Guideline Concordant N (%)	Crude OR (95% CI)	Demographic Adjusted OR (95% CI)	Comorbidity Adjusted OR (95% CI)	Insurance Adjusted OR (95% CI)
Colon						
White	46,272 (69.0)	20,822 (31.0)	1.14	1.14	1.13	1.10
Black	11,672 (66.2)	5,962 (33.8)	(1.10, 1.18)	(1.10, 1.18)	(1.10, 1.18)	(1.06, 1.14)
Rectum						
White	30,317 (56.7)	23,116 (43.3)	1.36	1.36	1.35	1.29
Black	4,442 (49.1)	4,608 (50.9)	(1.30, 1.42)	(1.30, 1.42)	(1.29, 1.42)	(1.24, 1.35)

6545 **Poster Session**

Use of modernized eligibility criteria in pancreatic cancer clinical trials. *First Author: Andrea N Riner, University of Florida, Gainesville, FL*

Background: In 2017, ASCO + Friends recommended modernized eligibility criteria to improve generalizability of clinical trial results. Traditional criteria contribute to disparities in trial participation, yet modernized criteria can equalize eligibility rates. We aimed to assess use of modernized eligibility criteria in pancreatic ductal adenocarcinoma (PDAC) clinical trials since the updated guidelines. **Methods:** Modernized eligibility criteria were obtained from ASCO + Friends guidelines. Clinicaltrials.gov was queried for "pancreas adenocarcinoma" trials from Jan. 1, 2018 onward and eligibility criteria were assessed for compliance with modernized criteria. Kruskal-Wallis and Fisher's exact tests were used to determine differences in compliance based on disease stage(s), starting year, phase, and funder. **Results:** In total, 108 clinical trials were identified - 31.5% for resectable, 56.5% for unresectable, 12.0% for both resectable/unresectable disease. Most trials were phase 1 (24.1%), phase 1l2 (15.7%) or phase 2 (45.4%). Funding sources included industry (38.0%), NIH (22.2%) and other sources (39.8%). No trial was compliant with all modernized criteria. Only 34.7% of trials allowed patients with ECOG performance status of 2. HIV+ patients were not allowed in 56.5% of trials. Only 7 trials (6.5%) were compliant with assessing renal function whereas 64.8% appropriately used upper limit of normal cutoffs for labs. Among trials that excluded patients for CHF, 59.6% used a classification system for exclusion. Specific cardiac abnormalities were excluded in 60.2% of trials. Prior malignancy was allowed in 71.3% of trials if treated > 2 years prior and concurrent malignancy, if stable, was allowed in 21.3% of trials. Prior PDAC treatment was allowed for 38.0% and required for 24.1% of trials. If prior treatment was allowed, 94% justified drug exclusions, 40.3% did not require a washout period, and 35.8% required recovery from prior adverse events. Stable/treated brain metastases were allowed in 33.8% of trials for unresectable cancer. Compliance with prior malignancy criteria improved from 2018-2019 to 2020-2022 (56.0% vs 84.5%, respectively; p = 0.001). Requirement of prior PDAC treatment was associated with disease stage (8.8% for resectable, 32.8% for unresectable, and 23.1% for both; p = 0.024), as was exclusion based on prior therapy (58.8% for resectable disease, 14.8% for unresectable, and 30.8% for both; p < 0.0001). Earlier trial phase was associated with prior treatment allowance (p = 0.002), whereas later phase trials were less likely to allow prior treatment (p = 0.021). NIH-funded trials required prior treatment (37.5%) more than industry (29.3%) or other (11.6%) funded trials (p = 0.034). **Conclusions:** Modernized eligibility criteria are inadequately implemented in PDAC clinical trials. Efforts to improve their use are warranted to produce more generalizable results and advance inclusivity. Research Sponsor: None.

6546 **Poster Session**

Concrete resource needs and frailty among older adults with cancer: The Cancer and Aging Resilience Evaluation (CARE) Registry. *First Author: Grant Richard Williams, The University of Alabama at Birmingham, O'Neal Comprehensive Cancer Center, Birmingham, AL*

Background: Concrete resource needs (CRN: insecurity of food, utilities, and/or housing) are important and modifiable indicators of poverty. Prior work among adults with chronic cardiometabolic diseases demonstrates that CRN-targeted interventions improve health outcomes. Poverty is associated with inferior health outcomes among patients with cancer. Frailty is a recognized state of increased vulnerability and is associated with increased toxicities from cancer therapies and reduced survival. The prevalence of CRN among older adults with cancer and its role in modifying the risk of frailty remains unknown. We aimed to (1) describe the prevalence of CRN and (2) examine the association between CRN and frailty among older adults with cancer. **Methods:** The CARE registry prospectively enrolls older adults (≥60y) with cancer seen at UAB as new patients. Single-item screening measures captured food, housing and utility insecurity in addition to the baseline CARE geriatric assessment beginning 8/2020. The 44-item CARE Frailty Index (based on the principles of deficit accumulation) was used to define frailty. Multivariable analysis examined association of CRN with frailty, adjusting for age, race, sex, education, employment, marital status, and cancer type and stage. **Results:** The cohort included 485 participants with a mean age at enrollment of 69y; 63.7% were male; 20.4% were non-Hispanic Black. The most prevalent cancer types included colorectal (33.0%), pancreatic (16.3%) and hepatobiliary (12.2%) cancers. Median time from cancer diagnosis to study enrollment was 35 days. The overall prevalence of CRN was 6.6% (insecurity of housing [2.9%], food [4.3%], and utilities [4.1%]). Participants with CRN were less educated (< HS: 21.9% vs. 9.9%, p= 0.01), more often widowed/divorced (53.1% vs. 35.1%, p= 0.003) and more likely to be disabled (43.8% vs. 12.4%, p< 0.001). Overall, 33.8% of patients were frail. In multivariable analysis, patients with CRN had a 6.24 higher odds of frailty (95% CI 1.72-22.7, p= 0.005) compared to those without CRN after adjustment for above-mentioned covariates. **Conclusions:** CRN represents a novel exposure that is independently associated with frailty. In order to inform a CRN-targeted intervention for the growing number of older adults with cancer, future work is warranted to examine the CRN construct in this population, including examination of more detailed screening measures and CRN-associated cancer outcomes. Research Sponsor: U.S. National Institutes of Health.

6547 **Poster Session**

A multilevel intervention increased accrual of Native Hawaiians and other Pacific Islanders to a national breast cancer screening trial. *First Author: Srue Wakuk, University of Hawaii Cancer Center, Honolulu, HI*

Background: The University of Hawaii Cancer Center (UHCC) Minority/Underserved NCI Community Oncology Research Program (Hawaii MU NCORP) provides access to NCI-sponsored clinical trials in Hawaii. The Hawaii MU NCORP is dedicated to increasing minority and underserved accruals to clinical trials. Native Hawaiian women have the highest breast cancer incidence and mortality; only 26% of Micronesian women in Hawaii over the age of 40 have ever had a mammogram. In 2018, the Hawaii MU NCORP became a recruitment site for the ECOG-ACRIN Tomosynthesis Mammographic Imaging Screening Trial (TMIST). A pilot study was launched in 2019, to support our NCORP recruitment of underrepresented Native Hawaiian and other Pacific Islander (NHPI) women to the TMIST study. Subsequently, specific funding was provided by the NCI's Center to Reduce Cancer Health Disparities that enabled the UHCC's Office of Community Outreach and Engagement (COE) to develop an effective multilevel recruitment strategy together with the Hawaii MIU NCORP. **Methods:** To foster community awareness of the TMIST study among NHPI women, the UHCC COE hired a Community Health Educator (CHE). The CHE, a Pacific Islander woman, utilized small group educational sessions to provide culturally and linguistically appropriate cancer prevention information and promote the TMIST study to NHPI women in Hawaii. The CHE worked in partnership with Hawaii MU NCORP clinical research associates (CRAs) in these efforts. In 2020, statewide COVID-19 health and safety protocols were enacted, limiting public group interactions in Hawaii. Despite this challenge, the CHE successfully adapted the in-person educational sessions on clinical trials and TMIST to conduct sessions using Zoom and Facebook Messenger. **Results:** Before the hire of the CHE in 2019, only one Pacific Islander (Micronesian) woman was recruited to the TMIST in Hawaii. The CHE conducted 21 community health events with 426 attendees from 2019 to 2021. The Hawaii MU NCORP NHPI TMIST enrollment went from the 9.9% in 2018 to 2019, to 20.1% in 2019 to 2020 and to 33% in 2020 to 2021. To date, 18 Micronesian, 52 Native Hawaiian and 6 Other Pacific Islander women out of 353 participants ware enrolled. **Conclusions:** The multilevel intervention of our CHE, in collaboration with NCORP staff providing clinical trial awareness training and community outreach, resulted in increasing the enrollment of NHPI women to the TMIST Trial. CHE-led community health education sessions on cancer prevention can be delivered using emergent technologies and social media. The use of culturally and gender concordant CHEs working with CRAs have the potential to increase awareness and accruals to cancer clinical trials. Research Sponsor: U.S. National Institutes of Health.

6548 **Poster Session**

Improving access to cancer genetic testing for underserved women in southeast Texas. *First Author: Darya Aleksandrovna Kizub, UT MD Anderson Cancer Center, Houston, WA*

Background: Hereditary breast cancer accounts for 5-10% of all cases, but only 20% of eligible women undergo NCCN guideline-concordant screening. We demonstrated previously that our simple genetic risk screening tool (GRST) and telegenetics improved adherence to genetic testing guidelines and increased high-risk cancer surveillance. Our objective was to identify women eligible for genetic testing using breast cancer screening clinics in underserved communities as entry points, reach them with our tailored program, and measure impact. **Methods:** This is a prospective study in women presenting for breast cancer screening at The Rose, which provides breast imaging to underserved patients in Houston, TX. Women who consented to participate filled out the GRST and provided socio-demographic information. Those at high risk for hereditary cancer after GRST scoring were provided with educational materials and sent a saliva-based genetic testing kit. When results included a pathogenic variant (PV) or variant of uncertain significance (VUS), individuals received telegenetic counseling and risk reduction resources. Others were notified of negative results by phone. The program included education for providers about importance of genetic testing. Socio-demographic characteristics were analyzed using descriptive statistics. All statistical tests were two-sided. **Results:** 501 women filled out the GRST. Median age was 52. Median annual salary was $45,000 (IQR 21-75K). 151 (36.3%) were uninsured. 252 (50.3%) identified as White, 230 (45.9%) as Hispanic/Latino, and 106 (21.2%) as Black/African American. 150 (33%) were eligible for genetic testing; 100 could be contacted. Of the 100, 41 declined testing, 40 were lost to follow-up, 19 agreed, and 15 (10% of those eligible) returned the kits. Results included 11 negative, 2 VUS, 1 PV (NF1). Among 41 who declined testing, reported reasons included not wanting to know the results or preference to follow-up with their primary care doctor in 11 (26.8%) each, not enough time or prior genetic testing in 6 (14.6%) each, no reason given by five, and perception that testing was unnecessary in two. Completion of genetic testing was not associated with insurance, salary, family history, or race/ethnicity ($p > 0.05$). **Conclusions:** Our study was successful in identifying underserved women at high risk of hereditary cancer who have not previously undergone genetic testing using a simple screening tool. We reduced barriers to genetic testing by working with a trusted community organization and using remote testing and telegenetics. We did not find any factors associated with genetic testing completion, though results are limited by small sample size. Given the low proportion of patients who completed testing, the next project phase will focus on improving convenience for patients and exploring patient and program-related reasons for non-completion of testing and strategies to overcome these. Research Sponsor: Susan G. Komen Foundation: CGPR-2019-TX105-THAC46-00012.

6549 **Poster Session**

Impact of depression among adolescents and young adults with cancer. *First Author: Edmund Men Qiao, Department of Radiation Medicine and Applied Sciences, University of California San Diego, La Jolla, CA*

Background: The incidence of adolescent and young adults (AYAs) with cancer continues to increase. The psychosocial burden of early cancer diagnosis within this unique AYA population remains poorly characterized. Without proper resources, these patients are likely to seek care in the acute care setting. For AYA patients, we evaluated the impact of malignancy on concurrent diagnosis with depression and on presenting to the emergency department (ED) with intentional self-injury. We further described the influence of concurrent depression diagnosis on hospital admission and extended length of stay (LOS) for AYA cancer patients. **Methods:** From the National Emergency Department Sample (NEDS), we identified patients between 15-39 years who presented to an ED in 2019. Diagnosis of cancer and depression were identified using International Classification of Diseases, 10th Revision coding. Separate multivariable logistic regressions evaluated the impact of cancer diagnosis on concurrent depression diagnosis and on presenting with intentional self-injury. For the subset of AYA cancer patients, multivariable logistic regressions evaluated the impact of depression on hospital admission and extended LOS (> 14 days). **Results:** We identified 10,570,148 AYA patients, and 35,035 had cancer (0.33%). Among AYA cancer patients, average age was 31 and the cohort skewed White (48.7%), female (58.1%), and with Medicaid insurance (48.4%). The prevalence of depression among AYA cancer patients was 9.6% vs. 4.4% for patients without cancer. On multivariable regression, AYA cancer patients had a 46% increased odds of depression diagnosis (odds ratio (OR), 95% confidence interval (CI): 1.46. [1.43-1.49] $P < 0.01$) and 32% increased odds of intentional self-injury (OR, 95% CI: 1.32 [1.19-1.47] $P < 0.01$) when compared to patients without cancer. Additional significant factors associated with depression diagnosis among AYA cancer patients were White race, female gender, and Medicaid insurance. Within AYA cancer patients, a concurrent diagnosis with depression was associated with ~3-fold increased odds of hospital admission (OR, 95% CI: 3.02 [2.90-3.14] $P < 0.01$) and a 31% increased odds of extended LOS (OR, 95% CI: 1.31 [1.23-1.39] $P < 0.01$). **Conclusions:** From this national sample, we found a significant association between cancer diagnosis and depression within AYA patients, with cancer diagnosis also increasing the risk of intentional self-injury. Furthermore, AYA cancer patients diagnosed with depression had increased risk of both hospital admission and extended LOS. Our results underscore the potential gap in psychological care for AYA cancer patients and highlight the need for stronger mental health resources for this at-risk population. Research Sponsor: None.

6550 **Poster Session**

Disparities in delayed diagnosis, access to treatment, and treatment delays among Hispanic men with metastatic prostate cancer. *First Author: Nishwant Swami, University of Massachusetts Medical School, Worcester, MA*

Background: Reporting racial/ethnic disparities in aggregate for Hispanics could obscure differences between subgroups given heterogeneity in social determinants of health. We sought to identify differences in delayed diagnosis, treatment status, and time to treatment among Hispanic subpopulations with metastatic prostate cancer. **Methods:** 2004-2017 data from the National Cancer Database (NCDB) was used to identify patients with prostate adenocarcinoma; patients were disaggregated by racial subgroup and Hispanic country-of-origin. Ordinal logistic regression defined adjusted odds ratios (aORs) with 95% CI of 1) presenting with Stage IV cancer, 2) receiving treatment, and 3) receiving delayed treatment (defined as treatment after 90 days). Sensitivity analysis was conducted for delayed treatment after 180 days. **Results:** Among 1,305,785 patients, Hispanic men had greater odds of presenting with stage IV prostate cancer compared with non-Hispanic White (NHW) men (aOR = 1.54 95% CI 1.50-1.58, $p < 0.001$). All Hispanic racial subgroups were more likely to present with stage IV cancer with highest odds observed in Hispanic Black men (aOR 1.68 95% CI 1.46-1.93, $p < 0.001$). Disparities were also observed in all country of origin subgroups, particularly for men of Mexican heritage (aOR 1.99 95% CI 1.86-2.12, $p < 0.001$). Among men with metastatic disease, Hispanic men were less likely to receive treatment than NHW men (aOR 0.60 95% CI 0.53-0.67, $p < 0.001$). Hispanic White patients were less likely to receive treatment compared with NHW men (Hispanic White aOR 0.58 95% CI 0.52-0.66, $p < 0.001$). Upon disaggregation by country of origin, disparities persisted, particularly for men of Dominican heritage (aOR 0.52 95%CI 0.28-0.98 $p = 0.044$). Hispanic men were more likely to experience treatment delays when compared to NHW men (aOR 1.38 95%CI 1.26-1.52 $p < 0.001$). All Hispanic racial subgroups experienced greater treatment delays, particularly Hispanic Black men (aOR 1.83 95%CI 1.22-2.75 $p = 0.002$). Men of Central or South American heritage had the greatest odds of treatment delays (aOR 1.48 95%CI 1.07-2.04 $p = 0.018$). Sensitivity analysis indicated consistent findings among Hispanic patients overall, Hispanic White patients, and patients of Mexican and Puerto Rican heritage. **Conclusions:** We found notable differences in stage IV cancer at presentation, treatment for metastatic disease, and delays in treatment when outcomes were stratified by racial subgroup and Hispanic country of origin. Future studies in Hispanic populations with disaggregated data are needed to characterize outcomes, study mediators of the observed variations, and develop targeted interventions. Research Sponsor: None.

6551 **Poster Session**

Variation of use of targeted therapies and molecular diagnostic testing by practice type for non-small cell lung cancer and colorectal cancer. *First Author: Thomas Roberts, Dana–Farber Cancer Institute, Boston, MA*

Background: Targeted therapies are important first-line treatments for many patients with non-small cell lung cancer (NSCLC) and colorectal cancer (CRC). All patients with newly-diagnosed metastatic NSCLC and CRC should undergo molecular diagnostic testing to guide treatment selection. **Methods**: We used 100% Medicare fee-for-service data from 2015 through 2019 to identify beneficiaries with incident metastatic NSCLC or CRC receiving systemic therapy and to assign beneficiaries to oncology practices. We then assessed for use of molecular diagnostic testing and targeted therapies in these cohorts. We used linear mixed effects models to assess patient and practice characteristics associated with molecular diagnostic testing and targeted therapy use. **Results:** Rates of molecular diagnostic testing increased between 2015 and 2019 for NSCLC and CRC. In 2019, rates of molecular diagnostic testing were 85% and 65% for NSCLC and CRC, respectively. Rates of targeted therapy use did not increase over time for NSCLC or CRC, and were 8% and 5%, respectively, in 2019. Compared to National Cancer Institute (NCI)-designated cancer centers, rates of molecular diagnostic testing for CRC were 3.7 percentage points lower at practices associated with non-academic hospitals and 10.6 percentage points lower at small independent practices. Rates of targeted therapy use for NSCLC were 4.8, 5.9 and 5.5 percentage points lower at academic medical centers, large independent practices and small independent practices, respectively, compared to NCI centers. **Conclusions:** Rates of molecular diagnostic testing for NSCLC and CRC increased in recent years, but testing rates remain below recommended levels, and targeted therapy use remains low. Substantial variation in testing and targeted therapy use by practice type suggest that the practice where a patient is treated may impact access to recommended testing and efficacious treatments. Research Sponsor: None.

Adjusted and unadjusted rates of use of molecular diagnostics and first-line targeted therapies in patients with metastatic non-small cell lung cancer and colorectal cancer.

	Molecular Diagnostics				Targeted Therapy Use			
	NSCLC		Colorectal Cancer		NSCLC		Colorectal Cancer	
Practice type	Unadjusted rate	Adjusted PP diff. (95% CI)	Unadjusted rate	Adjusted PP diff. (95% CI)	Unadjusted rate	Adjusted PP diff. (95% CI)	Unadjusted rate	Adjusted PP diff. (95% CI)
NCI Center (ref.)	78.9		56.9		16.6		5.0	
Academic center	78.3	-1.3 (-3.7 to 1.1)	57.2	0.9 (-3.1 to 4.8)	9.1	-4.8 (-6.5 to -3.2)	6.1	1.2 (-0.4 to 2.8)
Other hospital	79.2	-0.6 (-2.4 to 1.1)	54.4	-3.7 (-6.5 to -0.8)	8.0	-5.4 (-6.6 to -4.2)	4.8	0.3 (-0.9 to 1.5)
Large independent	80.0	-0.1 (-1.5 to 1.7)	54.9	-2.2 (-4.8 to 0.4)	7.4	-5.9 (-7.0 to -4.8)	4.4	-0.1 (-1.1 to 0.9)
Small independent	78.0	-1.3 (-3.0 to 0.4)	46.2	-10.6 (-13.4 to -7.8)	9.5	-5.5 (-6.7 to -4.3)	3.6	-1.1 (-2.3 to 0.02)

PP = percentage point.

6552 **Poster Session**

Medicare expenditures for discarded oncology therapies. *First Author: Caleb Scheckel, Mayo Clinic, Division of Hematology, Rochester, MN*

Background: Significant amounts of expensive oncology drugs are discarded resulting in waste and financial consequences for patients. Beginning in 2023, the Infrastructure Investment and Jobs Act (IIJA) will require drug manufacturers to refund Medicare for any single-use drugs where greater than 10% of the drug is wasted. We explored potential IIJA-associated savings through assessment of patterns in spending for discarded oncology agents between 2017-2020. **Methods:** We utilized the Medicare Part B Discarded Drug Units database from 2017-2020. Using J codes, we extracted spending and reimbursement data for discarded medications for antineoplastic and classical hematology therapies. The primary outcome was identification of therapies with high percentage of waste and the economic impact of retroactive application of the IIJA for discarded therapies. **Results:** Medicare Part B utilization data was extracted for a median 77 (64-152) oncologic therapies per year with median reimbursement for discarded treatments of $590 M ($566-616). From 2017-2020, bortezomib, romiplostim, and nab-paclitaxel were consistently among the top 5 therapies by value of wasted product. Pembrolizumab waste by value declined significantly after 2017 following transition to fixed dosing. In 2020, the top 5 therapies by value of wasted product were bortezomib, nab-paclitaxel, trastuzumab, romiplostim, and cabazitaxel with a value of $278 M. In 2020, the agents with the highest percentage of wasted product were bortezomib (27%), cabazitaxel (28%), decitabine (23%), topotecan (23%), and azacitidine (22%) with a collective discarded value of $160 M. Notably, these agents have weight-based dosing and single-use vials. Based upon the average number of drug claims per recipient and volume of product discarded, eliminating drug waste would allow an additional 6564 patients to receive treatment with discarded bortezomib. The number of additionally treated patients for the other top 5 agents: cabazitaxel (1216), decitabine (1509), topotecan (291), and azacitidine (2682). Retroactive application of IIJA policy would have impacted a median 20 (12-26) oncology agents resulting in median annual cost savings of $153 M (142-157) and the median annual spending on wasted oncology therapies would decline to $440 M (410-466). **Conclusions:** The IIJA would have yielded a median annual savings of $153 M in Medicare spending if applied retroactively. Given a 10% waste cutoff, a limited number of agents would be targeted by this legislation. In our study, we observe that drugs associated with weight-based dosing and single-use drug vials account for most drug waste. Strategies to minimize discarded units (through storage of unused product, approval of multi-dose vial formulations, or fixed-dose therapies) could yield substantial savings while enabling health equity in collaboration with communities with difficult access to these drugs. Research Sponsor: None.

6553 **Poster Session**

Rural-urban disparities in cancer mortality in the United States from 1999 to 2019. *First Author: Syed Hussaini, Duke University Medical Center, Durham, NC*

Background: U.S. cancer outcomes have improved in recent years, but it is unclear if these gains are realized in all geographic areas. We investigated US rural-urban disparities in age-adjusted cancer mortality rates (AAMRs) over a 20-year period. **Methods:** We identified cancer deaths from 1999 to 2019 in the CDC WONDER database. We classified populations into large metropolitan (≥1 million), small-or medium-sized metropolitan (50,000-999,999), and rural (<50,000) areas based on the 2013 U.S. Census classification. We calculated annual AAMRs per 100,000 individuals and stratified results by age, sex, and race/ethnicity. We estimated annual percentage changes (APC) in AAMR using robust linear regression models of the log-scale AAMR, including population size as weights, and assessed differential changes over time by geographic area with interaction tests. **Results:** There were 12,935,840 deaths attributed to cancer (50% large metropolitan, 31.2% medium/small metropolitan, and 18.7% rural). AAMRs were highest in rural areas with least annual improvement. AAMR in large metropolitan areas decreased from 204.5 to 142.6 (APC -1.74 (95% CI [-1.78, -1.7])), and in rural areas it decreased from 209 to 168.3 (APC -1.05 (95% CI [-1.09, -1])) (P < .001 for time trend). The absolute difference in AAMRs between large metropolitan and rural areas increased 5-fold, from 4.5 in 1999, to 25.7 in 2019. This trend was larger in elderly (>65), where rural-urban disparity grew 25-fold (P < 0.001). Non-Hispanic Blacks had higher AAMR than other racial/ethnic groups, and women had lower AAMR than men. **Conclusions:** In this national analysis of 20 years, rural residents suffered higher cancer mortality than their metropolitan counterparts resulting in widening disparities. Our findings inform program interventions possible through the recent reignition of the Cancer Moonshot in achieving geographic parity, and support ongoing congressional policy deliberations to increase access through re-investment in rural infrastructure. Research Sponsor: None.

AAMR and APC trends 1999-2019.

	All Areas		Large Metropolitan (n = 6,473,375)		Medium/Small Metropolitan (n = 4,039,500)		Rural Areas (n = 2,422,965)	
			AAMR		AAMR		AAMR	
	Overall APC (95% CI)	P	1999	2019	1999	2019	1999	2019
Overall	-1.53 [-1.6, -1.5]	N/A	205	143	204	152	209	168*
<25	-1.5 [-1.7, -1.4]	Reference	3.6	2.7	3.5	2.5	3.5	2.4
25-65	-1.7 [-1.8, -1.6]	0.018	109	71	112	82	120	96*
>65	-1.48 [-1.5, -1.4]	0.505	1159	830	1145	860	1154	930*
Male	-1.8 [-1.8, -1.8]	Reference	254	168	257	181	268	201*
Female	-1.41 [-1.4, -1.4]	<0.001	173	124	169	131	169	142*
White	-1.36 [-1.4, -1.3]	Reference	118	97	137	118	184	153*
Hispanic	-1.26 [-1.3, -1.2]	0.002	134	106	141	113	165	108*
Black	-2 [-2.0, -1.96]	<0.001	122	93	130	99	173	96*

P§ = P value for difference in change in AAMR over time between categories within each subgroup. Ref = reference for comparison. * = P < 0.001 when comparing rural to large metropolitan, within subgroups, estimated using interaction tests.

6554 **Poster Session**

The role of rurality in cancer treatment disruptions among patients with cancer diagnosed with SARS-CoV-2: An analysis of the ASCO Survey on COVID-19 in Oncology Registry. *First Author: Jessica Yasmine Islam, Moffitt Cancer Center, Tampa, FL*

Background: U.S. rural cancer patients experience multifactorial barriers to cancer treatment; however, little is known about the impact of the pandemic on cancer treatment delays or discontinuations (TDD) in the rural context. Our objective was to evaluate the role of rurality at both the patient and clinic level on cancer TDD among patients living with cancer with SARS-CoV-2 infection. **Methods:** We used data from the ASCO Survey on COVID-19 in Oncology Registry (March 2020-July 2021), which includes cancer patients diagnosed with SARS-CoV-2 (n = 3193). Data included patient demographics, SARS-CoV-2 treatment, cancer characteristics, and modifications to cancer treatment plans. Cancer-related TDD was defined as any treatment postponed > two weeks from the original scheduled date. Rurality was defined using the USDA Rural-Urban Commuting Area schema. We compared cancer characteristics, COVID-19 outcomes, and TDD by rurality of cancer patients, and TDD by rurality of oncology practices. We computed adjusted odds ratios (aOR) using multivariable logistic regression to evaluate rurality with TDD adjusting for age, race/ethnicity, sex, comorbidities, ECOG score, cancer extent, pandemic time period based on case peaks (< 06/2020, 06-12/2020, 01-07/2021), and COVID-19 severity. **Results:** Rural cancer patients (n = 499, 16%) with SARS-CoV-2 were mostly over 50 years (87%), female (57%), and NH-White (81%) with solid tumors (76%). Most rural patients received oncology treatment in urban areas (65%, p < 0.001). Rural patients were less likely to receive care through telemedicine (18%) compared to urban patients (26%) (p < 0.001). At SARS-CoV-2 diagnosis, rural patients were scheduled to receive drug-based therapy (72%), radiation therapy (8%), surgery (4%), or transplant (1%). Rural versus urban cancer patients with SARS-CoV-2 were less likely to experience TDD (41% vs. 51%) (p < 0.001). Among patients treated at rural oncology clinics, urban cancer patients were more likely to experience TDD (65%) compared with rural patients (47%) (p < 0.001). Similarly, among patients treated at urban oncology clinics, urban cancer patients were also more likely to experience TDD (51%) compared with rural patients (38%) (p < 0.001). In multivariable analyses, rural cancer patients were 28% less likely to experience TDD (aOR:0.72, 95% CI: 0.55-0.94) than urban cancer patients. Oncology practice rurality was not associated with TDD (aOR: 1.19, 95% CI: 0.81-1.76). **Conclusions:** Rural cancer patients were less likely to experience TDD than urban patients supporting the urban-rural paradox i.e., geographic distance to cancer care facilities is not consistently associated with treatment delivery in expected ways. Future work should focus on area-level factors of the rural cancer patient experience to disentangle potential reasons for TDD during the pandemic. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

6555 **Poster Session**

Access to definitive treatment and survival for intermediate-risk and high-risk prostate cancer at hospital systems serving health disparity populations. *First Author: Muhieddine Labban, Division of Urological Surgery and Center for Surgery and Public Health, Brigham and Women's Hospital, Harvard Medical School, Boston, MA*

Background: Socioeconomic and racial disparities in prostate cancer (PCa) can be attributed to patient-level and physician-level factors. However, there is growing interest in investigating the role of the facility of care in driving cancer disparities. Therefore, we sought to examine receipt of guideline-concordant definitive treatment, time to treatment initiation (TTI), and survival for men with PCa receiving care at hospital systems serving health disparity populations (HSDPs). **Methods:** We conducted a retrospective analysis of the National Cancer Database (2004-2016) among men with intermediate-risk or high-risk PCa eligible for definitive treatment. The primary outcomes were receipt of definitive treatment and TTI within 90 days of diagnosis. The secondary outcome was survival. We defined HSDPs as minority-serving hospitals – facilities in the highest decile of proportion of Non-Hispanic Black (NHB) or Hispanic cancer patients – and/or high-burden safety-net hospitals – facilities in the highest quartile of proportion of underinsured patients. We used mixed-effect models with facility-level random intercept to compare outcomes between HSDPs and non-HSDPs among the entire cohort and among men who received definitive treatment. We evaluated interactions between HSDP status and race for each of the outcomes. **Results:** The cohort included 821,931 men with intermediate-risk or high-risk PCa. We included 968 non-HSDPs (72.2%) and 373 HSDPs (27.8%) facilities. Treatment at HSDPs was associated with lower odds of receipt of definitive treatment (aOR 0.64; 95% CI 0.57-0.71; p < 0.001), lower odds of TTI within 90 days of diagnosis (aOR 0.74; 95% CI 0.68-0.79; p < 0.001), and worse survival (aHR 1.05; 95% CI 1.02-1.09; p = 0.003). However, no difference was found in survival among patients who received definitive treatment. NHB men at HSDPs had also worse outcomes than NHB men treated at non-HSDPs as well as NHW men treated at HSDPs (Table). **Conclusions:** Patients treated at HSDPs were less likely to receive timely definitive treatment and had worse survival. NHB men have worse outcomes than NHW at HSDPs. NHB men with PCa remain largely disadvantaged since they are more likely to be treated at hospitals with worse outcomes and have worse outcomes than other patients at those same institutions. Research Sponsor: American Cancer Society.

Interaction between race (NHW, n=634,917; NHB, n=119,166) and treatment at non-HSDP (n=603,346) versus HSDP facilities (n=150,737).

	Definitive Treatment		TTI within 90 days		Survival		Survival among men who received definitive treatment	
	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value
NHB at HSDP vs. NHW at HSDP	0.68 (0.66-0.71)	< 0.001	0.74 (0.72-0.76)	< 0.001	1.17 (1.12-1.23)	< 0.001	1.13 (1.07-1.19)	< 0.001
NHB at HSDP vs. NHB at non-HSDP	0.65 (0.58-0.73)	< 0.001	0.76 (0.70-0.82)	< 0.001	1.07 (1.00-1.14)	0.05	1.04 (0.97-1.12)	0.22

6556 **Poster Session**

Racial/ethnic disparities of cancer treatment disruptions among patients with breast cancer with SARS-CoV-2 infection: An analysis of the ASCO Survey on COVID-19 in Oncology Registry.

First Author: Jessica Yasmine Islam, Moffitt Cancer Center, Tampa, FL

Background: The COVID-19 pandemic has led to disruptions in cancer treatment delivery among breast cancer patients in the U.S. However, it is currently unknown whether racial/ethnic disparities exist in cancer treatment disruptions among patients with breast cancer and SARS-CoV-2 infection. **Methods:** We obtained data from the ASCO Survey on COVID-19 in Oncology Registry (March 2020-July 2021) describing breast cancer patients diagnosed with SARS-CoV-2 during their care treated at 46 practices across the US. Data included patient demographics, SARS-CoV-2 diagnosis and treatment, breast cancer characteristics, and modifications to cancer treatment plans. Breast cancer treatment delay or discontinuation (TDD) was defined as any treatment postponed more than two weeks from the originally scheduled date. We computed adjusted odds ratios (aOR) using multivariable logistic regression, accounting for non-independence of patients within hospitals to evaluate racial/ethnic disparities of TDD. Multivariable models were adjusted for age, sex, number of comorbidities, cancer extent, ECOG performance score, pandemic period based on case peaks (< 06/2020, 06-12/2020, 01-07/2021), and COVID-19 severity (death/hospitalization/ICU admission/mechanical ventilation). **Results:** Breast cancer patients (n = 804) with SARS-CoV-2 were mostly aged 50 years and above (75%) and urban residents (83%). The racial/ethnic makeup of the sample included: 13.3% non-Hispanic Black/African American (NH-Black), 11.7% Hispanic/Latinx, 4.9% American Indian/Alaskan Native (NH-AI/AN), 4.6% NH-Asian, and 65% NH-White. At SARS-CoV-2 diagnosis, 736 patients (91%) were scheduled to receive drug-based therapy (78%), radiation therapy (8%), or surgery (6%), of whom 39% experienced TDD. Across treatment modalities, the most commonly reported TDD reason from the clinic perspective was the patient's COVID-19 disease (~90%). Overall, NH-Black (62%), Hispanic/Latinx (44%), and NH-Asian (42%) adults with breast cancer and SARS-CoV-2 were more likely to experience TDD versus NH-White adults (34%) ($p < 0.001$). In multivariable analyses, NH-Black cancer patients were more likely to experience TDD compared to NH-White patients (aOR: 3.12, 95% CI: 1.96-5.47). The data suggest Hispanic/Latinx (aOR: 1.34, 95% CI: 0.78-2.30) breast cancer patients may also experience TDD, although not statistically significant. No association was observed among NH-Asian (aOR: 1.16, 95% CI: 0.50-2.73) or NH-AI/AN (aOR: 0.64, 95% CI: 0.28-1.52) breast cancer patients with TDD. **Conclusions:** Black or African American breast cancer patients are more likely to experience cancer care disruptions during the pandemic. Future research should evaluate the long-term impacts of care disruptions on breast cancer outcomes among minoritized US communities. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

6557 **Poster Session**

Rural disparities in oncology patient portal enrollment and use.

First Author: Bonny B. Morris, Wake Forest School of Medicine, Winston-Salem, NC

Background: Patient portals support patient access, engagement, and care coordination, yet could also widen the digital divide and exacerbate disparities among vulnerable populations. There is emerging evidence that racial/ethnic minority patients are less likely to use portals, yet prior research has not examined potential rural differences. We identified sociodemographic factors associated with portal enrollment and use among a racially and geographically diverse population of cancer patients. **Methods:** We retrospectively examined portal enrollment and use at an NCI-designated comprehensive cancer center from January 2015 until February 2022 among patients 18+ years old with a neoplastic disease diagnosis (ICD-10-CM C00-D49). Potential predictors included gender, race/ethnicity, marital status, age, rural (Rural-Urban Continuum Codes [RUCC] 4-9) vs nonrural (RUCC 1-3) residence, residential distance from the cancer center, and time since diagnosis. We used multivariable logistic regression to generate odds ratios (ORs) for portal enrollment and having ever sent a portal message, and Poisson regression to determine incidence rate ratios (IRRs) for number of logins and number of healthcare team interactions (portal messages or appointment requests), controlling for ICD-10 diagnosis (SAS 9.4). **Results:** We identified 11,333 patients (average age 67 years, 59% female, 24% rural, 10% Non-Hispanic Black, 1% Hispanic, 20% non-melanoma skin cancer, 14% breast cancer, 9% lung cancer). 36% of patients had enrolled in the portal, and of these, 80% had sent at least one message. Patients logged in a median of 203.5 times and had a median of 19 portal interactions. Rural residents were less likely to enroll in the portal than urban patients (28% vs 38%, $p < 0.0001$). Non-Hispanic Black patients and Hispanic/Latinx patients were less likely to enroll in the portal compared with non-Hispanic White patients (22% and 27%, respectively, vs 38.5%, $p < 0.0001$). Women, younger patients, more recently diagnosed cancer patients, and patients who were married/ partnered were significantly more likely to enroll. In multivariable analysis controlling for cancer type, rural patients were half as likely to enroll in the portal (OR: 0.48 [0.43-0.54]). Among those enrolled, rural residents were 25% less likely to have ever sent a portal message (OR: 0.75 [(0.62-0.92]), and had nearly half the login and interaction rates (IRR: 0.66 [0.66-0.67]; IRR: 0.58 [0.58-0.59], respectively). Patients who were Non-Hispanic Black, Hispanic, or unmarried were also significantly less likely to enroll or engage in the portal. **Conclusions:** Patient portals remain underutilized among cancer patients, despite an increased reliance on virtual communications in the COVID era. Interventions to support portal engagement among rural residents and racial/ethnic minority patients are needed to avoid potentially exacerbating health disparities. Research Sponsor: U.S. National Institutes of Health.

6558 **Poster Session**

Relationship of travel distance with patient demographics, advance care planning, and survival in early-phase clinical trials (EP-CTs).

First Author: Sienna Durbin, Massachusetts General Hospital, Boston, MA

Background: EP-CTs are often conducted at large academic centers, which may require some patients to travel further for their care. Little is known about either the distance EP-CT participants travel for their care or the association of distance traveled with patient characteristics and outcomes. **Methods:** We retrospectively reviewed the electronic health records of consecutive patients enrolled in EP-CTs at Massachusetts General Hospital from 2017-2019 to obtain patient characteristics (demographics and clinical factors) and outcomes (including time spent on trial, survival, and presence or absence of an advance care planning [ACP] discussion, defined as documentation of a code status or goals of care conversation in the medical record). We also used patients' home zip codes to derive the social deprivation index (SDI; a composite demographic measurement from 0-100 quantifying social determinants of health, with higher numbers indicating more disadvantage). To estimate distance traveled, we calculated the miles traveled in one direction driving from home zip code to trial site. We used descriptive statistics to compare patient characteristics and outcomes for those traveling < 50 miles (short distance) versus those traveling 50+ miles (long distance). **Results:** Among 421 patients (median age = 63.0 years, 56.9% female, 97.6% metastatic disease), median distance traveled was 36.4 miles. Half of patients (n = 217; 51.5%) traveled 50+ miles to receive care on trial. There were no significant differences between those traveling short and long distances in most patient characteristics evaluated, including age (60.9 vs 60.6 years; $p = 0.635$), sex (53.9% female vs 57.6%; $p = 0.447$), race (85.3% white vs 84.8%; $p = 0.346$), marital status (71.8% married vs 69.3%; $p = 0.586$), insurance (51% private vs 54.4%; $p = 0.266$), cancer type (22.5% GI vs 21.2%; $p = 0.666$), prior lines of therapy (52.5% one-two lines vs 51.2%; $p = 0.981$), and performance status (62.3% ECOG 1 vs 66.8%; $p = 0.270$. However, those with a higher SDI score were less likely to travel a long distance for trial participation (mean SDI 36.7 for short distance vs 30.5 for long distance; $p = 0.026$). Patients traveling a long distance were less likely to have a documented ACP discussion (48.8% vs 66.7%; $p < 0.001$). We found no significant difference in time spent on trial between those traveling short and long distances (mean days: 98 vs 93.5; $p = 0.175$) or in time from coming off trial to death (mean days: 147.7 vs 153.7; $p = 0.099$). **Conclusions:** We found that half of EP-CT participants travel 50+ miles in one direction to their trial site, with disparities in travel distance based on the social deprivation index. Notably, those traveling long distances were less likely to have a documented ACP discussion. Our findings suggest several unmet needs in the EP-CT population and highlight opportunities for future intervention development. Research Sponsor: None.

6559 **Poster Session**

Racial disparities in diagnostic follow-up following BIRADS 0 mammogram.

First Author: Ritika Manik, University of Pennsylvania, Philadelphia, PA

Background: Delays in follow-up after abnormal mammograms can lead to worse outcomes and may contribute to health disparities. BIRADS 0 mammograms necessitate additional diagnostic imaging, and BIRADS 4 or 5 mammograms should be followed by biopsy. The goal of this study was to investigate racial disparities in rates and timeliness of (1) diagnostic follow-up after a BIRADS 0 screening mammogram and (2) biopsy following a subsequent BIRADS 4 or 5 diagnostic mammogram. **Methods:** We included women ≥18 years old who underwent a screening mammogram at the Hospital of the University of Pennsylvania with an assessment of BIRADS 0 between September 2010 and February 2018. The distributions of time from screening to diagnostic mammogram and from BIRADS 4 or 5 diagnostic mammogram to biopsy were estimated using the Kaplan Meier method. Follow-up was censored at 365 days. Case-mix adjusted Cox proportional hazards models were used to estimate the association between race/ethnicity and time to diagnostic mammogram and biopsy. **Results:** We identified 6299 women (Asian/PI=257, Black=3223, Hispanic=124, White=2420, Other/Unknown=275) with 6880 BIRADS 0 screening mammograms during the study period. Following these BIRADS 0 mammograms, the overall rate of diagnostic mammograms within 365 days was 87.3% (n=6006 mammograms), with a rate of 90.6% (2432) for White women and 85.3% (2971) for Black women. For the 1151 BIRADS 4-5 diagnostic mammograms in the cohort, the overall rate of follow-up biopsies within 365 days was 91.8% (n=1057 biopsies), with a rate of 93.8% (396) for White women and 91.1% (575) for Black women. Compared to mammograms obtained by White women, those obtained by Black women were less likely to be followed up with a diagnostic mammogram (HR 0.71, 95% CI 0.63-0.80, p<0.001) and biopsy (HR 0.74, 95% CI 0.55-0.98, p=0.037) when indicated (Table). Almost 1/4 (24.2%, 95% CI 23.1-25.9%) of BIRADS 0 screening mammograms among Black women were not followed by diagnostic imaging within 30 days as compared to 14.6% among White women (95% CI 13.3-16.0%, p<0.001). 23.6% (95% CI 20.5-27.2%) of BIRADS 4-5 diagnostic mammograms among Black women were not followed up with biopsy within 30 days vs 18.7% for White women (95% CI 15.4-22.8%, p=0.61) (Table). These disparities persisted at 90 days. **Conclusions:** Racial disparities exist in rates of follow-up after BIRADS 0 mammograms. The additive effects of delays at each diagnostic step put Black women at disproportionately greater risk for worse outcomes. Research Sponsor: None.

	Adjusted HR for Diagnostic Mammogram	P-Value	% Without Diagnostic Mammogram 30 days Post-BIRADS 0 Mammogram	P-Value	Adjusted HR for Biopsy	P-Value	% Without Biopsy 30 days Post-Diagnostic Mammogram	P-Value
	HR (95% CI)	<0.001	% (95% CI)	<0.001	HR (95% CI)	0.037	% (95% CI)	0.61
White	Ref		14.6 (13.3-16.0)		Ref		18.7 (15.4-22.8)	
Black	0.71 (0.63-0.80)		24.2 (23.1-25.9)		0.74 (0.55-0.98)		23.6 (20.5-27.2)	

6560 **Poster Session**

Disparity of treatment-related adverse events and outcome in patients with early-onset metastatic colorectal cancer (mCRC). *First Author: Lingbin Meng, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

Background: While the incidence of newly diagnosed early-onset mCRC has been increasing, disparity of treatment-related adverse events (AE) and outcomes of this patient population has been inadequately studied with inconclusive findings. We aimed to evaluate such age-related disparity and explore potential underlying causes. **Methods:** We used individual patient data from 3 clinical trials in Project Data Sphere where 756 and 467 patients with mCRC received first-line FOLFOX in study 1 (NCT 00305188, NCT00272051) and study 2 (NCT00364013), respectively. Clinical NGS data of 763 patients with mCRC from prospectively maintained Moffitt Clinical Genomics Database were used to assess genomic alterations. Patients were categorized into 3 age groups: <50, 50-65, and >65 years. Continuous and categorical variables were compared with *t* test and χ^2 test, respectively. Kaplan-Meier method and log-rank test were used for survival analysis. Benjamini-Hochberg procedure was used to adjust for multiple comparisons. **Results:** Among 1986 patients included, 341 (17.2%) in the <50 group, 912 (45.9%) in the 50-65 group, 733 (36.9%) in the >65 group had similar baseline characteristics. Outcomes: Patients in the <50 group had shorter median OS compared to the 50-65 (15.5 vs 20.5 month, p=0.003) and >65 groups (15.5 vs 20.8 months, p=0.004) and shorter median PFS compared to the 50-65 (8.1 vs 9.4 month, p=0.039) and >65 groups (8.1 vs 8.6 months, p=0.07) in study 1. Findings were confirmed in study 2. Toxicity: Compared to other age groups, the <50 group had a higher incidence of severe (grade≥3) abdominal pain (8.4% vs 3.4%, p=0.01), severe anemia (6.1% vs 1.2%, p=0.001), nausea/vomiting (69.3% vs 58.8%, p=0.02), but lower incidence of severe diarrhea (6.1% vs 10.8%, p=0.02), severe neutropenia (25.7% vs 44.2%, p<0.001), and severe fatigue (4.5% vs 7.3%, p=0.02). The <50 group had earlier onset of nausea/vomiting (1.0 vs 2.3 weeks, p=0.01), mucositis (3.6 vs 5.4 weeks, p=0.05), and neutropenia (8.0 vs 9.0 weeks, p=0.04), and shorter duration of mucositis (0.6 vs 0.9 weeks, p=0.006). Outcomes + toxicity: In the <50 group, abdominal pain was associated with worse OS (HR 1.6, p=0.01). In contrast, fatigue (HR 0.66, p=0.03) and mucositis (HR 0.67, p=0.046) were associated with better OS. Neuropathy was associated with better PFS (HR 0.61, p=0.009). Genomics: Our NGS data showed that the <50 group had more ERBB2 amplification (10.5% vs 4.0%, p=0.04) and a trend of more TP53 mutations (80.2% vs 72.0%, p=0.07). These findings were confirmed in an independent mCRC cohort (n=471, MSK, Gastroenterology 2020). **Conclusions:** Patients with early-onset mCRC had worse outcome and unique treatment-related AE patterns. Distinct genomic profiles could explain some of the disparities. Our findings might improve a personalized management approach in patient selection for chemotherapy, counseling and AE monitoring. Research Sponsor: University of South Florida GME grant.

6561 **Poster Session**

Reducing oncology readmissions through a multidisciplinary discharge approach. *First Author: Samantha DiBenedetto, University of Virginia, Charlottesville, VA*

Background: Hospital readmissions are associated with increased health care utilization and unfavorable patient outcomes. Oncology patients have an increased risk of hospital readmission compared to the general patient population. The 30-day readmission rate for cancer patients at our institution is 27.7% which is higher than the reported national average of 20.2%. We sought to reduce 30-day hospital readmission rates by 25% for solid tumor oncology patients through a prospective integrated multidisciplinary discharge approach. **Methods**: Hospital readmissions for adult patients with a known solid tumor cancer diagnosis admitted to the oncology service at UVA from Jan 2019 – Apr 2019 were identified. Baseline information on tumor type, reason for readmission, interventions, length of stay (LOS), and inpatient morbidity and mortality (including ICU admission and transition to hospice) were collected via retrospective review. Qualitative and quantitative tools including process maps, cause-and-effect diagrams, Pareto charts, and priority matrix were used to identify potential areas for intervention. Two PDSA cycles were implemented: daily multidisciplinary discharge rounds with physicians, nursing, social work, case management, and PT/OT (PDSA1), and a templated discharge email to patients' primary oncology team including attending oncologist, mid-level providers, nurse coordinator, pharmacist, and urgent care team (PDSA2). An SPC chart with 3-σ limits and t-test of unequal variance with 2-sided p-value was used to evaluate impact on readmission rates from baseline to PDSA2. **Results**: Following PDSA1 (May 2019 – Oct 2019), the 30-day readmission was 25.7%; PDSA2 was postponed due to COVID-19, however the 30-day readmission rate remained stable during the pandemic. Following PDSA2 (Sept 2021 – Dec 2021), the 30-day readmission rate was 18.2% corresponding to an absolute decrease of 34.3% which was statistically significant ($p \leq 0.05$). This was associated with a trend towards increased LOS, rate of ICU admission, and case-mix severity index although not statistically significant. There was no significant difference in inpatient mortality or transition to hospice (Table). **Conclusions**: Implementation of multidisciplinary discharge rounds and templated discharge communication resulted in a significant decrease in rate of 30-day readmissions for solid tumor oncology patients. There was a trend towards increased LOS and ICU admissions without increased inpatient mortality. Improvement in discharge email compliance and implementation of an urgent symptom clinic may further reduce the 30-day readmission rate. Research Sponsor: None.

	Baseline (n=424)	PDSA1 (n=1231)	PDSA2 (n=231)	P-value
30-day readmission rate (%)	27.7	25.7	18.2	0.046
Average LOS (days)	5.8	5.7	10.0	0.076
ICU admissions (%)	9.1	14.7	16.7	0.339
Inpatient mortality (%)	5.2	3.1	4.8	0.977
Transition to hospice (%)	15.6	16.0	16.7	0.845
Case mix index	1.66	1.68	1.94	0.287

6562 **Poster Session**

Acceptability of a machine learning-powered clinical decision support system aiding serious illness conversation and its impact on clinical outcomes: A pilot study. *First Author: Teja Ganta, Tisch Cancer Institute, Division of Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: Patients with advanced cancer that utilize end of life planning see benefits including better quality of life and medical care that is more consistent with their values. We developed a 30-day mortality predictive model using a machine learning algorithm and integrated it into a clinical decision support system (CDSS) that encourages clinicians to use the serious illness conversation (SIC) guide—a standardized questionnaire and conversational tool that facilitates end-of-life planning. The CDSS was piloted in the thoracic oncology clinic. We evaluated clinicians' use of this system and its impact on patient outcomes. **Methods:** Between 4/14/21-1/15/22, information about patients identified by the model was sent to clinical teams via the electronic health record (EHR) to assess eligibility for a SIC. We reviewed the EHR for patients identified, SIC completion, and level of agreement by oncologists with the model. We evaluated the SIC guide responses using descriptive statistics and assessed differences in rates of hospice referral, hospital visits, and 30-day mortality by SIC completion status. Chi-squared test was used for testing association. **Results:** 94 patients were evaluated for SIC eligibility. Of these, oncologists agreed with 48 (51%) model predictions and SIC was completed for 28 (58%) of those patients. A median of 2.5 SIC eligibility assessments per week were completed, with a median time of 4 days from prediction to assessment. Likewise, a median of 1 SIC per week was completed, with a median time of 20 days from SIC eligibility assessment to conversation. Regarding the responses to the SIC guide, out of 28 patients, 75% have an appropriate understanding of their illness; 64% want to be fully informed of their medical information while 21% prefer information to be limited. Common patient goals were "being comfortable" (54%), "being at home" (29%) and "being independent" (25%). The most prevalent patient fears were "family concerns" (29%) or "physical suffering" (25%). The clinician who performs the SIC most often recommended an "additional conversation with physician" (39%), "conversation with family" (36%), or "referral to palliative care" (18%). SIC completion was associated with an increased rate of enrollment in hospice (33% vs 14%, P= 0.03) on univariate analysis. SIC was not associated with a difference in 30-day mortality or hospital visits. Multivariable analysis is ongoing. **Conclusions:** The machine-learning powered CDSS was adopted by the oncology care team within a reasonable timeframe. However, even if an oncologist used and agreed with the CDSS, the rate of eventual completion of SIC was not 100%. Additional barriers to SIC will be studied to optimize the CDSS. SIC completion may lead to increased enrollment in hospice and should continue to be studied as a standard component of comprehensive cancer care. Research Sponsor: None.

6563 **Poster Session**

Updated health-related quality of life of patients with TRK-fusion cancer treated with larotrectinib in clinical trials. *First Author: Shivaani Kummar, Stanford Cancer Center, Stanford University, Palo Alto, CA*

Background: *NTRK* gene fusions have been identified as oncogenic drivers in patients (pts) with TRK fusion cancer across multiple solid tumors. Larotrectinib, a highly selective, CNS-active TRK inhibitor has shown high response rates, durable disease control, and a favorable safety profile in pts with TRK fusion cancer and is approved in over 40 countries. Larotrectinib has demonstrated rapid health-related quality of life (HRQOL) improvement in a group of 57 adult and pediatric pts (Kummar et al, *Curr Prob Canc* 2021). Here, we report updated HRQOL results for larger group of pts treated with larotrectinib. **Methods:** HRQOL data were collected in two ongoing trials (NCT02576431, NCT02637687) of larotrectinib in pts with TRK-fusion cancer using the EORTC QLQ-C30, EQ-5D-5L questionnaires and were analyzed descriptively and longitudinally. Scores from the EORTC QLQ-C30 Global Health Status (GHS), EQ-5D-5L VAS range from 0 to 100, with higher scores indicating better QOL. We also calculated the proportion of pts with either below normal or normal and above normal HRQOL scores against values in the literature for the US general population. **Results:** By July 2021, 113 adults with TRK-fusion cancer had received larotrectinib and completed the baseline (BL) and ≥ 1 post-BL questionnaire. The majority of pts had clinically meaningful HRQOL improvements during treatment (Table). For EORTC QLQ-C30 GHS, most adults maintained or improved scores from BL at or above the normal population level category. HRQOL improvements (change from BL > 0) occurred after ~2 months of treatment in 75% of adults. Median duration of pts with sustained improvement in EORTC QLQ-C30 GHS, and EQ-5D-5L VASs was 12.5 months (range, 1.8-34.1), and 12.9 months (range, 1.8-34.0), respectively. HRQOL results were consistent across multiple data cuts. **Conclusions:** Patients with TRK-fusion cancer treated with larotrectinib continued to have rapid, clinically meaningful, and sustained improvements in HRQOL. Clinical trial information: NCT02576431, NCT02122913, NCT02637687. Research Sponsor: Bayer HealthCare and Loxo Oncology.

6564 **Poster Session**

Readmission risk identification: Implementation of a patient-centered interview. *First Author: Raquel E. Reinbolt, The Ohio State University Comprehensive Cancer Center, Arthur G. James Cancer Hospital, Columbus, OH*

Background: Unplanned 30-day readmissions in the cancer population are common. There are few large studies describing cancer patients' readmission perspective. To better define predisposing factors associated with readmission, our Nurse Case Manager team implemented a patient-focused survey. **Methods:** Cancer patients readmitted to The James Cancer Hospital from May 2020-December 2021 were included. Readmission events were defined as an inpatient hospital readmission within 30 days of the patient's prior hospitalization. Team members conducted a 16-question survey immediately following readmission to evaluate the patients' perspective on factors that may have contributed to their readmission; results were recorded. **Results:** A total of 3,333 readmissions were unplanned, 109 planned, 22 listed as other; 3,464 patients completed interviews (Table). During their index admission, most patients reported receiving (90%) and understanding (89%) discharge education/instructions. Upon index discharge, most patients (62%) were discharged on a new medication; the majority reported filling their prescription (95%) and taking it as instructed (98%). Nearly all patients had a post-index hospitalization follow up appointment scheduled, but only 58% reported attending. The primary reason reported for not attending was readmission prior to the appointment. Just over 50% of patients received a post-index hospital stay phone call. Some patients (6% yes; 58% unanswered) felt services at discharge would have been helpful. Most patients (51%) contacted their provider regarding worrisome symptoms experienced prior to being readmitted. Pain (18%), fever (11%), and shortness of breath (10%) were the most commonly reported symptoms that prompted returning to the hospital. **Conclusions:** To our knowledge, this is the largest study to date of cancer patients' own perspective of their 30-day readmission. More immediate post-hospitalization follow up and increased deployment of tailored discharge services represent areas of opportunity identified to decrease readmission rates. Symptom-specific interventions may also be impactful. Due to the negative downstream effects readmissions have on the healthcare system, it is critical to develop risk mitigation strategies incorporating patient-reported experience. Research Sponsor: None.

To patient/caregiver:	Yes	No	Unanswered or N/A	I Don't Remember
Did you contact your provider about worrisome symptoms after discharge	1775	1445	244	-
Did you receive education re: discharge needs	3126	63	273	2
Did you understand the discharge instructions	3085	40	339	-
Were you sent home on a new medication	2138	1012	314	-
Would discharge services have been helpful	207	1242	2015	-
Was a hospital follow up appointment scheduled	3180	62	222	-
If yes, did you attend	1842	1215	123	-
Did you receive a post hospital follow up phone call	1877	1054	521	12
If no, would a call have been helpful	216	722	116	-

6565 **Poster Session**

Implementing proven methods in a community-based health system to improve breast cancer screening rates during the COVID-19 pandemic. *First Author: Celine Fadel, Northeast Georgia Medical Center, Gainesville, GA*

Background: There are reduced screening rates across the United States secondary to the COVID-19 pandemic; the additional anticipated deaths from breast and colorectal cancer, secondary to reduced screening, is approximated at 10,000 people. A study of thirty-two health systems in Georgia noted an 8% decrease in screening mammography compared to pre-pandemic rates. To help reverse the decline, Northeast Georgia Medical Center (NGMC) participated in the "Return to Screening" initiative, in conjunction with the American Cancer Society (ACS). A quality improvement project was performed at the community-based hospital system to increase breast cancer screening rates, using a multidisciplinary approach with a focus on health care disparities. **Methods:** The initial goal was to increase screening mammograms by 10% (n = 14,364) from June 1st to December 1st 2021. Interventions were selected by a multidisciplinary team of NGMC researchers, clinical providers, and oncology administrators. Interventions varied in category, encompassing unique patient and provider-specific approaches. The evidence-based interventions were tailored to address health care disparities in the local population. This included identification and quantification of cultural groups in the community to ensure quality patient access. Integrative collaboration consisted of intermittent meetings to certify consistent communication, project reflection and identification of barriers. The selected interventions were executed monthly, with simultaneous data tracking of mammography rates. **Results:** From June 1st to December 1st 2021, a total of forty evidence-based interventions were successfully implemented. Analysis of screening rates demonstrated a 15% increase across the allotted time period, corresponding to an average of 1,302 mammograms monthly (n = 15,284). This exceeded the initial anticipated goal of increasing screening by 10% (n = 14,364). Analysis of mammography results identified 331 new cases of breast cancer diagnosed within the allotted period, a 7% mean diagnosis rate increase. Certain planned interventions were unable to be conducted and required modification due to limitation of the ongoing pandemic; however, this solidified the use of social media and virtual participation as effective methods of community outreach. **Conclusions:** We identified key methods to engage the local community and successfully increased rates of screening mammography. Interventions were tailored to the local population, ensuring patient-centered tools and a personalized approach to medicine. The multidisciplinary, consistent collaboration with stakeholders ensured quality of care for the local patient population. This project demonstrates the importance of local community engagement to impact national cancer screening rates, and thus, ensure earlier detection of breast cancer. Research Sponsor: American Cancer Society.

6566 **Poster Session**

Evaluation of inpatient chemotherapy among patients with cancer. *First Author: Giulia Petrone, Icahn School of Medicine/Mount Sinai Morningside-West Hospital, New York, NY*

Background: Administration of inpatient chemotherapy (IC) is associated with more aggressive end of life care, reduced use of palliative care (PC) and decreased quality of life (QOL). This study aims to identify risk factors associated with overutilization of IC. **Methods:** We conducted a retrospective chart review of all admissions where IC was administered at an academic center between January 2016 and December 2017. Patients (pts) were stratified by solid tumors (ST) versus hematologic malignancies (HM) and urgency for IC was assessed. We evaluated other variables which can impact patient care such as length of stay (LOS), reason for admission and for IC. Descriptive statistics and odds ratios (OR) were estimated from logistic regression models with mixed-effect taking into account correlations from multiple admissions per patient. All tests were two-sided and statistical significance was considered when p<.05. **Results:** We analyzed 880 admissions (17% ST). Table 1 summarizes outcomes. HM pts required frequent direct admission for IC compared to ST. ST pts (p<.0001), pts >65 years (p=0.004) and pts with KPS ≤50% (p<.0001) were most likely admitted for cancer complications rather than for IC. LOS (>7 days) was significantly longer in HM admissions (p=0.0001), among pts with stage 4 cancer (p=0.014) and KPS ≤50% (p=0.0001). ST (p=0.006) and pts with KPS ≤50% (p=0.0001) received IC for a non-urgent indication significantly more often than HM. In 20% of ST admissions, pts received IC because the admission coincided with a non-urgent planned cycle compared to 3% of HM. In the adjusted analysis, tumor type was the most important factor correlated with urgency of IC (OR 0.42, 95% CI: 0.25-0.72; p=0.001). ST pts (p=0.0001), older pts (p=0.004) and pts with KPS ≤50% (p=0.0001) were less likely to respond to chemotherapy. Only 15% of HM admissions and 46% of ST admissions had a PC consult. 60-day mortality was significantly higher in ST pts than HM (p=0.002). **Conclusions:** IC is associated with poorer outcomes for pts with advanced stage ST, pts with poor functional status and pts admitted for acute indications. Additionally, ST pts have a higher mortality after IC compared to HM. Utilization of IC should be standardized to account for different patient characteristics and to reduce the incidence of non-urgent administration. Based on this data, we created a standardized protocol to better assess the appropriateness of IC to improve patient care, QOL, and reduce chemotherapy and healthcare utilization at the end of life. Research Sponsor: None.

	ST N=147 (%)	HM N=733 (%)	P-value
Reason for admission			<.0001
Symptoms/Cancer			
Complications/POD/Other	88 (60)	135 (18)	
Direct admission for IC	59 (40)	597 (81)	
Reason for IC			0.006
Admitted during planned cycle/Symptoms/POD	92 (63)	160 (22)	
IC required	55 (37)	573 (78)	
Non-urgent indication	50 (34)	140 (19)	0.0001
No response to IC	63 (43)	139 (19)	0.0001
Mortality within 60 days of admission	22 (20)	43 (9)	0.002

6567 **Poster Session**

Lisocabtagene maraleucel (liso-cel) as second-line (2L) treatment (tx) for R/R large B-cell lymphoma (LBCL) in patients (pt) not intended for hematopoietic stem cell transplantation (HSCT): Patient-reported outcomes (PRO) from the phase 2 PILOT study. *First Author: Leo I. Gordon, Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL*

Background: PILOT (NCT03483103) evaluated liso-cel, an autologous, CD19-directed, CAR T cell product, as 2L tx in pts with R/R LBCL not intended for HSCT. We analyzed changes in health-related quality of life (QOL) with respect to functioning and symptoms in PILOT. **Methods:** Adults with R/R LBCL after first-line tx were eligible. Pts were deemed not candidates for high-dose chemotherapy and HSCT by their physician and met ≥ 1 frailty criteria: age ≥ 70 yr, ECOG PS = 2, DLCO ≤ 60%, LVEF < 50%, CrCl < 60 mL/min, or ALT/AST > 2 × ULN. Pts completed EORTC QLQ-C30, FACT-LymS, and EQ-5D-5L (health utility index [HUI] and VAS) at screening (baseline [BL]), pre-tx (within 7 days before lymphodepletion), preinfusion on day of liso-cel infusion (Day 1), post-tx on Days 29, 60, 90, 180, 270, 365, 545, and 730/end of study, or at PD. The PRO-evaluable set included all pts with BL and ≥ 1 post-BL assessments. Linear mixed-effects models for repeated measures assessed the least squares (LS) mean change from BL for visits with ≥ 10 pts. Meaningful change from BL was calculated using responder definitions (in points): 10 for EORTC QLQ-C30, 3 for FACT-LymS, 0.08 for EQ-5D-5L HUI, and 7 for EQ-VAS. **Results:** Among the PRO-evaluable set, completion rates were high (≥ 80%) across most visits for all measures. For EORTC QLQ-C30, mean BL fatigue was meaningfully worse than in a general noncancer population (difference of > 10 points). Overall LS mean changes through Day 545 showed significant improvements in EORTC QLQ-C30 fatigue and pain, FACT-LymS, and EQ-VAS (Table). Improvement for lymphoma symptoms was also clinically meaningful. Fatigue improvement was clinically meaningful with a more sensitive minimal important difference of 4 (Cocks et al, 2012). Significant worsening was not observed for any outcome. In individual patient-level analysis, 70% of pts demonstrated meaningful improvement in FACT-LymS at month 6. **Conclusions:** Liso-cel meaningfully improved fatigue and FACT-LymS scores without negatively impacting other QOL measures. These data support the clinical evidence of liso-cel as a potential new 2L tx in pts with R/R LBCL not intended for HSCT. Clinical trial information: NCT03483103. Research Sponsor: Juno Therapeutics, a Bristol-Myers Squibb Company.

Overall score changes for primary outcomes of interest.

Instrument	Outcome	LS mean change (95% CI)	*P* value
EORTC QLQ-C30 (n = 56)	Global health status/QOL[a]	2.77 (–0.36, 5.91)	0.082
	Physical functioning[a]	–1.67 (–4.88, 1.53)	0.298
	Role functioning[a]	–3.21 (–8.01, 1.60)	0.187
	Cognitive functioning[a]	–0.55 (–3.50, 2.41)	0.711
	Fatigue[b]	–6.94 (–10.34, –3.55)	< 0.001
	Pain[b]	–4.12 (–7.62, –0.62)	0.022
FACT-Lym	FACT-LymS[a] (n = 49)	4.08 (2.55, 5.61)	< 0.001
EQ-5D-5L	HUI[a] (n = 55)	0.02 (–0.02, 0.06)	0.341
	EQ-VAS[a] (n = 54)	4.35 (1.27, 7.43)	0.006

[a]Higher change indicates improved functioning from BL; [b]Lower change indicates improved symptoms from BL.

6568 **Poster Session**

Polypharmacy and premature aromatase inhibitor (AI) discontinuation in older women with breast cancer. *First Author: Elizabeth Joyce, University of Michigan Health System, Ann Arbor, MI*

Background: Treatment with AI therapy for at least five years is recommended to reduce risk of cancer recurrence in postmenopausal women with hormone-positive breast cancer, but up to 50% prematurely discontinue their AI. Prior studies have demonstrated higher rates of nonadherence in older patients. Higher rates of comorbidities are also present in older patients, many of which require treatment with prescription medications. However, in prior studies, the impact of polypharmacy on AI persistence in older women has been variable. We evaluated the relationship between use of prescription and over-the-counter (OTC) medications and AI discontinuation in older women in a randomized controlled trial of AI therapy. **Methods:** In the Exemestane and Letrozole Pharmacogenetics (ELPh) trial, postmenopausal women with stage 0-III hormone-positive breast cancer were randomized to receive exemestane or letrozole and followed for two years. Prescription medication and OTC supplement usage was prospectively collected. Only enrolled participants at least 65 years of age were included in this analysis. Univariate and multivariable Cox proportional hazards models evaluated the association between baseline prescription medications, OTC medications, initial assigned AI medication, and time to discontinuation of initial AI. **Results:** 131 women at least 65 years old with baseline medication and OTC supplement information were identified. The average age was 70.4 (SD 5). 58 participants (44%) were randomized to exemestane and 73 (56%) to letrozole. 21% had previously received tamoxifen and 18% received taxane-based chemotherapy. The average number of prescription medications at AI initiation was 4.95, and 127 patients reported taking at least one. The average number of OTC medications was 3.23, and 107 patients reported taking at least one. There was no difference in number of prescription medications or OTC medications by study arm. As previously reported, exemestane was associated with premature discontinuation (HR 1.92 [95%CI 1.06-3.50], p = 0.032). Controlling for AI, the risk of discontinuation decreased by 12% for every additional prescription medication (HR 0.88 [95%CI 0.78-0.99], p = 0.038). OTC medication use was not significantly associated with AI duration. **Conclusions:** Increased prescription medication usage at AI initiation was associated with decreased risk of premature discontinuation of AI. Further research is needed to evaluate this interaction and identify characteristics that impact AI persistence in older women with breast cancer. Clinical trial information: NCT00228956. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

6569 **Poster Session**

When and how to deliver oncology supportive care resources: An adolescent and young adult perspective. *First Author: Betty Roggenkamp, Independent Consultant, Chicago, IL*

Background: The Coleman Supportive Oncology Collaborative for Adolescents and Young Adults (CSOC AYA) is a multi-institution Chicago-based quality improvement collaborative consisting of representation from AYA-focused oncology teams at six hospitals and national patient advocacy organizations**.** Coping with cancer as an AYA is challenging given their complex and unique phases of life and dichotomy between pediatric and adult care. AYAs with cancer are a recognized underserved population within the cancer community and have unique supportive care needs that are often unmet. The CSOC AYA focuses on improving access to resources for supportive care. **Methods:** We implemented an online survey across six cancer treatment centers (5 academic, 1 community) engaging 50 AYAs. Participants were newly diagnosed (2), currently on treatment (18), or off treatment (30). Participant age range was representative of AYAs (< 18years: 2%, 18 – 24: 36%, 25 – 34: 55%, and 35-39: 7%). Reported race was 60% Caucasian, 10% Black, 18% Latino, 8% Asian, 2% American Indian, and 2% other. Questions were asked to inform which supportive resources were desired by patients, when the resources would be most useful during the care continuum, and the preferred methods to receive information. **Results:** Greater than 54% percent of respondents desire social/emotional resources and peer connection at diagnosis. During treatment and after treatment, > 71% and > 56% respectively, desire guidance regarding nutrition/diet and physical activity/exercise, in addition to social/emotional support and peer connection (See table). Preferred methods to receive information were identified: 72% via email or text, 60% in person, and 45% via a patient portal. **Conclusions:** The CSOC AYA survey identified the type of supportive care resources AYAs need, when they are wanted, and their preferred methods for receiving them. Optimizing accessibility and availability of supportive care resources can enable AYA self-management and has the potential to improve quality of life. These survey results will serve as the basis for a patient-facing online intervention implemented throughout the care continuum with the intent to improve supportive care access for AYAs with cancer. Research Sponsor: The Coleman Foundation.

At which point in your cancer care would these support resources be helpful?			
n = 50	% Diagnosis	% During Treatment	% Off Treatment
Nutrition/diet guidance	42	82	56
Physical activity/exercise guidance	40	76	64
Social/emotional support	65	78	69
Connecting to other AYAs	54	71	65

6570 **Poster Session**

Changes in Functional Assessment of Cancer Therapy: General (FACT-G) to predict treatment response and survival outcomes in patients with metastatic gastrointestinal (GI) cancer. *First Author: Joy X. Jarnagin, Massachusetts General Hospital, Boston, MA*

Background: The FACT-G contains 27 questions within 4 subscale domains [Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, Functional Well-Being] related to health-related quality of life (QOL) in the past 7 days, with higher scoring indicating better QOL. In this prospective cohort study, we assessed longitudinal FACT-G data with treatment response and survival outcomes among patients with metastatic GI cancer. **Methods:** From 5/2019-11/2021, we enrolled patients at Massachusetts General Hospital with metastatic GI cancer to study before their treatment start. We collected the FACT-G survey at baseline (start of treatment) and 1-month later. We then used regression models to assess associations of 1-month changes in FACT-G with treatment response and survival outcomes (progression-free survival [PFS] and overall survival [OS]). For treatment response, clinical benefit was defined as decreased or stable tumor burden versus progressive disease at the time of first scan. All models were adjusted for baseline values of each respective variable. **Results:** We enrolled 203 of 262 patients approached (77.5% enrollment); 160 had 1-month follow-up data (median age = 63.0 years [range: 28.0-84.0 years], 66.3% male, 45.6% pancreaticobiliary cancer). For treatment response, 66.3% experienced a clinical benefit and 33.8% had progressive disease at the time of first scan (mean time to first scan = 2.7 months). Increases in FACT-G Total were predictors for treatment response (OR = 1.05, p = 0.0028), and improved PFS (HR = 0.98, p = 0.026) and OS (HR = 0.98, p = 0.038). Increases in FACT-G Emotional were associated with clinical benefit at the time of first scan (OR = 1.18, p = 0.0024), improved PFS (HR = 0.94, p = 0.023), and improved OS (HR = 0.93, p = 0.012). Improvement in FACT-G Physical were predictors for clinical benefit at time of first scan (OR = 1.08, p = 0.038) and better PFS (HR = 0.96, p = 0.038), while increases in FACT-G Functional were associated with improved PFS (HR = 0.96, p = 0.034) and OS (HR = 0.96, p = 0.019). Finally, changes in FACT-G Social were only associated with treatment response (OR = 1.16, p = 0.011). **Conclusions:** We found that 1-month increases in FACT-G can predict for treatment response and improved survival outcomes in patients with metastatic GI cancers. Notably, the FACT-G Total and FACT-G Emotional subscore predicted for all three outcomes of interest, while the FACT-G Social only predicted for clinical benefit at first scan. These data support previous findings indicating the possible use of early changes in patient-reported outcomes as a biomarker for early treatment response while emphasizing the growing need to integrate more patient-centric interventions into clinical care for cancer patients. Clinical trial information: NCT04776837. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

6571 **Poster Session**

Physician awareness of immune-related adverse events from checkpoint inhibitors. *First Author: Ahmed Bilal Khalid, Indiana University School of Medicine, Indianapolis, IN*

Background: Immune checkpoint inhibitors (ICIs) have been one of the most significant developments in Oncology over the last decade. Despite being very effective for certain patient subsets, they have a unique side effect profile different from conventional chemotherapy that can manifest as immune-related adverse events (IRAEs). With increasing ICI use, clinicians will increasingly encounter these adverse events and thus, adequate knowledge on recognition and management of IRAEs is very important. **Methods:** To assess physician knowledge on IRAEs of ICIs, an online survey was administered to resident physicians in internal medicine (IM), emergency medicine (EM) and family medicine (FM) as well as to faculty physicians in IM, and FM at 3 tertiary care hospitals in Indiana. **Results:** We sent the survey to 413 physicians out of which 155 responded with a response rate of 38%. Out of 155 physicians, 110 were residents and 45 were faculty (27 hospitalists and 17 primary care physicians). Pembrolizumab was identified as a checkpoint inhibitor correctly by 79% of physicians, nivolumab by 64% and ipilimumab by 55%. Twenty-five percent of physicians incorrectly believed infliximab and adalimumab were ICIs. Most physicians (93%) were able to identify the gastrointestinal tract as an IRAE site whereas only 57% and 67% were able to identify cardiovascular and renal systems as an IRAE site, respectively. Fifty-nine percent of physicians believed steroids negatively affect efficacy of ICIs and should be used with caution to treat IRAEs. Sixty-five percent of physicians incorrectly thought endocrinopathies due to IRAEs are usually reversible. Most physicians (79%) believed IRAEs most commonly manifest in the first 6 months of treatment. Forty-five percent of FM residents considered antibiotics as the mainstay of treatment in ICI associated immune mediated colitis; this was significantly different from EM (15%) and IM (8%) residents(p = 0.0004). When comparing between residency programs, on a scale of 0-100, IM residents felt significantly more comfortable identifying IRAEs secondary to ICIs (27.1±24.2) when compared to EM (12.2±12.7) and FM residents (9.4±13.8; p = 0.0009). There was no significant difference among IM (19.8±20.1), EM (11.9±13.6), and FM residents (11.6±18.9; p = 0.11) when comparing how comfortable they were in treating IRAEs. When asked what the best way would be to learn about IRAEs, 36% chose printed material and algorithms, 30% picked online teaching module and 30% chose one time in-person lecture from an Oncologist. **Conclusions:** Resident and faculty physicians in multiple specialties are not comfortable in the management and treatment of IRAEs due to ICIs. Given that most of these physicians are usually the first point of contact with patients, physician education on identification and treatment of IRAEs is needed. Early detection of these toxicities is critical for their resolution. Research Sponsor: None.

6572 **Poster Session**

Implementation of a precision medicine thoracic (PREDICT) service using reflex testing in a large academic-community practice network. *First Author: Debora S. Bruno, Case Western Reserve University, Cleveland, OH*

Background: Broad genomic testing is necessary for treatment of patients with stage IV non-small cell lung cancer (NSCLC). This quality improvement initiative aims to implement a precision medicine service for NSCLC patients at a hybrid academic-community practice oncology network. **Methods:** Following IRB approval, network tumor registries were queried for retrospective newly diagnosed stage IV NSCLC from 01/2016 through 12/2018. PREDICT was implemented in 08/2021. It consists of: 1) system-wide reflex testing of newly diagnosed stage IV NSCLC patients by an in-house solid tumor focused assay (hybrid DNA/RNA next-generation sequencing (NGS) panel previously reported) and PD-L1 testing, 2) PREDICT navigator, 3) molecular tumor board (MTB), 4) integrated information portal for real-time updates on samples processing, results and treatment recommendations by the MTB. We compared prospective data (08/2021 through 01/2022) after PREDICT with retrospective practice assessment. Comparisons between the groups were conducted using independent samples t-test / Wilcoxon rank sum test for continuous variables and Chi-square test/Fisher's exact test for categorical variables. **Results:** Of 861 retrospective patients identified in the compiled registry of stage IV NSCLC, 626 were eligible. Since PREDICT launch in 08/2021, 103 eligible prospective patients have been identified. Prospective patients are slightly older (mean age 70.9 vs 68 years old; $p = 0.013$), with no other significant demographic or clinical differences identified. Rates of NGS testing obtained within 90 days of biopsy date (BxD) increased significantly (94.1% vs 60.8%; $p < 0.0001$) after PREDICT. Turnaround times (TAT) from BxD to test results were significantly shorter for both NGS (12 vs 18 days; $p < 0.0001$) and PD-L1 (7 vs 10 days; $p = 0.007$) after PREDICT. A trend towards higher rates of actionable alterations (EGFR, ALK, ROS1, RET, BRAF, MET14 skipping, NTRK1/2/3) was noted: 19.6% vs 13% ($p = 0.071$). Targeted therapy use increased from 6.8% to 15.6% ($p = 0.002$) in the overall cohort. No differences in time to treatment initiation (TTI) after PREDICT have been identified to this point, with a median of 34 and 35 days for the prospective and retrospective groups, respectively. **Conclusions:** Implementing a precision medicine service for thoracic oncology patients has led to significantly higher rates of NGS testing for patients with stage IV NSCLC in a large hybrid academic-community practice network. Launching of this initiative resulted in significantly shorter TAT for both NGS and PD-L1 test results. A trend towards higher rates of actionable alterations has been identified. Targeted therapy use has increased significantly overtime, potentially due to higher availability of precision medicine drugs in the current era. Research Sponsor: AstraZeneca/NCCN.

6573 **Poster Session**

Association of modifiable factors with financial burden and health literacy among patients with cancer. *First Author: Betina Yanez, Northwestern University Feinberg School of Medicine, Chicago, IL*

Background: Cancer patients are at a higher risk of financial burden compared to those with other chronic illnesses and those without cancer. Additionally, cancer patients with low health literacy are at risk for poor health outcomes and poor self-management. Aside from factors such as education and insurance, there is limited information on the role of modifiable factors in predicting financial burden and health literacy. The aim of this study was to identify risk factors associated with financial burden and health literacy among cancer patients. **Methods:** Participants were 2,260 adult, English- or Spanish-speaking patients who were recruited from an NCI-designated cancer center in the Chicagoland area as part of a trial on symptom management. Participants completed measures on depressive symptoms and anxiety using the Patient-Reported Outcomes Measurement Information System (PROMIS). Financial burden was assessed using a Comprehensive Score for Financial Toxicity (COST FACIT) item (FT12) and health literacy was assessed by the Single Item Literacy Screener (SILS). Additional information on insurance and cancer diagnosis were extracted from medical records. The area deprivation index (ADI) was calculated using national percentile rankings for the patient's block group. All patient-reported outcomes were assessed at study baseline. Cross-sectional logistic regression models were fit with the FT12 item [dichotomized as high (somewhat/quite a bit/very much) vs. low (not at all/a little bit) financial burden] and SILS [dichotomized as high (quite a bit/extremely) vs. low (not at all/a little bit/somewhat) health literacy] as separate outcomes. The primary covariates of interest were anxiety and depressive symptoms T-scores (dichotomized reflect normal limits vs. elevated distress). Analyses were adjusted for socio-demographic and clinical characteristics. **Results:** After adjusting for covariates, significant associations of greater financial burden were PROMIS depression [odds ratio (OR): 1.63 (95% CI: 1.22-2.19)] and PROMIS anxiety (OR: 1.60; 95% CI: 1.22-2.10). In addition, higher ADI score, lower education, unemployment, and low health literacy were significantly associated with greater financial burden. PROMIS depression (OR: 2.15; 95% CI: 1.38-3.40) was associated with low heath literacy, along with disability/leave of absence, Medicare/Medicaid/uninsured and lower education. **Conclusions:** Modifiable factors are associated with financial burden and health literacy. These results support the systematic screening for financial burden and health literacy in addition emotional well-being. Interventions targeting the modifiable factors elucidated in this study may further efforts to provide quality and equitable comprehensive cancer care. Future work should evaluate the potential causal pathways between depression, health literacy, and financial burden. Research Sponsor: U.S. National Institutes of Health.

6574 **Poster Session**

Standardized documentation of advanced care planning to facilitate goal-concordant care in a large gynecologic oncology practice. *First Author: Pamela T. Soliman, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Advanced care planning (ACP) involves sharing of knowledge related to prognosis, treatment options, and patient values/goals, among the patient, their caregivers, and the clinical care team. These goals of care (GOC) discussions are critical at different time points during the care of a cancer patient, but are not performed or documented consistently in most oncology practices. The American Society of Clinical Oncology recommends that documentation of advance directive discussions, a component of ACP, take place by the third office visit for patients with newly diagnosed invasive cancer. We implemented a quality improvement initiative to improve ACP discussion and documentation in our large gynecologic oncology practice. **Methods:** As part of an institution-wide effort called "Mind the Gap: bridging the gap between patients' perception of their oncologic situation and the reality thereof", we identified 3 critical timepoints for which a GOC discussion and ACP documentation was recommended in the outpatient setting. These time points included: (1) by the 3rd visit for new patients with an invasive cancer, (2) preoperative (within 30 days of surgery), and (3) at time of treatment/chemotherapy change. Providers were educated on the key components of ACP documentation including surrogate decision maker and goals of cancer treatment. Standard templates were used to document these discussions for easy identification in the electronic health record. Metrics for each faculty team were shared monthly with the entire department. The department goal was to reach a cumulative goal > 60% completion for all patients in each of the 3 clinical time points within 6 months. **Results:** The proposed plan and education on ACP standard documentation was presented to 22 gynecologic oncologists during a faculty retreat in 10/2020. Baseline data from 8/2020 was shared revealing that ACP documentation was completed in 24% of new patients, 1% of preoperative, and 19% at treatment change. At the 6-month assessment (5/2021), ACP documentation was completed in 83.6% of new patients, 79.8% of preoperative, and 63% of patients at the time of treatment change. At one year (10/2021), ACP documentation was completed on 88.6% of new patients, 70.3% of preoperative, and 59% of patients at the time of treatment change. There was variability among providers in documentation of ACP for new patients (range 50-100%), preoperative (range 0-100%) and treatment change (range 12.5-100%). **Conclusions:** Through a departmental initiative, we were able to successfully encourage more frequent goals of care discussions and their standardized documentation, which was maintained at 1 year. We are currently evaluating the impact of this program on end-of-life quality metrics including chemotherapy within 14 days, ICU stay within 30 days and multiple hospital admissions within 30 days of end of life. Research Sponsor: None.

6575 **Poster Session**

Next-generation sequencing (NGS): How often is testing performed too late? *First Author: Meena Sadaps, Cleveland Clinic, Cleveland, OH*

Background: With the emergence of precision oncology over a decade ago, NGS and the utility of targeted therapies have readily been incorporated into standard-of-care (SOC) practices. Still in many cases, NGS is only done after patients (pts) have failed several lines of treatment and/or their performance status (PS) has declined. We aim to further evaluate the timing of NGS as it pertains to patients' clinical disease course. **Methods:** All patients with incurable solid tumor malignancies undergoing NGS testing at our institution from January 2020 to December 2021 were included. Our genomics team (including medical oncologists, bioinformaticians, and a genetic counselor) routinely reviews all NGS results on a biweekly basis to assess for actionable alterations that would be eligible for on-label therapy (tx), clinical trials, and/or off-label consideration for targeted tx that has been FDA approved in another histology. Baseline demographics for pts such as age and gender, in addition to oncologic history, performance status, and date of death were collected via in-depth chart review utilizing the electronic medical record system. **Results:** We reviewed NGS results for 1767 pts, of which 1455 (82.4%) had genomic tumor board (GTB) recommendations for an actionable alteration. Of the 1767 pts, 33 were deceased at time of results review. The most common histology amongst the deceased were lower gastrointestinal tract (24.2%), genitourinary (18.2%), lung and pancreatic (15.2% each). At time NGS was ordered, 11 (33.3%) had received no prior tx, 8 (24.2%) had received one line of systemic tx, and 14 (42.4%) had received 2 or more lines of systemic tx. The average time from when NGS was ordered to results being reported was 17.9 days. The median time from when NGS was ordered to date of death was 26 days. At time NGS was ordered, 39% of pts had an ECOG PS of 0-1, 34% had an ECOG PS of 2, and 27% had an ECOG PS of 3-4. All 33 of these pts had actionable alterations for which GTB recommendations were made. All of these pts were matched to at least one clinical trial while 21.9% were recommended for an on-label tx as well. 54.5% of these pts were receiving care at regional facilities while 45.5% were receiving care at main campus. **Conclusions:** In our experience, all patients who were deceased at time of NGS review had an actionable alteration, for which there was a treatment recommendation made. In a rapidly evolving field where novel targeted therapies are on the rise, the rate of actionability is increasing, and NGS is now SOC, we are still seeing pts get testing done only after the receipt of multiple lines of systemic tx and/or once their PS has declined. These pts may benefit from earlier NGS testing, which would have opened up additional therapies earlier on in the course of their disease, when their PS was also likely to be more optimal. Further work is necessary to determine if early NGS testing makes a significant clinical impact on survival. Research Sponsor: None.

6576 **Poster Session**

An examination of translated content on NCI-designated cancer websites with a focus on breast and colorectal cancer. *First Author: Minira Aslanova, Mount Sinai Beth Israel, New York, NY*

Background: One unforeseen implication of the pandemic has been a greater reliance on health information sharing via the Internet. This is complicated by the fact that many healthcare websites and online resources fail to consider Limited English Proficiency (LEP) when designing websites that relay essential health information. We aimed to quantify the extent to which NCI-Designated Cancer Center websites provide language accessibility. **Methods:** Over the course of 2021, we performed a cross-sectional review of translation services and available languages on NCI-Designated Cancer Center websites. This study was particularly focused on both breast cancer and colorectal cancer portions of these websites. The primary out-comes were as follows: option of translated content, presence of more than one language, and method by which the translation was performed (written text vs. Google scholar). We referred to the 2015 US language map for the percentage of LEP by state. **Results:** Of the 71 NCI-Designated Cancer Centers, 56 (78.9%) were without translation, and 15 (21.1%) used either manual translation or displayed a link for Google translate. Of the 15 centers who offered translated content on their website, 15/15 (100%) had more than one language available in the drop down list. Spanish (100%) was the most common language available. In terms of Limited English Proficiency, 25 of 71 (35.21%) NCI-Designated Cancer Centers were located in states where greater than 10% of the population is defined as having LEP, and yet, only 5 of these centers (20.0%) had languages other than English featured. We observed no significant relationship between the state LEP percentile and the number of NCI-Designated Cancer Centers offering website translation services within that state. Additionally, no appreciable differences in language availability were observed between breast cancer and colorectal cancer. **Conclusions:** Overall, only a fraction of NCI-Designated Cancer Centers actually translate the content of their websites. In New York for example, despite having the highest percentage of residents with LEP at 19.345%, only one of ten NCI-Designated Cancer Centers within the state had a website with language translation. We believe this represents a missed opportunity as language inaccessibility may contribute to delays in care for non-English speaking patients, particularly in a post pandemic world, further exacerbating health care disparities among patient populations. Research Sponsor: None.

6578 **Poster Session**

Contemporary real-world associations between performance status and clinical outcomes in patients with cancer: A retrospective cohort study. *First Author: Deepika Kumar, Hematology/Oncology Fellowship Program, Kaiser Permanente, San Francisco, CA*

Background: The ECOG-PS (Eastern Cooperative Oncology Group Performance Status) scale is often used to guide cancer care, but the degree to which it predicts contemporary real-world clinical outcomes, in general and within certain patient groups, is relatively unknown. This retrospective cohort study examined associations between ECOG-PS levels and adverse outcomes in cancer patients with diverse patient characteristics. **Methods:** Various patient characteristics and nurse-rated ECOG-PS scores (range: 0-4) were recorded for all 21,730 adult patients with cancer receiving intravenous systemic therapy between 01/01/2017 and 12/31/2019 at 18 Kaiser Permanente Northern California cancer centers. Differences in baseline characteristics by ECOG-PS scores were evaluated using chi-square tests for categorical variables and ANOVA for continuous variables. Univariable and multivariable Cox Proportional Hazard models were used to test the ability of ECOG-PS to predict the occurrence of adverse clinical outcomes, including 1-month emergency department (ED) visits and hospitalizations, and 6-month mortality. **Results:** Overall, 42.5% of patients had ECOG-PS = 0, 42.5% had ECOG-PS = 1, 10.5% had ECOG-PS = 2, 4% had ECOG-PS = 3 and 0.4% had ECOG-PS = 4. Most patients were women (58%), non-Hispanic White (61%), English speakers (93%) and married/domestic partners (63%). African Americans, men, older patients, and those with higher Charlson comorbidity index or Stage IV cancer were found to have higher ECOG-PS levels (all $p < 0.001$). In multivariable analysis, ECOG-PS of 3-4 were associated with higher ED visits (HR 3.85, 95% CI [3.47-4.26]), hospitalizations (HR 4.7, [4.12-5.36]) and mortality (HR 7.34, [6.64-8.11]), compared with ECOG-PS = 0. Upper gastrointestinal (GI) and Stage IV cancers were associated with a higher risk of ED (upper GI: HR 2.39, [2.12-2.68], (stage IV: HR 1.31, [1.21-1.42]), hospitalization (HR 2.67, [2.27-3.13], (HR 1.51, [1.35-1.68]), and mortality rates (HR 3.37, [2.97-3.81], (HR 1.82, [1.68-1.98]), compared to Breast and Stage I cancers; however, advanced age was not associated with these outcomes. Interactions between ECOG-PS and cancer type as well as ECOG-PS and age group were statistically significant ($p < 0.001$), such that ECOG-PS was more predictive of adverse outcomes in younger patients and those with breast cancer. **Conclusions:** In this contemporary real-world cohort, multivariable analysis showed that ECOG-PS, cancer type and stage were strong predictors of ED visits, hospitalizations and mortality; however, advanced age was not. These results also show that ECOG-PS is more predictive of clinical outcomes in certain patient groups. Our findings may have implications on the use of ECOG-PS for clinical decision making. Research Sponsor: None.

6579 **Poster Session**

Overall survival (OS) of patients with TRK fusion–positive cancer receiving larotrectinib versus standard of care (SoC): A matching-adjusted indirect comparison (MAIC) using real-world data (RWD). *First Author: Carsten Bokemeyer, University Medical Center Hamburg-Eppendorf, Hamburg, Germany*

Background: Larotrectinib trials in Tropomyosin Receptor Kinase (TRK) fusion cancer population were single arm trials and therefore limited comparative effectiveness data with larotrectinib are available.MAIC is typically used to balance population characteristics to facilitate cross-study comparisons. The objective of this study was to use MAIC to compare efficacy of the highly specific TRK inhibitor larotrectinib vs. SoC. **Methods:** Individual patient data from larotrectinib trials (NCT02122913, NCT02637687, NCT02576431) were compared with published aggregate SoC data from patients with locally advanced/metastatic TRK fusion cancer identified in the Flatiron Health/Foundation Medicine clinico-genomic database (Demetri et al. Ann Oncol. 2021). Prior to matching, eligible patients were ^{3}18 years and had to have received ≤4 lines of prior therapy (LoPT). Patients were matched on available common baseline characteristics (Table). Overall survival was the only endpoint assessed and was defined as time from locally advanced/metastatic disease diagnosis to death. The analyses included: 1) a log-rank test of equality to test whether the two groups were similar before larotrectinib initiation; and 2) estimation of treatment effect of larotrectinib vs. SoC. Hazard ratios (HRs) were used to compare the 2 groups. MAIC assumes that all observed and unobserved prognostic factors are adjusted for in the analysis. **Results:** 85 larotrectinib patients and 28 SoC patients were included. After matching, log-rank testing suggested no difference between the 2 groups *(P*=0.26), and larotrectinib was associated with a 78% lower risk of death (adjusted HR: 0.22 [95% confidence interval: 0.09, 0.54]; *P*=0.001), compared to SoC. **Conclusions:** This analysis suggests longer overall survival with larotrectinib, compared to SoC, in adult patients with TRK fusion cancer. The current analysis was limited to the prognostic variables available in the RWD. Further data are warranted to confirm those results. Research Sponsor: Bayer.

Baseline characteristic, %	Flatiron/FMI (Demetri et al. 2021)	Larotrectinib (before-matching)	Larotrectinib (after-matching)	Baseline characteristic, %	Flatiron/FMI (Demetri et al. 2021)	Larotrectinib (before-matching)	Larotrectinib (after-matching)
NTRK1	82.0	42.4	81.8	*Brain metastases*	17.9	9.4	17.9
Age ≥ 65 y	39.3	29.4	39.2	*Breast*	4.0	1.2	4.0
*ECOG 0-1**	50.0	87.1	50.2	*Salivary gland*	7.0	21.2	7.1
*Lines of therapy since diagnosis, 0-2**	71.4	77.7	71.5	*NSCLC*	18.0	12.9	18.0
Stage at diagnosis, 0-II	17.9	20.0	17.9	*Soft tissue sarcoma*	21.0	22.4	21.0
Stage at diagnosis, III-IV	64.3	61.2	64.3	*Colorectal*	32.0	5.9	31.8

*Matching performed on multiple categories.

6580 **Poster Session**

Real-world trends of PARPi maintenance treatment uptake and progression-free survival (PFS) in patients (pts) with newly diagnosed advanced ovarian cancer (AOC) in the United States. *First Author: John K Chan, Palo Alto Medical Foundation, Palo Alto, CA*

Background: Since 2018, the FDA has approved 2 PARP inhibitors (PARPi), niraparib and olaparib, for first-line (1L) maintenance therapy for OC. Using real-world population data, we assessed trends of 1L PARPi maintenance treatment uptake and PFS of pts with newly diagnosed AOC. **Methods**: Pts diagnosed with AOC between January 1, 2017, and June 30, 2021, who completed 1L chemo were identified from the nationwide Flatiron Health electronic health record (EHR)-derived de-identified database. We calculated descriptive statistics describing pt demographics, clinico-pathological characteristics, and 1L treatment patterns. The use of PARPi or active surveillance (AS) was identified during a 120-day period after the last dose of 1L chemo. The end of the 1L treatment identification period was defined as the index date. Time to next treatment was used as a proxy for PFS and was defined as time from the index date to the next therapy, last clinical activity, end of study period, or death. Kaplan-Meier methods and Cox models were used to analyze the PFS endpoint. **Results**: A total of 705 pts were included in the study; 166 received PARPi monotherapy (PARPi mono) and 539 underwent AS after completion of 1L chemo. Median age was 68 y for AS vs. 65 y for PARPi mono (Table). Median time from last chemo to initiation of PARPi mono was 48.5 d. Median follow-up was 20.6 mo for AS and 10.9 mo for PARPi mono. In the overall group, median PFS (mPFS) was 9.53 mo for AS vs. not reached (NR) for PARPi mono. In those with *BRCA* mutations (*BRCA*m), corresponding mPFS was 11.4 mo vs. NR and for *BRCA* wild type (*BRCA*wt) was 9.1 mo vs. 13.5 mo. On multivariate analysis, 1L PARPi maintenance was an independent predictor for improved PFS when compared to AS in all pts (HR, 0.47; 95% CI, 0.34-0.63), *BRCA*m (HR, 0.17; 95% CI, 0.07-0.41) and *BRCA*wt (HR, 0.50; 95% CI, 0.35-0.72). Stage IV at initial diagnosis, no debulking surgery, residual disease, and *BRCA*wt status were associated with poorer PFS. Trends analysis over the 4-year study period showed PARPi mono use increased from 6% in 2017 to 53% in 2021. **Conclusions**: This real-world analysis shows that adoption of PARPi mono in the 1L maintenance setting in pts with newly diagnosed AOC has increased to 53% in 2021. PARPi use, when compared with AS, was associated with significantly improved mPFS in both pts with *BRCA*m and *BRCA*wt. Research Sponsor: GlaxoSmithKline.

	AS N=539	PARPi mono N=166	*P* value
Median age at index, y	68 (59.0-75.0)	65 (56.0-72.8)	<0.01*
IQR, y			
Group stage at initial diagnosis, n (%)			<0.05*
III	383 (71.1)	103 (62.0)	
IV	156 (28.9)	63 (38.0)	
Debulking surgery before index, n (%)			0.655
Yes	492 (91.3)	154 (92.8)	
No/unknown	47 (8.7)	12 (7.2)	
Residual disease status, n (%)			0.495
No residual disease	245 (45.5)	78 (47.0)	
Residual disease	150 (27.8)	51 (30.7)	
Unknown	144 (26.7)	37 (22.3)	
***BRCA* status, n (%)**			<0.001*
***BRCA*m**	41 (7.6)	52 (31.3)	
Not *BRCA*m	361 (67.0)	103 (62.0)	
Unknown	137 (25.4)	11 (6.6)	

6581 **Poster Session**

Changes in cancer-related mortality during the COVID-19 pandemic in the United States. *First Author: Jingxuan Zhao, American Cancer Society, Atlanta, GA*

Background: The coronavirus disease 2019 (COVID-19) pandemic resulted in delayed medical care that may have led to increased death rates in 2020 among people with medical conditions such as cancer. This study examined changes in cancer-related mortality between 2019 and 2020. **Methods:** We used the US 2019-2020 Multiple Cause of Death database from the CDC WONDER to identify cancer-related deaths, defined as decedents with invasive or noninvasive cancer as a contributing cause of death (ICD-10 codes: C00-C97 and D00-D09). We compared age-standardized cancer-related annual and monthly mortality rates (per 100,000 person-years and person-months, respectively) in January-December 2020 (pandemic) versus January-December 2019 (pre-pandemic) overall and stratified by rurality and place of death. We calculated the 2020 excess death by comparing the numbers of observed death with the projected death based on age-specific cancer-related death rate from 2015 to 2019. **Results:** The number of cancer-related deaths was 686 054 in 2020, up from 664 888 in 2019, with an annual increase of 3.2%. Compared to the number of projected deaths for 2020 (666 286), the number of cancer-related excess deaths was 19 768 in 2020. Annual age-standardized cancer-related mortality rate (per 100,000 person-years) continuously decreased from 173.7 in 2015 to 162.1 in 2019, while it increased to 164.1 in 2020 (2020 vs 2019 rate ratio (RR): 1.013, 95% confidence interval (CI): 1.009 - 1.016). The cancer-related monthly mortality rate was higher in April 2020 (RR: 1.032, 95% CI: 1.020 – 1.044) when healthcare capacity was most challenged by the pandemic, subsequently declined in May and June 2020, and higher mortality rates were again observed each month from July to December 2020 compared to 2019. In large metropolitan areas, the largest increase in cancer-related mortality was observed in April 2020, while in non-metropolitan areas, the largest increases occurred from July to December 2020, coinciding with the time-spatial pattern of COVID-19 incidence in the country. Compared to 2019, cancer-related mortality rates were lower from March to December 2020 in medical facilities, hospice facilities, and nursing homes or long-term care settings but higher in decedent's homes. **Conclusions:** The COVID-19 pandemic led to significant increases in cancer-related deaths in 2020 versus 2019. Ongoing evaluation of the spatial-temporal effects of the pandemic on cancer care and outcomes is warranted, especially in relation to patterns in vaccine uptake and COVID-19 hospitalization rates. Research Sponsor: None.

Age-standardized cancer-related mortality rates in 2019 and 2020.

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
2019*	14.15	12.67	13.94	13.16	13.67	13.12	13.43	13.54	13.18	13.87	13.48	13.84
2020*	14.05	13.01	13.86	13.58	13.36	12.90	13.72	13.78	13.36	13.90	13.79	14.80
Rate ratio	0.99	1.03	1.00	1.03	0.98	0.98	1.02	1.02	1.01	1.00	1.02	1.07

*Rate per 100,000 person-months.

6582 **Poster Session**

Frailty status derived from the electronic medical record to predict survival and health care utilization in veterans with lung and gastrointestinal cancers. *First Author: Sudha Yarlagadda, Baylor College of Medicine, Houston, TX*

Background: Frailty is associated with increased vulnerability to stressors. Although frailty is a predictor of survival, traditional frailty assessments are not feasible in clinical practice. Frailty indexes (FI) derived from the electronic medical record (EMR) are an alternate approach. There is limited data for the association between EMR-FI and cancer-related outcomes including survival and health care utilization. **Methods:** We identified a cohort of patients diagnosed with lung or gastrointestinal cancer from 2016-2020 using VA administrative files. We used the Veterans Affairs-FI (VA-FI), a validated 31-item cumulative deficit FI, to define three groups: robust (≤0.1), prefrail (0.1-0.2), frail (> 0.2). Cox proportional hazard analyses were conducted to evaluate survival. Logistic regression analyses were performed to examine healthcare utilization. All models were adjusted for age, gender, race, Charlson comorbidity index, and stage. **Results:** Among 37,439 patients (age: 70±8.6 years), the majority were prefrail (36.8%) or frail (24.1%). Prefrail patients had a 13% increased risk of death compared to robust patients (adjusted hazard ratio [aHR] 1.13; 95% CI 1.10-1.16), while frail patients had a 52% increased risk (aHR 1.52; 95% CI 1.47, 1.57). Pre-frail and frail patients had increased odds of 1-year ED visits (adjusted odds ratio [aOR] 1.33; 95% CI 1.27 - 1.40 and aOR, 1.88, 95% CI 1.77-2.00, respectively). Frailty status was associated with increased odds of 1-year all-cause hospitalization among prefrail (aOR 1.09; 95% CI 1.03-1.15) and frail patients (aOR 1.26; 95%CI: 1.18, 1.34). **Conclusions:** Frailty measured by EMR data is significantly associated with survival and healthcare utilization among patients with lung and gastrointestinal cancers, independent of stage. Further study is warranted to develop EMR-FI as a risk stratification tool for personalized cancer treatment decisions. Research Sponsor: Veterans Affairs.

6583 **Poster Session**

What is driving declines in oncology-prescribed opioids? *First Author: Tarlise Townsend, NYU Grossman School of Medicine, New York, NY*

Background: Patients with cancer have experienced sharp declines in opioid prescribing during the past decade, raising concerns about insufficient pain management in a population with high rates of undertreated pain. It is unclear whether these declines are driven by certain oncology subspecialties, payors, or clinical guidelines regarding opioid prescribing released in/after March 2016. **Methods:** We conducted time series analyses using 2006-2019 IQVIA Longitudinal Prescription Data, which represents up to 92% of all U.S. prescription fills. Using log-linear regression stratified by group, we estimated annual percent change in opioid receipt by: subspecialty (medical oncology MO, radiation oncology RO, and surgical oncology SO); payor (third-party; Medicare, including Medicare Part D; Medicaid; cash/out-of-pocket); and pre- versus post-March 2016. Opioid receipt outcomes included: monthly fills of any opioid; monthly fills of extended-release/long-acting (ER/LA) opioids; and monthly number of patients receiving long-term opioid therapy (LTOT). Outcomes were per 1,000 survivors to account for temporal changes in cancer prevalence. **Results:** Between 2006 and 2019, 14,301,900 opioid fills were prescribed by oncologists to 3,476,354 distinct patients. Across all outcomes, MO had the highest levels of dispensing, followed by RO, then SO; for example, in 2006 MO dispensed 6.2 fills per 1,000 survivors (compared to 1.9 fills among RO, and 0.5 among SO). We observed substantial declines in all opioid outcomes. Per 1,000 survivors, there was an annual decline of: 5.7% (95CI: 5.1-6.3; total unadjusted decline 2006-2019=70.2%) in the rate of all opioid fills; 4.9% (95CI: 4.1-5.6; total unadjusted decline=66.8%) in ER/LA fills; 3.2% (95CI: 1.5-5.0; total unadjusted decline=56.2%) in LTOT fills, and 1.9% in average daily dose (95CI: 1.9-2.0; total unadjusted decline=29.8%). The annual decline in opioid fills prescribed by MO (7.1%, 95CI: 6.6-7.7) was sharper than for RO (5.9%, 95CI: 5.4-6.4) and SO (5.2%, 95CI: 4.7-5.7). Annual declines were steepest among fills paid out-of-pocket (14.5%, 95CI: 13.9-15.0), followed by those paid by Medicaid (13.1%, 95CI: 12.5-13.6), third-party payors (9.3%, 95CI: 8.7-9.9), and Medicare (2.4%, 95CI: 1.8-3.1). Declines in every outcome accelerated following clinical guidelines released in/after 2016. **Conclusions:** Opioids prescribed by oncologists declined dramatically across groups and outcomes. Medical oncologists were responsible for a disproportionate share of opioid fills in 2006, and for the sharpest declines. Out-of-pocket fills declined more sharply than fills covered by insurance and clinical guidelines may have contributed to accelerating declines. While de-escalation of opioid therapy may reduce risk of opioid-related harms to cancer survivors, care is needed to ensure cancer-related pain is appropriately treated. Research Sponsor: U.S. National Institutes of Health.

6584 **Poster Session**

Analysis of genomic alterations and treatment landscape in patients with advanced tumors using real-world data for precision oncology. *First Author: Kubra Karagoz, Sema4, Stamford, CT*

Background: Analysis of real-world data is critical for clear understanding of treatment effectiveness. Here, we explore the clinical utility of next-generation sequencing (NGS) and the impact of mutational landscapes on targeted therapy and outcomes in almost 10,000 patients in real-world setting. **Methods:** We constructed a data analysis platform that integrated NGS results with machine and manually curated electronic medical records data from a single large healthcare system. We assessed eligibility for a targeted therapy based on the constellation of mutations detected by NGS, investigated whether a matched therapy was given and how this affected patient outcome. **Results:** The study comprised of 9848 patients with NGS results across 90 cancer types including lung (2208;22%), colorectal (1495;15%), multiple myeloma (1153;12%), breast (783;8%), and prostate (480;5%) and other remaining cancers (3,729; 38%) from 2011 to 2021. Overall, 95% of patients had a positive NGS result, of whom 6364 (65%) had a targetable mutation in 34 genes per any NCCN guidelines in any cancer type. Of these, 2930 (46%) were late-stage (3-4). 820 patients across 31 cancer types received any of 54 targeted therapies based on an NGS result; 605/820 (74%) were stage 3-4; overall 605/2930 (21%) of all tested stage 3-4 patients received targeted therapy. Overall stage 4 patients with a targetable mutation who were treated with a targeted therapy had better 5-year overall survival (OS) than patients who did not (HR = 0.71, 95% CI 0.57-0.89, p = 0.003). We further analyzed important biomarkers in specific cancers. Stage 4 lung cancer patients carrying *EGFR, ALK, ROS1* or *MET* alteration and receiving targeted therapy had better 5-year OS (HR 0.56, 95% CI 0.40-0.80, p = 0.001). We observed that multiple myeloma patients carrying *KRAS* and *NRAS* mutation received off-label Trametinib, however it did not improve their OS (HR 1.28, 95% CI 0.76-2.15, p = 0.4). Moreover, there are 665 patients with tumor mutational burden (TMB) across 64 cancer types. TMB has been categorized into high (55, 8%), intermediate (177, 27%) and low (433, 65%). OS was significantly longer in TMB-low patients compared to TMB-high and TMB-intermediate patients across all cancers (HR 0.63, 95% CI 0.43-0.92, p = 0.016). There are 5051 patients with microsatellite instability status across 72 cancers categorized into high (828, 16%), and low (4223, 84%) with no significant survival difference between groups. **Conclusions:** We show that real-world data offers important insights into clinical practice and patient outcome, with respect to genomic alterations and associated targeted therapies. Moreover, we have built an analytics platform which allows users to ask relevant clinical questions around outcome of patients treated with targeted therapy by genomics biomarker and potential to identify off-label use and clinical response in any cancer type. Research Sponsor: None.

6585 **Poster Session**

Persistent high-risk opioid use in lymphoma survivors following treatment.

First Author: Katherine Ann Stafford, Mount Auburn Hospital, Cambridge, MA

Background: Opioid analgesia has an important role in treating cancer pain but can place survivors at risk for long-term adverse effects, including misuse, abuse, and overdose. While opioid use has been studied in surgical oncology patients, little is known about long-term use and outcomes for patients with hematologic malignancies who primarily receive non-surgical treatment. We evaluated the association between opioid use during lymphoma treatment and persistent high-risk opioid use. **Methods**: We conducted a retrospective cohort study using IBM Watson Health MarketScan Commercial Claims and Encounters Data from 2000-2019, containing claims for employer-sponsored privately insured individuals in the US. We identified opioid-naïve adults age 18-64 years at their first diagnosis of Hodgkin (HL) or Non-Hodgkin lymphoma (NHL) who had outpatient cancer therapy lasting 90-240 days (including ≥3 episodes of outpatient chemotherapy). Using outpatient pharmacy claims, we categorized each patient's opioid exposure during cancer treatment to no exposure, moderate [1-7 days supply], or high [> 7 days supply]. Follow-up began 60 days after patients' final cancer treatment and continued up to 365 days or until an outcome or censoring event. High-risk opioid use was defined as ≥120 days cumulative supply, ≥3 consecutive months of opioid prescriptions, or a prescription with ≥90 morphine milligram equivalents per day. We used time-to-event methods to estimate cumulative incidence and hazard ratios across exposure groups. **Results**: There were 4380 opioid-naïve lymphoma patients in the cohort. 42.5% had HL and 57.5% had NHL. Median age at diagnosis was 46 years (IQR 32-56) and median treatment duration was 147 days (IQR 112-166). 55.0% of patients were male. During cancer treatment, 42.8% of patients had no opioid exposure, 28.1% had moderate, and 29.1% had high. Among the no-opioid-exposure group, the 1-year cumulative incidence of high-risk opioid use was 1.7%. Compared to this no-exposure group, the hazard ratios for moderate and high exposure were 2.6 (95% CI 1.5-4.6) and 9.0 (95% CI 5.6-14.4), respectively, after adjustment for cancer treatment duration, age, cancer type, and calendar time. A sensitivity analysis comparing patients diagnosed 2000-2009 vs. 2010-2019 found that hazard ratios remained consistent between the two time periods; however, there was a decrease in the absolute incidence of high-risk opioid use by approximately half. **Conclusions:** In this cohort study of opioid-naïve lymphoma patients, higher opioid exposure during cancer treatment was associated with a higher likelihood for persistent high-risk opioid use in the year following cancer treatment. The absolute incidence of high-risk opioid use decreased over time and may be due to increased awareness of the opioid epidemic. Close clinical follow-up in the post-treatment period may be warranted for patients at high risk of adverse outcomes. Research Sponsor: None.

6586 **Poster Session**

Time at home among older adults with acute myeloid leukemia based on treatment intensity: A SEER-Medicare analysis.

First Author: Daniel R. Richardson, University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: Older adults with acute myeloid leukemia (AML) have identified time at home (TAH) as a critical outcome when deciding on treatment. No study to date has fully explored TAH for older adults with AML. **Methods**: We identified a cohort of adults age ≥66 years with a new diagnosis of AML from the SEER-Medicare linked database from 2004-2016. Individuals were stratified into high-intensity chemotherapy [HIC] v. hypomethylating agent [HMA] v. other using claims. The primary outcome was TAH, quantified by subtracting the total number of person-days spent in hospitals and skilled nursing facilities from the number of person-days survived. Demographics, comorbidities, frailty, and transfusion dependence were considered covariates. **Results**: 7,946 adults were included. 2,824 (36%) received HIC, 2,542 (32%) HMA, and 2,580 (33%) other. Mean age was 75 years (HIC: 73; HMA: 78; other: 76). The cohort was predominantly White (88%, Black 5%; Asian 3%; Hispanic 1%) and male (57%). Median survival was 7 months (HIC: 9; HMA: 8). Median total TAH was 151 days (Mean 426, Range 0-1825). Adults receiving HIC spent less time at home and more time hospitalized than those receiving HMAs each month in the first year (Table). Differences in TAH between HIC and HMA cohorts were most pronounced in the first 3 months (1st: 49.5% v. 86.5%; 2nd: 68.2% v. 84.1%; 3rd: 77.3% v. 86.8%). Total TAH over 12 months was lower for those receiving HIC v. HMA (51.7% [187 days] v. 56.9% [205 days]). Transfusion dependence (≥ 1/month) was associated with decreased TAH at 1 month (OR 0.81, p<0.001) and 12 months (OR 0.90, p=0.04). Other covariates were not associated with TAH. **Conclusions**: Although intensive chemotherapy resulted in slightly longer survival, older adults treated with HMAs had more time at home. Treatment decision-making should incorporate patient preferences for prolonging survival v. increasing time at home. The effect of new treatments (eg, venetoclax) on time at home should be evaluated in future studies. Research Sponsor: Lineberger Comprehensive Cancer Center.

Percentage of person-days spent at home (Time at home) and hospitalized by month after treatment among older adults with AML, by treatment intensity (High intensity [HIC] v. hypomethylating agent [HMA]).

Month after treatment	N alive, All adults	N alive, HIC	N alive, HMA	Time at home, All adults	Time at home, HIC	Time at home, HMA	Hospitalized, All adults	Hospitalized, HIC	Hospitalized, HMA
1	7946 (100%)	2824 (100%)	2542 (100%)	62.9%	49.5%	86.5%	35.6%	49.6%	12.1%
2	6962 (88%)	2642 (93%)	2347 (92%)	75.0%	68.2%	84.1%	22.5%	29.5%	13.8%
3	5961 (75%)	2317 (82%)	2095 (82%)	82.2%	77.3%	86.8%	15.5%	20.4%	11.5%
4	5339 (67%)	2138 (75%)	1879 (73%)	85.5%	81.1%	89.2%	12.7%	17.1%	9.4%
5	4885 (61%)	1979 (67%)	1720 (68%)	87.2%	83.5%	89.8%	11.4%	15.1%	9.0%
6	4470 (56%)	1827 (64%)	1572 (62%)	89.1%	86.2%	91.5%	9.9%	12.9%	7.6%
9	3581 (45%)	1492 (52%)	1247 (49%)	90.5%	88.0%	91.7%	8.6%	11.3%	7.2%
12	2924 (37%)	1205 (42%)	1020 (40%)	91.7%	89.9%	92.3%	7.6%	9.5%	7.1%

6588 **Poster Session**

Do publicly available OncoGenomic databases represent the population? A comparative analysis.

First Author: Danielle Brazel, UC Irvine Healthcare, Orange, CA

Background: Large publicly available databases are important repositories for analyses of clinicogenomic research used for identifying clinically relevant biomarkers. Diversity among individuals in these repositories is key for ensuring applicability of findings to patient populations. **Methods:** We compared two publicly available pancancer databases from academic institutions: The Cancer Genome Atlas (TCGA) and United States (US) institutions from the American Association for Cancer Research (AACR) Project GENIE version 11.0 (APG) with cancer incidence statistics from The US Cancer Statistics (USCS) in 2018, the most recently available data. We compared demographic data from key individual cancer types (Lung, Colorectal, Prostate, Breast, Gliomas, and Leukemias) for gender, race, and ethnicity. Frequencies are displayed as percentages and compared by Chi-Squared method. **Results:** The USCS includes 1,708,921 new cases in 2018 while the TCGA includes 12,958 cases and APG includes 109,041 cases. Women account for 49.5% of all cancer diagnosis and similarly 50.4% of all cases in AACR and 51.2% of TCGA cases. Table summarizes key demographic differences. Amongst all cancer types, 78% of all US cancers occur in White patients however 84% and 83% of patients were White in AACR and TCGA respectively. 16% of prostate cancer cases occur in Black patients, but only 9% (n = 328/3993) of AACR and 11% (n = 51/484) of TCGA cases were Black ($p < 0.01$). However, while Black patients are only 2% of all breast cancer diagnoses, they accounted for 9% (n = 841/9871) of AACR and 16% (n = 203/1343) of TCGA cases $p < 0.01$). Patients of Hispanic ethnicity were underrepresented amongst the population and all single tumor types with Hispanics accounting for 8% of cases in USCS but only 5% in the AACR and TCGA ($p < 0.01$). Pancreatic and lung cancers, which have historically short survivals, both had lower median ages at sequencing compared to the median age of diagnosis. Median age of sequencing for pancreatic cancers was 65 in both TCGA and AACR, while median age at diagnosis in US is 70. Median age at diagnosis of lung cancers is 71 years in US, however median age was 67 in both AACR and TCGA. **Conclusions:** Patients with advanced age and minority races are underrepresented in publicly available American databases. To make informed analyses from genomic databases, the diversity of the population must be reflected in these databases and efforts must be made to increase representation of underrepresented groups. Research Sponsor: None.

	USCS	APG	TCGA	USCS	APG	TCGA	USCS	APG	TCGA
Cancer Type	All			Prostate			Pancreatic		
Total	1,708,921	109,041	12,958	211,893	3,993	484	52,546	4,777	316
Male	51%	44%	50%	100%	99%	100%	52%	53%	55%
White	78%	84%	83%	77%	86%	86%	82%	87%	90%
Black	10%	7%	10%	16%	9%	11%	13%	5%	4%
Asian	3%	6%	6%	2%	3%	3%	4%	5%	6%
Native American	1%	0%	0%	0%	0%	0%	1%	0%	0%
Hispanic	8%	5%	5%	7%	4%	2%	9%	6%	4%
Median Age (y)	66	62	61	67	67	61	70	65	65

6589 **Poster Session**

Real-world utilization and comparative effectiveness of treatment options in cancer-associated thrombosis: A propensity score weighed analysis.

First Author: Irbaz Bin Riaz, Mayo Clinic, Phoenix, AZ

Background: Real-world utilization and comparative effectiveness of direct oral anticoagulants (DOACs), low molecular weight heparin (LMWH) and warfarin for cancer-associated venous thromboembolism (VTE) treatment remains largely unexplored. **Methods:** De-identified administrative claims data (OptumLabs - Data Warehouse) for adult active cancer patients with acute VTE (1/1/2012-9/30/2019) were assessed for utilization patterns, recurrent VTE, and major bleeding differences between DOACs, LMWH, and warfarin. Patients were followed up till the end of treatment. Patients who crossed over to other anti-coagulants within the follow up period were excluded. Multinomial logistic regression was used to assess predictors of anticoagulant administration. Kaplan-Meier curves were used to evaluate the differences in time to medication discontinuation among the three groups. Propensity score (PS) and inverse probability of treatment weighting were used to balance baseline differences between groups. Standardized difference (SD) was used to assess the balance of covariates after weighting and SD < 10% was considered acceptable. Weighted Cox proportional hazards regression with a robust variance estimator was then used to assess outcomes in PS weighted groups. **Results:** A total of 5100 patients met the inclusion criteria; 49.3% filled DOACs (n = 2512), 29.2% LMWH (n = 1488), and 28.6% warfarin (n = 1460). Median treatment duration was around 3.2 months for DOACs and warfarin, and 1.8 months for LWMH (*P*-value < 0.01). Multinomial regression analysis showed that younger patients were more likely to be prescribed LMWH (OR 0.97 95% CI: 0.97-0.98) as compared to DOACs. Patients with lung (OR 2.07 95% CI: 1.12-3.65; OR 1.87 95% CI: 1.04-3.37), urological (OR: 1.94 95% CI:1.08-3.49; OR: 2.04 95% CI: 1.12-3.73), gynecological (OR 4.25, 95% CI: 2.31-7.82; OR 2.31 95% CI: 1.22-4.39) and colorectal cancer (OR 2.26 95% CI: 1.20-4.32; OR 2.51; 95% CI: 1.32-4.79) were more likely to be prescribed LMWH or warfarin respectively, compared to DOACs. VTE recurrences were more frequent for patients receiving LMWH (HR: 1.47; 95% CI: 1.14-1.90) or warfarin (HR: 1.46; 95% CI: 1.13-1.87) compared to DOACs. LMWH, but not warfarin, was associated with greater major bleeding rates compared to DOACs (HR: 2.27; 95% CI: 1.62-3.20). All-cause mortality rates were also significantly higher for patients receiving LMWH, but not warfarin compared to DOACs (HR: 1.61; 95% CI: 1.15-2.25). **Conclusions:** Patients with cancer associated VTE remain on anti-coagulation for a remarkably short duration in real-world clinical practice. DOACs and warfarin may offer better compliance than LMWH. Patients receiving DOACs have a lower risk of VTE recurrence, less major bleeding, and improved mortality. Warfarin may still be considered for patients with contraindications to DOACs and non-compliant to LMWH. Research Sponsor: Internal funding.

6590 **Poster Session**

Comparison of outcomes for Hispanic and non-Hispanic patients with advanced renal cell carcinoma in the International Metastatic Renal Cell Carcinoma Database.

First Author: Kripa Guram, VA San Diego Healthcare System, San Diego, CA

Background: Epidemiologic studies suggest that Hispanic patients with renal cell carcinoma (RCC) have worse outcomes than non-Hispanic White patients (NHW). It is unclear if this disparity is related to inherent biological differences or patients' social determinants of health (SDOH). Utilizing the International Metastatic Renal Cell Carcinoma Database (IMDC) of patients with RCC primarily receiving care at academic medical centers, we investigated outcomes of Hispanic and NHW patients with advanced RCC. **Methods:** Eligible patients included patients who self-reported being non-Black Hispanic or NHW with locally advanced or metastatic RCC initiating systemic therapy. The primary endpoint was overall survival (OS) and secondary endpoint was time to treatment failure (TTF) for the first-line therapy. Kaplan Meier curves were constructed for OS and TTF. Cox regression was used to estimate hazard ratios (HR) adjusted for confounding variables. **Results:** The cohort included 1,563 patients, of which 181 (11.6%) were Hispanic. Most patients were male (74%) with clear cell histology (82%). IMDC risk groups were 18%, 58%, 24% for favorable, intermediate, and poor risk, respectively, and were similar by ethnic groups. Compared to NHW, Hispanic patients were younger at diagnosis (median 57 vs 59 years, p = 0.036), less likely to have > 1 metastatic site (61% vs 77%, p < 0.001) and bone metastases (24% vs 33%, p = 0.009). 1,178 patients (124 Hispanic vs. 1,054 NWH) received treatment before 2018, 385 patients (57 Hispanic vs. 328 NWH) received treatment during or after 2018. With regards to first line therapy, the majority received tyrosine kinase inhibitor (TKI) monotherapy (70%), 10% received immunotherapy (IO) + IO, 9% received TKI + IO, 4% received IO monotherapy, and 8% received other treatments. Median TTF was 7.8 months (95% Confidence Interval (CI): 6.2-9.0) in Hispanic patients and 7.5 months (95% CI: 6.9-8.1) in NHW patients. On multivariable analysis, there was no significant difference in TTF between Hispanic and NHW patients (HR 1.05, 95% CI: 0.89-1.25, p = 0.558). Significant predictors of TTF were presence of unfavorable site of metastases, histology, IMDC risk group, and therapy type. Median OS was 38.0 months (95% CI: 28.1-59.2) in Hispanic patients and 35.7 months (95% CI: 31.9-39.2) in NHW patients. On multivariable analysis, there was no significant difference in OS between Hispanic and NHW patients (HR 1.07, 95% CI: 0.87-1.32, p = 0.544). Significant predictors of OS were number of metastatic sites, presence of unfavorable metastasis, histology, IMDC risk group, and therapy type. **Conclusions:** In this analysis, we did not detect a difference in OS or TTF for Hispanic patients with RCC. Our data suggest that access to care (as available in a tertiary cancer hospital) can mitigate the historic difference in outcomes in Hispanic versus NWH patients. Research Sponsor: None.

6591 **Poster Session**

Cost effectiveness of reduced intensity conditioning and transplantation of unrelated umbilical cord blood versus HLA haploidentical related bone marrow for adults with hematologic malignancies.

First Author: Lotte Maria Gertruda Steuten, Office of Health Economics, London, United Kingdom

Background: BMT CTN 1101 was a Phase III randomized controlled trial evaluating the comparative effectiveness of unrelated umbilical cord blood (UCB) versus HLA-haploidentical related donor bone marrow (haplo-BM) cell sources for hematopoietic cell transplantation (HCT) in patients with high-risk hematologic malignancies (leukemias, lymphomas). We report results of an economic evaluation conducted as part of the clinical trial. **Methods:** 368 patients (90% of planned accrual) enrolled from 33 centers in the U.S. were randomly assigned to unrelated UCB (n=186) or haplo-BM (n=182) transplant. Healthcare utilization and costs were estimated using propensity-score matched cohorts of BMT patients in the OptumLabs Data Warehouse for trial participants <65 years, and Medicare claims for trial participants ≥65 years. Cost-effectiveness was calculated from payer perspectives (commercial, Medicare) over a 20-year time horizon from time of transplant. Weibull models (best fit based on AIC/BIC) were used to extrapolate survival from 5-year trial follow-up data. Trial participant surveys (EQ-5D) were used to derive health state utilities for estimating Quality-Adjusted Life Years (QALYs). One-way and probabilistic sensitivity analyses were conducted to assess uncertainty in results. Outcomes were discounted at 3% annually. **Results:** At 5-year follow-up, overall survival was 42% for haplo-BM versus 36% for UCB (P=.06). Over a 20-year time horizon, haplo-BM is expected to be more effective and more costly for <65 year-olds and in ≥65 year-olds it is expected to be more effective and less costly. In one-way uncertainty analyses, for persons <65, the cost/QALY result was most sensitive to life years and health state utilities. For persons ≥65, life years were more influential than costs and health state utilities. Using probabilistic sensitivity analysis, for persons <65 there was a 43% chance that haplo-BM was cost-effective using a willingness to pay threshold of $150k/QALY and 52% at a $200K/QALY threshold. **Conclusions**: Results from a large national clinical trial indicate that compared to UCB, haplo-BM was moderately cost-effective for patients aged <65 years, and less costly and more effective for persons ≥65 years. Haplo-BM is a fair value choice for commercially insured patients with high-risk leukemia and lymphoma who require HCT. For Medicare enrollees, haplo-BM is a preferred choice when considering costs and outcomes. Research Sponsor: U.S. National Institutes of Health.

	LY	QALY	Cost	ICER (cost/LY gained)	ICER (cost/QALY gained)
<65 Commercial					
UCB	6.91	5.33	$712,904		
Haplo-BM	7.76	5.96	$838,858		
Increment	*0.86*	*0.63*	*$118,953*	*$138,736*	*$189,799*
≥65 Medicare					
UCB	4.39	3.82	$721,450		
Haplo-BM	5.47	4.71	$547,330		
Increment	*1.07*	*0.90*	*$-174,119*	*Haplo-BM is more effective and less costly than UCB*	

ICER = incremental cost-effectiveness ratio, LY = life years.

6592 **Poster Session**

A quantitative analysis of escalating antineoplastic medication price increases.

First Author: Michail Alevizakos, Beth Israel Deaconess Medical Center, Boston, MA

Background: Established antineoplastic medication prices are overall increasing, yet the yearly trend and additive cost of such increases relative to overall antineoplastic spending is often unclear. **Methods:** We accessed the yearly reimbursement files from Medicare Part B for parenteral antineoplastic agents (codes J8501-J9999) for the years 2010-2020 and adjusted all values to 2020 USD to account for inflation. We calculated an initial inflation-adjusted price-per-claim for every medication at the time of medication entry to the database and compared that price with the yearly price-per-claim that Medicare reimbursed. For medications whose price had increased beyond the initial inflation-adjusted price, we multiplied the annual differences with the total annual claims of the medication reimbursed in order to calculate the additional cost accrued by Medicare for every affected year. We only included medications with total annual cost >10 million USD/yr in our analysis. **Results:** Price increases were noted in 70.9% of already established medications annually (median 74.5%, range 52.17-81.48%). This led to an average additional extra cost of 311 million USD (range 156-492 million USD) annually, for a total of 3.1 billion USD over the 10 years of observation. This extra cost represented 4.6-9.3% of the total Medicare Part B spending for antineoplastic medications annually and this percentage rose yearly by a statistically significant 0.43% (95% CI 0.14%-0.73%, $P = 0.01$; R^2 0.59) in absolute terms (Table). Rituximab (1,003 million USD), trastuzumab (421 million USD), and bevacizumab (326 million USD) accumulated the highest extra costs. **Conclusions:** The majority of established parenteral antineoplastics are affected by escalating price increases beyond the rate of inflation. Year-by-year, these increases occupy a progressively larger part of overall Medicare Part B spending. Since Medicare does not negotiate medication price nor receives rebates but rather relies on average market prices, these increases likely affect other U.S. markets as well. Research Sponsor: None.

Price increases of Medicare Part B antineoplastic medications with cost >10 million USD/yr.

Year	Established medications	Medications with price increase	% Medications with price increase	Extra cost due to price increases[1]	Total spending for antineoplastic medications[1]	% of extra cost on total spending
2011	23	17	73.91	212	3819	5.55
2012	23	15	65.22	231	3609	6.4
2013	23	12	52.17	156	3184	4.9
2014	24	13	54.17	196	3239	6.05
2015	27	20	74.07	303	3273	9.26
2016	25	19	76	338	3809	8.87
2017	27	22	81.48	342	4149	8.24
2018	31	25	80.65	436	4668	9.34
2019	32	24	75	492	5303	9.28
2020	34	26	76.47	405	5013	8.08

1. in million USD.

6593 **Poster Session**

Cost effectiveness of adjuvant olaparib for BRCA-mutated, early-stage breast cancer.

First Author: Christie Zettler, Columbia University Medical Center, New York, NY

Background: An interim analysis of the OlympiA trial found that olaparib given in the adjuvant setting can improve distant disease-free and overall survival for patients with early-stage, BRCA-mutated breast cancer; however, the cost-effectiveness of adjuvant olaparib is unknown. This study aimed to evaluate the cost-effectiveness of adjuvant olaparib in patients with early-stage, BRCA-mutated breast cancer. **Methods:** We used a decision-analytic model to compare outcomes of treatment with and without one year of oral olaparib after completion of systemic therapy in 42-year-old women with BRCA-mutated, early-stage breast cancer. Olaparib's effectiveness was based on the OlympiA trial, and other model parameters were identified from the literature. We calibrated the model to reflect the 1-, 2-, and 3-year distant disease-free survival (DDFS) and overall survival (OS) observed in the OlympiA trial, and we assumed that olaparib reduced the risk of distant recurrence only in the first 3 years. Olaparib was estimated to cost $14,523 per month. Average lifetime costs were estimated from a health care system perspective in 2021 $ US, and incremental cost-effectiveness ratios (ICER) were estimated as $ per quality-adjusted life-year (QALY) gained. Costs, life-years, and QALYs were discounted by 3% annually. **Results:** Simulating the OlympiA trial, DDFS for the olaparib arm was 94.3% at 12 months, 90.0% at 24 months, and 87.5% at 36 months, compared to placebo with DDFS of 90.2%, 83.9%, and 80.4% respectively. Similarly, OS for the olaparib arm was 98.1%, 94.8%, and 92.0% compared to 96.9%, 92.3%, and 88.3% with placebo at 12, 24, and 36 months respectively. In the base case, adjuvant olaparib was associated with a 1.21-year increase in life expectancy and a 1.15-QALY increase at an incremental cost of $131,167 compared to placebo. The resulting ICER was about $114,500/QALY gained. At a willingness-to-pay threshold of USD$150,000/QALY, olaparib was cost effective at its current price. Results were sensitive to assumptions about the effectiveness of olaparib and its impact on quality of life. **Conclusions:** Adjuvant olaparib is cost-effective for women with early-stage, BRCA-mutated breast cancer at the current price of olaparib in the U.S. and at a willingness-to-pay threshold of $150,000. As such, clinicians and payers should consider adjuvant olaparib as a cost-effective option for this patient population. Research Sponsor: None.

	Olaparib	No olaparib	Incremental
Life-years	17.41	16.20	1.21
QALYs	16.79	15.64	1.15
Cost	$307,186	$176,019	$131,167
$ per LY gained	-	-	$108,402
$ per QALY gained	-	-	$114,496

6594 **Poster Session**

Trends in low-value oncology care during the COVID-19 pandemic. *First Author: Ravi Bharat Parikh, University of Pennsylvania, Philadelphia, PA*

Background: Low-value services, which provide minimal patient benefit while entailing costs and risks, are prevalent in cancer care. Shifts in cancer care delivery during the COVID-19 pandemic to minimize exposure provided opportunities for health systems and clinicians to prioritize higher-value over low-value oncology services. **Methods:** In this retrospective cohort study, we investigated the association between the COVID-19 pandemic period and low-value cancer care practices using administrative claims from the HealthCore Integrated Research Environment, consisting of ~65 million members managed by 14 health plans across the US. We identified commercial or Medicare Advantage members diagnosed with breast, colorectal, or lung cancer between January 2015 and March 2021. Low-value cancer care practices were identified from peer-reviewed medical literature, including ASCO and ASTRO Choosing Wisely campaigns and evidence-based pathways. Five low-value practices were studied: (1) conventional fractionation instead of hypofractionation for early-stage breast cancer; (2) off-pathway systemic therapy; (3) non-guideline-based antiemetic use for minimal-, low-, or moderate-to-high-risk chemotherapies; (4) Positron Emission Tomography/Computed Tomography (PET/CT) instead of conventional CT for staging; and (5) aggressive end-of-life care (chemotherapy ≤14 days, multiple emergency department visits ≤30 days, ICU utilization ≤30 days, hospice initiation ≤3 days, and/or no hospice before death). We used linear probability models to evaluate the association between the COVID-19 period (March to December 2020) and the 5 outcomes, adjusting for patient, facility, geographic and temporal characteristics. **Results:** Among 204,581 members (mean age 63.1, 139,488 [68.1%] female), 83,593 (40.8%) had breast cancer, 56,373 (27.5%) had colon cancer, and 64,615 (31.5%) had lung cancer. Rates of low-value care were similar in pre-COVID vs. COVID periods: conventional radiotherapy: 22.1% vs. 9.4%; off-pathway systemic therapy: 36.7% vs. 43.2%; non-guideline-based antiemetics: 61.2% vs. 58.1%; PET/CT imaging: 39.9% vs. 41.3%; aggressive end-of-life care: 75.8% vs. 73.3%. In adjusted analyses, the COVID-19 period was associated with no changes in off-pathway therapy (adjusted percentage point difference [aPPD] 0.82, SD 0.08, p = 0.33), PET/CT imaging (aPPD 0.10, SD 0.005, p = 0.83), and aggressive end-of-life care (aPPD 2.71, SD 0.02, p = 0.16). Small changes in conventional radiotherapy (aPPD 3.93, SD 0.01, p < 0.01) and non-guideline-based antiemetics (aPPD -3.62, SD 0.006, p < 0.01), were noted. **Conclusions:** The shock of the COVID-19 pandemic did not meaningfully change several metrics of low-value cancer care. Broader changes to payment and incentive design should be considered to turn the tide toward higher-value cancer care. Research Sponsor: U.S. National Institutes of Health.

6595 **Poster Session**

Systematic performance status assessment by primary care providers in patients with advanced cancer and its impact on referral to palliative care and cost in a value-based practice. *First Author: Roberto Enrique Ochoa, Chen Medical Centers, Miami, FL*

Background: Value Based (VB) Care model has been growing in the primary care (PrC) Medicare population, its role in oncology and integration with VB PrC has not been well defined. Key initiatives in VB include reducing hospitalizations by multidisciplinary management of chronic conditions. Earlier Palliative Care (PaC) has shown to favorably impact outcomes. Eastern Cooperative Oncology Group Performance Status (ECOG-PS) is a validated tool used for decision making. Poor PS is associated with worse outcomes and futile end of life care; Guidelines recommend using ECOG-PS to decide on involvement of PaC in patients (pts) with metastatic cancer (mCa). ECOG-PS is subject to significant variability among oncologists and rarely used by PrC providers (PCPs). We created a standardized system for ECOG-PS documentation and monitoring by PCPs in a VB model in a large Medicare Advantage (MA) population with the goal of increasing earlier PaC referrals. **Methods:** Pts with mCa managed by PCPs in a multi-state MA practice were identified via EMR from February 2021 to September 2021. At every visit, an automated alert asked PCPs to determine pts' ECOG-PS and for those ≥ 2, recommendation to refer to PaC. PCPs were trained on use of the tool and were given a script to discuss with pts the role of PaC. Hospital admissions as well as total cost of care was measured in pts comanaged by PCP's & PaC versus those managed by PCPs &Oncology without PaC. Statistical analysis between the groups was done using Pearson's Chi-squared test with Yates' continuity correction. **Results:** An ECOG-PS was measured in a total of 565 pts with mCa during the study period. Median age was 73 years, 40% were ≥75 yrs. 55% were female. Breast, Prostate, Lung, Colorectal and Gyn ca accounted for 75% cases. ECOG was documented in 97% of patients; 250 (44%) had ECOG ≥ 2, 124 (22%) had ECOG ≥ 3. Of those PaC referral was done by the PCP in 70%, in total 69 patients were comanaged by PC vs 181 who did not. Pts that had PaC involvement were 43% less likely (RR 0.57 [95%CI 0.33,0.98 p = 0.043]) to be admitted compared to patients without PC. Pts without PaC that were admitted had 238% higher admission days per 1,000 pts compared to pts comanaged by PaC. Total medical costs of pts comanaged by PaC was 86% lower after PaC involvement $18,541 3-months prior vs $2,742 3-months after PaC involvemen, driven by lower part A and part B costs (p=0.001) **Conclusions:** ECOG PS monitoring of pts with mCa by PCPs was very successful, easy to perform and implement in a PrC. Poor PS is common in this medicare advantage population. PaC involvement in pts with poor ECOG-PS was associated with lower admission rates at the end of life, and significantly lower total medical costs. Research Sponsor: None.

	PC	No PC
Median Age (range)	73 (60-94)	73 (46-95)
%Male	36	48
Breast (%)	18	19
Prostate (%)	22	22
Colorectal (%)	6	8
Lung (%)	12	19
Gyn (%)	13	6
ECOG>2 (%)	21	23
Admissions (%)	12 (17%)	59 (33%)

6596 **Poster Session**

The financial toxicity order set: A simple intervention to better connect patients with resources. *First Author: Bridgette Thom, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Rising cancer care costs have led to significant hardship for patients and caregivers, defined as "financial toxicity." Prior research has focused on experiences of financial toxicity and identified risk factors, but there are limited interventions, despite a growing need for both patient-level and systems-based solutions. We present a novel electronic medical record (EMR) financial toxicity order that streamlines referrals for financial assistance and/or counseling for patients in need. **Methods:** A multidisciplinary team developed, tested, and implemented an EMR order set to refer patients directly to patient financial services, due to specific financial concerns. Following a 3-month service-based pilot, the order set was activated enterprise-wide March 2021. All team members could place the order, and referrals were tracked on an institutional dashboard. Order indications and frequency of orders across patient and provider demographics were evaluated. **Results:** From March-December 2021, 617 orders were placed for 580 unique patients, by 272 individuals across 49 services. Nurses placed 45% of orders, followed by advanced practice providers (20%) and attending physicians (14%). Primary indications for the order included high/outstanding balance or out-of-pocket costs (41%), difficulty meeting basic needs (i.e., transportation, food; 30%), co-payment assistance (28%), or out-of-network insurance (11%); 29% of referrals included multiple reasons. Most orders (69%) were placed for patients on active treatment. Compared to the distribution of institutional averages by age, more patients 30-39 years (8% of all orders vs. 5% of all patients), 50-59 years (22% of all orders vs. 19% of all patients), and 60-69 years (33% of all orders vs. 26% of all patients) received an EMR financial toxicity order. Compared to institutional race and ethnicity averages, Black patients (15% of all orders vs. 9% of all patients) and Hispanic patients (12% of all orders vs. 7% of all patients) were over-represented among orders. Disease sites over-represented among orders included breast (25% of orders vs. 21% of patients) and lung (10% of orders vs. 7% of patients); and Hodgkin's lymphoma (8% of orders vs. 5% of patients). More female patients received orders than their representation among patients (62% of orders vs. 57% of patients). **Conclusions:** Our findings represent a first step toward improving the process by which patients experiencing financial toxicity are referred to relevant counseling and tangible financial resources. Multilevel interventions are necessary to address financial toxicity, and hospital-based EMR interventions represent progress in empowering the care team to connect patients to available resources. Categorizing the amount and type of financial help provided as a result of the EMR order is next, and efforts to proactively screen patients for financial toxicity risk are underway. Research Sponsor: None.

6597 **Poster Session**

Longitudinal changes in financial burden in patients with colorectal cancer treated with curative intent: Primary results of EAQ162CD. *First Author: Sheetal Mehta Kircher, Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL*

Background: We prospectively assessed financial burden (FB) due to treatment costs among patients with colorectal cancer (CRC) recruited by NCI Community Oncology Research Program (NCORP) sites. **Methods:** Patients with newly diagnosed CRC treated with curative intent enrolled through NCORP sites and completed the FACIT Comprehensive Score for Financial Toxicity (COST) instrument at 0-, 3, 6, and 12 months. Higher COST score (range 0-44) indicates greater financial well-being. Effects of demographic, clinical, self-efficacy and safety net affiliation on FB were assessed using linear mixed modeling with compound symmetry covariance structure to account for measurement correlation from the same subject. **Results:** In 450 patients (mean age 61, 47% female, 84% white, 64% colon, 31% rectal) attrition was comparable across demographics, clinical variables and baseline FB. Higher COST score was linearly correlated with time. Increasing age, income less than $60,000 (vs. less than $29,999), higher self-efficacy, and higher neighborhood socioeconomic status (nSES) predicted a higher COST score; these effects were not moderated by time. Chemotherapy receipt, insurance type, and treatment at a safety net hospital did not predict COST score. **Conclusions:** Among those with CRC treated with curative intent in community settings, FB improves over the 12 months post diagnosis. Individual and neighborhood level social determinants of health are protective from financial fragility. Research Sponsor: U.S. National Institutes of Health.

Predictors of COST.

	Baseline		3 mo		6 mo		12 mo		Coefficient (95% CI)*	p-value*
	N	%	N	%	N	%	N	%		
Total	450	100	298	100	270	100	215	100		
Age	61.0 (12.0, 65.0)		61.5 (12.3, 65.0)		61.7 (12.3, 65.0)		62.1 (11.9, 55.0)		0.20 (0.04, 0.36)	0.012
Mean (SD, Range)										
Income	136	30.2	82	27.5	74	27.4	59	27.4		<0.001
$30,000- 59,999									2.09 (-1.65, 5.83)	
$60,000+	192	42.7	134	45.0	120	44.4	105	48.8	7.45 (3.62, 11.29)	
Up to $29,999	111	24.7	70	23.5	63	23.3	46	21.4	Ref	
Not Answered	11	2.4	12	4.0	13	4.8	5	2.3	-1.25 (-11.78, 9.28)	
nSES	118	26.2	78	26.2	74	27.4	57	26.5		0.0388
Quartile 2 (53.0-55.5)										
Quartile 3 (55.5-58.1)	95	21.1	61	20.5	60	22.2	48	22.3		
Quartile 1 (<=53.0)	120	26.7	79	26.5	68	25.2	50	23.3		
Quartile 4 (>58.1)	117	26.0	80	26.8	68	25.2	60	27.9		
Mean (SD, Range)	55.8 (4.0, 21.5)		55.9 (4.1, 21.5)		55.9 (4.0, 21.1)		56.1 (4.0, 21.1)		0.36 (0.02, 0.70)	
Self-efficacy	6.8 (2.4, 9.0)		6.8 (2.4, 9.0)		7.0 (2.3, 9.0)		7.2 (2.2, 9.0)		2.13 (1.53, 2.73)	<0.001
Mean (SD, Range)										
COST	450, 23.5 (11.9, 44.0)		298, 24.6 (12.3, 44.0)		270, 25.5 (12.2, 44.0)		215, 28.8 (11.7, 44.0)		N/A	N/A
N, Mean (SD, Range)										

Adjusted for age, gender, race, marital status, education, income, insurance, chemo, comorbidities, safety net affiliation, stage, cancer type, FACT-G7, self-efficacy, nSES, and employment.

6598 **Poster Session**

National trends in post-launch cancer prescription drug prices and the impact of generic entry, 2014-2020. *First Author: Danielle Rodin, Princess Margaret Hospital Cancer Centre, Toronto, ON, Canada*

Background: The high prices of branded 'on patent' cancer prescription drugs and the impact of competition on them is of importance to patients, physicians, payers and policymakers. The objective of this study is to quantify trends in the prices of all currently approved cancer drugs and to evaluate the impact of loss of exclusivity and generic entry on prices using national and contemporaneous data. **Methods:** Observational study of cancer drug prices from the IQVIA National Sales Perspectives from January 2014 to December 2020. The compound annual growth rate (CAGR) of drug prices was calculated for branded and generic drugs by therapeutic class (chemotherapy, targeted therapy, and supportive therapy). An event study empirical strategy and ordinary least squares regression was used to determine the relationship between the natural logarithm of prices and loss of exclusivity and generic entry. **Results:** The study cohort included 184 cancer drugs (37% chemotherapy, 51% targeted therapy, and 12% supportive therapy), of which 105 were always branded, 18 were always generic and 18 underwent loss of exclusivity and generic entry during the study period. Prices of branded chemotherapies and targeted therapies increased by 2.24% (0.79% CPI-adjusted) and 2.83% (1.07% CPI-adjusted) annually, whereas generics decreased by 12.63% (-14.14% CPI-adjusted) and 20.15% (-21.57% CPI-adjusted), respectively. Prices of branded supportive therapies decreased by 0.73% (-2.40% CPI-adjusted), while generics increased by 1.28% but decreased with CPI-adjustment (-0.45). Loss of exclusivity and generic entry was associated with statistically significant decreases in generic drug prices, but increases in branded drug prices after CPI-adjustment; these effects are concentrated in chemotherapies and targeted therapies. **Conclusions:** We found that cancer drug prices increased, after adjusting for inflation, particularly among branded chemotherapies and targeted therapies. Generic entry mitigates these price increases, but only a handful of cancer drugs experienced competition in the study period. Drug prices are key determinants of cancer-related spending, and many cancer patients remain underinsured. Although this data reflects net prices before discounts to providers and pharmacies, patient out-of-pocket costs are based on the list price. Our findings are critical to informing current efforts to improve cancer treatment affordability. Research Sponsor: American Cancer Society.

6599 **Poster Session**

Cost-effectiveness of adjuvant chemotherapy for patients with high-risk stage II and stage III colon cancer in South Africa. *First Author: Yoanna S Pumpalova, Columbia University Irving Medical Center, New York, NY*

Background: Colon cancer (CC) incidence is rising globally, and case fatality rates are greatest in low-income settings, such as South Africa (SA). Adjuvant chemotherapy is standard of care for high-risk stage II and stage III CC in the US. We evaluated the cost-effectiveness of adjuvant chemotherapy for CC in SA public hospitals. **Methods:** We developed a decision-analytic Markov model comparing lifetime costs and outcomes for 60-year-old high-risk stage II and stage III CC patients treated in a SA public hospital with no adjuvant chemotherapy, versus: capecitabine and oxaliplatin (CAPOX) for 3 or 6 months or capecitabine for 6 months. High-risk stage II was defined as ≥1 of: T4 disease; poorly differentiated tumor; lymphovascular/perineural invasion; <12 lymph nodes dissected, bowel obstruction/perforation. Transition probabilities were derived from clinical trials estimating toxicity, disease recurrence, and survival. Costs from a SA societal perspective and utility estimates were obtained from literature and local expert opinion. The primary outcome was the incremental cost-effectiveness ratio (ICER) in international dollars (I$) per disability-adjusted life year (DALY) averted, with a willingness-to-pay (WTP) threshold equal to 2021 GDP/capita of SA (I$13,764). **Results:** CAPOX for 3 months was the cost-effective strategy for stage III CC at a lifetime cost of I$5,284 and 5.55 DALYs averted, compared to no adjuvant treatment. All other strategies were absolutely dominated. For high-risk stage II CC, CAPOX for 3 months was the cost-effective strategy (ICER = I$711/DALY averted). No adjuvant chemotherapy was on the efficiency frontier, with a lower lifetime cost, but no DALYs averted. The results of one-way deterministic sensitivity analyses showed that the model is most sensitive to CC recurrence rate. In a probabilistic sensitivity analysis, CAPOX for 3 months was optimal in 88% of iterations for high-risk stage II CC and 79% of iterations for stage III CC. **Conclusions:** CAPOX for 3 months is the cost-effective adjuvant treatment for high-risk stage II and stage III CC in SA public hospitals. This strategy offers the highest quality of life benefit for the lowest cost and is well within the WTP threshold for SA. The optimal strategy in other settings will vary according to local WTP thresholds. Base case estimates of cost-effectiveness, in order of cost. Research Sponsor: U.S. National Institutes of Health.

Strategy	Cost (I$[a])	DALYs averted	Incremental DALYs averted	ICER[b]
High-Risk Stage II				
No Adjuvant Chemotherapy	3,517	0.00	0.00	0.00
CAPOX 3 months	4,598	1.52	1.52	711
Capecitabine 6 months	4,883	0.93	-0.59	Dominated
CAPOX 6 months	6,153	0.97	-0.55	Dominated
Stage III				
CAPOX 3 months	5,284	5.55	0.00	0.00
Capecitabine 6 months	5,594	4.01	-1.53	Dominated
CAPOX 6 months	6,668	5.28	-0.27	Dominated
No Adjuvant Chemotherapy	8,169	0.00	-5.55	Dominated

[a]I$1.00 = ZAR7.097; [b]In I$/DALY averted, relative to optimal strategy.

6600 **Poster Session**

Oncologist consideration of patient health insurance coverage and out-of-pocket costs for genomic testing in treatment decision. *First Author: Kewei Shi, American Cancer Society, Atlanta, GA*

Background: Use of genomic testing, especially multi-marker tumor panels, is increasing in the United States. Not all tests and related treatments are covered by health insurance, which can result in substantial patient out-of-pocket (OOP) costs. Although most patients are concerned about OOP costs, little is known about oncologists' treatment decisions with respect to patient health insurance coverage and OOP costs for genomic testing. **Methods:** We identified 1,049 oncologists who reported using multi-marker tumor panels from the 2017 National Survey of Precision Medicine in Cancer Treatment. Separate multivariable ordinal logistic regression analyses were used to assess the associations of oncologist, practice, and patient characteristics and the oncologist ratings of the importance of health insurance coverage and OOP cost for genomic testing as part of treatment decisions. **Results:** Among oncologists, 47.3%, 32.7% and 20.0% reported that patient insurance coverage for genomic testing was very important, somewhat important, and a little/not important, respectively, in treatment decisions. 56.9%, 28.0%, and 15.2% reported patient OOP costs for genomic testing were very, somewhat, or a little/not important in treatment decisions, respectively. In adjusted ordinal logistic regression analyses, oncologists who used next-generation gene sequencing tests were more likely to report patient health insurance and OOP costs for testing as important (odds ratio (OR) = 2.0; 95% confidence interval (CI): 1.2, 3.5) and (OR = 2.1; 95%CI: 1.2, 3.7), respectively) in treatment decisions. Oncologists with more years of experience, who treated solid tumors (rather than only hematological cancers), worked in practices without molecular tumor boards for genomic tests, and with higher percentages of patients insured by Medicaid or self-paid/uninsured also reported insurance coverage or OOP costs for testing were important in treatment decisions (all $p < 0.05$). **Conclusions:** Physician, practice, and patient characteristics were associated with oncologists' ratings of the importance of patient health insurance and OOP costs in treatment decisions. Identifying factors that influence physicians' priorities in treatment decisions may inform the development and targeting of interventions to support patient and physician discussions about oncology care. Research Sponsor: None.

6601 **Poster Session**

Price variability of pembrolizumab in New York City from 2016-2021. *First Author: Syed Hussaini, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD*

Background: There is poor compliance among cancer centers with price transparency rules set forth by the CMS in 2021. Service charges higher than what a hospital reasonably expects to be reimbursed may both prevent competitive price shopping by the consumer and result in catastrophic financial toxicity for small payors and under/uninsured individuals. We investigated variability in the charged and reimbursed payments for pembrolizumab infusion within one metro area utilizing Medicare claims. **Methods**: Medicare claims data from 2016 through 2021 for all pembrolizumab (HCPCS J9271) infusions in a hospital outpatient department were selected from the Definitive Healthcare claims database for medical oncology providers in New York City (NYC). Average charges, reimbursements, and total claims were obtained for the 6 largest prescribers by volume. Annual percentage changes (APC) were calculated to evaluate trends during study period. Prices are presented as inflation adjusted numbers (charged and reimbursed; 2021 dollars). Analyses were performed in Excel (Microsoft Corp). **Results**: Our analysis included 5 NCI-designated cancer centers (NCI-A, NCI-B, NCI-C, NCI-D) of which 1 was PPS (Prospective Payment System)-exempt (NCI-PPS). One hospital was non-NCI and 4 hospitals were part of the discounted 340B Drug Pricing Program (NCI-A, NCI-B, NCI-D, Non-NCI). From 2016 to 2021, total Medicare claims increased 793 to 1537, and total payments to all centers increased from $5.4M to $16.3M. NCI-PPS comprised 61% of claims, and 65% of total payments in 2021. Average charge for pembrolizumab in 2021 ranged from $20,130 (NCI-PPS) to $155,825 (NCI-D/340B). During study period, APC ranged from +1.7% (NCI-A/340B) to +25.4% (NCI-D/340B). Despite wide variability in charged amounts for Medicare claims, reimbursed amounts were similar across centers (range: $6227-9623, 2021). **Conclusions**: There is significant variability in charges for pembrolizumab in Medicare claims with price increases outpacing the annual rate of inflation. Within NYC, the highest charges were from a 340B hospital; NCI-PPS had higher volume and total payments but consistently lower charged prices each year. Our study highlights extreme price variability, and has policy implications for price transparency requirements and uniform rate setting to establish payment levels and control rate of annual growth. Research Sponsor: U.S. National Institutes of Health.

Center	340-B	2016	2017	2018	2019	2020	2021	APC
NCI-PPS	No	14.7 (47)	16.8 (47)	18.6 (43)	17.5 (47)	19.8 (48)	20.1 (48)	6.7
NCI-A	Yes	-	34.6 (26)	35 (18)	35.2 (18)	41 (20)	36.2 (17)	1.7
NCI-B	Yes	22.8 (36)	19.4 (40)	24 (25)	24.5 (25)	27.8 (27)	28.7 (26)	5.6
NCI-C	No	26.6 (25)	32.4 (26)	34 (18)	34.8 (18)	41 (21)	46 (19)	25.4
NCI-D	Yes	51.4 (8)	61.4 (8)	78.5 (5)	83 (5)	114 (5)	155.8 (5)	11.8
Non-NCI	Yes	-	-	40 (16)	40 (16)	42 (16)	50 (16)	8

Note: Inset numbers include average charged price of pembrolizumab in USD in thousands, and percentage reimbursed from Medicare in parenthesis.

6602 **Poster Session**

Self-reported financial difficulties among patients with multiple myeloma and chronic lymphocytic leukemia: An Alliance for Clinical Trials in Oncology study. *First Author: Rena M. Conti, University of Chicago, Chicago, IL*

Background: Treatment advances have greatly improved survival and quality of life among blood cancer patients, yet significant financial costs are a growing concern. **Methods:** We conducted an observational, prospective survey in 2019-2020 to estimate the self-reported prevalence of financial difficulty among multiple myeloma (MM) and chronic lymphocytic leukemia (CLL) patients and identify sociodemographic correlates of financial difficulty. Patients with an MM or CLL diagnosis >/= 18 years of age were recruited from NCI NCORP sites of care. Financial difficulty was measured in a previously validated single question from the EORTC QLQ C30 and a composite measure of five questions from the EORTC QLQ C30. **Results:** 521 MM and CLL patients were registered to the study, 416 patients were administered all or part of the patient survey, for an overall response rate of 79.8%. 16.8% of respondents reported experiencing financial difficulty in response to the single item question and 58.6% reported experiencing financial difficulty in response to the composite measure. Respondents reporting financial difficulty to both measures had reported household incomes of less than $60,000, identified their highest education levels as a high school diploma or GED, had more than one medical comorbidity and used an expensive oral chemotherapeutic agent to treat their blood cancer. **Conclusions:** Blood cancer patients treated at NCI NCORP sites are experiencing financial difficulties. Results of this study aim to inform physician, site of care and policy efforts to improve access among cancer patients. Clinical trial information: NCT03870633. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

Patient report of financial difficulty by selected sociodemographic and treatment characteristics.

	Total	Reported Financial Difficulty (Primary Endpoint)	Composite Score Financial Difficulty (Secondary Endpoint)
N=	416	70 (16.8%)	244 (58.7%)
Insurance Type, n (%)			
Public Insurance, n (%)	100 (32.5%)	26 (37.1%)	91 (37.3%)
Private insurance, n (%)	89 (28.9%)	26 (37.1%)	64 (26.2%)
Private and Public Insurance	118 (38.3%)	17 (24.3%)	88 (36.1%)
Mean (SD) number of comorbidities	5.1 (3.94)	5.2 (3.79)	5.2 (4.23)
Reported Household Income < $60,000 n (%)	141 (45.8%)	53 (75.7%)	142 (58.2%)
Education, n (%)			
High School Diploma/GED or below	132 (42.9%)	44 (62.9%)	123 (50.4%)
Associates or Bachelor's Degree	119 (38.6%)	17 (24.3%)	81 (33.2%)
Above Bachelor's Degree	50 (16.2%)	8 (11.4%)	35 (14.3%)
Receiving an Expensive Oral Therapeutic, n (%)*	193 (62.7%)	43 (61.4%)	148 (60.7%)

BOLD indicates statistically significant, reporting results of logistic regressions with p-values<0.05. *Patients who were currently receiving one of the following oral therapeutics were classified as receiving an expensive oral therapeutic, including Ixazomib Citrate, Lenalidomide, Panobinostat, Pomalidomide, Thalidomide, Chlorambucil, Ibrutinib, Idelalsib, Venetoclax.

TPS6603 **Poster Session**

A randomized study to measure and enhance the health-related quality of life in patients with cancer receiving immune checkpoint modulators (ME-Q). *First Author: Marcos Aurelio Fonseca Magalhaes Filho, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Existing data demonstrate the impact of Immune checkpoint modulators (ICMs) on Health-Related Quality of Life (HRQOL), but this was from studies that used HRQOL tools developed for patients treated with chemotherapy and/or radiation. To address this gap, we developed a toxicity subscale to cover important immune-related adverse events (irAEs) to combine this subscale with the generic FACT-G to measure HRQOL in patients treated with ICMs, the FACT-ICM. This trial proposes to validate the use of the FACT-ICM as a tool for HRQOL measurement and simultaneously to assess the benefit of remote symptom monitoring and management using a new electronic platform developed specifically for patients receiving ICMs. **Methods:** Participants will be randomized (1:1) before starting their standard of care ICM therapy to either usual care or the monitoring arm. The ME-Q platform uses a web-based application to enable remote monitoring of patient symptoms and HRQOL, allowing all participants enrolled in both the usual care or monitoring arms to complete the FACT-ICM and other questionnaires (DART, Health Resource Utilization, Decision regret scale, post-study system usability questionnaire) at set time points. Patients on the monitoring arm will have their electronic responses sent automatically, and new or significant worsening symptoms of clinical concern will generate an alert to the advanced practicing nurse (APN) responsible for replying to the patient and acting on responses. Via phone or a video teleconference, the nurse will perform a targeted assessment and provide standardized clinical advice and interventions based on well-established clinical algorithms and international guidelines for the management of irAEs. The APN will inform the patient's clinical team about the patient's responses and obtain the treating team's input and agreement on a proposed treatment plan. Patients enrolled in the usual care arm will respond to the questionnaires; however, their responses are not transmitted to their clinical team. The primary objective will be to validate the PRO tool for HRQOL measurement, and the secondary objective is to improve HRQOL in cancer patients receiving ICMs by remote monitoring and symptom management using the ME-Q electronic platform. We estimate that a total sample size of 266 patients (divided into two arms) achieves 90% power to detect an effect size of 0.4 in mean score changes (from baseline to 4 months) between arms using a two-sample t-test with a two-sided significance level of 0.05. Enrolment is to be completed in 2 years. Research Sponsor: None.

TPS6604 **Poster Session**

Assessment of adolescent and young adult oncology patient and provider perspectives in Philadelphia (AYA-4P). *First Author: Christopher Terry, Sidney Kimmel Cancer Center, Philadelphia, PA*

Background: The overall cancer incidence continues to increase in adolescent and young adult patients (AYAs), defined by the National Cancer Institute as individuals diagnosed between the ages of 15-39. Both disease biology and psychosocial needs are unique for young adults living with cancer. AYAs are more likely to have challenges related to work, insurance, relationships, fertility and emotional distress. Studies demonstrate that specialized supportive care improves outcomes such as health-related quality of life, mental health, and physical functioning. Most AYA oncology programs are developed without patient input and affiliated with pediatrics. The Sidney Kimmel Cancer Center (SKCC) at Jefferson is an adult oncology group serving over 900 new patients annually between the ages of 18-39, but does not have a formal AYA program. With guidance from patient advocates and other validated tools, a unique survey-based needs assessment was created by SKCC to provide data for the development of a comprehensive, patient-centered model of care for AYAs. **Methods:** A one-time survey will be administered electronically to participants through Qualtrics. Solicitation from SKCC and the Young Adult Cancer Connection, a local patient advocacy group, will occur via social media and email aggregation. Eligible patients are those who received the majority of their cancer care within 30 miles of Philadelphia between the ages of 18-39. Eligible healthcare providers include current advanced practice providers or physicians who have practiced at SKCC for at least 1 year. There are no hypotheses being tested or primary outcome variables, therefore no sample size calculations were performed. A $10 Amazon card is offered as incentive for the patient-directed survey to improve response rates and reach at least 100 completed surveys. The provider survey includes no completion incentive. Each survey should take no longer than 20 minutes to complete and no follow-up is required. Surveys are multiple choice with a single open-ended, free response question at the end for additional comments. Categorical survey responses will be summarized using frequencies and percentages. Descriptive statistics and data visualization will be used to characterize the patient demographics and summarize awareness, experiences, and priorities of the participants. Primary objectives of the surveys are to assess AYAs' current perspective of age-specific medical services and psychosocial support in Philadelphia, as well as to assess the knowledge and perspective of providers of the current care and available services for AYAs at SKCC. The secondary objective is to identify patient preferences and areas for improvement. By using the data generated from the surveys, SKCC will be more informed in their patient-centric approach to program development in an effort to improve the overall care for Philadelphia's AYA oncology community. Research Sponsor: Sidney Kimmel Cancer Center Cancer Awareness, Research, Engagement and Support (CARES) Program.

TPS6605 **Poster Session**

Implementation of the Avera/Sema4 oncology and analytics protocol (ASAP). *First Author: Casey B. Williams, Avera Cancer Institute, Sioux Falls, SD*

Background: Precision medicine represents a new era in oncology and population health. Comprehensive molecular profiling and hereditary cancer testing are increasingly important in the routine management of many malignancies, yet may not be widely adopted in many practices and leads to patients not consistently receiving care recommended by current national guidelines such as NCCN and ASCO. In addition, available targeted DNA sequencing panels may be limited to only defined drivers and lack detection in precancerous conditions. Whole exome sequencing (WES) combined with whole transcriptome sequencing (WTS) represent an expanded testing approach that identifies additional genetic changes beyond standard commercial panel tests. Current evidence suggests that WES/WTS is feasible to carry out in routine clinical practice, with improved detection of somatic alterations compared to smaller panels, and the promise to enhance access to targeted therapies and clinical trials. The primary purpose of the ASAP study is to understand the breadth of molecular characteristics present in participants cared for in a large integrated community-based health system, by linking comprehensive molecular profiles with clinical data extracted and curated from the electronic medical record. **Methods:** Avera Health is a large, Midwestern, predominantly rural vertically integrated health system with six regional cancer centers and over 40 oncology outreach sites across South Dakota and surrounding states. The ASAP study was initiated in November 2021 in GYN and as of February, the study is enrolling in the Otolaryngology clinic and expected to open in medical oncology and hematology in March/April 2022. The study will expand to include additional cancer centers outside of Sioux Falls later in 2022 and is anticipated to be open for accrual for 5 years. Enrolled participants are expected to receive WES/WTS and proteomics on their primary tumor and metastatic sites were feasible as well as hereditary testing, pharmacogenomics (PGx) and microbiome profiling. Liquid biopsies will be performed every 3 months while on treatment or when treatment is changed, in follow up to coincide with scheduled radiographic testing, and as part of annual routine surveillance. For participants not diagnosed with cancer, each participant will receive hereditary testing, PGx, microbiome, and a liquid biopsy at least annually. Participants also consent to sharing their electronic health information. Future stages of this work will employ natural language processing (NLP) methods to develop algorithms to help identify opportunities to improve patient outcomes. Projected enrollment is 1000 participants in year 1, 1500 participants in year 2, and up to 3000 annually thereafter. Approximately 50 patients have consented as of February 1 2022. Clinical trial information: NCT05142033. Research Sponsor: Sema4, TheraLink.

TPS6606 **Poster Session**

NHS-Galleri Trial Design: Equitable study recruitment tactics for targeted population-level screening with a multi-cancer early detection (MCED) test.

First Author: Charles Swanton, Cancer Evolution and Genome Instability Laboratory, The Francis Crick Institute, London, United Kingdom

Background: Cancer is a leading cause of premature death globally. Early detection can reduce cancer mortality by reducing the number of cancers diagnosed at a late stage. A blood-based MCED test (Galleri) was developed that can detect cancer signals and predict cancer origin with a single blood draw. The NHS-Galleri trial is a randomized controlled trial (RCT) assessing the clinical utility of this MCED test in a targeted screening population alongside current screening programs. Screening adherence is lower among certain individuals (eg, those with lower socioeconomic status), despite healthcare being free at the point of access in England. NHS-Galleri utilizes innovative strategies to optimize equity in study recruitment, with the goal of enrolling a representative sample. **Methods:** This pragmatic, blinded RCT is currently enrolling 140,000 asymptomatic participants by inviting ~1.3 million residents aged 50-77 in select postcodes of England via the NHS DigiTrials service. Regions were selected to include areas of high cancer mortality, socioeconomic deprivation, and ethnic diversity; eligible participants will be identified from these regions. A variety of methods are employed to enroll a representative study population (defined as including a reasonable number of participants from all socioeconomic statuses and all major ethnic minority groups). These methods include the use of mobile phlebotomy clinics that facilitate access in economically deprived areas, monitoring of participant representativeness by postcode with dynamic adjustment of enrollment, providing interpreters and wheelchair accessibility, and targeted local campaigns. Blood will be collected at 3 annual visits (baseline, year 1, year 2) unless cancer is diagnosed. After baseline blood collection, participants will be randomized 1:1 to the intervention (blood sample analyzed by the MCED test) or control (blood sample stored for potential future MCED testing) arm. Only participants in the intervention arm with "cancer signal detected" will have results returned and be referred for investigations and possible treatment. Participants in the intervention arm without "cancer signal detected" and all in the control arm will remain blinded and return for annual visits. All participants will be reminded to continue guideline-based screening and report unusual/concerning symptoms to a doctor. The primary study objective is a significant reduction in the absolute numbers of stage III & IV cancers diagnosed in the intervention versus control arm 3.5 years after randomization. Cancer-specific mortality will be assessed during trial follow-up. Exploratory endpoints include assessing the primary objective by participant age, gender, socioeconomic status, and ethnicity. Clinical trial information: ISRCTN91431511. Research Sponsor: GRAIL, LLC.

7000 **Oral Abstract Session**

Effects of age, obesity, and body surface area on asparaginase-associated toxicities during acute lymphoblastic leukemia induction therapy: A report from the Children's Oncology Group.

First Author: Etan Orgel, Childrens Hospital Los Angeles, Los Angeles, CA

Background: Asparaginase is integral to pediatric-inspired regimens (PIR) to treat acute lymphoblastic leukemia (ALL) in adolescents and young adults (AYA). However, asparaginase-associated toxicities (AAT) often preclude delivery of planned therapy. Older age, obesity and/or large body surface area (BSA) have been associated with higher risk of AAT in PIR, but data are conflicting, and the impact of dose modification based on these factors is unknown. **Methods:** We examined induction toxicity data from patients ages 1-30 years enrolled in the frontline Children's Oncology Group (COG) trials for high-risk B-ALL (AALL0232, 2004-2011) and T-ALL (AALL0434, 2007-2014). During Induction, patients received pegaspargase (2,500 IU/m^2 without prescribed dose-capping) plus daunorubicin, vincristine, and prednisone or dexamethasone. AAT were defined as CTCAE v4 hyperbilirubinemia (Grade ≥3), elevated alanine aminotransferase (ALT) (Grade ≥4), thrombosis (any), or pancreatitis (any, included consolidation phase). Obesity was classified using population norms as body mass index (BMI) ≥30 (or ≥95th percentile for age/sex). BSA was analyzed continuously and dichotomized at 1.5 m^2 (equivalent to pegaspargase 3,750 IU, the threshold for permissible dose-capping in PIR). The association of AAT with end-Induction minimal residual disease (MRD) ≥0.01% was assessed. **Results:** Among 4,925 patients, 25% were ≥15 years, 39% had BSA >1.5m^2, and 18% had obesity. Multivariable logistic analyses inclusive of BMI and BSA together found increased risk for any AAT in age groups ≥10 years (10-15y, odds ratio (OR) 2.0, 15-20y OR 2.2, ≥21 OR 3.3, p=0.002). Only patients with both obesity and high BSA (>1.5m^2) were at additional risk (OR 3.3, p<0.0001). Similarly, risks for hyperbilirubinemia, ALT elevations, and thrombosis were increased in patients with both high BSA and obesity (OR 3.5, 95% confidence interval [CI] 2.2-5.7), OR 3.3, 95%CI 1.7-6.6, and OR 3.1 95%CI 1.5-6.5, respectively), but not in those with high BSA without obesity. The risk of hyperbilirubinemia was greater with increasing obesity (p<0.0001) and was also higher in all age groups ≥10 years (OR 6.3-7.9, p<0.0001). Age was not associated with thrombosis or ALT elevation; risk for pancreatitis was associated with Hispanic ethnicity, but not with age, BMI, or BSA. AAT were not associated with pooled trial MRD ≥0.01%. **Conclusions:** We report here the largest dataset of AAT in children and AYAs receiving ALL Induction therapy without routinely prescribed dose-capping of pegaspargase. Risk for AAT was increased in patients >10 years and in those with obesity, but not high BSA alone. Dose capping may not be necessary for children and AYAs with high BSA without obesity. Prospective studies of AAT pharmacogenomics and modifiable risk factors will support safer dosing in PIR. Clinical trial information: NCT00075725, NCT00408005. Research Sponsor: U.S. National Institutes of Health.

7001 **Oral Abstract Session**

Efficacy and safety of intramuscular (IM) recombinant *Erwinia* asparaginase in acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (LBL): The Children's Oncology Group (COG) AALL1931 study.

First Author: Luke Devon Maese, Huntsman Cancer Institute, University of Utah, Primary Children's Hospital, Salt Lake City, UT

Background: The inability to receive L-asparaginase (ASNase) therapy due to hypersensitivity is associated with inferior outcomes in patients with ALL or LBL. JZP458, a recombinant *Erwinia*-derived ASNase from a *Pseudomonas fluorescens* expression platform, is approved by the FDA for patients with ALL/LBL who have developed hypersensitivity to *E. coli*–derived ASNase. Here, we report the efficacy and safety of IM JZP458 from COG AALL1931, a phase 2/3, open-label, multicenter, pharmacokinetic (PK) study. **Methods:** Eligible patients with ALL/LBL had a grade ≥3 allergic reaction or silent inactivation to a pegylated *E. coli*–derived ASNase. Each remaining dose of pegylated *E. coli*–derived ASNase was replaced with 6 doses of IM JZP458 on Monday/Wednesday/Friday (M/W/F) over 2-weeks. Three dosing cohorts were enrolled: Cohort 1a, 25 mg/m^2 M/W/F; Cohort 1b, 37.5 mg/m^2 M/W/F; Cohort 1c, 25 mg/m^2 M/W and 50 mg/m^2 F. Efficacy was assessed by the proportion of patients who achieved the last 72-hour (primary endpoint) or 48-hour (key secondary endpoint) nadir serum asparaginase activity (NSAA) levels ≥0.1 IU/mL in the first treatment course. A population PK (PPK) model was developed based on SAA data from AALL1931 to characterize the PK of JZP458 and to inform dosing decisions. **Results:** 167 patients were enrolled for IM dosing (Cohort 1a, n = 33; Cohort 1b, n = 83; Cohort 1c, n = 51). The median (range) age was 10 (1, 25) years. The median (range) of JZP458 courses received was 5 (1, 14) for Cohort 1a, 5 (1, 15) for Cohort 1b, and 4 (1, 11) for Cohort 1c. Mean (95% CI) SAA levels (IU/mL) at 72-hour were 0.16 (0.12, 0.19) for Cohort 1a, 0.33 (0.27, 0.39) for Cohort 1b, and 0.47 (0.35, 0.59) for Cohort 1c; and 0.45 (0.37, 0.53), 0.88 (0.76, 1.01), and 0.66 (0.54, 0.77), respectively, at 48-hour. Simulated data from the PPK model matched the observed data well. For Cohort 1c, the proportions of patients (95% CI) achieving NSAA levels ≥0.1 IU/mL at the last 72- and 48-hour in Course 1 were 90% (81%, 98%) and 96% (90%, 100%), respectively, based on observed data; and were 92% (91%, 93%) and 94% (93%, 95%) based on modeled data. The Table shows the rates of treatment-related adverse events (TRAEs; all grades) of interest per cohort. Overall, TRAEs leading to discontinuation included pancreatitis (6%), drug hypersensitivity (4%), anaphylactic reaction (2%), increased alanine aminotransferase (1%), and hyperammonemia (1%). There were no TRAEs leading to death. **Conclusions:** The totality of the results from AALL1931 demonstrate the positive benefit-risk profile of the IM JZP458 dosing regimen of 25 mg/m^2 M/W and 50 mg/m^2 F with a safety profile consistent with other asparaginases. Clinical trial information: NCT04145531. Research Sponsor: Jazz Pharmaceuticals.

Patients, n (%)	Cohort 1a n=33	Cohort 1b n=83	Cohort 1c n=51
Allergic reactions	2 (6)	11 (13)	3 (6)
Pancreatitis	0	6 (7)	6 (12)
Thrombosis	0	2 (2)	0
Hepatotoxicity	3 (9)	19 (23)	11 (22)

7002 **Oral Abstract Session**

MOMENTUM: Phase 3 randomized study of momelotinib (MMB) versus danazol (DAN) in symptomatic and anemic myelofibrosis (MF) patients previously treated with a JAK inhibitor.

First Author: Ruben A. Mesa, UT Health San Antonio, San Antonio, TX

Background: MMB, an oral JAK1/2 and ACVR1/ALK2 inhibitor, showed clinical activity on MF symptoms, RBC transfusion requirements (anemia), and spleen volume in the SIMPLIFY trials. This pivotal phase 3 study of MF patients (pts) previously treated with a JAK inhibitor (JAKi) tested MMB vs DAN on key symptom, anemia, and spleen volume endpoints at 24 weeks (wks). **Methods:** Eligibility: Primary or post-ET/PV MF; DIPSS high risk, Int-2, or Int-1; MF Symptom Assessment Form Total Symptom Score (MFSAF TSS) ≥10; Hgb <10 g/dL; prior JAKi for ≥90 days, or ≥28 days if RBC transfusions ≥4 units in 8 wks or Gr 3/4 thrombocytopenia, anemia, or hematoma; palpable spleen ≥5 cm. Stratification: TSS, palpable spleen, and RBC units transfused. JAKi taper and washout was ≥21 days. Randomization: 2:1 to MMB 200 mg QD plus DAN placebo or DAN 600 mg QD plus MMB placebo for 24 wks, after which pts could receive open-label MMB. Assessments: Pt reported symptoms using a daily eDiary and spleen volume by MRI or CT. The primary endpoint was TSS response (≥50% reduction from baseline [BL]) rate at wk 24. Secondary endpoints, assessed sequentially at wk 24, were RBC transfusion independence (TI) rate, splenic response rate (SRR; ≥25% reduction in volume from BL), change from BL in TSS, SRR (≥35% reduction from BL) and rate of zero transfusions since BL. **Results:** 94 of 130 (72%) MMB pts and 38 of 65 (58%) DAN pts completed the 24-wk randomized treatment (RT) phase. Median BL TSS were 28 (MMB) and 26 (DAN), Hgb were 8.1 (MMB) and 7.9 (DAN) g/dL, and platelets were 97 (MMB) and 94 (DAN) x10^9/L. BL TI was 13% (MMB) and 15% (DAN). Prior JAKi was ruxolitinib in 195 pts (100%) and fedratinib in 9 pts (5%). All primary and key secondary endpoints were met (Table). Most common Gr ≥3 TEAEs in the RT phase of the study were thrombocytopenia (MMB, 22%; DAN, 12%) and anemia (MMB, 8%; DAN, 11%). Gr ≥3 infections occurred in 15% of MMB and 17% of DAN pts. Peripheral neuropathy occurred in 5 (4%) of MMB (all Gr ≤2) and 1 (2%) of DAN (Gr ≤2) pts in the RT phase, and none discontinued study drug. Overall, TEAEs led to study drug discontinuation in 18% of MMB and 23% of DAN pts in RT phase. A trend toward improved OS up to wk 24 was seen with MMB vs DAN (HR=0.506, p=0.0719). **Conclusions:** In symptomatic and anemic MF pts, MMB was superior to DAN for symptom responses, transfusion requirements, and spleen responses with comparable safety and favorable survival. MMB may address a critical unmet need, particularly in MF pts with anemia. Clinical trial information: NCT04173494. Research Sponsor: Sierra Oncology, Inc.

Wk 24 Endpoint	Test	MMB	DAN	p-value
TSS response rate (primary), %	Superiority	24.6	9.2	0.0095
TI rate, %	Non-inferiority	30.8	20.0	0.0064 (one-sided)
SRR ≥25%, %	Superiority	40.0	6.2	<0.0001
TSS change from BL*	Superiority	-9.36	-3.13	0.0014
SRR ≥35%, %	Superiority	23.1	3.1	0.0006
Zero transfusion rate, %	Superiority	35.4	16.9	0.0012

*Least-squares mean from mixed model for repeated measures.

7003 **Oral Abstract Session**

Rusfertide (PTG-300) treatment in phlebotomy-dependent polycythemia vera patients.

First Author: Ronald Hoffman, The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY

Background: Polycythemia (PV) patients with hematocrit (HCT) levels > 45% are at an increased risk of thrombosis and are treated with therapeutic phlebotomy (TP) alone or in combination with cytoreductive agents. Current therapies are not effective in reaching a HCT < 45% or uniformly tolerated. Rusfertide (PTG-300) is a hepcidin mimetic being developed as a non-cytoreductive option to consistently control HCT at < 45% in PV patients. **Methods:** We report results from two Phase 2 trials investigating the activity of rusfertide in PV patients. The first (NCT04057040) was conducted in patients with excessive erythrocytosis despite TP (3 or more in the 6 months prior to enrolling) ± cytoreductive therapy with a HCT < 45% at study entry. This study comprised 1) a 28-week open-label dose finding phase; 2) a 12-week double-blind randomized (1:1) withdrawal; and 3) a 3-year open-label extension with all subjects receiving rusfertide. Rusfertide doses,10-120 mg, were self-administered SQ weekly and adjusted monthly to maintain HCT < 45%. The second study (NCT04767802) enrolled poorly controlled PV patients with HCT > 48% at study entry despite TP ± hydroxyurea. Rusfertide dosing was initiated as 40 mg twice weekly and reduced to once weekly dosing when HCT < 45% was reached. **Results:** As of December 2021, 63 subjects were enrolled in Study 1. TP alone was the most common treatment (n = 30). The mean number of TP in the 28 weeks prior to enrollment was 4.63 and was 0.43 after treatment. On rusfertide, patients consistently maintained HCT < 45%, essentially eliminating TP, had normalization of serum ferritin, MCV values and iron deficiency. Rusfertide-treated patients also reported a statistically significant improvement in symptom burden at week 28. 20 subjects were enrolled in Study 2. TP with hydroxyurea was the most common treatment (n = 12). Mean HCT was 50.7% pre-treatment and mean time to reach HCT < 45% without TP was 4.79 weeks with persistently well controlled HCT thereafter. Rusfertide significantly reduced erythrocyte counts by ~1.2x10^6/μL within 8 weeks of treatment. In both trials rusfertide did not result in changes in the number of WBC; clinically not meaningful transient increases in platelet numbers were noted. Rusfertide was well tolerated, with mostly grade 1-2 adverse events (AE). The most common AEs were injection site reactions. These were typically transient, manageable with topical therapies, and did not lead to study withdrawal. **Conclusions:** Rusfertide, when added to standard therapy, demonstrated robust activity in managing PV patients with sub-optimally controlled erythrocytosis in 2 trials, enrolling patients with HCT < 45% (Study 1), and HCT > 48% (Study 2). Taken together, these data show that the non-cytoreductive rusfertide, is a promising novel agent for PV patients which leads to sustained HCT control < 45%. A pivotal Phase 3 study is scheduled to begin in 2022. Clinical trial information: NCT04057040 and NCT04767802. Research Sponsor: Protagonist Therapeutics, Inc.

7004 **Oral Abstract Session**

Efficacy and safety results from ASCEMBL, a phase 3 study of asciminib versus bosutinib (BOS) in patients (pts) with chronic myeloid leukemia in chronic phase (CML-CP) after ≥2 prior tyrosine kinase inhibitors (TKIs): Week 96 update. *First Author: Delphine Rea, Hôpital Saint-Louis, Paris, France*

Background: Asciminib is the first BCR::ABL1 inhibitor to specifically target the ABL Myristoyl Pocket (STAMP). In the ASCEMBL primary analysis, asciminib had superior efficacy and better safety/tolerability than BOS in pts with CML-CP after ≥2 prior TKIs. After a median follow-up of 2.3 years (16.5 months' additional follow-up since primary analysis), we report efficacy and safety results (cutoff: October 6, 2021). **Methods:** Eligible pts were adults with CML-CP after ≥2 prior TKIs, with intolerance or lack of efficacy per 2013 European LeukemiaNet. Pts were randomized 2:1 to asciminib 40 mg twice daily or BOS 500 mg once daily, stratified by major cytogenetic response (MCyR) status (Ph+ metaphases ≤35%) at baseline. The key secondary endpoint was major molecular response (MMR) rate at wk 96. **Results:** 233 pts were randomized to asciminib (n=157) or BOS (n=76). At cutoff, treatment was ongoing in 84 (53.5%) and 15 (19.7%) pts, respectively; the most common reason for discontinuation was lack of efficacy in 38 (24.2%) and 27 (35.5%) pts, respectively. MMR rate at wk 96 (per ITT) was higher on asciminib (37.6%) than BOS (15.8%). The difference, adjusting for baseline MCyR, was 21.7% (95% CI, 10.5%-33.0%; 2-sided *P*=.001). More pts on asciminib than BOS, respectively, had *BCR::ABL1*^{IS} ≤1% (45.1% vs 19.4%) at wk 96. The probability of maintaining MMR and *BCR::ABL1*^{IS} ≤1% for ≥72 wk was 96.7% (95% CI, 87.4%-99.2%) and 94.6% (95% CI, 86.2%-97.9%), respectively, on asciminib and 92.9% (95% CI, 59.1%-99.0%) and 95.0% (95% CI, 69.5%-99.3%), respectively, on BOS. Median duration of exposure was 103.1 (range, 0.1-201.1) wk on asciminib and 30.5 (range, 1.0-188.3) wk on BOS. Despite the longer duration of asciminib exposure, safety/tolerability of asciminib continued to be better than that of BOS (Table). No new on-treatment deaths were reported since the primary analysis. Most frequent (>10%) grade ≥3 adverse events (AEs) on asciminib vs BOS were thrombocytopenia (22.4%, 9.2%), neutropenia (18.6%, 14.5%), diarrhea (0%, 10.5%), and increased alanine aminotransferase (0.6%, 14.5%). **Conclusions:** After >2 years of follow-up, asciminib continued to show superior efficacy and better safety/tolerability vs BOS. Responses were durable, with more pts on asciminib in MMR. Additionally, more pts on asciminib had *BCR::ABL1*^{IS} ≤1%, a milestone response in later lines associated with improved survival. These results continue to support the use of asciminib as a new CML therapy, with the potential to transform standard of care. Clinical trial information: NCT03106779. Research Sponsor: Novartis Pharmaceuticals Corporation.

Overview of AEs.

	Asciminib n=156[a]		BOS n=76	
n (%)	All grades	Grade ≥3	All grades	Grade ≥3
AEs	142 (91.0)	88 (56.4)	74 (97.4)	52 (68.4)
AEs leading to discontinuation	12 (7.7)	12 (7.7)	20 (26.3)	15 (19.7)

[a] 1 pt developed cytopenia after randomization and was not treated per investigator's decision.

7005 **Oral Abstract Session**

Overall survival by *IDH2* mutant allele (R140 or R172) in patients with late-stage mutant-*IDH2* relapsed or refractory acute myeloid leukemia treated with enasidenib or conventional care regimens in the phase 3 IDHENTIFY trial. *First Author: Stéphane De Botton, Gustave Roussy, Villejuif, France*

Background: *IDH2* gene mutations (m*IDH2*) occur in up to ~20% of patients (pts) with acute myeloid leukemia (AML), most commonly as R140Q (in ~75% of cases) or R172K (~25%) point mutations. The functional effects and prognostic relevance of m*IDH2*-R140 and m*IDH2*-R172 can vary (Papaemmanuil 2016). In the randomized, phase 3 IDHENTIFY trial, enasidenib (ENA), an oral mIDH2 inhibitor, did not significantly improve overall survival (OS) vs conventional care regimens (CCR) as salvage treatment (Tx) for older pts with m*IDH2* relapsed/refractory (R/R) AML in ITT analysis, but a trend for improved OS with ENA was detected in pts with *IDH2*-R172 mutations. We further investigated OS and correlative biomarkers in IDHENTIFY pt subgroups defined by m*IDH2* variant (R140/R172). **Methods:** This open-label trial (NCT02577406) enrolled pts ≥ 60 years of age who had received 2 or 3 prior AML Tx. Pts were preselected to a CCR (azacitidine, intermediate- or low-dose Ara-C, or supportive care), and were then randomized 1:1 to ENA 100 mg/d or CCR in 28d cycles. Co-occurring gene mutations were identified by targeted next-generation sequencing (37-gene panel) of bone marrow mononuclear cell (BMMC) DNA. Total 2-HG levels were determined by LC/MS. **Results:** Of 319 pts enrolled, 88 pts (28%; 43 ENA, 45 CCR) had m*IDH2*-R172 and 229 (72%; 115 ENA, 114 CCR) had m*IDH2*-R140. Median baseline (BL) 2-HG levels were similar between Tx arms and m*IDH2* variant subgroups, as were *IDH2* variant allele frequencies. Pts with m*IDH2*-R172 had fewer median BL co-mutations (4 [range 2–8]) than did pts with m*IDH2*-R140 (5 [1–11]) ($P < 0.0001$). The most frequently co-occurring mutations were *SRSF2* and *RUNX1* in the R140 cohort (59% each) and *DNMT3A* in the R172 cohort (57%). Compared with the R172 cohort, the R140 group was enriched with *SRSF2, FLT3* (-ITD/-TKD), *NPM1, RUNX1,* and *JAK2* mutations, whereas *DNMT3A* and *TP53* mutations were more common in the R172 group. In Cox multivariate analysis including m*IDH2* variant (R140/R172), *DNMT3A* mutation status, and number of gene mutations at BL, m*IDH2*-R172 was significantly ($P = 0.04$) correlated with improved OS (vs. R140) in the ENA arm, whereas the number of BL gene mutations was significantly ($P < 0.01$) associated with OS in the CCR arm. Median OS in the R172 subgroup was 14.6 mo with ENA vs 7.8 mo with CCR (HR, 0.59 [95%CI 0.35-0.98]; $P = 0.039$) and 1-yr survival rates were 62% and 30%, respectively. In m*IDH2*-R140 pts, median OS was 5.7 mo in both Tx arms (0.93 [0.70-1.24]; $P = 0.61$), and 1-year survival rates were 29% and 25% with ENA and CCR, respectively. **Conclusions:** Mutational burden and co-mutational profiles differed between pts with m*IDH2*-R140 and m*IDH2*-R172 R/R AML. ENA improved survival outcomes for pts with *IDH2*-R172 mutations, with median OS and 1-year survival rate approximately double those in the CCR arm. Clinical trial information: NCT02577406. Research Sponsor: Celgene, a Bristol-Myers Squibb Company.

7006 **Oral Abstract Session**

Pre-MEASURE: Multicenter evaluation of the prognostic significance of measurable residual disease testing prior to allogeneic transplantation for adult patients with AML in first remission. *First Author: Chris S. Hourigan, Laboratory of Myeloid Malignancies, Hematology Branch, National Heart Lung and Blood Institute, National Institutes of Health, Bethesda, MD*

Background: Measurable residual disease (MRD) prior to allogeneic hematopoietic cell transplantation (alloHCT) is associated with increased relapse and death in patients with acute myeloid leukemia (AML) in cytomorphological complete remission (CR). We recently demonstrated AML MRD detected in pre-alloHCT blood by DNA-sequencing was associated with increased relapse and decreased overall survival in patients randomized to reduced intensity conditioning (RIC) versus myeloablative conditioning (MAC). The clinical utility of such ultra-deep next-generation sequencing (NGS-MRD) had not yet been reported in a large multi-center cohort. **Methods:** Patients aged 18 or older who underwent first alloHCT between 2013-2017 for AML in first CR (CR1), reported to be *FLT3, NPM1, IDH1, IDH2* and/or *Kit* mutated at diagnosis, with a pre-conditioning remission blood sample available in the CIBMTR biobank were eligible for this study. Ultra-deep anchored multiplex PCR-based NGS-MRD for the above mutations was performed on 500ng gDNA with error-corrected variant calling as previously described. The pre-specified statistical analysis plan was registered on OSF. **Results:** Of 457 patients with a sample available, 448 had sufficient clinical annotation and DNA for analysis. 147 of these 448 patients (33%) experienced relapse at a median of 5.6 months post-alloHCT. NGS-MRD was positive in 129 pre-alloHCT patient samples (29%), averaging 1.35 mutation(s)/patient (range: 1-4). 173 mutations were detected with a median VAF of 0.18% (range: 0.0054-62%), most frequently *FLT3-ITD* (n = 43 patients), *NPM1* (n = 48), and *IDH2* (n = 46). Testing positive by NGS-MRD prior to alloHCT was associated with a 3yr RFS of 36% (95% CI: 28-45%) compared with 56% (51-62%) in those testing negative ($p < 0.001$). Detection of *NPM1* and/or *FLT3-ITD* mutations prior to alloHCT was associated with a 3yr relapse probability of 55% (43-67%) and RFS of 26% (16-37%). NGS-MRD impact was modified by conditioning intensity: positive patients receiving RIC/NMA had the highest relapse of 57% at 3yr, testing negative followed by RIC/NMA had the same relapse rate at 3yr (35%) as those who tested positive but received MAC ($p < 0.001$). At three years, those positive for *FLT3-ITD* and/or *NPM1* mutations prior to RIC/NMA alloHCT had a relapse probability of 67% (50-83%) with a RFS of 19% (8-33%). HR for relapse if NGS-MRD positive pre-alloHCT in CR1 was 2.3 ($p < 0.001$, 95% CI 1.6-3.1) when adjusting for conditioning intensity and age group. **Conclusions:** In this largest cohort of NGS-MRD testing prior to alloHCT for AML reported to date, we confirm the ability to identify patients in CR1 but at high-risk of subsequent relapse. This evidence provides the foundation for future precision medicine approaches to reduce post-transplant AML relapse. Research Sponsor: U.S. National Institutes of Health.

7007 **Oral Abstract Session**

Long-term results of a phase 2 trial of crenolanib combined with 7+3 chemotherapy in adults with newly diagnosed FLT3 mutant AML. *First Author: Eunice S. Wang, Roswell Park, Buffalo, NY*

Background: Crenolanib is a potent type I FLT3 inhibitor active against FLT3- ITD, TKD and variant mutations. We report the long-term outcomes of a phase II trial evaluating crenolanib combination therapy in patients (pts) with newly diagnosed FLT3 mutant AML. **Methods:** Pts (≥ 18 yrs) with newly diagnosed FLT3-AML received 7+3 induction with cytarabine 100 mg/m^2/d for 7 days and daunorubicin (DNR) (<60 yrs: 90 mg/m^2; ≥60 yrs: 60 mg/m^2) or idarubicin (IDA 12 mg/m^2) for 3 days. Crenolanib 100 mg TID was administered starting on day 9 until 72 hrs prior to next chemotherapy. Re-induction was allowed. Up to 4 cycles of HiDAC consolidation (<60 yrs: 3 g/m^2; ≥60 yrs: 1g/m^2) was allowed. Eligible pts could proceed to transplant. Crenolanib maintenance therapy was offered for 1 yr after HiDAC or transplant. **Results:** 44 pts (22 male) with a median age of 57 yrs (range 19-75) were treated; 15 (34%) pts were >60 yrs. 7 pts had initial WBC >100,000/μL (2 had WBC >200,000). 4 pts had AML following MDS/MPN. 39 (89%) pts had intermediate risk cytogenetics, 3 (7%) had adverse risk, and 2 were unavailable. 33 (75%) pts had *FLT3-ITD*, 8 (18%) had *TKD*, and 3 (7%) had *ITD* and *TKD* mutations. 11 pts had concomitant *NPM1*/*DNMT3A* mutations, 11 pts had secondary AML-type mutations, and 2 pts had *TP53*. 28 pts received DNR/crenolanib; 16 pts received IDA/crenolanib. Overall CRc (CR + CRi) was 73% (32/44) after one induction cycle; 86% (38/44) after two cycles. CRc rates > 80% were noted in pts ≤ 60 yo, *FLT3-ITD* mutations, concomitant *FLT3/DMT3A/NPM1* mutations, intermediate risk cytogenetics, and WBC ≥ 100,000/μL. Median time to count recovery was 30 days. MRD-negative CRc was achieved in 94% of evaluable pts (17); 22 pts underwent HSCT. The most common treatment related adverse events (AE) were diarrhea (66%), nausea (57%) and febrile neutropenia (52%). Grade ≥3 AE included febrile neutropenia (50% pts), diarrhea (18%), nausea (6%), and rash (6%). No QTC prolongation was observed. 6 pts required crenolanib dose reduction during induction. High levels of serum crenolanib were achieved and maintained throughout therapy. With a median follow-up of 45 mos (4.4-54.9), the median OS for all pts has not been reached with 57% of pts alive. Median EFS for all pts was 45 mos. In younger pts (≤ 60 yo) OS was 69% and EFS 62%. Cumulative incidence of relapse was 15%. In older pts (61-75), 80% achieved CR/CRi, and median OS was 20 mos. Mutational analysis demonstrated clearance of multiple variant FLT3 mutations and no new FLT3 clones at relapse in pts completing protocol therapy. **Conclusions:** Long-term outcomes of a phase 2 trial of crenolanib combined with 7+3 induction and consolidation in adults with newly diagnosed *FLT3* mutant AML demonstrate high response rates (CRc 86%). With a median follow-up of 45 mos, median OS has not been reached. A phase 3 trial (NCT03258931) randomizing pts with newly diagnosed *FLT3* mutant AML to crenolanib vs midostaurin with 7+3 is ongoing. Clinical trial information: NCT02283177. Research Sponsor: Arog Pharmaceuticals, Inc.

7008 **Clinical Science Symposium**

Autologous CD19-directed CAR T cells produced by novel PrimeCAR manufacture platform exhibit safety, efficacy, and long persistence profiles in relapsed/refractory B-lineage acute leukemia (r/r B-ALL). *First Author: Shiqi Li, 920th Hospital of Joint Logistics Support Force of People's Liberation Army of China, Kunming, China*

Background: CD19 chimeric antigen receptor (CAR) T cell therapy has shown promising efficacy in the r/r B-ALL. However, the life-threatening side effects especially high grades of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) limited its wide application. To overcome these limitations, we established a novel PrimeCAR platform based on moderate activation and short expansion to manufacture MC-1-50, an autologous CD19-directed CAR T cell. Our preclinical study showed that MC-1-50 exerted a great efficacy and less cytokines secretion. **Methods:** In this Phase I /II study (NCT04271410), CAR T cells were manufactured by PrimeCAR platform, which reduces manufacture periods to about 2 days. T cells were transducted with a lentiviral vector encoding a humanized CD19 specific scFv following 4-1BB and CD3ζ cytoplasmic domain. Patients (pts) received single-dose of MC-1-50 at dose level 1 (1×10^5 CAR+/kg), level 2 (3×10^5 CAR+/kg), and level 3 (1×10^7 CAR+ totally, ranged 1.67-3.85×10^5 CAR+/kg). Pts were pre-conditioned with fludarabine (25-30 mg/m^2) and cyclophosphamide (200-300 mg/m^2) daily for 3 days. Toxicity was graded by CTCAE , CRS and ICANS were graded by ASTCT criteria. **Results:** As of Feb 10, 2022, 13 pts with r/r B-ALL were infused with MC-1-50. Disease characteristics and outcomes are shown in the table. No DLTs were reported. Eleven pts (84%) experienced CRS, including 7 (54%) at grade 1 and 4 (30%) at grade 2, no ≥ 3 CRS were observed. One pts (7%) experienced grade 1 ICANS, no ≥ 2 ICANS occurred. The Tmax for IL-6 was detected around day 11 (123.3±165.16 pg/ml). There were similar low secretion features of other cytokines, which is consistent with low CRS and ICANS. In all dose levels, 13 pts finished 1M evaluation and the CR rate in 1M is 100%. Four pts finished 3M evaluation and the CR rate in 3M is 75%, 1 pts relapsed at the month 3 with CD19 mutation. One pts had a CR statue at the month 11. Cmax for CAR copy number in 3 dose levels are similar and the average number of Cmax of CAR is 275901.6 copies/ug genomic DNA. **Conclusions:** PrimeCAR platform could produce CAR T cells in very short time with high percentage of T_{scm}. Treatment of r/r B-ALL at very low dose resulted in excellent safety profile, while exhibited a promising efficacy. That make this PrimeCAR platform potential for outpatient administration in the future. Clinical trial information: NCT04271410. Research Sponsor: Chongqing Precision Biotech Co., Ltd.

Disease characteristics and safety outcomes.

ID	Age	Gender	Prior HSCT	Tumor burden	Dose	CRS	ICANS
01	17	M	Y	71%	1×10^5/kg	2	/
02	39	F	N	83%	1×10^5/kg	1	/
03	26	M	N	52%	1×10^5/kg	1	/
04	34	M	N	69%	3×10^5/kg	2	/
05	21	M	N	79%	3×10^5/kg	1	/
06	23	F	N	83%	3×10^5/kg	1	/
07	39	F	N	79%	1×10^7 total	2	/
08	52	F	N	58%	1×10^7 total	1	/
09	22	F	N	35%	1×10^7 total	1	/
10	70	F	N	45%	1×10^7 total	/	/
11	54	M	N	0%[a]	1×10^7 total	/	/
12	38	F	N	30%	1×10^7 total	1	/
13	8	M	Yes	25%	1×10^7 total	2	1

[a]The patient has only extramedullary lesions.

7009 **Poster Discussion Session**

A phase II trial of a chemotherapy-free combination of ponatinib and blinatumomab in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL). *First Author: Nicholas James Short, The University of Texas MD Anderson Cancer Center, Department of Leukemia, Houston, TX*

Background: Ponatinib and blinatumomab are highly active in Ph+ ALL. A chemotherapy-free combination of these agents may lead to durable remissions and reduce the need for stem cell transplant (SCT) in first remission. **Methods:** In this phase II study, adults with newly diagnosed (ND) Ph+ ALL, relapsed/refractory (R/R) Ph+ ALL, or CML in lymphoid blast phase (CML-LBP) received up to 5 cycles of blinatumomab. Ponatinib 30mg daily was given during cycle 1 and decreased to 15mg daily once a complete molecular response (CMR) was achieved. After completion of blinatumomab, ponatinib was continued for at least 5 years. All patients (pts) received 12 doses of prophylactic IT chemotherapy. **Results:** Between 2/2018 and 1/2022, 55 pts were treated (35 ND, 14 R/R and 6 CML-LBP). Baseline characteristics and responses are shown in Table. Among 23 pts with ND Ph+ ALL evaluable for response, 22 (96%) achieved CR/CRi; 1 pt had early death due to myelosuppression from prior chemotherapy. Among 13 evaluable pts with R/R Ph+ ALL, 12 (92%) achieved CR/CRi. The CMR rates for the ND, R/R and CML-LBP cohorts were 64%, 71%, and 17% after cycle 1 and were 85%, 79%, and 33% overall, respectively. In the ND cohort, 4/17 evaluable pts (24%) achieved CMR in the peripheral blood within 1 week, and 9/15 (60%) within 2 weeks. The median follow-up is 11 months (range, 1-46+ months). Among the 35 pts in the ND cohort, 33 pts (94%) are alive and in continuous remission. Only 1 pt in the ND underwent SCT in first remission (due to persistent MRD positivity), and no relapses have been observed. The 2-year EFS and OS rates in the ND cohort are 93%. Among the 13 responding pts in the R/R cohort, 6 (46%) underwent SCT. The 2-year EFS and OS rates for the R/R cohort are 42% and 61%, and for the CML-LBP cohort are 33% and 60%, respectively. Most side effects were grade 1-2 and were consistent with the known toxicity profile of the two agents individually. Two pts discontinued ponatinib due to toxicity (1 due to stroke and 1 due to DVT). One pt discontinued blinatumomab due to recurrent neurotoxicity. **Conclusions:** The chemotherapy-free combination of ponatinib and blinatumomab was safe and effective in Ph+ ALL and CML-LBP. Longer follow-up continues to demonstrate durable remissions, particularly in ND Ph+ ALL, even without SCT in first remission. Clinical trial information: NCT03263572. Research Sponsor: Amgen and Takeda.

Baseline characteristics.

Characteristic N (%) / median [range]	Category	ND Ph+ ALL N = 35	R/R Ph+ ALL N = 14	CML-LBP N=6
Age (years)		57 [22-83]	38 [24-61]	69 [29-82]
CD19 expression		99.8 [74.9-100]	99.9 [98.6-100]	99.7 [98.3-99.9]
BCR-ABL1 transcript		26 (74)	13 (93)	0
	p190	9 (26)	1 (7)	6 (100)
	p210			
Line of therapy	Frontline	35 (100)	0	4 (67)
	Primary refractory	0	2 (14)	0
	Salvage 1	0	6 (43)	1 (17)
	Salvage 2+	0	6 (43)	1 (17)
Response				
CR		21/23 (91)	11/13 (85)	4/6 (67)
CR/CRi		22/23 (96)	12/13 (92)	5/6 (83)
CMR after 1 cycle		21/33 (64)	10/14 (71)	1/6 (17)
CMR overall		28/33 (85)	11/14 (79)	2/6 (33)

7010 **Poster Discussion Session**

Two-year follow-up of KTE-X19, an anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, in adult patients (Pts) with relapsed/refractory B-cell acute lymphoblastic leukemia (R/R B-ALL) in ZUMA-3. *First Author: Bijal D. Shah, Moffitt Cancer Center, Tampa, FL*

Background: Brexucabtagene autoleucel (KTE-X19) is an autologous anti-CD19 CAR T-cell therapy approved in the US to treat adult R/R B-ALL based on the ZUMA-3 study. The overall complete remission (CR) rate (CR + CR with incomplete hematologic recovery [CRi]) was 71% (95% CI, 57-82) after 16.4 mo median follow-up (N = 55; Shah et al. *Lancet* 2021). Here, we report updated outcomes with longer follow-up in these pts and in a larger pooled analysis of Phase (Ph) 1 and 2 pts who received the pivotal dose of KTE-X19. **Methods:** Eligible adults (≥18 years) had R/R B-ALL and received a single infusion of KTE-X19 at the pivotal dose (1×10^6 CAR T cells/kg) following leukapheresis and conditioning chemotherapy. The primary endpoint was CR/CRi rate by central review. **Results:** As of 23 July 2021, median follow-up was 26.8 mo (range, 20.7-32.6) for treated Ph 2 pts (N = 55). The CR/CRi rate per central review was 71% (95% CI, 57-82; 56% CR; 15% CRi). Eleven pts (20%; 8 CR and 2 CRi) proceeded to subsequent allogeneic stem cell transplant (alloSCT). Median duration of remission (DOR) censored at subsequent alloSCT was 14.6 mo (9.4-not estimable [NE]); not censored: 18.6 mo (9.6-NE); 6/39 responders (15%) had ongoing responses at data cutoff. Median (95% CI) relapse-free survival (RFS) was 11.6 mo (2.7-20.5) censored at subsequent alloSCT and 11.7 mo (2.8-20.5) not censored at subsequent alloSCT; 18-mo RFS rates (95% CI) were 35% (20.5-50.6) and 42% (28.0-55.0), respectively. Median (95% CI) overall survival (OS) was 25.4 mo (16.2-NE) among all KTE-X19-treated pts and not reached (25.4-NE) in pts with CR (n = 31). For Ph 1/2 pts (N = 78) who received the pivotal KTE-X19 dose (median follow-up: 29.7 mo; range 20.7-58.3), the CR/CRi rate by independent review was 73% (95% CI, 62-82). Medians (95% CI) for DOR, RFS, and OS were 18.6 mo (9.6-NE), 11.7 mo (6.1-20.5), and 25.4 mo (16.2-NE), respectively. A subgroup analysis revealed that in pts aged 18-39 (n = 36), 40-59 (n = 27), and ≥60 (n = 15) years, the CR/CRi rates (95% CI) were 69% (52-84), 70% (50-86), and 87% (60-98); 24-mo OS rates (95% CI) were 48% (30-64), 54% (33-71), and 57% (28-78), respectively. In pts with pre-KTE-X19 infusion marrow blast percentages > 25 to ≤50 (n = 12), > 50 to ≤75 (n = 14), and > 75 to 100 (n = 30), CR/CRi rates (95% CI) were 83% (52-98), 86% (57-98), and 57% (37-75); 24-mo OS rates (95% CI) were 58% (27-80), 55% (26-77) and 37% (19-55), respectively. There were no new safety signals; the proportion of treated Ph 2 pts with Gr ≥3 treatment emergent adverse events was unchanged since prior data cutoff. One pt had an ongoing neurologic event of Gr 1 finger numbness. **Conclusions:** With longer follow-up and an expanded data set by independent review, outcomes remain durable in adults with R/R B-ALL, most of whom were heavily pretreated, with median OS not yet reached in pts with CR. Long-term safety was favorable. Clinical trial information: NCT02614066. Research Sponsor: Kite, a Gilead Company.

7011 **Poster Discussion Session**

Updated results from a phase II study of mini-hyper-CVD (mini-HCVD) plus inotuzumab ozogamicin (INO), with or without blinatumomab (Blina), in older adults with newly diagnosed Philadelphia chromosome (Ph)-negative B-cell acute lymphoblastic leukemia (ALL). *First Author: Walid Macaron, MD Anderson Cancer Center, Houston, TX*

Background: INO and Blina improve overall survival (OS) in patients (pts) with relapsed/refractory B-ALL. The use of these agents in older adults in the frontline setting may allow for use of less chemotherapy and improve remission duration and OS compared to standard therapies. **Methods:** Pts ≥60 years with newly diagnosed Ph-negative B-cell ALL received mini-HCVD for up to 8 cycles. Initially, INO was given at 1.3-1.8mg/m^2 on day 3 of cycle 1 and 0.8-1.3mg/m^2 on day 3 of cycles 2-4. Rituximab (if CD20+) and prophylactic IT chemotherapy were given for the first 4 cycles. Responding pts received POMP maintenance for up to 3 years. Beginning with pt #50, INO was given in fractionated doses each cycle (0.6 mg/m^2 on day 2 and 0.3 mg/m^2 on day 8 of cycle 1; 0.3 mg/m^2 on day 2 and 8 of cycles 2-4) and 4 cycles of Blina were given following 4 cycles of mini-HCVD plus INO. Maintenance was with 12 cycles of POMP and 4 cycles of Blina (1 cycle of Blina after 3 cycles of POMP). **Results:** Characteristics of the 80 pts are shown in Table. 6 pts were in complete remission (CR) at enrollment. Among 74 evaluable pts, 73 (99%) responded (CR in 89%). MRD negativity by flow was achieved in 80% of pts after 1 cycle and in 94% overall. The 30-day mortality rate was 0%. Among 79 responders, 11 (14%) relapsed, 4 (5%) underwent SCT, 33 (42%) remain in ongoing continuous remission, and 31 (39%) died in remission. Notably, 6 pts (8%) developed veno-occlusive disease, 1 after subsequent SCT. With a median follow-up of 55 months, the 5-year continuous remission and OS rates were 76% and 47%, respectively. Age ≥70 and poor-risk cytogenetics were associated with worse outcomes. The inferior outcomes in pts ≥70 years was primarily due to higher rates of death in CR. The 5-year OS for pts age 60-69 years without poor-risk cytogenetics (n=37), age 60-69 with poor-risk cytogenetics (n=13), age ≥70 without poor-risk cytogenetics (n=24) and age ≥70 with poor-risk cytogenetics (n=6) were 69%, 39%, 36% and 0%, respectively. **Conclusions:** The combination of mini-HCVD plus INO, with or without Blina, in older adults with newly diagnosed Ph-negative ALL resulted in an overall response rate of 99% and a 5-year OS rate of 47%. Particularly favorable outcomes were seen in pts age 60-69 years without poor-risk cytogenetics (5-year OS: 69%). Chemotherapy-free regimens may improve outcomes in pts age ≥70 years, and novel agents/regimens are still needed for those with poor-risk cytogenetics. Clinical trial information: NCT01371630. Research Sponsor: Pfizer and Amgen.

Patient characteristics.

Characteristic	Category	N (%) / Median [range]
Age (years)		68 [60-87]
	≥70	30 (38)
Karyotype	Diploid	26 (33)
	HeH	5 (6)
	Ho-Tr	12 (15)
	Tetraploidy	3 (4)
	Complex	3 (4)
	t(4;11)	1 (1)
	Misc	15 (19)
	IM/ND	15 (19)
CNS disease at diagnosis		4 (5)
CD19 (%)		99.5 [26-100]
CD22 (%)		96.9 [27-100]
CD20	≥ 20%	44/73 (60)
***TP53* mutation**		24/61 (39)

7012 **Poster Discussion Session**

Health inequities in survival of patients with acute lymphoblastic leukemia in Peru: A single tertiary institution experience.

First Author: Evelyn Pamela Espinoza-Morales, Universidad Privada San Juan Bautista, Lima, Peru

Background: Acute Lymphoblastic Leukemia (ALL) in Latino countries is characterized by high incidence and worst outcomes compare to other ethnicities. However, the actual epidemiological characterization of ALL in South America remains unknown. The lack of registries, uniform treatment and prospective protocols have been pointed out for these disparities. Also, biological, and social aspects of this disease play an important role that has not been well examined. We aimed to evaluate the survival of patients with acute lymphoblastic leukemia according to demographic characteristics with emphasis in the place of residence. **Methods:** We performed an analytical retrospective cohort study with subjects diagnosed and treated for ALL during the period 2016-2018 at the Peruvian national cancer center (INEN, Instituto Nacional de Enfermedades Neoplasicas). INEN is currently the main center dedicated to diagnosing and treat acute leukemias for patients without social neither private insurance. Also, INEN is located at the capital city (Lima-Peru). The calculated sample size was 378 patients. Patient data were obtained from the epidemiological registry and corroborated with the national registry of mortality (RENIEC, Registro Nacional de Identificacion y Estado Civil Overall survival probabilities according to demographic characteristics were estimated using the Kaplan-Meier curve; in addition, the Log-rank test and Cox regression were used. **Results:** A sample of 378 patients were included during the study period (N = 588), of which 212 (56.8%) were male, 42% were between 0-10 years, 24% in 46-65 years. Regarding the characteristics at diagnosis, 80% were Ph(-) BCP-ALL and 69% corresponded to high-risk groups. At 42 months of follow-up, the median survival of the patients was 29 months (95% CI: 23.3-34.6), and the overall survival at three years was 44.8%. Overall survival in males (48.8%) was higher than in females (39.5%). According to the range of age, the highest survival was in the group of 0-10 years (70%), followed by 11-20 years (36.8%) and the lowest survival was in 46- 65 years (12.5%). Furthermore, overall survival in Lima (51.5%) was higher than in the country-side (39.7%). There was a statistically significant association ($p < 0.05$) between survival and sex ($p = 0.042$), age range ($p = 0.000$) and place of residence ($p = 0.005$); according to the Log-rank test. **Conclusions:** We report a lower survival among all age groups in ALL compared to international working groups. Living in a country-side region represents a significant factor for dismal survival in our cohort. Specialized health care access to diagnosis and treatment should be warranted for patients with geographical limitations and programs to ensure it must be implemented. Research Sponsor: None.

7013 **Poster Discussion Session**

Impact of socioeconomic status on survival after CD19 CART therapy.

First Author: Haley Newman, Children's Hospital of Philadelphia, Philadelphia, PA

Background: CD19-directed chimeric antigen receptor T cell (CART) therapy has dramatically improved survival for children with relapsed/refractory (r/r) B-cell acute lymphoblastic leukemia (B-ALL). While significant socioeconomic (SES) outcome disparities exist for children with newly diagnosed B-ALL, the impact of SES on CART access and outcomes is poorly described. Using the largest single-center pediatric CART experience, we investigated the hypothesis that poverty-exposed children would have inferior survival outcomes compared to unexposed children. **Methods:** Retrospective cohort study of US pediatric patients treated on CD19 CART clinical trials or with commercial tisagenlecleucel at Children's Hospital of Philadelphia from 2012-2020. Poverty was the primary exposure, defined at the household-level by insurance status (public vs private). Neighborhood opportunity was defined by census-derived Childhood Opportunity Index (COI) (low [q1-2] vs high [q3-4]). Overall survival (OS) and relapse-free survival (RFS) were evaluated by Kaplan Meier methods, and association with exposures by Cox regression models. **Results:** Among 206 patients, 36% were household poverty exposed, 24.9% low COI, 21.4% identified as Hispanic, 7.3% non-Hispanic Black, 63.6% non-Hispanic White, and 7.7% non-Hispanic Other. Household-poverty exposure was similar between local and referred patients (32.4% vs 36.7%). Patients unexposed to poverty at the household level or with high COI presented to CART with high disease burden (37.1% vs 26%, $p = 0.049$, 37.9% vs. 29.7%, $p = 0.002$). In multivariate analysis adjusting for age, race/ethnicity, disease burden, relapse status, and inotuzumab exposure, there were no significant differences in OS by householdverty (HR 0.86, 95%CI 0.50-1.48, $p = 0.575$) or low COI (HR 1.03, 95%CI 0.53-1.99, $p = 0.932$). Low COI was associated with inferior RFS (HR 2.26, 95%CI 1.34-8.80, $p = 0.002$). There was no significant difference in RFS by household-poverty (HR 0.84, 95%CI 0.48-1.44, $p = 0.520$). **Conclusions:** Household poverty was not associated with inferior survival outcomes in pediatric patients who received CART for r/r B-ALL. Patients with low neighborhood opportunity had increased hazard of relapse, a finding that requires investigation of the COI components underlying this association. Patients of higher proxied SES were more likely to have high disease burden, an access inequity potentially reflecting referral pattern bias or greater ability of advantaged families to advocate for CART. Future institutional and multi-center studies should utilize patient-reported social determinants of health to investigate mechanisms driving these disparities and guide care delivery interventions to improve equity in access and outcomes. Clinical trials: NCT01626495, NCT02435849, NCT02374333, NCT02228096, NCT02906371 Research Sponsor: None.

7014 **Poster Discussion Session**

Challenges and outcomes of treating acute myeloid leukemia (AML) in resource-constrained settings.

First Author: Sahitya Dangudubiyyam, All India Institute of Medical Sciences, New Delhi, India

Background: Acute myeloid leukemia (AML) is a heterogeneous disease. Improvement in supportive care, has considerably improved AML induction outcomes, decreasing induction deaths to <5% in recent studies. However, induction deaths during AML treatment in resource constraint settings remains as high as 25% in young adults. In this study we explore various challenges encountered in treating AML patients in one of the largest public sector teaching hospitals in India. **Methods:** Consecutive patients diagnosed with AML and registered in our clinic from January 1, 2018 to December 31, 2019, were included. **Results:** Of 316 patients diagnosed with AML, only 181 (57%) were able to get admitted to our institute for remission induction treatment. Median time from diagnosis to treatment initiation was 9.5 days (range, 0-232 days). Almost half (N=88; 49%) of admitted patients had infections at the time of admission. Among these, 31 (35%) had invasive fungal infection; 14 possible, 15 probable, and 2 proven. Fifty-two (29%) patients died prior to starting their remission induction therapy. Induction mortality in our cohort is 40%. Primary induction failure and primary refractory disease were noted in twenty (18%), and 5 (4%) patients respectively. Only 1 patient was able to get all three high dose cytarabine (HIDAC) consolidations on time. Median time to first HIDAC was 39.5 days (range, 28-91). Of 83 patients who were candidates for consolidative allogeneic hematopoietic cell transplantation (HCT), only ten (12%) patients were able to get transplanted. Median time to HCT from CR1 was 3.8 months (range, 1.89-12.8). The median event free survival (EFS) was 1.7 months (95%CI, 1.03-2.5) and median overall survival was 2.5 months (95%CI, 1.6-3.6). The median EFS in favourable risk, intermediate risk and adverse risk AML was 3.6 months, 3.7 months, and 3.4 months respectively. Likewise the median OS was 8.8 months, 11.8 months and 7.4 months in the three risk strata respectively. **Conclusions:** Outcomes of AML treatment in our cohort are discordant with that reported from the West. Our study identifies various challenges in treating AML in resource-constraint setting. Strategies need to be formulated to overcome these challenges. Research Sponsor: None.

Baseline characteristics.

Characteristic	No of patients (%)
Age, years (median)	
< 19	34 (19%)
19 – 60	127 (70%)
> 60	20 (11%)
Sex	
Males	107 (59%)
ELN 2017 risk stratification	
Favourable risk	36 (21%)
Intermediate risk	67 (39%)
Adverse risk	16 (9%)
Unknown	52 (31%)
Hyperleucocytosis at presentation	42 (23%)
Baseline TLS	18 (10%)
Remission induction therapy given	122 (67%)
Conventional chemotherapy	89 (73%)
3 + 7	86 (70%)
3 + 7 plus TKI	3 (2.5%)
Palliative	24 (20%)
Azacytidine	16 (13%)
Low dose cytosar	4 (3%)
Azacytidine plus venetoclax	4 (3%)
Hybrid regimens	6 (5%)
Azacytidine followed by 3+7	5 (4%)
Low dose cytosar followed by azacytidine	1 (1%)

7015 **Poster Discussion Session**

Navitoclax plus ruxolitinib in JAK inhibitor-naive patients with myelofibrosis: Preliminary safety and efficacy in a multicenter, open-label phase 2 study.

First Author: Francesco Passamonti, Department of Medicine and Surgery, University of Insubria, Varese, Italy

Background: Ruxolitinib (RUX), a Janus kinase (JAK) 1/2 inhibitor, is the current standard of care for patients (pts) with myelofibrosis (MF) that improves splenomegaly and disease symptoms with limited impact on disease biology. Many pts lose response over time, highlighting an unmet need for novel therapies. Navitoclax (NAV) is an oral, small-molecule inhibitor of BCL-X_L and BCL-2 that has a synergistic effect when used in combination with JAK inhibitors to enhance apoptosis. This ongoing, open-label, multicenter, phase 2 trial (NCT03222609) is evaluating the efficacy and safety of NAV with/without RUX in pts with MF. Here, we report results from JAK inhibitor-naïve pts treated with NAV+RUX. **Methods:** Enrolled pts had primary or secondary MF with splenomegaly (DIPSS ≥INT-1) and did not receive prior JAK-2 therapy or bromodomain and extraterminal motif (BET) inhibitors. Pts initiated NAV at 100 mg QD or 200 mg QD if baseline (BL) platelet count was $\leq 150 \times 10^9$/L or $>150 \times 10^9$/L, respectively. RUX was given BID with starting dose based on BL platelet count per local label. The primary endpoint was spleen volume reduction of ≥35% (SVR_{35}) from BL at wk 24. Key secondary endpoints were ≥50% reduction in total symptom score (TSS_{50}), bone marrow (BM) fibrosis reduction, and anemia response. Adverse events (AEs) were monitored throughout the study. **Results:** As of Oct 04, 2021, 32 pts received NAV+RUX. Median duration of f/u was 6.1 (range, 1.9 18.6) mos. 28 (88%) pts received NAV 200 mg and 4 (13%) received 100 mg OD. Median age was 69 (44 83) yrs, and median spleen volume was 1889.08 cm^3 (645.6 7339.6). Median NAV and RUX exposures were 24.1 (5.1 80.9) and 20.1 (0.1 80.1) wks, respectively. 31 (97%) pts reported ≥1 AE (Grade ≥3 AEs, 25 [78%]; serious AEs, 6 [19%]). Most common Grade ≥3 AEs were anemia (34%), thrombocytopenia (31%), and neutropenia (19%). 3 (9%) and 2 (6%) pts reported an AE leading to NAV and RUX discontinuation, respectively, and 2 (6%; 1 PD, 1 cardiac disorder unrelated to NAV) AEs led to death ≤30 days after last NAV dose. SVR_{35} was achieved by 52% of evaluable pts at wk 24 (SVR_{35} in INT-2, 50%; HR, 33%) and by 76% at any time on treatment (Table). Median time to first SVR_{35} was 12.1 (11 47) wks. **Conclusions:** The combination of NAV+RUX was well tolerated and demonstrated early and robust reductions in spleen volume, anemia, and BM fibrosis in pts without prior JAK-2 inhibitor exposure. SVR_{35}, TSS_{50}, and BM fibrosis improved over time. Clinical trial information: NCT03222609. Research Sponsor: AbbVie.

Key endpoints.

	NAV+RUX n/N (%)
SVR_{35} at wk 24	11/21 (52)
SVR_{35} at any time post BL	16/21 (76)
TSS_{50} from baseline to wk 24	5/16 (31)
TSS_{50} at any time post BL	9/16 (56)
Total anemia response[a]	6/11 (55)
Reduction in bone marrow fibrosis grade from BL by ≥1grade at any time post BL	6/20 (30)

BL, baseline [a]Total anemia response = transfusion independence (TI) in pts with BL Hb<10 g/dl with Hb increase ≥ 2g/dl + TI in those who were transfusion-dependent at BL.

7016 **Poster Discussion Session**

Phase 1/2a study of the IRAK4 inhibitor CA-4948 as monotherapy or in combination with azacitidine or venetoclax in patients with relapsed/refractory (R/R) acute myeloid leukemia or lyelodysplastic syndrome.

First Author: Guillermo Garcia-Manero, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: CA-4948 is a novel oral inhibitor of interleukin-1 receptor-associated kinase 4 (IRAK4) and FLT3. IRAK4 is critical in triggering inflammation, oncogenesis, and survival of cancer cells. Genetic mutations in the splicing factors *SF3B1* and *U2AF1* drive overexpression of a highly active long isoform of IRAK4 and have been associated with disease progression and poor prognosis of high-risk myelodysplastic syndrome (HR-MDS) and acute myeloid leukemia (AML). **Methods:** This is an open-label, phase 1/2a dose escalation and cohort expansion trial (NCT04278768). In phase 1 Dose Escalation, patients with R/R AML or HR-MDS are treated with CA-4948 monotherapy. Phase 1b includes 2 arms of combination therapy: CA-4948 + azacitidine (AZA) and CA-4948 + venetoclax (VEN). The primary objectives of this study are to assess the safety, clinical activity, and identify the Recommended Phase 2 Dose (RP2D) of CA-4948 as monotherapy or in combination with AZA or VEN in R/R AML or HR-MDS. The Phase 2a Dose Expansion includes patients for CA-4948 monotherapy: R/R AML with *FLT3* mutation, or AML and HR-MDS R/R to HMA with *U2AF1* or *SF3B1* mutations. **Results:** As of December 16th, 2021, 49 patients have been treated in the phase 1 portion, of whom 43 started by September 30th, allowing 2 on-study disease assessments. The median number of prior therapies was 2 (range 1-5). Four monotherapy dose levels of CA-4948 were tested (200 to 500 mg orally BID). No dose-limiting toxicities were observed at 200 mg and 300 mg BID. No Grade 4 or 5 treatment-related AEs (TRAEs) were reported, and all the TRAEs were manageable. Reversible, manageable Grade 3 rhabdomyolysis occurred in 1/26 (4%) patients at 300 mg BID, 2/17 (12%) at 400 mg BID, and 1/3 (33%) at 500 mg BID. RP2D was determined as 300 mg BID. Of 43 patients starting before Sept 30th, 2021, 14 had *SF3B1*, *U2AF1* or *FLT3* mutations and demonstrated more promising efficacy. In the 5 evaluable AML patients with spliceosome mutations, 40% reached CR/CRh (1 CR, 1 CRh), both with study duration >6 months. In the 7 spliceosome-mutated HR-MDS patients, 57% reached marrow CR, including 1 with RBC transfusion independence and 1 proceeding to HSCT. One of the three *FLT3*-mutated AML reached CR, and 2 became *FLT3*-negative. Among the 29 patients without *SF3B1/U2AF1/FLT3* mutations, 1 reached CR and 2 PR. Phase 1b and Phase 2a are ongoing. RNA-seq on selected samples showed decrease in relative expression of IRAK4-long isoforms with response to CA-4948. **Conclusions:** CA-4948 is well tolerated and effective in heavily pretreated AML and HR-MDS patients, especially in those with *U2AF1/SF3B1/FLT3* mutations. No dose-limiting myelosuppression was reported, suggesting CA-4948 may be a candidate for combination therapy. Accrual of Phases 1b and 2a is ongoing. Clinical trial information: 04278768. Research Sponsor: Curis.

7017 **Poster Discussion Session**

Magrolimab in combination with azacitidine for untreated higher-risk myelodysplastic syndromes (HR-MDS): 5F9005 phase 1b study results.

First Author: David Andrew Sallman, Moffitt Cancer Center, Tampa, FL

Background: Magrolimab is a monoclonal antibody that blocks CD47, a "don't eat me" signal overexpressed on cancer cells. CD47 blockade by magrolimab induces macrophage-mediated phagocytosis of tumor cells and is synergistic with azacitidine (AZA) via upregulation of "eat me" signals. Here we report final Phase 1b data in patients (pts) with untreated HR-MDS (NCT03248479). **Methods:** Pts with previously untreated intermediate-/high-/very high-risk MDS per IPSS-R received magrolimab IV as a priming dose (1 mg/kg) followed by ramp-up to a 30 mg/kg weekly or Q2W maintenance dose. AZA 75 mg/m^2 was administered IV or SC on Days 1–7 of each 28-day cycle. Primary endpoints were safety/tolerability and complete remission (CR) rate. **Results:** 95 pts (median age 69 years [range 28, 91]) were treated. IPSS-R risk was intermediate, high, or very high in 27%, 52%, and 21%, respectively. MDS was therapy-related in 22%; 26% (n=25) had a *TP53* mutation and 62% had poor-risk cytogenetics (27% complex). Median (range) number of cycles was 6 (1, 27). The most common TEAEs included constipation (68%), thrombocytopenia (55%), anemia (52%), neutropenia (47%), nausea (46%), and diarrhea (44%). The most common Grade 3/4 TEAEs included anemia (47%), neutropenia (46%), thrombocytopenia (46%), and WBC count decreased (30%). 6 pts discontinued treatment due to AEs. 60-day mortality was 2%. Median Hb change from baseline (BL) at first post-dose sample was –0.7 g/dL (range –3.1, +2.4). CR and objective response (OR) rates were 33% and 75% with 31% of evaluable OR pts with abnormal cytogenetics at BL having cytogenetic CR. Median time to first OR, duration of CR (DCR), duration of OR, and PFS were 1.9, 11.1, 9.8, and 11.6 mos. OS rates at 12 and 24 mos were 75% and 52%, respectively (median NR with 17.1 mos follow-up for OS). For patients evaluated with sequential WES with a VAF cutoff of 5%, 3 of 3 pts with *TP53* mutation who achieved CR had TP53 VAF <5% by C5D1. Favorable outcomes were observed in both *TP53* mutant (40% CR, median OS 16.3 months) and wildtype pts (31% CR, median OS NR; Table). **Conclusions:** Magrolimab+AZA was well tolerated with promising efficacy in pts with untreated HR-MDS including those with *TP53*-mut and *TP53*-wt disease. A Phase 3 trial of magrolimab/placebo+AZA (ENHANCE: NCT04313881) is ongoing. Clinical trial information: NCT03248479. Research Sponsor: Gilead Sciences, Inc.

Outcome	All N=95*	*TP53*-wt MDS N=61	*TP53*-mut MDS N=25
Objective response rate, %†	75	79	68
CR, % (95% CI)	33 (23, 43)	31 (20, 44)	40 (21, 61)
Marrow CR, %	32	38	20
SD w/HI, %	11	10	8
DCR, median (95% CI) mos	11.1 (7.6, 13.4)	12.9 (8.0, NR)	7.6 (3.1, 13.4)
Marrow CR with HI/Any HI, %	17/59	20/61	12/56
Converted to RBC transfusion independence, %	14	10	24
PFS, median (95% CI) mos	11.6 (9.0, 14.0)	11.8 (8.8, 16.6)	11.0 (6.3, 12.8)
OS, median (95% CI) mos	NR (16.3, NR)	NR (21.3, NR)	16.3 (10.8, NR)

*9 pts included in all pts had missing TP53 status. †Defined as CR+ PR + marrow CR + SD w/HI. HI, hematologic improvement; NR, not reached; SD, stable disease.

7018 **Poster Discussion Session**

A phase Ib/II study of ivosidenib with venetoclax +/- azacitidine in IDH1-mutated hematologic malignancies.

First Author: Curtis Andrew Lachowiez, M.D. Anderson Cancer Center, Houston, TX

Background: Isocitrate dehydrogenase-1 mutations (*IDH1*$^+$) result in production of the oncometabolite 2-hydroxyglutarate, arrested differentiation, and increased dependence on the anti-apoptotic protein BCL-2, enhancing susceptibility to the BCL-2 inhibitor venetoclax (VEN). Herein, we report the completed P1b portion of the P1b/II study combining the IDH1 inhibitor ivosidenib (IVO; 500 mg PO daily D15-continous) with VEN (D1-14), with or without azacitidine (AZA; 75mg/m^2 D1-7 every 28 days). **Methods:** Eligible patients age 18 with *IDH1*$^+$ MDS, newly diagnosed (ND: de novo and secondary/treated secondary AML) or relapsed/refractory (R/R) AML were enrolled into 4 dose levels (DL): DL1 (IVO+VEN 400 mg), DL2 (IVO+VEN 800 mg), DL3 (IVO+VEN 400 mg+AZA), DL4 (IVO+VEN 800 mg+AZA). Primary objectives included safety and tolerability, and IWG defined overall response (ORR: CR+CRi+CRh+PR+ MLFS). **Results:** 31 patients (DL1: 6, DL2: 6, DL3: 13, DL4: 6) enrolled with a median follow-up of 26 months. Median age was 67 years (range: 44-84). 71% had AML (ND: N = 14, R/R: N = 8), 29% (N = 9) had MDS. ELN risk was intermediate and adverse in 19% (N = 6) and 55% (N = 17). Median baseline *IDH1*$^+$ VAF was 23% (5%-48%). Median time on study was 6.4 (range: 4 -not reached [NR]) months. The ORR was 94% (DL1: 67%, DL2-DL4: 100%); Composite CR (CRc: CR+CRi+CRh) was 87% (DL1: 67%, DL2: 100%, DL3: 85%, DL4: 100%). 63% of AML patients attained measurable residual disease negative CRc by multiparameter flow cytometry (ND-AML: 64%, R/R-AML: 60%). Addition of AZA increased MRD clearance in ND-AML compared to the doublet regimen (86% vs. 25%, p: 0.09). *IDH1*$^+$ mutation clearance by digital droplet PCR (sensitivity: 0.1-0.25%) was attained in 67% of patients (ND-AML: 83%, R/R-AML: 50%, MDS: 50%) following cycle 5. 35% of patients required dose reductions for cytopenias (DL2: 2 [33%], DL3: 6 [46%], DL4: 3 [50%]). Grade 3-5 adverse events (AEs) occurring in 10% of patients included febrile neutropenia (29%; one episode resulted in death in a R/R-AML patient relapsing on study) and pneumonia (23%). AEs of special interest (AESI) included grade 3 tumor lysis syndrome in two patients (dose-limiting toxicity in one), and differentiation syndrome in 4 (G2: N = 2, G3: N = 2) patients. All AESIs were transient and reversible. Median EFS and OS were 36 and 42 months. 24-month OS was 71% (95% CI: 55-91; [ND-AML: 67%, R/R-AML: 50%, MDS: 100%]). MRD-negative CRc improved OS (median NR vs. 8 months, p: 0.002) in ND and R/R-AML. 100% of patients (N = 4) relapsing after *IDH1*$^+$ clearance demonstrated no *IDH1*$^+$ at relapse. Based on efficacy and toxicity, DL3 (IVO+-VEN400+AZA) was the recommended phase 2 dose. **Conclusions:** IVO+VEN +/- AZA is an effective treatment for *IDH1*$^+$ myeloid malignancies with an expected toxicity profile and notable efficacy across disease groups. Single-cell sequencing and CyTOF correlatives will also be presented. Phase 2 enrollment is ongoing. Clinical trial information: NCT03471260. Research Sponsor: V foundation Award, LLS Career Scholar Award, Conquer Cancer Foundation of the American Society of Clinical Oncology.

7019 **Poster Discussion Session**

Molecular characterization of clinical response in patients with newly diagnosed acute myeloid leukemia treated with ivosidenib + azacitidine compared to placebo + azacitidine.

First Author: Stéphane De Botton, Institut Gustave Roussy, Villejuif, France

Background: Acute myeloid leukemia (AML) is a disease with a dynamic mutational landscape; 6–10% of patients (pts) have somatic mutations in isocitrate dehydrogenase 1 (*IDH1),* which can drive oncogenesis. Ivosidenib (IVO) is a potent oral targeted inhibitor of mutant IDH1 (mIDH1). IVO 500 mg QD + azacitidine (AZA) 75 mg/m^2 SC or IV for 7 days in 28-day cycles was shown to significantly improve event-free survival (HR = 0.33 [95% CI 0.16, 0.69], p = 0.0011), median overall survival (24.0 vs 7.9 months), and complete remission + partial hematologic recovery rates (CR/CRh; 52.8% vs 17.6%) vs placebo (PBO) + AZA in the double-blind phase 3 AGILE study (NCT03173248) in pts with newly diagnosed *IDH1*-mutated AML (ND-AML). *IDH1*-mutation clearance (*IDH1*-MC) and baseline co-mutation analysis from AGILE is reported. **Methods:** Genomic DNA from bone marrow mononuclear cells (BMMCs) or peripheral blood mononuclear cells (PBMCs), and/or bone marrow aspirate (BMA) were used for molecular studies. *IDH1*-MC analysis on BMMCs was performed by BEAMing digital PCR (limit of detection 0.02%-0.04%). BMA, BMMCs and PBMCs were utilized for co-mutational analysis by next-generation sequencing, ACE Extended Cancer Panel (detection limit 2%). **Results:** 146 pts were randomized: 72 to IVO+AZA; 74 to PBO+AZA. Median (range) baseline m*IDH1* variant allele frequency in BMMCs was 36.7% (3.1–50.5) in the IVO+AZA arm and 35.5% (3.0–48.6) in the PBO+AZA arm. Updated IDH1-MC data (October 2021) from 47 IVO+AZA and 32 PBO+AZA treated pts with at least 1 on-treatment sample demonstrated *IDH1*-MC in 21/35 (60%) IVO+AZA pts achieving CR/CRh vs 4/11 (36%) PBO+AZA pts. In CR/CRh pts with time points available after *IDH1*-MC, suppression of the m*IDH1* was durable and *IDH1*-MC maintained in all subsequent samples in 17/17 (100%) IVO+AZA treated pts and 1/3 (33%) PBO+AZA pts. Further analysis of baseline co-mutations on 120 pts (IVO+AZA: n = 58; PBO+AZA: n = 62) showed that *DNMT3A*, *SRSF2*, and *RUNX1* were the most frequent in both treatment arms. Importantly, comparison of CR/CRh and non CR/CRh responses by cohort did not identify any single gene or pathway associated with an inferior outcome in IVO+AZA pts compared to PBO+AZA pts ($p < 0.05$, Fisher's Exact test). Several genes (*DNMT3A*, *RUNX1*, *SRSF2*, *STAG2*) and pathways (Differentiation, Epigenetics, Splicing) were associated with improved outcomes with IVO+AZA, including the RTK pathway, which was previously reported to be associated with primary resistance to IVO monotherapy. Further analysis of patient subgroups, including R132 variants (i.e., R132C vs R132S), will be presented. **Conclusions:** These data suggest that improved clinical outcomes with IVO+AZA are associated with sustained clearance of the m*IDH1* clone including pts with disease that harbor mutations implicated in resistance to IVO monotherapy (e.g., with RTK pathway mutations). Clinical trial information: NCT03173248. Research Sponsor: Agios Pharmaceuticals, Inc. Servier Pharmaceuticals LLC has completed the acquisition of Agios' oncology business.

7020 **Poster Discussion Session**

Tolerability and efficacy of the first-in-class anti-CD47 antibody magrolimab combined with azacitidine in frontline TP53m AML patients: Phase 1b results.

First Author: Naval Guastad Daver, Department of Leukemia, MD Anderson Cancer Center, Houston, TX

Background: Magrolimab is a monoclonal antibody blocking CD47, a "don't eat me" signal overexpressed on cancer cells such as acute myeloid leukemia (AML). This blockade induces phagocytosis of tumor cells and is synergistic with azacitidine (AZA) via upregulation of "eat me" signals. We report data from a Phase 1b trial of magrolimab+AZA in frontline *TP53*-mutant (*TP53*m) AML. **Methods:** Patients (pts) with frontline AML not suitable for intensive chemotherapy received IV magrolimab starting with a priming dose (1 mg/kg) followed by ramp-up to 30 mg/kg QW or Q2W as maintenance dose. AZA 75 mg/m^2 was given IV or SC on Days 1–7 of each 28-day cycle. Primary endpoints were safety/tolerability and complete remission (CR) rate by ELN 2017 criteria. **Results:** 72 *TP53*m AML pts were treated (Table). Common all-grade TEAEs were constipation (52.8%), diarrhea (47.2%), febrile neutropenia (45.8%), nausea (43.1%), fatigue (37.5%), decreased appetite (37.5%), thrombocytopenia (31.9%), peripheral edema (30.6%), and cough (30.6%). Most common Grade 3+ TEAEs were febrile neutropenia (37.5%), anemia (29.2%; Grade 3, 26.4%; Grade 4, 2.8%), thrombocytopenia (29.2%), pneumonia (26.4%), and neutropenia (20.8%). Objective response rate (ORR) by intent-to-treat was 48.6% (33.3% CR, 8.3% CR with incomplete hematologic recovery [CRi] / CR with partial hematologic recovery [CRh], 1.4% morphologic leukemia-free state [MLFS], 5.6% partial response). Stable disease was reported in 16.7%, progressive disease (PD) in 5.6%. 30- and 60-day mortalities were 8.3% and 18.1%, respectively. Response assessment was unavailable in 4.2% who discontinued due to AEs and 6.9% due to other, prior to the C3D1 assessment. Median time to CR/CRi was 2.2 months (mos; range 1.7–7.2) and to CR was 3.0 mos (range 1.8–9.6). 45.2% (14/31) of evaluable CR/CRi/CRh/MLFS pts achieved negative MRD by flow cytometry (investigator reported). Of 24 CR patients, 8 had a longitudinal *TP53* VAF assessment, and 5/8 (63%) had VAF decreased to ≤5%. Treatment was stopped due to SCT in 9 pts (12.5%), PD 26 (36.1%), death 8 (11.1%), AE 13 (18.1%), and other 14 (19.4%). Median durations of CR and CR/CRi were 7.7 mos (95% CI: 4.7, 10.9) and 8.7 mos (95% CI: 5.3, 10.9), respectively. Median overall survival (OS) for the 72 pts was 10.8 mos (95% CI: 6.8, 12.8) with median follow up 8.3 mos. **Conclusions:** In high-risk frontline *TP53*m AML pts unsuitable for intensive chemotherapy, magrolimab+AZA showed durable responses and encouraging OS in a single-arm study. A Phase 3 trial in *TP53*m AML (ENHANCE-2; NCT04778397) of this combination vs standard of care is ongoing. Clinical trial information: NCT03248479. Research Sponsor: Gilead Sciences, Inc.

Baseline characteristics.

	N = 72
Age, years (range)	73 (31, 89)
ECOG	
0-1	61 (84.7%)
2	11 (15.3%)
ELN Cytogenetic risk	
Favorable	1 (1.4%)
Intermediate	2 (2.8%)
Adverse	57 (79.2%)
Unknown	12 (16.7%)
AML with MDS-related changes	34 (47.2%)
Therapy-related AML	15 (20.8%)

7021 **Poster Session**

Enrichment of high-risk innate immune cells in Hispanic and Black children with B-acute lymphoblastic leukemia.

First Author: Julie R. Gilbert, Aflac Cancer and Blood Disorders Center, Emory University and Children's Healthcare of Atlanta, Atlanta, GA

Background: Black and Hispanic children with B-acute lymphoblastic leukemia (B-ALL) experience worse outcomes compared to their non-Hispanic white (NHW) counterparts. Immune-based therapies have improved the outcomes of children with B-ALL, however, impact of racial/ethnic background on immune microenvironment is less studied. **Methods:** BM from 61 children with newly diagnosed B-ALL(Hispanic = 21, Black = 17, NHW = 23) was obtained via the Aflac Biorepository. High-dimensional analysis was performed utilizing single cell mass cytometry with 61 markers to characterize T, NK and myeloid cells. Data was analyzed using Cytobank and high-dimensional visualization platforms such as ViSNE. Clinical data including self-reported race/ethnicity and NCI-risk classification were obtained for all samples. **Results:** Multidimensional analysis was carried out for each cell population to dissect race/ethnicity-associated differences. ViSNE clustering of NK cells identified 3 different NK populations, including a distinct population of mature CD57+ NK cells with Tbet^{hi}, HLADR^{hi}, granzymeB^{hi}, CD27- phenotype. The distribution of NK subsets was highly impacted by race/ethnicity. Hispanic (H) patients had higher proportions of CD57+ mature NK cells when compared with other groups, (40 ± 4% vs 33 ± 2%; p = 0.03) with pronounced differences apparent within standard risk (SR) patients. H-SR had higher proportion of CD57+ NK cells compared to other SR patients (mean H-SR 43.4 ± 5.87% vs 26.3 ± 2.87% p = 0.0049). ViSNE clustering of myeloid cells identified 5 clusters based on patterns of cell surface markers, including a distinct CD11c+CD16+DR^{hi} inflammatory/non-classical myeloid population. Further analysis showed that NHW-SR patients have significantly lower proportions of CD16+DR+ myeloid cells compared to Hispanic, Black and NHW-HR patients (mean NHW-SR 3.67 ± 2.56% vs Others 10.8 ± 7.87% p = 0.0394). Notably, a phenotypically similar population has recently been implicated in leukemic progression in preclinical models (Witkowski et al, Cancer Cell 2020). In contrast to innate cells, T cell clusters were broadly comparable between different racial/ethnic groups. **Conclusions:** These studies provide detailed single-cell proteomic analysis and highlight the impact of racial/ethnic background on immune microenvironment in pediatric B-ALL. Our data identify differences in innate immunity with enrichment of high-risk immune-populations in Hispanic and Black children and depletion of inflammatory myeloid populations in NHW-SR children with B-ALL. These variations may contribute to the observed differences in outcomes and may impact application of immune therapies in racial/ethnic groups. Research Sponsor: Aflac Pilot Grant.

7022 **Poster Session**

Mutational landscape and clinical characterization of over 17,000 patients with myeloid malignancies using real-world data.

First Author: Taylor J. Jensen, Laboratory Corporation of America, Durham, NC

Background: Myeloid neoplasms represent a broad spectrum of hematological disorders for which somatic mutation status in key driver genes is important for diagnosis, prognosis and treatment. Here we summarize the findings from 17,181 clinical samples analyzed by a targeted next generation sequencing (NGS) laboratory developed test. Samples were analyzed comprehensively and as part of individual cohorts specific to acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and myeloproliferative neoplasms (MPN). **Methods:** Whole blood or bone marrow samples from patients with cause-for-testing for hematological symptoms were submitted for analysis by a referring clinician. DNA was extracted and assayed by a targeted, NGS panel to detect and report single nucleotide variants and small indels within 50 genes associated with myeloid malignancies and sequenced on Illumina DNA sequencers (Illumina, San Diego, CA). Results were reviewed, orthogonally confirmed unless previously validated, and reported by clinical laboratory directors. Disease status or symptoms were taken from test requisitions for each patient. **Results:** Overall, 34,581 Tier I, II, or III somatic variants were detected. The mean number of variants reported per patient was 1.98. This number increased with age ($p < 0.001$) and was highest in patients with AML. Mutations in genes associated with FDA-approved therapies (*FLT3*, *IDH1*, *IDH2*, *KIT*, and *JAK2*) were observed in 22.3% (3836) patients while 28.0% of samples had mutations considered diagnostically relevant by the WHO. Clinical trials are in progress for therapies targeting *TP53*, *NPM1*, and *CEBPA* mutations and were observed in 12.5% (2144) of samples. *FLT3, NPM1* and *RUNX1* mutation which are diagnostic for AML were found in 29.0% (646 of 2225) of AML samples. Pair-wise mutation analyses found 21 mutually exclusive pairs including between genes associated with RNA splicing (*SF3B1*, *SRSF2* and *U2AF1*; OR < 0.29, $p < 0.001$) suggesting possible candidates for targeted therapy. The clinically favorable co-mutation of *NPM1* with *FLT3* internal tandem duplicate was significantly enriched (OR = 7.4, $p < 0.001$) in the AML population. Co-occurrence of *ASXL1* with *RUNX1* mutations which independently confer adverse risk was also enriched in AML (OR = 3.9, $p < 0.001$). Some patients (1021; 6.3%) were tested at multiple time-points with 48.8% showing loss or gain of a mutation between sample dates, potentially the result of tumor evolution and/or therapeutic intervention. **Conclusions:** This study shows that parallel testing of multiple genes in addition to the canonical driver mutations encompasses the mutations contributing to the etiology of these diseases. Despite the breadth of different mutations observed for myeloid neoplasms, consistent patterns are routinely observed that can help the clinician tailor the treatment and chart the progression of these diseases for each patient. Research Sponsor: Laboratory Corporation of America.

7023 **Poster Session**

Updated efficacy and safety report of a phase I trial of donor-derived CD7 CAR T cells for T-cell acute lymphoblastic leukemia.

First Author: Jing Pan, State Key Laboratory of Experimental Hematology, Department of Hematology, Beijing Boren Hospital, Beijing, China

Background: Results of a phase I trial of donor-derived CD7 chimeric antigen receptor (CAR) T cells for relapsed or refractory T-cell acute lymphoblastic leukemia (r/r T-ALL) (Pan et al. *J Clin Oncol* 2021;39:3340-3351) have been reported previously, and are updated now. **Methods:** The target dose is 1×10^6 (±30%) CAR T cells per kg of body weight. Patients with prior stem cell transplantation (SCT) received CAR T cells from prior SCT donors, while patients without SCT history received CAR T cells from new donors who also provided stem cells for transplantation post CAR T therapy. The primary endpoint was safety with efficacy secondary. Survival status were continuously followed up while severe adverse events (SAEs) were recorded until receiving other anti-leukemia therapy. **Results:** Nineteen (95%) of twenty enrolled patients responded and were followed up with a median time of 15.8 months (range 13-18.3) until Feb, 14th, 2022. Short-term adverse events included grade 3 or higher cytokine release syndrome (10%) and grade 1-2 graft-versus-host disease (GVHD, 60%), which were all reversible. Six late-onset (> 30 days post-infusion) severe adverse events (SAEs) occurred in 5 responders. Two had been reported previously. Four SAEs were newly observed, including a grade 4 intestinal GVHD at month 11 and a grade 5 pneumonia at month 12.3 in one patient, a grade 5 *Pseudomonas Aeruginosa* pneumonia at month 8.7 in one patient, and a grade 3 cytomegalovirus (CMV) encephalitis at month 11 which recovered at month 13.3 in another patient. All severe infections occurred in patients with no further therapy, and the total T cells in them reached a median count of 300.03/μL (range 121.46-512.83), which were substantially lower than normal levels despite steadily increasing. The objective response and complete remission rate was 95% and 85% at day 30 post-infusion. Of 19 responders that were followed up, two (11%) withdrew for other therapy at day 55 and 271 respectively. Of 10 (53%) patients who received no further therapy, all had continuously detectable CAR T cells until the last visit, three remained in remission, three had a relapse (one CD7+, and two CD7-), and four died of infection; Seven (37%) patients proceeded to SCT and no CAR T cells were detectable after SCT, and among them two remained in remission, four had a relapse (three CD7+, and one CD7-), and one died of transplant-related mortality. Patients relapsed at a median time of 6 (range 4-10.9) months. The one-year progressive-free survival (PFS) and overall survival (OS) rates were 51.6% (95% CI, 24.7-78.4%) and 72.5% (95% CI, 51.9-93.0%). **Conclusions:** Donor-derived CD7 CAR T cell therapy showed encouraging activity in treating r/r T-ALL. Relapse emerges as major issues impeding long-term outcomes. CD7-negative relapse was commonly observed under CAR T cell surveillance. Late onset GVHD and infections may occur and should be carefully managed. Clinical trial information: ChiCTR2000034762. Research Sponsor: the National Key R&D program.

7024 **Poster Session**

Phase 1/2 study of SEL24/MEN1703, a first-in-class dual PIM/FLT3 kinase inhibitor, in patients with *IDH1*/*2*-mutated acute myeloid leukemia: The DIAMOND-01 trial.

First Author: Giovanni Martinelli, Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori" (IRST)IRCCS, Meldola, Italy

Background: Mutations in the FLT3 tyrosine kinase are the most frequent ones that occur in adults with acute myeloid leukemia (AML) and can co-occur with mutations in *IDH1* or *IDH2* (collectively *IDH*m) in up to 30% of cases. SEL24/MEN1703 is an orally available, dual PIM/FLT3 kinase inhibitor. Preliminary results from the phase 1/2 first-in-human DIAMOND-01 trial (NCT03008187) evaluating single-agent SEL24/MEN1703 showed activity in adults with relapsed/refractory (R/R) *IDH*m AML, where 3/8 *IDH*m patients (pts) responded. Here we report the first safety and efficacy results from an additional expansion cohort of the DIAMOND-01 trial in 20 pts with R/R *IDH*m AML. **Methods:** Pts with IDHm R/R AML and no standard therapeutic options were eligible. The recommended dose of 125 mg SEL24/MEN1703 was given orally, once daily for 14 days over a 21-day cycle until disease progression or unacceptable toxicity. The primary endpoint was safety; adverse events (AEs) were graded according to NCI-CTCAE v4.03. The secondary endpoint was anti-leukemic activity including overall response rates (ORR). **Results:** As of 10 Jan 2022, 14 pts were enrolled in the IDHm cohort. Median age was 68 years (range 37-79). Four pts had AML secondary to myelodysplastic syndrome and 7 pts had intermediate cytogenetic risk. The median number of prior lines was 2 (range 1-3). Seven pts had IDH2, 1 had IDH1/2, and 4 had IDH1 mutations. Concomitant mutations in FLT3/ITD were detected in 2 pts. Median duration of treatment was 2 cycles (range 1-8). Safety data (N = 12) showed that serious treatment-emergent AEs (TEAEs; ≥5%) were pneumonia (33%), and skin infection and gastroenteritis clostridial (8% each). These were all unrelated to study drug. Drug-related TEAEs were liver injury, overdose, and hyponatremia (8% each). The drug-related liver injury occurred in a pt who was concomitantly receiving other drugs with known hepatotoxic potential. Grade ≥3 TEAEs (≥10%) were pneumonia (33%) and asthenia (17%), both unrelated to study drug. No differentiation syndrome was observed. Of the 7 pts who completed ≥1 treatment cycle and had ≥1 post-baseline assessment or clear disease progression, ORR was 28.6%; 1 pt achieved CRi at cycle (C) 3 and underwent hematopoietic stem cell transplant, 1 pt had PR at C4 (confirmed at C7 and still on treatment), 4 had disease progression, 1 discontinued for AE not drug-related. Among the 7 remaining pts, 3 discontinued before completion of C1 without progression or response, while 4 pts were ongoing and have not yet had any post-baseline assessment. **Conclusions:** Preliminary results in the IDHm cohort confirm that SEL24/MEN1703, a first in class, orally available, dual PIM/FLT3 inhibitor, has a manageable safety profile and single-agent activity in pts with R/R IDHm AML. Updated results will be presented at the congress. Clinical trial information: NCT03008187. Research Sponsor: Menarini Ricerche SpA.

7025 **Poster Session**

BTX-1188, a first-in-class dual degrader of GSPT1 and IKZF1/3, for treatment of acute myeloid leukemia (AML) and solid tumors.

First Author: Aparajita Hoskote Chourasia, BioTheryX, Inc., San Diego, CA

Background: BTX-1188 is a first-in-class oral molecular glue that degrades GSPT1 and IKZF1/3 and is currently in phase 1 clinical trials for treatment of hematologic and solid malignancies. Targeted protein degradation of cereblon neosubstrates is clinically validated in the treatment (tx) of hematologic malignancies (Lu 2014, Zou 2020). **Methods:** Cell viability in BTX-1188-treated cells and patient samples was measured by CellTiter-Glo 2.0 assay (Promega). Substrate degradation and apoptosis profiles were analyzed by immunoblots of protein lysates from cells treated with DMSO or BTX-1188. Vehicle, or 30 or 40 mg/kg IP BTX-1188, was used in athymic nude mice AML xenograft models. **Results:** BTX-1188 is a rapid, deep, and potent degrader of GSPT1 and IKZF1/3 and inhibitor of Myc in several cancer cell lines (Table). Proteomics and immunoblot analysis of AML cell line, MV-4-11, shows significant degradation of GSPT1 and IKZF1 after 2 h tx with 100 nM BTX-1188 ($P<1x10^{-5}$) and 6 h tx with 3 nM BTX-1188 (>90% of GSPT1), respectively, indicating rapid and potent neosubstrate degradation. BTX-1188 also durably degrades GSPT1 where tx with 30 nM for 6 h followed by washout maintains significantly lower levels of GSPT1 and sustained apoptosis for up to 24 h. Owing to IKZF1/3 degradation, BTX-1188 has immunomodulatory properties as seen by inhibition of proinflammatory cytokines (IL-1β, IL-6, TNFα) and induction of IL-2 by LPS and αCD3-stimulated PBMCs, respectively. This approach is expected to improve clinical outcomes and reduce toxicities associated with pure GSPT1 degradation (CC-90009), thus expanding the therapeutic window of BTX-1188. Functionally, BTX-1188 is cytotoxic in various cancer cell lines such as Myc-driven lines (IC_{50} range: 0.5-10 nM) and primary human AML patient samples (IC_{50} range: 0.4-1.5 nM), including relapsed/refractory-, cytarabine- and venetoclax-resistant samples. The durability of GSPT1 degradation and sustained apoptosis in response to BTX-1188 tx is further reflected in in vivo efficacy models where daily or intermittent dosing of BTX-1188 results in potent and sustained antitumor activity. **Conclusions:** These preclinical data show that BTX-1188 is a promising drug candidate for AML and other tumor types. Its immunomodulatory properties owing to IKZF1/3 degradation may prevent systemic inflammatory dose-limiting toxicities associated with pure GSPT1 degradation (Uy 2019). BTX-1188 has entered phase 1 clinical studies for advanced solid tumors and AML. DC_{50} (nM) or inhibitory concentration (nM) of BTX-1188 at 6 h of Tx. Research Sponsor: BioTheryX, Inc.

Human cell line	GSPT1	IKZF1	IKZF3	c-Myc	n-Myc
DOHH-2 (lymphoma)	0.2	1	1	1	–
ABC-1 (NSCLC)	2	–	–	NI	11
NCI-H1155 (NSCLC)	2	–	–	NI	10–30
KNS-42 (glioma)	4	–	–	NI	3
SU-DHL-2 (DLBCL)	3	–	–	28	–
Daudi (Burkitt lymphoma)	2	–	–	~12–15	–

DC_{50}, degradation concentration; DLBCL, diffuse large B cell lymphoma; NI, no impact; NSCLC, non-small cell lung cancer.

7026 **Poster Session**

Acute myeloid leukemia with *KMT2Ar* and association with risk of bleeding and early mortality.

First Author: Daniel Nguyen, University of Texas Health Science Center McGovern Medical School, Houston, TX

Background: Acute myeloid leukemia (AML) with rearrangement of *KMT2A* is characterized by chemotherapy resistance and high rates of relapse. However, additional causes of treatment failure or early mortality have not been well-defined in this entity. **Methods:** In a retrospective analysis, we compared causes and rates of early mortality following induction treatment between a cohort of adults with *KMT2Ar* AML (N=172) and an age-matched cohort of patients (pts) with normal karyotype (NK) AML (N=522). **Results:** The 30 and 60-day (60d) mortality in pts with *KMT2Ar* AML were significantly higher compared to those with NK AML, with rates of 10% (17/172 pts) and 15% (26/172 pts) in KMT2Ar AML vs 4% (20/522 pts) and 7% (38/522 pts) in NK AML, respectively (P=0.004). Among those who died within 60d, the most common contributing cause in *KMT2Ar* was respiratory failure without a clear infectious etiology in 38% (10/26 pts) vs 11% (4/38 pts) in NK AML (P=0.01). We found 42% (11/26 pts) with *KMT2Ar* AML who died within 60d were either diagnosed with or had high clinical suspicion for diffuse alveolar hemorrhage (DAH) that warranted empiric therapy vs 18% (7/38 pts) with NK AML (P=0.05). Given the high occurrence of DAH in *KMT2Ar* AML, we set out to quantify bleeding events and recorded major and minor bleeds as defined by the International Society of Thrombosis and Haemostasis. We found 65% (17/26 pts) with *KMT2Ar* AML had at least one bleeding event vs 32% (12/38 pts) with NK AML (P=0.01). There was a significantly higher frequent occurrence of major bleeds (rate ratio=6.22; P=0.005) and total bleeding events (rate ratio=4.5; P=0.001) in *KMT2Ar* AML vs NK AML. *KMT2Ar* was associated with disseminated intravascular coagulopathy (DIC), as 93% of evaluable pts (14/15 pts) vs 54% (7/13 pts) in NK AML had overt DIC before death. Longitudinal trajectories of DIC parameters of pts who died within 60d showed significantly higher prothrombin time levels (P=0.008) in *KMT2Ar*. In a multivariate analysis, *KMT2Ar* and a monocytic phenotypic were the only independent predictors of any bleeding event in pts who died within 60d (OR 3.5, 95% CI 1.4-10.4, P=0.03; OR 3.2, 95% CI 1.1-9.4, P=0.04). **Conclusions:** *KMT2Ar* AML is associated with higher early mortality and an increased risk of bleeding and coagulopathy compared with NK AML. Early recognition and aggressive management of DIC and coagulopathy are important considerations that could mitigate the risk of death during induction treatment. Research Sponsor: None.

Characteristics of bleeding events.

Characteristic	*KMT2Ar*	Normal Karyotype	*P*
60-day mortality	26/172 (15%)	38/522 (7%)	0.004
Respiratory failure, non-infectious	10/26 (38%)	4/38 (11%)	0.01
Diffuse alveolar hemorrhage	11/26 (42%)	7/38 (18%)	0.05
Pts with ≥1 bleeding event	17/26 (65%)	12/38 (32%)	0.01
Evaluable pts with overt DIC before death	14/15 (93%)	7/13 (54%)	0.03
Major bleeding events[a]	10	6	0.005
Total bleeding events[a]	24	14	0.001

[a] Proportional rates for recurrent events.

7027 **Poster Session**

A phase 1b/2 study of TP-0903 and decitabine targeting mutant TP53 and/or complex karyotype in patients with untreated acute myeloid leukemia ≥ age 60 years: Phase 1b interim results.

First Author: Alice S. Mims, The Ohio State University Comprehensive Cancer Center, Columbus, OH

Background: TP-0903 is a multi-kinase inhibitor designed to target AXL, a receptor tyrosine kinase, and also inhibits cell cycle regulators such as Chk1/2 and other AML associated kinases. TP-0903 has shown prior anti-tumor activity at a safe dose in solid tumors. In pre-clinical AML studies, TP-0903 shows potent cytotoxicity in *TP53* mutant (*TP53*m) AML cell lines, an adverse prognostic genomic sub-group of AML. TP-0903 also had synergistic activity with decitabine (dec) in *TP53*m AML and prolonged survival in xenograft and genetically engineered mouse models. We report here on the initial safety and clinical results from the Leukemia and Lymphoma Society's ongoing Beat AML phase 1b/2 (Ph1b/2) trial of TP-0903 in combination with dec (ClinicalTrials.gov NCT03013998). **Methods:** Newly diagnosed AML pts ≥60 years with *TP53*m and/or complex karyotype (≥3 abnormalities) were selected for a Ph1b/2 dose escalation study of TP-0903 combined with dec. Seven Ph1b pts were given TP-0903 every 28-day cycle from days 1-21 (Dose level (DL) 1 = 37 mg/day) and dec IV days 1-10 (20 mg/m^2). A standard 3+3 design was used to evaluate the safety and tolerability. Nine additional patients enrolled onto Ph2 at DL1, but further assessments of safety, pharmacokinetics (PK) and correlative data was used to update the final recommended Ph2 dose (RP2D) of TP-0903 to DL-1 (25 mg/day) with dec. **Results:** At data cutoff (10Jan2022), 16 total pts were accrued. Ph1b treated 7 pts at DL1, 6 were DLT evaluable, and no DLTs were observed. Ph2 enrolled and treated 9 pts at DL1 before concerns of delayed count recovery led to the reduction of the Ph2 dose of TP-0903 to DL-1 (25 mg/day). For all 16 pts treated at DL1, 1 pt achieved CR, 4 pts CRh, and 1 pt CRi, for a composite CR (CR/CRh/CRi) rate of 37.5% (95% CI, 15.2-64.6), with 4 pts achieving MRD negativity by central flow cytometry. For the remaining 10 pts, 1 pt achieved MLFS (6%), 6 pts had stable disease (37.5%), 1 pt had treatment failure (6%), and 2 pts were not evaluable (12.5%) due to withdrawal of consent and death from early disease progression. Two pts (1 CR and 1 CRh) proceeded to stem cell transplantation. The most common grade 3 and above treatment-related AEs include decreased neutrophil counts (37.5%), platelet counts (31.3%), and anemia (18.8%). Finally, PK and correlative data analysis looking at soluble Axl and Gas6 also supported reduction to DL-1. **Conclusions:** Initial results with DL1 suggest that TP-0903/dec shows preliminary clinical activity in the prognostically poor *TP53*m/complex karyotype AML sub-group, with 4 pts achieving MRD negative status out of 6 patients who achieved a CR/CRh/CRi (66%). After further patients were treated on DL1, the toxicity profile and correlative data supported the de-escalation to DL-1 as the RP2D. The Ph2 study is ongoing to determine the clinical activity of this new RP2D (DL-1). Clinical trial information: NCT03013998. Research Sponsor: Sumitomo Dainippon Pharma Oncology, Leukemia & Lymphoma Society.

7028 **Poster Session**

Phase I study of donor-derived CD5 CAR T cells in patients with relapsed or refractory T-cell acute lymphoblastic leukemia. *First Author: Jing Pan, State Key Laboratory of Experimental Hematology, Department of Hematology, Beijing Boren Hospital, Beijing, China*

Background: Despite the manageable safety and encouraging efficacy of donor-derived CD7 chimeric antigen receptor (CAR) T cells in relapsed or refractory T-cell acute lymphoblastic leukemia (r/r T-ALL) (Pan et al. *J Clin Oncol* 2021;39:3340-3351), a considerable proportion of responding patients eventually relapsed with CD7 antigen loss. CAR T cells targeting another antigen, CD5, which is expressed on blasts of over 80% T-ALL cases, may be capable of treating these patients. Here we present early safety and efficacy results of a phase I trial of donor-derived CD5 CAR T cells in T-ALL. **Methods:** CD5 CAR T cells that resist fratricide by deletion of CD5 gene (Preclinical data in Dai et al. *Mol Ther* 2021;29:2707-2722) were manufactured. Patients with prior stem cell transplantation (SCT) (group A) received CAR T cells from prior SCT donors, while patients without SCT history (group B) received CAR T cells from new donors who also provided stem cells for transplantation post CAR T therapy. The trial using bayesian optimal interval phase I/II design to explore optimal biological dose (OBD) from the initial dose of 1×10^6 (±20%) CAR T cells/kg in each group. If manufactured cells were not sufficient, patients could be treated at a low dose of 5×10^5 (± 20%)/kg. The primary endpoint was safety with efficacy secondary. **Results:** Five patients who had CD7-negative relapsed after CD7 CAR therapy were enrolled and received prior SCT donor-derived CD5 CAR T cells between Oct 8th, 2021 and Dec 14th, 2021. Four patients were on initial dose level, while one patient was on low dose level. This early report has approved by the Data and Safety Monitoring Committee, and indicated the OBD in group A was 1×10^6 (±20%) /kg. No DLT occurred. Adverse events within 30 days included grade 3-4 hematologic toxicity in all (100%) which already existed before enrollment, grade 1-2 cytokine release syndrome in 4 (80%), grade 1 graft-versus-host disease in 1 (20%), grade 2 rash maculo-papular in 3 (60%). One patient developed late grade 5 epstein-barr virus infection accompanied by hemophagocytic lymphohistiocytosis at 2.7 months post-infusion. All five patients achieved complete remission at day 30, and remained MRD-negative with a median follow-up time of 2.7 (range, 1.8-4.1) months. In three patients, low level of CD7 CAR T cells were still detectable for one month post-infusion, but CD5 CAR T cells dominated and persisted well until last visit. Patient CD5-positive healthy T cells were depleted, while CD5-negative T cells increased to a median count of 133 (range, 13-299)/μl at one month, although they were still much lower than normal level. **Conclusions:** We report the safety and efficacy of donor-derived CD5 CAR T cells in r/r T-ALL. And the depletion of CD5-positive healthy T cells was commonly observed. Longer follow-up assessment is needed to determine the durable remission and the functional immune system reconstitution. Clinical trial information: NCT05032599. Research Sponsor: the National Key R&D program.

7029 **Poster Session**

Assessing eligibility for non-intensive chemotherapy (IC) randomized clinical trials (RCT) in patients (pts) with newly diagnosed (ND) AML from the Connect Myeloid Disease Registry. *First Author: Harry Paul Erba, Duke University, Durham, NC*

Background: Pts with AML in RCTs often do not reflect the population seen in clinical practice due to strict eligibility criteria. This study evaluated criteria from a recent RCT of non-IC against a broad cohort of real-world pts with AML from the Connect® Myeloid Disease Registry (NCT01688011). **Methods:** Pts were stratified into 3 groups based on the non-IC phase 3 VIALE-A trial eligibility criteria: 1) "eligible" pts who would have met all VIALE-A inclusion criteria; 2) "unfit" pts who would have been ineligible for VIALE-A due to ≥ 1 of the following: abnormal liver/kidney function, high ECOG, recent prior malignancy, comorbidities score ≥ 2 by ACE-27, hepatic grade ≥ 1, AIDS grade ≥ 1; 3) "fit" pts who would have been ineligible for VIALE-A because they would have qualified for IC (defined as: ≤ 74 y of age, low ECOG, no apparent cardiovascular/renal comorbidities, and did not meet any criteria in #2). Baseline characteristics were summarized by eligibility group. Overall survival (OS) by group was estimated using the Kaplan–Meier method. Induction regimens were categorized as IC (any regimens containing 7+3, MEC, CLAG, FLAG) or venetoclax (VEN)-based. Hazard ratios (HRs) for induction regimens among each group were estimated using Cox models adjusted for age, ELN risk, ECOG, frailty score, and comorbidity index. **Results:** Of 734 enrolled pts with AML (Dec 2021), most were male (61%) and white (84%); median age 71 y (range 55–97). Only 26% of pts (n = 192) were eligible for a non-IC RCT, 45% (n = 327) were ineligible due to unfitness, and 29% (n = 215) were ineligible due to overall fitness. The main reason for non-IC RCT ineligibility was high overall comorbidity grade (n = 265 [36%]). Fit pts intended to undergo transplant more often compared with unfit pts. Median OS for eligible, unfit, and fit pts were 14, 10, and 22 months, respectively. Among unfit pts, those receiving IC had significantly longer OS compared with pts receiving a VEN-based regimen (median OS 14 vs 6 months, respectively; HR: 0.51, 95% CI: 0.27–0.98, $P = 0.042$; Table). Eligible pts who received IC tended to have shorter median OS (13 months) vs pts who received VEN-based therapies (23 months; not sig.). **Conclusions:** The majority of pts with ND AML in the Registry would have been ineligible for a non-IC RCT due to being too fit or unfit. Pts ineligible for an RCT due to unfitness but who received IC maintained an OS benefit vs those receiving VEN-based therapies. This analysis suggests that non-IC RCTs may be excluding pts who appear unfit but can potentially tolerate IC and experience improved survival outcomes. Clinical trial information: NCT01688011. Research Sponsor: Bristol Myers Squibb.

Median OS for IC versus VEN-based therapy by RCT eligibility.

	1) Eligible		2) Unfit		3) Fit	
	ICn = 31	VEN-basedn = 27	ICn = 76	VEN-basedn = 33	ICn = 69	VEN-basedn = 10
Median OS, months	13	23	14	6	19	NE[a]
HR (95% CI)	1.45 (0.66–3.17)		0.51 (0.27–0.98)*		NE[a]	

*$P < 0.05$; [a]Not estimated due to small sample size.

7030 **Poster Session**

Safety and efficacy of casein kinase 1α and cyclin dependent kinase 7/9 inhibition in patients with relapsed or refractory AML: A first-in-human study of BTX-A51. *First Author: Brian Ball, City of Hope, Duarte, CA*

Background: Inactivation of p53 and overexpression of Mcl1 are common mechanisms that cancer cells use to evade apoptosis. BTX-A51 is a novel, oral, direct inhibitor of casein kinase 1α (CK1α) and cyclin dependent kinase 7 and 9 that robustly increases p53 protein levels via CK1α inhibition while preferentially decreasing super-enhancer transcription of *Myc and Mcl1,* enabling selective apoptosis of leukemia cells. Here, we report the interim results of the first-in-human (FIH) study of BTX-A51 in patients (pts) with R/R AML. **Methods:** The study utilizes a hybrid accelerated titration with single pt cohorts and a Bayesian optimal interval design in dose escalation. The primary objective is to determine the maximum tolerated dose and recommended Phase 2 dose (RP2D) of BTX-A51. Secondary objectives include evaluating the anti-leukemic activity, pharmacokinetics (PK), and pharmacodynamics (PD). **Results:** As of 25 January 2022, 30 pts (28 with AML; 2 with HR-MDS) enrolled at dose levels between 1 and 42 mg; 2 pts remain on treatment. Monotherapy doses between 1 and 42 mg were administered orally 3 days/week (wk) (3 wk in a 28-day cycle) and at 21 mg (4 wk in a 28-day cycle). Baseline characteristics include median age 75 years, median number of prior therapies 3, 97% received prior treatment with venetoclax, 97% had prior HMA, and 43% had prior induction failure. The most common treatment-emergent AEs (TEAEs) were hypokalemia, nausea, vomiting, diarrhea, and hypotension. The most common Grade 3 or higher TEAEs were anemia, febrile neutropenia, platelet count decreased, and hypokalemia. DLTs included grade 3 hepatic failure at the 42 mg dose in 1 pt and grade 3 alkaline phosphatase elevation in 1 pt at the 21 mg dose. All events resolved after holding study drug. Plasma PK of BTX-A51 was roughly dose-proportional between 1 and 42 mg with accumulation based on AUC between Day 1 and Day 5. Estimated half-life was between 18 and 55 hours. Among the 30 pts with R/R AML and MDS, CR/CRi rate was 10% (3/30) with 1 pt at the 11 mg and 2 pts at the 21 mg dose levels attaining CRi. Bone marrow (BM) blast reduction > 50% occurred in 4 patients including the 3 responders, all at the 11 and 21 mg dose levels. All 4 pts with > 50% BM blast reduction had RUNX1 mutations; 9 pt with RUNX1 enrolled in the trial. The median duration of response for pts achieving CR/CRi was approximately 1.5 month. Responses were not observed in MDS pts. PD data will be provided in the full presentation. Based on the clinical data from dose escalation, the RP2D is 21 mg administered 3 days/wk for 4 wk of a 28-day cycle. **Conclusions:** In this FIH study, monotherapy BTX-A51 demonstrated an acceptable safety profile and promising antileukemic activity in pts with heavily pretreated R/R AML. The 21 mg dose administered 3x/wk for 4 wk was identified as the RP2D. RUNX1 mutations were enriched among responders and pts attaining > 50% BM blast reduction. Clinical trial information: NCT04243785. Research Sponsor: None.

7031 **Poster Session**

Lower-intensity CPX-351 + venetoclax for patients with newly diagnosed AML who are unfit for intensive chemotherapy. *First Author: Geoffrey L. Uy, Washington University School of Medicine, St. Louis, MO*

Background: CPX-351 (US: Vyxeos; Europe: Vyxeos liposomal) is a dual-drug liposomal encapsulation of daunorubicin and cytarabine in a synergistic 1:5 molar ratio. CPX-351 is approved for newly diagnosed, therapy-related AML or AML with myelodysplasia-related changes in patients (pts) who are candidates for intensive chemotherapy (IC) and aged ≥1 year in the US and adults in Europe. However, the appropriate dosage of CPX-351 in pts unfit for IC may be different from the label dosage. Venetoclax (VEN; BCL-2 inhibitor) + low-dose cytarabine has demonstrated efficacy in unfit pts with AML, and drug synergism/additivity in preclinical studies provided a rationale for combining CPX-351 + VEN clinically. Our study evaluates the safety and efficacy of lower-intensity CPX-351 + VEN in adults with newly diagnosed AML who are unfit for IC. **Methods:** This is an ongoing, open-label, phase 1b study (NCT04038437). Pts who achieve at least partial remission after 1 or 2 cycles may receive up to 4 similar cycles in the dose-exploration phase (DEP) or up to 8 similar cycles in the expansion phase (EP). Pts are assessed for response (morphology, measurable residual disease [MRD]) and monitored for safety and survival. **Results:** The data include 31 pts enrolled by 9/15/2021, with a data cutoff of 12/2/2021: 4 pts in DEP at dose level 1 (CPX-351 20 units/m^2 on Days 1 and 3 + VEN 400 mg on Days 2 to 21 of each cycle), 7 pts in DEP at dose level 2 (CPX-351 40 units/m^2 + VEN 400 mg), and a total of 20 pts in DEP and EP at dose level 1b (CPX-351 30 units/m^2 + VEN 400 mg; established as the recommended phase 2 dose). Pts were unfit for IC based on age ≥75 y (n = 15) or health (ECOG PS of 2 to 3 and/or comorbidities [n = 16]). Median age was 74 y (range: 60, 90); 65% were male; 77% had *de novo* AML; 58% had poor-risk disease; and 23% had a *TP53* mutation. Nonhematologic treatment-emergent adverse events (TEAEs) in ≥20% of pts were diarrhea (26%), cough (23%), dyspnea (23%), and nausea (23%). Hematologic grade ≥3 TEAEs were reported in 17 (55%) pts; no nonhematologic grade ≥3 TEAE was reported in > 10% of pts. There were no deaths by Day 30; mortality at Day 60 was 13%, with deaths due to myocardial infarction unrelated to therapy (n = 1), worsening lung infection (n = 1), and disease progression (n = 2). Median (IQR) recovery times were 30 d (22, 34.5) to neutrophils ≥500/μL and 21 d (21, 27) to platelets ≥50,000/μL. Complete remission (CR) or CR with incomplete neutrophil or platelet recovery (CRi) was achieved by 16/28 (57%) evaluable pts. All 16 of these pts achieved remission (CR or CRi) after the first cycle. MRD negativity was achieved by 12/16 (75%) pts with CR or CRi, primarily after Cycle 1 (Cycle 1: n = 8; Cycle 2: n = 2; Cycle 3: n = 1; Cycle 4: n = 1). Survival data are not yet mature. **Conclusions:** Lower-intensity CPX-351 + VEN was generally well tolerated in adults with newly diagnosed AML who are unfit for IC and showed promising initial efficacy, with CR or CRi in the majority of pts. Clinical trial information: NCT04038437. Research Sponsor: Jazz Pharmaceuticals.

7032 **Poster Session**

Health-related quality of life (HRQoL) with enasidenib versus conventional care regimens in older patients with late-stage mutant-*IDH2* relapsed or refractory acute myeloid leukemia (R/R AML). *First Author: Courtney Denton Dinardo, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Enasidenib (ENA) is an oral inhibitor of mutant-IDH2 (mIDH2) proteins. In the phase 3 IDHENTIFY trial, ENA improved event-free survival (EFS), overall response, and complete remission rate vs conventional care regimens (CCR) ($P < 0.01$ for all) in patients (pts) ≥ 60 years of age with m*IDH2* R/R AML with 2 or 3 prior treatments (Tx) (DiNardo 2021). Pt-reported HRQoL was a secondary trial endpoint. **Methods:** IDHENTIFY is an open-label, randomized trial (NCT02577406). Pts were preselected to a CCR (SC azacitidine, intermediate- or low-dose Ara-C, or supportive care) and then randomized 1:1 to ENA 100 mg/d or CCR in 28-d cycles. Key HRQoL endpoints were mean changes from baseline (CFB) overall and by clinical response in the Global Health Status/QoL, Physical Functioning, Role Functioning, Fatigue, and Dyspnea domains of the EORTC QLQ-C30 questionnaire, and in EQ-5D-5L utility index (UI) and visual analogue scale scores. The QLQ-C30 and EQ-5D-5L were assessed on D1 of each Tx cycle (C) and at end of Tx. Minimally important differences (MIDs) in CFB scores within or between Tx arms were based on accepted thresholds. Sensitivity analysis using imputed data on CFB was conducted using pattern mixture modeling. **Results:** HRQoL-evaluable cohorts included 118/158 (74.7%) pts in the ENA arm and 80/161 (49.7%) in the CCR arm; 40 ENA pts and 81 CCR pts were not evaluable due to missing data at baseline (BL; 22 ENA and 51 CCR) and/or at ≥1 post-BL visit (26 ENA and 69 CCR). Pts ineligible for HRQoL analyses had lower response rates and worse EFS and overall survival than HRQoL-evaluable pts. Overall QLQ-C30 completion rates in the ENA and CCR arms were 79% and 65%, respectively ($P < 0.001$). While there was no meaningful improvement or worsening from BL (ie, exceeding MID) within either Tx arm in the key QLQ-C30 domains, scores worsened during initial Tx cycles and then improved with continued Tx. Mean EQ-5D-5L scores also worsened during early cycles in both Tx arms, with meaningful UI deterioration in the ENA arm from C2 through C7. However, between-group comparisons showed no consistent differences between ENA and CCR in mean CFB. Sensitivity analysis with imputation of missing CFB data showed worsened HRQoL compared with non-imputed data in the CCR arm but not with ENA. In the ENA arm, clinical responders reported relatively stable mean HRQoL scores over time, and non-responders showed no meaningful differences in CFB vs the CCR arm. **Conclusions:** HRQoL measures tended to worsen during early cycles in both Tx arms and gradually improved with continued Tx. Data should be interpreted with caution as only approximately one-half of pts in the CCR arm were HRQoL-evaluable. ENA improved clinical efficacy measures vs CCR without compromising HRQoL in older pts with R/R AML. Clinical trial information: NCT02577406. Research Sponsor: Celgene, a Bristol-Myers Squibb Company.

7033 **Poster Session**

Targeting signaling pathways vulnerabilities for the treatment of IKZF1-deleted ph-negative B lymphoblastic leukemia. *First Author: Rohit Gupta, Baylor College of Medicine, Houston, TX*

Background: Approximately 20% of children diagnosed with B lymphoblastic leukemia (B-ALL) will suffer a relapse, and most adults with B-ALL have a poor prognosis. Genome-wide association studies of B-ALL patients have identified frequent deletions of the gene *IKZF1,* encoding the master regulator of lymphoid development, IKAROS. These deletions are associated with therapy resistance, increased risk of relapse, and inferior survival. Currently, how loss of IKAROS function contributes to therapy resistance and increased risk of relapse is not fully understood. We used CRISPR-Cas9 genome editing to develop human B-ALL cell lines with various *IKZF1* deletions that genetically and phenotypically recapitulate those occurring in patients. Using these isogenic cell lines, we have previously shown *IKZF1* deletion results in cell-intrinsic chemoresistance and increased activation of the JAK/STAT signaling pathway (Rogers, Gupta et al. 2021). **Methods:** Given JAK/STAT is often dysregulated in poor-prognosis leukemia, we investigated the potential mechanisms of aberrant JAK/STAT activation and the therapeutic potential of targeting JAK/STAT in our engineered cell lines. We treated our cells with SH-4-54 (STAT3/5 inhibitor) or tofacitinib (JAK1 inhibitor) alone and in combination with dexamethasone. To elucidate how loss of IKAROS mediates an increase in JAK-STAT activity, we also performed RNAseq of known pathway regulators, comparing *IKZF1* wild-type with *IKZF1* knockout. **Results:** The JAK/STAT negative regulator *Suppressor of Cytokine Signaling 2 (SOCS2)* was significantly downregulated with *IKZF1* deletion, validated by RTqPCR and immunoblotting. We further analyzed publicly-available RNAseq data from > 650 pediatric B-ALL samples, finding that *SOCS2* expression is significantly lower in patients with low *IKZF1*expression (likely corresponding to *IKZF1* deletion) compared to those with high *IKZF1* expression. When we treated our engineered cell lines with tofacitinib or SH-4-54, *IKZF1* wild-type cells were sensitive to each compound, suggesting JAK/STAT signaling plays a vital role in cell survival. In contrast, the *IKZF1*-deleted cells were relatively resistant to JAK/STAT inhibitors alone. However, in combination with dexamethasone, treatment of cells with sub-IC50 levels of SH-4-54 or tofacitinib resulted in re-sensitization to glucocorticoid-induced apoptosis. **Conclusions:** Our findings support that *IKZF1* deletion leads to a targetable upregulation of the JAK/STAT pathway that, when inhibited, results in relative re-sensitization to dexamethasone. JAK/STAT pathway upregulation in *IKZF1* deleted cells may be mediated by decreased expression of *SOCS2.* These results provide initial promise for targeting these vulnerabilities for the treatment of this poor-prognosis disease. Research Sponsor: AOA Carolyn L. Kuckein Medical Student Grant, ASH HONORS medical student award, Rally Foundation for Childhood Cancer Research, Hyundai Hope on Wheels Scholar Award, Andrew McDonough B+ Research Foundation.

7034 **Poster Session**

A phase II study of hyper-CVAD with sequential blinatumomab (Blina), with or without inotuzumab ozogamicin (INO), in adults with newly diagnosed B-cell acute lymphoblastic leukemia (ALL). *First Author: Nicholas James Short, The University of Texas MD Anderson Cancer Center, Department of Leukemia, Houston, TX*

Background: Blina and INO are highly effective in relapsed/refractory B-cell ALL and are associated with high rates of measurable residual disease (MRD) clearance. Use of these agents in the frontline setting may improve outcomes. **Methods:** Patients (pts) 14-59 years of age with newly diagnosed Philadelphia chromosome (Ph)-negative B-cell ALL, including pts who had received no more than 1 prior cycle of chemotherapy, were eligible. Pts received hyper-CVAD alternating with high-dose MTX/Ara-C for up to 4 cycles, followed by 4 cycles of Blina. Pts with CD20+ disease received 8 doses of an anti-CD20 antibody. Eight doses of IT chemotherapy were given. Maintenance was with alternating blocks of POMP (maintenance cycles 1-3, 5-7, 9-11, and 13-15) and Blina (maintenance cycles 4, 8, and 12). Beginning with pt #39, INO at a dose of 0.3 mg/m2 on day 1 and 8 was added to the 2 cycles of MTX/Ara-C and to 2 cycles of Blina (4 total cycles with INO). **Results:** Characteristics of the 58 treated pts (38 without INO and 20 with INO) are summarized in Table. Among 45 pts with active disease at study entry, 100% achieved CR. Overall, 76% achieved MRD negativity by flow cytometry after induction and 95% at any time over the course of therapy. The median follow-up of the entire cohort is 26 months (range, 3-61+ months). Overall, 5 pts (9%) relapsed, 18 (31%) underwent transplant in first remission (including an additional 2 pts who relapsed post-transplant), 2 (3%) died in CR, and 33 (57%) remain in continuous remission without transplant. All relapses occurred in pts with established poor-risk features and no relapses have occurred beyond 2 years. For the entire cohort, the estimated 3-year OS is 85% and the 3-year continuous remission duration is 84%. No relapses or deaths have occurred in the INO group, and the estimated 1-year OS is 100%. Treatment was overall well-tolerated. One patient discontinued Blina due to recurrent grade 2 neurotoxicity. No pts have discontinued INO due to toxicity and no cases of veno-occlusive disease have been observed. **Conclusions:** Hyper-CVAD with sequential Blina is highly effective as frontline treatment of Ph-negative B-cell ALL. The addition of INO to this regimen was safe and early results are encouraging, with no relapses observed to date. Clinical trial information: NCT01371630. Research Sponsor: Amgen and Pfizer.

Patient characteristics.

Characteristic N (%) / median [range]	Overall (N=58)	HCVAD + Blina (N=38)	HCVAD + Blina + Ino (N=20)
Age (years)	34 [17-59]	37 [17-59]	24 [18-47]
WBC (x10^9/L)	4.1 [0.5-553]	3.12 [0.5-360.9]	8.1 [1.2-553]
CD20 ≥20%	27/49 (55)	17/33 (52)	10/16 (63)
CD19 (%)	99.7 [91.4-100]	99.8 [97-100]	99.1 [91.4-100]
CD22 (%)	96.3 [23.4-99.9]	96.1 [23.4-99.9]	97 [52.8-99.8]
TP53 mutation	14/53 (26)	6/32 (19)	3/16 (19)
Karyotype			
Diploid	18 (31)	11 (29)	7 (35)
Ho-Tr	8 (14)	6 (16)	2 (10)
Complex	4 (7)	3 (8)	1 (5)
HeH	4 (7)	3 (8)	1 (5)
KMT2Ar	5 (9)	3 (8)	2 (10)
Others	19 (33)	12 (32)	7 (35)

7035 **Poster Session**

Autologous CD7-targeted CAR T-cell therapy for refractory or relapsed T-cell acute lymphoblastic leukemia/lymphoma. *First Author: Liping Zhao, State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Haihe Laboratory of Cell Ecosystem, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences &Peking Union Medical College, Tianjin, China*

Background: Refractory or relapsed (r/r) T-cell acute lymphoblastic leukemia/lymphoma (T-ALL/LBL) has a poor prognosis. Our previous report showed that donor-derived CD7 CAR-T cell therapy could induce remission of r/r T-ALL, but graft-versus-host disease (GVHD) occurred in some patients (Pan et al. J Clin Oncol 2021;39:3340-3351). We recently conducted a phase I trial to evaluate autologous CD7 CAR-T therapy in r/r T-ALL/LBL, which may avoid GVHD while showing the efficacy; here we report the early result with the approval of the Data and Safety Monitoring Committee and Institutional Review Board (IRB). **Methods:** The patients who had CD7$^+$ r/r T-ALL/LBL and no leukemia cells in peripheral blood were eligible for this phase I trial (NCT04840875). The CD7 CAR construct included an endoplasmic reticulum anchor domain fused to a CD7 binding domain to prevent CD7 expression on cell surface, which contributed to minimize CAR T cell fratricide. CAR T product was checked to ensure lack of tumor contamination before infusion. The trial followed a "3+3" dose escalation process. Adverse events and efficacy were primary and secondary endpoints. **Results:** A total of 5 patients (Pt1-5), with a median age of 3.8 years (range, 1.9-13), were enrolled between Sept 2021 and Jan 2022. At enrollment, Pt1 had mediastinal mass and blasts in pleural fluid; Pt4 was in central nervous system (CNS)-3 status; Pt2, 3 and 5 had marrow disease with a median burden of 1.35% (range, 0.07%-7.31%). Pt1, 2 and 3 received 5×10^5 (±20%) cells/kg; Pt5 received 1×10^6 (±20%) cells/kg; Pt4 received cells below the target dose. Three patients had cytokine release syndrome (CRS), including one grade 3; the median onset was on day 5 (range, 1-9) with the median duration of 4 days (range, 3-14). No patient had neurotoxicity, GVHD or infection. Grade 3-4 hematological toxicity occurred in all five patients, which recovered to grade 2 within 30 days. On one month post-infusion, four patients achieved complete remission, and one patient (Pt4) still had leukemia cells in the cerebrospinal fluid. With the median follow-up time of 62 days (range, 35-136), one patient (Pt1) underwent stem cell transplantation (SCT) on 2.9 months post-infusion, and had a CD7$^-$ relapse on 1.4 months post-SCT; the other three responders remained in MRD$^-$ CR. In the four patients who received target dose, the median peak CAR T cell count in peripheral blood was 4.27×10^2/uL (range, 2.49-5.61) by flow cytometry, and all five patients had detectable CAR transgene by PCR on their last visits. There was a decrease of CD7-positive normal T cells and an increase of CD7-negative counterparts in all responders. **Conclusions:** Autologous CD7 CAR T cell therapy was safe and effective in the induction of remission in r/r T-ALL/LBL patients, without signs of GVHD. Longer follow-up time of more cases will be used to further evaluate this therapy. Clinical trial information: NCT04840875. Research Sponsor: the National Key R&D Program of China (2019YFA0110200).

7036 **Poster Session**

Quizartinib (QUIZ) with decitabine (DAC) and venetoclax (VEN) is active in patients (pts) with FLT3-ITD mutated acute myeloid leukemia (AML): A phase I/II clinical trial. *First Author: Musa Yilmaz, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: QUIZ, a potent 2nd generation FLT3 inhibitor (FLT3i) demonstrated synergy with VEN in AML cell lines and PDX models (Mali Haematologica 2020). We evaluated the safety and efficacy of DAC + VEN + QUIZ triplet in patients with newly diagnosed (ineligible for intensive induction chemotherapy) or relapsed/refractory (R/R; up to 5 prior chemotherapies) FLT3 ITD mutated AML. **Methods:** All pts received 10 days of DAC (20 mg/m2) in Cycle 1. Pts underwent day 14 bone marrow (BM) biopsy, and VEN (400 mg/day starting from day1) was put on hold in pts with BM blasts ≤ 5% or aplasia. Those with day14 BM blast >5% continued VEN for 21 days during cycle 1. In subsequent cycles, DAC was reduced to 5 days. QUIZ (30 or 40 mg/day) was administered daily continuously. **Results:** Overall, 28 pts were enrolled and evaluable at the time of this report. Of the 23 pts with R/R AML (median 3 [range 1-5] prior therapies, 78% with ≥1 prior FLT3i including prior gilteritinib (GILT) in 70%, and 39% had a prior ASCT), 78% achieved CRc (3 CR, 15 CRi) with 6/16 and 5/18 responders FLT3-PCR and multicolor flow cytometry (MFC) negative, respectively. Pts with RAS/MAPK mutations had the lowest response rates (Table). Interestingly, no emergent TKD mutations were noted at relapse after the triplet but 3/8 evaluable pts had emergent RAS/MAPK mutations. 60-day mortality rate was 5%. Of 5 patients with newly diagnosed AML (median age 69), all achieved CRc (2 CR, 3 CRi) with 4/5 and 2/4 responders FLT3-PCR and MFC negative, respectively. 60-day mortality was 0. 2 pts developed hematologic DLT with 40 mg/day QUIZ dose (grade 4 neutropenia with a <5% cellular BM lasting ≥42 days). Hence, QUIZ 30 mg/day dose was determined as RP2D for the triplet. Grade 3/4 non-hematologic toxicities included lung infections (42%) and neutropenic fever (30%). No QTcF prolongations >480 msec were noted. With a median follow-up (f/u) of 13 months, the median OS was 7.6 months in R/R cohort (1-year OS of 30%). 8/18 responding R/R pts (including 5/8 prior GILT exposed pts) underwent ASCT with a median OS of 19 vs 8 months in those who underwent ASCT versus not (p=0.26). Of the 5 frontline responding pts median OS was 14.5 months, 2 were alive in CR, 1 died in CR1 post-ASCT, 2 died due to relapsed disease at the last f/u. **Conclusions:** DAC + VEN + QUIZ is active in R/R FLT3-ITD mutated AML pts, with CRc rates of 78% and the median OS of 7.6 months. Interestingly, RAS/MAPK mutations but not emergent TKD mutations were associated with primary and secondary resistance to the triplet. Accrual continues, and updated clinical, NGS, and mass cytometry (CyTOF) data will be presented. Clinical trial information: NCT03661307. Research Sponsor: Daiichi-Sankyo.

CRc rates in R/R AML, n=23.

Subgroups	n/N (%)
Prior GILT	12/16 (75)
No Prior GILT	6/7 (85)
Prior HMA + VEN	8/11 (72)
No Prior HMA + VEN	10/12 (83)
DNMT3A +	8/12 (66)
DNMT3A -	10/10 (100)
NPM1 +	7/9 (77)
NPM1 -	11/13 (84)
RAS/MAPK* +	2/5 (40)
RAS/MAPK* -	16/17 (94)

*RAS/PTPN11/CBL/NF1/BRAF.

7037 **Poster Session**

Phase 2 study of ASTX727 (cedazuridine/decitabine) plus venetoclax (ven) in patients with relapsed/refractory acute myeloid leukemia (AML) or previously untreated, elderly patients (pts) unfit for chemotherapy. *First Author: Farhad Ravandi, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: ASTX727, is an oral formulation of the fixed dose combination of decitabine and cytidine deaminase inhibitor cedazuridine (100 mg/35 mg). We investigated whether a total oral therapy regimen of ASTX727+ven is feasible and safe. **Methods:** Pts aged ≥18 years (yrs) with relapsed/refractory AML (R/R) or pts with AML aged ≥ 75 or 18 -74 with comorbid conditions prohibiting intensive chemotherapy were eligible to participate (frontline-FL). Other eligibility criteria included adequate renal and hepatic function, and an ECOG performance status (PS) of≤2. ASTX727 is administered daily on days 1-5 of each cycle and ven on days 1-28 of the first cycle after a dose ramp up of 100-200-400 mg over 3 days (with tumor lysis prophylaxis precautions and with ven dose adjustments as needed). A bone marrow exam is performed on day 21±3 days and ven is held if blasts < 5% to allow count recovery. Cycles are repeated every 4-8 weeks and ven is administered for 21 days in subsequent cycles. **Results:** Between March 2021 and January 2022, 28 pts (15 FL and 13 R/R) have been treated on the study. The median age is 75 yrs (range, 47-90) with FL cohort 81 and R/R cohort 72. 9 FL pts (60%) were ≥80 and 5 (30%) 70-80 yrs. In R/R cohort 9 pts (69%) were 70-80 yrs. The median PS is 2 (range 0-3) and in the R/R cohort, the median number of prior treatments is 2 (range, 1-4). In the FL cohort 5 (33%) had normal and 6 (40%) a complex karyotype; 3 had other. In the R/R cohort, 15% had normal karyotype, 46% complex and 31% others. Mutations of note in the frontline cohort were RUNX1 (33%), ASXL1 (33%), DNMT3A (7%), TET2 (40%) and TP53 (20%). The overall response rate (ORR) including complete response (CR), CR with incomplete count recovery (CRi) and morphological leukemia free state (MLFS) in the FL cohort is 61% (4 CR, 4 CRi, 1 MLFS and 3 non-responders). 3 pts received only one day of therapy for severe adverse events unrelated to therapy (1 due to ischemic stroke, 1 septic shock and 1 debilitation) and were not evaluable for response. In the R/R cohort, the ORR was 45% (2 CR, 2 CRi, 2 MLFS with 5 non-responders and 2 not evaluable). The median number of cycles received is 2 (range, 1-5) for both cohorts. With a median follow-up of 5 months, the median survival for the FL cohort has not been reached (range, 0.6 – 7.3) and is 7.2 (range, 0.8-7.3) months for the R/R cohort. Grade 3 or higher adverse events directly attributable to therapy were mainly myelosuppression-related and included neutropenic infections in 3 (11%) and elevation of liver enzymes in 1 (4%) pt. **Conclusions:** Total oral therapy of ASTX727+ven is safe and feasible, particularly in the advanced elderly population, and demonstrates significant efficacy in pts unfit for chemotherapy both in the FL and R/R settings. Clinical trial information: NCT04746235. Research Sponsor: Taiho.

7038 **Poster Session**

Impact of induction approach on post-stem cell transplant (SCT) outcomes in older adults with newly diagnosed acute myeloid leukemia (AML). *First Author: Faustine Ong, The University of Texas MD Anderson Cancer Center, Department of Leukemia, Houston, TX*

Background: The optimal induction regimen for older patients (pts) with AML who are eligible for SCT is not well-established. **Methods:** This is a retrospective analysis of 127 pts age ≥60 years with newly diagnosed AML who underwent allogeneic SCT in first remission between 9/2012 and 7/2021 at our institution. Pts with previously treated secondary AML were excluded. Pts were divided according to induction therapy received: intensive chemotherapy (IC) (n = 44), lower-intensity therapy (LIT) without venetoclax (VEN) (n = 36), and LIT with VEN (n = 47). We compared overall survival (OS), relapse-free survival (RFS), cumulative incidence of relapse (CIR) and non-relapse mortality (NRM) according to the induction regimen received. **Results:** Pts who received IC were younger than those who received LIT with or without VEN (median age: 63 vs. 68 years; P < 0.0001) and were more likely to have an ECOG performance status of 0 at time of AML diagnosis (34% vs. 14%; P = 0.02). Cytomolecular risk was well-balanced between the 3 arms; the rates of adverse cytomolecular features in the IC, LIT without VEN and LIT with VEN groups were 43%, 50%, and 55%, respectively. Donor sources and degree of HLA matching were similar in the 3 groups. Most pts (92%) in the LIT with VEN group received reduced-intensity conditioning prior to SCT, compared with 54% and 58% in the IC and LIT without VEN groups, respectively. The majority of pts achieved CR/CRi prior to SCT (IC cohort:100%, LIT without VEN: 94%, LIT with VEN: 92%); the rest had MLFS as best response. The rate of measurable residual disease (MRD) negativity by flow cytometry prior to SCT was higher in the LIT with VEN group (69%), compared with IC (58%) and LIT without VEN (49%) (P = 0.14). The median number of cycles of chemotherapy prior to SCT was 3 in all groups. The median post-SCT follow-up was 37 months. The 2-year CIR was similar in pts who received IC or LIT with VEN (18% and 19%, respectively) and was highest in pts who received LIT without VEN (36%). The 2-year NRM was lowest in pts with LIT with VEN (11%), as compared with IC or LIT without VEN (27% and 22%, respectively) (P = 0.02 for IC vs. LIT with VEN). The 1-year post-SCT RFS for pts who received IC, LIT without VEN and LIT with VEN was 58%, 50%, and 75%, respectively, and the 2-year RFS was 54%, 42% and 62%. The 1-year post-SCT OS was 63%, 58%, and 84%, respectively, and the 2-year OS was 58%, 44% and 73%. OS was statistically superior for LIT with VEN compared with LIT without VEN (P = 0.02) and there was a trend towards superior OS with LIT with VEN compared to IC (P = 0.17). **Conclusions:** LIT with VEN was associated with similar rates of CIR and lower NRM compared with IC. Despite the older age of pts in the LIT with VEN cohort, their post-SCT survival outcomes were noninferior, and possibly superior, to those who received IC. These results suggest that LIT with VEN is a valid induction strategy for older SCT-eligible pts with newly diagnosed AML. Research Sponsor: None.

7039 **Poster Session**

Donor-derived T cells specific for tumor antigen and multiple pathogens for prevention of relapse and infection after haemopoietic stem cell transplant (HSCT) for myeloid malignancies (the INTACT trial). *First Author: Wei Jiang, The Westmead Institute for Medical Research, The University of Sydney, Westmead, Australia*

Background: Disease relapse and infection cause significant morbidity and mortality after allogeneic HSCT for acute myeloid leukemia (AML) and myelodysplasia (MDS). Wilms' tumour 1 (WT1) and preferentially expressed antigen in melanoma (PRAME) are both commonly overexpressed in these conditions. We assessed the safety of a novel combination of tumour associated antigen (TAA) and multipathogen (MP) specific T cells administered prophylactically after HSCT in a phase 1 trial. **Methods:** Patients with overexpression of WT1 or PRAME by ddPCR on diagnostic tumour samples were eligible. TAA and MP specific T cells were *ex vivo* expanded from stem cell donors by stimulating apheresis derived mononuclear cells with tumour, viral or fungal peptides. T cells specific for CMV, EBV, Adenovirus (AdV) and Aspergillus (Asp) antigens were produced separately and pooled in equal parts into a MP product. Patients received 1 infusion of MP specific and up to 4 infusions of TAA specific T cells at 4-weekly intervals from 28 days post HSCT (cell dose $2x10^7/m^2$ per infusion). **Results:** Ten HSCT recipients have received a total of 38 infusions. Median age was 48 years (17-67), disease AML (n = 6) or high risk MDS (n = 4), DRI intermediate (n = 4) or high (n = 6), conditioning myeloablative (n = 8) or reduced intensity (n = 2), donor source sibling (n = 7) or matched unrelated (n = 3). Median expression of WT1 on diagnostic bone marrow was 1442 copies/10^4 copies ABL (0-3870), PRAME 131 copies/10^4 copies ABL (4-12300). Patients received WT1 (n = 4), PRAME (n = 5) or both WT1 and PRAME specific T cells (n = 1). Mean tumour antigen specificity in the TAA product was 1.4% and 13.3% of CD3+ cells for WT1 and PRAME respectively. Mean total pathogen specificity in the MP product was approximately 44% (CMV = 14.0%, EBV = 14.8% and AdV = 11.6% of CD3+ cells, Asp = 14.8% of CD4+ cells). All patients received MP specific T cells. No immediate infusion related adverse events were reported. At a median 540 days post transplant (80-1265), 8 of 10 patients remain alive and in complete disease remission. Two patients did not proceed after completing 3 of 5 infusions due to the development of graft versus host disease (GVHD); both are in remission. There were 2 deaths; one patient with progressive disease who had persistent high risk MDS pre and post HSCT, and one with multiorgan failure who had multiple post transplant complications (venoocclusive disease, sepsis, GVHD), both prior to infusion. Low level viral reactivations occurred (CMV n = 5, EBV n = 7, BKV n = 3, HHV6 n = 4, AdV n = 1), however none required treatment and there were no cases of viral tissue disease or EBV PTLD. There were no invasive fungal infections. **Conclusions:** Prophylactic infusions of donor derived WT1/PRAME and multipathogen specific T cells post HSCT are well tolerated and associated with low rates of infection and relapse. Clinical trial information: NCT02895412. Research Sponsor: Western Sydney Local Health District.

7040 **Poster Session**

Long-term outcomes of newly diagnosed CRLF2 rearranged B-cell ALL.

First Author: Jayastu Senapati, Department of Leukemia, M.D. Anderson Cancer Center, Houston, TX

Background: CRLF2 rearranged B-ALL, a subtype of Ph-like ALL, constitutes a high-risk subset of B-ALL with poor outcomes with chemotherapy. Targeted therapies such as blinatumomab (blina) or inotuzumab (ino) may improve treatment outcomes for these patients (pts). **Methods:** We retrospectively analyzed pts with newly diagnosed B-ALL (diagnosed between 01/2001 and 12/2021) at our center who had documented CRLF2 overexpression. Initial therapy, including use of ino and blina in CR1 were noted. Outcomes measures included CR/CRi, MRD response, RFS and OS. **Results:** A total of 76 pts with a median age of 38 years (yrs) (range, 18-80) were identified, of which 70% were males and 81% were of Hispanic ethnicity. All pts had overexpression of CRLF2 documented by flow cytometry or gene expression profile. A subset of pts (n=37) had a concomitant CRLF2 FISH performed with all confirming CRLF2 rearrangement. Baseline disease parameters, treatment and outcomes are detailed in Table. Sixty-five pts (85%) received Hyper-CVAD based induction therapy (HCVAD, n=51; mini-HCVD, n=14) and 11 (15%) received augmented BFM. Among the HCVAD/mini-HCVD treated pts, 37% received blina in CR1 during consolidation at a median of 3.6 months after starting induction therapy, 34% received ino in CR1 (most commonly starting in cycle 1 as part of mini-HCVD + ino regimen) and 22% received both ino and blina in CR1. We focus on the outcomes of 65 pts treated with HCVAD/mini-HCVD. The median follow-up was 18 months (mos). CR/CRi rate after C1 among HCVAD/mini-HCVD treated pts was 52/65 (80%) with 25/47 (53%) MRD evaluable pts achieving MRD-neg post C1. The median RFS and OS was 17.6 and 26.6 mos, respectively. CR/CRp rate after C1 among pts who received mini-HCVD + ino in C1 was 100% (14/14) with 79% MRD-neg. On landmark analysis to the time to blina initiation, blina treated pts had similar RFS and trended for improved OS. A total of 19/65 (30%) had allo-SCT in CR1; all were MRD-neg prior to allo-SCT. Landmark analysis for OS based on time to allo-SCT (6 mos) favored SCT in CR1 (47.2 vs. 17.6 mos, p=0.04). **Conclusions:** Despite improvements in treatment options, CRLF2 overexpressed B-ALL continue to have inferior outcomes. Earlier initiation of targeted therapies might improve outcomes. Research Sponsor: None.

Disease and treatment parameters.

Parameters		N (%) or median [range] (N=76)
Age, yrs		38 [18-80]
Gender, male		53 (70)
Ethnicity	Hispanic	62 (81)
Baseline parameters	WBC (x 10^9/L)	17 [1-602]
	Platelets (x 10^9/L)	39 [3-195]
	PB blasts (%)	72 [0-98]
	BM blasts (%)	89 [29-98]
	CNS positive	10 (80)
Cytogenetics and molecular	Diploid karyotype	28 (37)
	CRLF2 mutation (n=31)	4 (13)
	JAK2 mutation (n=45)	13 (29)
	JAK1 mutation (n=31)	9 (29)
Frontline regimen	Augmented BFM	11 (15)
	HCVAD/mini-HCVD	65 (85)
	- Chemotherapy alone	32/65 (49)
	- with blina	24/65 (37)
	- with ino	22/65 (34)
	- with both ino and blina	14/65 (22)
Response with HCVAD/mini-HCVD therapy	CR/CRp (EOC1) MRD negative EOC1 among CR/CRp[#]	52/65 (80) 25/47 (53)

[#]5 missed samples.

7041 **Poster Session**

Decreasing HPK1 expression in CD19 CAR-T cells: A novel strategy to overcome challenges of cell therapy for adult (r/r) B-ALL.

First Author: Na Zhang, Department of Hematology, Xijing Hospital, Xi'an, China

Background: Since the FDA approved the first CD19 CAR T cell therapy (Kymriah) for pediatric and young adult patients with relapsed or refractory (r/r) B-cell acute lymphoblastic leukemia (ALL), cytokine release syndrome (CRS) has still been a life-threatening toxicity that limits the full therapeutic potential in adults [1,2]. So far, Tecartus was the first and only approved CAR-T cell therapy for adult r/r B ALL, which was based on results from ZUMA-3 study. CRS occurred in 92% patients, and neurologic toxicities occurred in 87% patients in ZUMA-3 study[3], suggesting that therapeutic developments are needed to ensure more safe options for adult B-ALL. Our preclinical data demonstrated that CAR-T cells with decreased HPK1 expression had enhanced antitumor effects and did not induce higher grade CRS [4]. Thus, the first-in-human clinical study is ongoing to test CD19 CAR-T cells with decreased HPK1 expression (XYF19 CAR-T cells) for adult (r/r) B-ALL (NCT04037566). **Methods:** Dose-escalation study was initiated to explore the safety and efficacy of XYF19 CAR-T cells in adult r/r B-ALL. 11 eligible adult r/r B-ALL patients were enrolled. The cell dosage of XYF19 was significantly lower than Tecartus and Kymriah, participants were infused with XYF19 CAR-T cells: 3 at low dose (2.0×10^5/kg), 5 at medium dose (5.0×10^5/kg), and 3 at high dose (1.0×10^6/kg). All patients received a conditioning regimen of IV fludarabine (30mg/m^2/d) for 4 days and cyclophosphamide (500mg/m^2/d) for 2 days. **Results:** 30 days after infusion with XYF19 CAR-T cells, 8 of the 11 (72.7%) patients had achieved complete remission (CR) or CR with incomplete count recovery (CRi). Considering the low dosage of XYF19 and that the CR/CRi rate is 71% with Tecartus [2] and 69% with Kymriah [3], the clinical response of XYF19 is similar or even the highest in these three studies. Strikingly, in this clinical trial, no patient has yet experienced dose-limiting toxicity. No grade 3 or higher CRS occurred in XYF19 treated patients, while Grade 3 or higher CRS was observed in 26% of patients with Tecartus [2], and 72% of patients with Kymriah[3]. No neurologic events occurred in the current study, while the incidence of neurological events was 51% with Tecartus [2] and 43% with Kymriah[3]. Thus, XYF19 is a strong potential novel treatment for CD19 CAR-T cell therapy in adult B-ALL. **Conclusions:** Treatment with XYF19 CAR-T cells promises a novel treatment that can alleviate some of the stern challenges of CD19 CAR-T cell therapy for adult patients with r/r B-ALL. In the current study, this treatment showed robust activity against adult (r/r) B-ALL without > Grade 2 toxicity. This efficacy and safety will be demonstrated in further trials with larger sample sizes. References: [1] Blood. 2021; 19;138 (7): 531–543. [2] Lancet.398(10299):491-502. [3] J. Biol. Chem. 287,34091–34100. [4] Cancer Cell. 2020; 38; 1-16. Clinical trial information: NCT04037566. Research Sponsor: National Natural Science Foundation of China 81970190, China NCRCH 2020ZKMC01.

7042 **Poster Session**

Hematologic improvements with ivosidenib + azacitidine compared to placebo + azacitidine in patients with newly diagnosed acute myeloid leukemia.

First Author: Hartmut Dohner, Ulm University Hospital, Ulm, Germany

Background: Ivosidenib (IVO) is a potent oral targeted inhibitor of mutant isocitrate dehydrogenase 1 (mIDH1). IVO plus azacitidine (AZA) significantly improved event-free survival (EFS), overall survival and complete remission + partial hematologic recovery rates compared with placebo (PBO) + AZA, in patients (pts) with newly diagnosed *IDH1*-mutant acute myeloid leukemia (AML) in the Phase 3 AGILE trial (NCT03173248). Here we report blood count recovery results from the AGILE trial. **Methods:** Pts were randomized 1:1 to IVO 500 mg QD + AZA 75 mg/m^2 SC or IV for 7 days in 28-day cycles (n = 72), or PBO+AZA (n = 74). Red blood cell (RBC)/platelet transfusion history were assessed at screening and follow-up. Bone marrow (BM) and peripheral blood samples were obtained at screening, and during weeks 9, 17, 25, 33, 41, 53, and every 24 weeks thereafter, and at end of treatment and during EFS follow up. Samples were analyzed at each local site according to ICSH guidelines. **Results:** In the IVO+AZA and PBO+AZA arms, 4.2% and 5.5% of pts, respectively, received concomitant granulocyte colony-stimulating factor. Hemoglobin levels steadily increased from baseline at a similar rate in both treatment arms. Mean platelet count recovered from baseline values in the IVO+AZA and PBO+AZA arms (71.0 and 92.6 x 10^9/L, respectively) as early as week 9 of treatment (171.1 and 155.1 x 10^9/L, respectively) and continued to steadily increase thereafter in the treated population. In pts receiving IVO+AZA, mean neutrophil counts rapidly increased from baseline (0.99 x 10^9/L) to week 2 (2.05 x 10^9/L) and week 5 (4.07 x 10^9/L), and then generally stabilized to within the normal range to study end (last available cycle value; ~2.0 x 10^9/L). Mean neutrophil counts initially declined with PBO+AZA before slowly recovering to near-normal levels after 36-40 weeks. The increased blood counts were accompanied by a rapid decrease in the mean BM blast percentage from 54.8% at baseline to 12.0% and 7.2% at week 9 and 17, respectively, in IVO+AZA treated patients and were maintained for 149 weeks. The decline in BM blasts was slower in the PBO+AZA arm (53.7%, 34.6% and 19.6% at baseline, week 9 and week 17, respectively). Among patients who were RBC/platelet transfusion-dependent at baseline (~54.0% in both groups), 46.2% in the IVO+AZA group achieved RBC/platelet transfusion independence compared with 17.5% in the PBO+AZA arm (1-sided p = 0.0032). Additionally, fewer adverse events of febrile neutropenia (28.2% vs 34.2%) and infections (28.2% vs 49.3%) were reported in the IVO+AZA arm compared to the PBO+AZA arm. **Conclusions:** IVO+AZA demonstrated a significant clinical benefit compared with PBO+AZA and this subanalysis demonstrated a rapidly improved recovery of blood counts and a reduced dependence on RBC and/or platelet transfusion. Moreover, rates of febrile neutropenia and infections were reduced with IVO+AZA. Clinical trial information: NCT03173248. Research Sponsor: Agios Pharmaceuticals, Inc. Servier Pharmaceuticals LLC has completed the acquisition of Agios' oncology business.

7043 **Poster Session**

V-FAST master trial: Preliminary results of treatment with CPX-351 plus midostaurin in adults with newly diagnosed *FLT3*-mutated acute myeloid leukemia.

First Author: James K. McCloskey, John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ

Background: CPX-351 (US: Vyxeos; Europe: Vyxeos liposomal), a dual-drug liposomal encapsulation of daunorubicin and cytarabine in a synergistic 1:5 molar ratio, is approved for newly diagnosed, therapy-related AML or AML with myelodysplasia-related changes in patients aged ≥1 year in the US and in adults in Europe. In a phase 3 study in older adults with newly diagnosed, high-risk/secondary AML, CPX-351 significantly improved overall survival and remission rates versus conventional 7+3, with a comparable safety profile. Preclinical data suggest CPX-351 may have synergistic activity with targeted agents, including the FLT3 inhibitor midostaurin (MID). Herein, we report preliminary results for the cohort of adults treated with CPX-351 + MID in the V-FAST (Vyxeos – First Phase Assessment with Targeted Agents) trial. **Methods:** V-FAST is an open-label, multicenter, multiarm, nonrandomized, phase 1b master trial (NCT04075747) to evaluate the safety and preliminary efficacy of CPX-351 combined with targeted agents (midostaurin, venetoclax, enasidenib). Eligible adults in the CPX-351 + MID cohort were aged 18 to 75 years, had newly diagnosed AML with a *FLT3* internal tandem duplication (ITD) or tyrosine kinase domain (TKD) mutation, were fit for intensive chemotherapy, and had an ECOG performance status of 0 to 2. The dose-exploration phase (3+3 design) determined a recommended phase 2 dose of CPX-351 100 units/m^2 (daunorubicin 44 mg/m^2 + cytarabine 100 mg/m^2) on Days 1, 3, and 5 + MID 50 mg BID on Days 8 to 21. There were no dose-limiting toxicities, and additional patients were enrolled in the expansion phase at this dose. **Results:** A total of 23 patients received CPX-351 + MID and had sufficient data to be included in the analysis (cutoff date: 1/20/2022). Patient baseline characteristics are shown in the Table. Treatment-emergent adverse events (TEAEs) in ≥40% of patients included febrile neutropenia (78%), nausea (65%), increased alanine aminotransferase (57%), leukopenia (57%), thrombocytopenia (57%), headache (43%), and hyponatremia (43%). All patients experienced a grade 3/4 TEAE, primarily hematologic events. Nonhematologic grade 3/4 TEAEs in ≥2 patients included pneumonia (17%), lung infection (13%), and hyperglycemia (9%). There were no grade 5 TEAEs and no deaths on or before Day 60. Complete remission was achieved by 18/22 (82%) evaluable patients after the first induction cycle. **Conclusions:** Preliminary results from the V-FAST trial suggest CPX-351 + MID is feasible, with a manageable safety profile and promising remission rates in adults with newly diagnosed AML who have a *FLT3* mutation. Clinical trial information: NCT04075747. Research Sponsor: Jazz Pharmaceuticals.

	N = 23
Median (range) age	66 (40, 74) years
Aged <60 years	22%
Male / female	48% / 52%
Favorable / intermediate / poor risk disease	4% / 65% / 30%
ECOG PS 0 / 1 / 2	26% / 65% / 9%
***de novo* AML**	78%
AML with antecedent hematologic disorder	13%
Therapy-related AML	4%

7044 **Poster Session**

Efficacy and safety of venetoclax in combination with azacitidine or decitabine in an outpatient setting in patients with untreated acute myeloid leukemia.

First Author: Sudhir Manda, Arizona Oncology, The US Oncology Network, Tucson, AZ

Background: Venetoclax (Ven), a highly selective BCL-2 inhibitor, combined with hypomethylating agents (HMAs) azacitidine (Aza) or decitabine (Dec) is approved for the treatment of newly diagnosed acute myeloid leukemia (ND AML) in patients (pts) who are ineligible to receive intensive chemotherapy. Previous clinical studies initiated Ven + HMA in an inpatient setting due to concerns of tumor lysis syndrome (TLS). This Phase 3b, single-arm, multicenter, open-label study (NCT03941964) evaluated the efficacy and safety of Ven + HMA in a US community-based outpatient setting. **Methods:** Pts with ND AML who were ineligible to receive intensive chemotherapy, had no evidence of spontaneous TLS at screening, and were deemed an appropriate candidate for outpatient initiation of Ven + HMA by the investigator were eligible. Pts received Ven (400 mg) in combination with Aza (75 mg/m^2) or Dec (20 mg/m^2) for up to 6 cycles during the study period. Pts could continue receiving commercially acquired Ven after the study period. All pts received TLS prophylaxis. The primary endpoint was the composite complete remission (CR) rate (CR + CR with incomplete hematologic recovery [CRi]) per modified International Working Group criteria. Secondary endpoints included CR or CRi rates and transfusion independence (TI). TLS was assessed per Howard criteria (Howard. *N Engl J Med*. 2011;364:1844). **Results:** At the 19 Oct 2021 cutoff date, 60 pts were enrolled and treated (Ven + Aza, n=30; Ven + Dec, n=30). Efficacy outcomes are shown in the Table. The composite CR rate was 58%. CR and CRi rates were 13% and 45%, respectively. Most pts (>50%) maintained TI, and 41% and 57% of pts dependent on red blood cells or platelets, respectively, converted to TI. Bone marrow blast clearance was achieved in 42 pts (70%) at a median 26 days after treatment initiation. The most common (≥50%) AEs were anemia (75%), neutrophil count decrease (55%), white blood cell count decrease (52%), and nausea (50%). Serious AEs occurred in 67% of pts, most commonly (≥15%) febrile neutropenia (28%) and sepsis (15%). Two pts (3%) had TLS; neither event led to treatment discontinuation. Of pts who achieved blast clearance, 12/42 (29%) had a new event of myelosuppression post-blast clearance and prior to the next cycle. **Conclusions:** The results of this US community-based study indicate that Ven + HMA is an effective treatment option for pts with ND AML and, with appropriate TLS prophylaxis and monitoring, can safely be initiated in an outpatient setting. Clinical trial information: NCT03941964. Research Sponsor: AbbVie.

Efficacy outcomes.

	Ven + Aza (n=30)	Ven + Dec (n=30)	All Pts (N=60)
Composite response rate, n (%)	17 (57)	18 (60)	35 (58)
CR, %	13	13	13
CRi, %	43	47	45
TI conversion rate, n/N (%)			
Red blood cell	3/8 (38)	4/9 (44)	7/17 (41)
Platelet	1/3 (33)	3/4 (75)	4/7 (57)
TI maintenance rate, n/N (%)			
Red blood cell	10/19 (53)	13/19 (68)	23/38 (61)
Platelet	18/26 (69)	18/25 (72)	36/51 (71)

7045 **Poster Session**

Incorporating patient-reported outcome data into a hematopoietic cell transplant survival calculator.

First Author: Bronwen E. Shaw, CIBMTR (Center for International Blood and Marrow Transplant Research), Department of Medicine, Medical College of Wisconsin, Milwaukee, WI

Background: The Center for International Blood and Marrow Transplant Research (CIBMTR) provides a validated 1-year Overall Survival (OS) calculator to estimate outcomes for individual patients prior to allogeneic Hematopoietic Cell Transplant (HCT) to inform risk. The calculator considers pre-HCT clinical and demographic characteristics, but not patient-reported outcome (PRO)s. Pre-HCT PRO scores have been associated with OS. We hypothesized that adding the baseline PRO score to the calculator will enhance its performance in predicting OS. **Methods:** In addition to established covariates,we considered pre-HCT PRO scores, collected on five (published) prospective randomized clinical trials performed through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). Measures used were the SF36 physical component score (PCS) and mental component score (MCS), and the FACT-BMT Trial outcome index (TOI). We also investigated inclusion of a single question from the SF36: In general, would you say your health is: excellent/very good/good vs fair/poor. Patients were ≥18. **Results:** 1,033 patients were included, 341 (33%) completed only the SF36, 339 (33%) only the FACT-BMT and 353 (34%) both, per study design. HCT occurred 2004-2014, and the population was diverse with respect to disease, stage, demographics, and transplant characteristics. When adjusted for clinical characteristics, the PCS was significantly predictive of mortality (HR=0.88, 95%CI 0.81-0.96, p=0.0021), while the MCS and TOI were not. The single general health question was also significantly associated with mortality (HR=0.52, 95%CI 0.35-0.74, p=0.0004). Addition of PRO scores to the calculator did not result in a significant change in the model's predictive ability as measured by Harrell's concordance statistic (Table). **Conclusions:** In this large analysis, we confirmed the significant, independent association of pre-HCT PRO scores with OS. We showed, for the first time in this setting, that a single general health question is as accurate as the full SF36 measure for predicting survival, but we did not find support for the hypothesis that adding PROs to the calculator improved its performance. Estimates of baseline PRO measure effect on mortality and model concordance statistics at 1-year post-HCT. Research Sponsor: U.S. National Institutes of Health, Other Government Agency.

Model	Hazard ratio (HR) of mortality (95% confidence interval); p-value	Harrell's C statistic
SF36		
Clinical covariates (CC) only		0.7098
CC + PCS*	0.88 (0.81-0.96); p=0.0021	0.7195
CC + MCS*	1.03 (0.95-1.11); p=0.4692	0.7097
CC + General health (Excellent/very good/good vs fair/poor)	0.52 (0.35-0.74); p=0.0004	0.7214
FACT-BMT		
CC		0.7090
CC + TOI*	0.95 (0.90-1.00); p=0.0588	0.7086

*HR for PCS, MCS and TOI reflects death risk ratio corresponding to 5 unit change in predictor Funding: R21 HL140314, U24-CA76518, U24HL138660, K23 HL141445, U10HL069294.

7046 **Poster Session**

Association of frailty with clinical and financial outcomes of allogeneic hematopoietic stem cell transplant.

First Author: Sara Sakowitz, David Geffen School of Medicine, UCLA, Los Angeles, CA

Background: Considered the only curative therapy for many hematological conditions, allogeneic hematopoietic stem cell transplantation (alloHSCT) is increasingly used in older patients. Yet, chronological age alone has been found to be an inaccurate predictor of posttransplant sequelae. More recently, the concept of frailty has emerged as a better marker of physiologic reserve. While formal frailty instruments have not been widely adopted due to their resource intensive nature, we applied a previously-validated coding-based approach to examine the association of frailty with in-hospital outcomes of alloHSCT. **Methods:** All adults (≥ 18 years) undergoing alloHSCT for hematological malignancies were identified in the 2010-2019 Nationwide Readmissions Database. The previously-validated binary Johns Hopkins Adjusted Clinical Groups indicator was used to classify patients as frail. In this algorithm, the presence of diagnoses across various domains, including malnutrition, dementia, and decubitus ulcer, constitute frailty. Regression models were developed to evaluate the independent association of frailty with in-hospital mortality, periprocedural complications, length of stay, hospitalization costs, and 30-day non-elective readmissions. **Results:** Of an estimated 48,161 patients, 9.8% were considered frail. Frail patients were not significantly older (51.8 ± 15.0 vs 51.6 ± 14.2, p = 0.685), but had higher Elixhauser scores (2.8 ± 1.3 vs 2.0 ± 1.3, p < 0.001). After adjustment, frailty was associated with increased odds of in-hospital mortality (AOR 2.22; 95% CI 1.68-2.94; P < 0.001), as well as infectious (AOR 1.44, 95% CI 1.18-1.76; P < 0.001) and respiratory (AOR 1.69, 95% CI 1.41-2.02; P < 0.001) complications. Frailty was also associated with greater risk of acute graft-vs-host disease (AOR 1.39, 95% CI 1.12-1.72; P = 0.003) and CMV (AOR 1.72, 95% CI 1.27-2.33; P < 0.001) or invasive fungal infection (AOR 1.49, 95% CI 1.07-2.06; P = 0.017). Further, frailty was linked to increased likelihood of non-home discharge (AOR 1.29, 95% CI 1.03-1.61; P = 0.026), 30-day non-elective readmissions (AOR 1.29, 95% CI 1.11-1.50; P = 0.001), and significant increases in length of stay (+6.05 days, 95% CI 4.41-7.69; P < 0.001) and costs (+$36,660, 95% CI 27,413-45,907; P < 0.001). **Conclusions:** Among patients undergoing alloHSCT, frailty, as measured by an administrative tool, was independently associated with increased in-hospital mortality, complications and overall resource use. Inclusion of frailty in risk models may better aid benchmarking efforts and inform shared-decision making. Research Sponsor: None.

(%)	Non-Frail n = 43,465	Frail n = 4,697	P
Age (Years)	51.6 (51.2-52.0)	51.8 (51.0-52.6)	0.685
Female	18,207 (41.9)	2,041 (43.4)	0.183
Elixhauser Comorbidity Index	2.0 (2.0-2.1)	2.8 (2.7-2.9)	< 0.001
Payer			0.001
Private	26,766 (61.8)	2,634 (56.2)	
Medicare	8,933 (20.6)	1,090 (23.3)	
Medicaid	5,251 (12.1)	647 (13.8)	

7047 **Poster Session**

Non-myeloablative allogeneic blood or marrow transplantation (AlloBMT) with post-transplant cyclophosphamide (PTCy) for peripheral T-cell lymphoma (PTCL): Improved outcomes with peripheral blood (PB) allografts and increased total body irradiation (TBI) to 400 cGV.

First Author: Cole Harris Sterling, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD

Background: The use of PTCy for graft-versus host-disease (GVHD) prophylaxis has revolutionized alloBMT, but there is limited published experience in PTCL. **Methods:** All patients with PTCL who received a non-myeloablative alloBMT using PTCy-based GVHD prophylaxis between January 2004 and December 2020 at Johns Hopkins Hospital were analyzed. Standard population statistics were used. **Results:** Sixty-five patients were identified. The median age was 59 years (range, 24-75 years). Lymphoma histology included PTCL-not otherwise specified (n=24), ALK-negative anaplastic large cell lymphoma (n=14), angioimmunoblastic T-cell lymphoma (n=7), enteropathy-associated T-cell lymphoma (n=6), hepatosplenic T-cell lymphoma (n=4), and other (n=10). Eleven patients were in first complete remission (CR1, 17%). The remaining patients were in first partial remission (PR1) or underwent salvage therapy to at least PR prior to transplant. Forty-eight patients received an alloBMT from a haploidentical related donor (74%), 10 from a fully matched donor (15%), and 7 from a mismatched unrelated donor (mMUD, 11%). All patients received non-myeloablative conditioning with fludarabine, cyclophosphamide, and TBI. The graft source was bone marrow (BM) in the first 46 patients (71%). Because of relatively high relapse rates, in 2018 we began using PB and increased TBI from 200 to 400 cGy; the remaining 19 patients (29%) received this regimen. GVHD prophylaxis was PTCy, mycophenolate mofetil, and a calcineurin inhibitor or sirolimus. With a median follow up of 2.8 years, the 3-year progression-free survival (PFS) for the entire cohort was 39% (95% confidence interval [CI] 28-54%), and the 3-year overall survival (OS) was 43% (95% CI 31-58%). The cumulative incidence (CuI) of relapse and non-relapse mortality (NRM) at 1 year was 25% (95% CI 14-35%) and 12% (95% CI 4-20%), respectively. Among 29 cases of GVHD (45%), 2 were grade 3-4 acute GVHD (3%) and 3 were severe chronic GVHD (5%). Univariate analysis including age, histology, mMUD, PB/400cGy, and CR1 revealed only PB/400 cGy TBI as a significant predictor of survival, relapse, or NRM. Outcomes by source. **Conclusions:** AlloBMT with non-myeloablative conditioning and PTCy is safe and well-tolerated in patients with PTCL. Our preliminary data suggest increasing TBI dose to 400 cGy and using PB allografts may offer improved disease control and better survival outcomes, though additional studies are needed to confirm these findings. Research Sponsor: None.

	3-yr PFS	3-yr OS	1-yr CuI relapse	1-yr CuI NRM
BM/200cGy TBI	30% (95% CI 19-47%)	34% (95% CI 22-51%)	33% (95% CI 19-46%)	11% (95% CI 2-20%)
PB/400cGy TBI	66% (95% CI 43-100%)	70% (95% CI 47-100%)	5% (95% CI 0-16%)	16% (95% CI 0-33%)
p-value	0.035	0.043	0.012	0.600

7048 **Poster Session**

Impact of prior solid tumor on outcomes of allogeneic hematopoietic stem cell transplantation for AML or MDS. *First Author: Aya Albittar, University of Washington, Seattle, WA*

Background: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) offers a definitive treatment of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). Prior solid tumor (PST) is felt to portend a worse post-transplant prognosis. The aim of this study was to evaluate the impact of PST history on allo-HSCT outcome. **Methods:** We retrospectively identified patients with AML or MDS who underwent first allo-HSCT at the Fred Hutchinson Cancer Research Center between 2010 and 2018. Cox regression analysis was used to identify factors associated with mortality among patients with PST, and to compare outcomes of patients with and without PST. Multivariable models were fit, adjusting for cytogenetic risk level, time from PST diagnosis to transplant, receipt of reduced-intensity conditioning (RIC), and age at transplant. Survival estimates were obtained using the Kaplan-Meier method. **Results:** 1198 patients were included for analysis, of which 101 had a history of PST. After a median follow up of 1301 days among survivors, there was a total of 558 deaths and 322 relapses among all patients. Patients with history of PST were older (62.5 vs 54.9 yrs) and a higher proportion received RIC (52.5% vs 27.3%). The most common PSTs included breast (38/101, 38%), prostate (13/101, 13%), colon (9/101, 9%), thyroid (8/101, 8%), and uterine (7/101, 7%). Among those with known staging (n = 66), stage 1 (28/66, 42%) was the most common, followed by stage 2 (17/66, 26%) then stage 3 (15/66, 23%). The most common therapies provided were surgery (95/101, 95%), cytotoxic chemotherapy (41/101, 41%), radiation (45/101, 45%), and endocrine therapy (25/101, 25%). The unadjusted hazard ratio (HR) of mortality in the PST group relative to the non-PST group was 1.10 (95% confidence interval [CI] 0.83-1.47, p = 0.52). After adjustment for patient age, disease, patient/donor CMV status, KPS, cytogenetic risk, source of stem cells, and donor type, the adjusted HR was 0.91 (95% CI 0.68-1.22, p = 0.59). The unadjusted HR for relapse was 1.15 (95% CI 0.79-1.67, p = 0.48), and adjusted HR was 1.11 (0.76-1.11, p = 0.61). Among patients with PSTs, high-risk cytogenetics were associated with increased mortality (adjusted HR = 2.21; 95% CI 1.16-4.2, p = 0.016) and relapse (adjusted HR = 1.91; 95% CI 1.01-3.60, p = 0.047). Longer time from PST diagnosis to transplant led to a numerically increased mortality in the unadjusted (HR = 1.05; 95% CI 1.00-1.11, p = 0.057) and adjusted (HR = 1.05; 95% CI 1.00-1.11, p = 0.69) models treating time as a continuous linear variable. **Conclusions:** In our study, a history of PST did not impact overall survival or relapse rate among patients who underwent first allo-HSCT for AML or MDS. As in the overall population, post-transplant outcomes were primarily driven by cytogenetic risk level. However, it is likely that selection of patients with PST for transplantation was biased based on overall risk assessment. Research Sponsor: None.

7049 **Poster Session**

Bosutinib (BOS) in newly diagnosed chronic myeloid leukemia (CML): Gastrointestinal (GI), liver, effusion, and renal safety characterization in the BFORE trial. *First Author: Jorge E. Cortes, Georgia Cancer Center, Medical College of Georgia at Augusta University, Augusta, GA*

Background: Efficacy and safety of BOS vs imatinib (IMA) in patients (pts) with newly diagnosed chronic phase CML was assessed in the phase 3 BFORE trial. Here we characterize the safety profile of BOS after 5 yrs follow-up, with a focus on GI, liver, effusion and renal treatment-emergent adverse events (TEAEs). **Methods:** Pts who received ≥1 dose of BOS (n=268) or IMA (n=265) 400 mg/d in BFORE were included. Adverse events (AEs) of special interest were analyzed by selecting prespecified MedDRA terms to generate TEAE clusters. Final database lock: June 12, 2020. **Results:** Median duration of treatment (Tx) was 55 mo for pts receiving BOS or IMA; respective median (range) dose intensity was 393.6 (39–583) vs 400.0 (189–765) mg/d. Any grade TEAEs occurred in 98.9% and 98.9% of BOS- vs IMA-treated pts. Most common newly occurring TEAEs (any grade) after 12 mos were increased lipase (9.0%) with BOS, and diarrhea (8.3%) with IMA. In BOS- vs IMA-treated pts, 25.4% vs 14.3% had AEs leading to permanent Tx discontinuation; the majority discontinued in yr 1 (14.2% vs 10.6%). Most frequent AEs leading to discontinuation were increased ALT (overall, 4.9%; yr 1, 4.5%) with BOS vs thrombocytopenia (overall, 1.5%; yr 1, 1.5%) with IMA. GI, liver, effusion and renal TEAEs, respectively, occurred in 79.9%, 44.0%, 6.0% and 10.4% (maximum grade 3/4 [G3/4]: 9.0%, 26.9%, 1.1% and 2.2%) of BOS- vs 61.5%, 15.5%, 2.3% and 9.8% (G3/4: 1.1%, 4.2%, 0.4% and 0.8%) IMA-treated pts. One grade 5 renal TEAE occurred in the BOS arm and was not considered related to Tx. Cumulative rates per Tx yr are shown in the Table. Most common GI TEAEs were diarrhea (BOS vs IMA: 75.0% vs 40.4% [G3/4: 9.0% vs 1.1%]) with BOS, and nausea (37.3% vs 42.3% [G3/4: 0% vs 0%]) with IMA. In both arms, the most common liver, effusion and renal TEAEs, respectively, were increased ALT and/or AST (34.0% vs 8.3% [G3/4: 22.0% vs 2.3%]), pleural effusion (5.2% vs 1.9% [G3/4: 0.7% vs 0.4%]) and increased blood creatinine (6.7% vs 8.3% [G3/4: 0.4% vs 0.4%]). GI, liver, effusion and renal TEAEs infrequently led to Tx discontinuation (1.9%, 7.8%, 0.7% and 0.7% vs 1.1%, 0.8%, 0% and 0.4%). **Conclusions:** The safety profiles of BOS and IMA in BFORE were distinct, with no new safety signals identified after 5 yrs follow-up. Onset of TEAEs occurred primarily during yr 1 (eg, GI and liver), with an increased incidence of some TEAEs (eg, effusion and renal) in later yrs. Discontinuations due to AEs generally occurred early into Tx, with few due to GI, liver, effusion and renal AEs. These safety results support the use of first-line BOS as a standard of care in pts with CP CML. Clinical trial information: NCT02130557. Research Sponsor: Pfizer.

Cumulative rate of pts with GI, liver, effusion and renal TEAEs by yr.

	BOS n=268					IMA n=265				
%	Yr 1	2	3	4	5+	Yr 1	2	3	4	5+
GI	76.5	78.0	79.5	79.5	79.9	52.8	56.6	58.5	61.1	61.5
Liver	39.2	41.4	42.2	42.9	44.0	11.7	13.6	14.0	14.3	15.5
Effusion	2.2	3.0	4.5	6.0	6.0	1.5	1.5	1.5	1.5	2.3
Renal	6.0	7.8	8.2	9.7	10.4	6.0	8.3	8.7	8.7	9.8

7050 **Poster Session**

Treatment-free remission (TFR) in patients with chronic myeloid leukemia (CML) following the discontinuation of tyrosine kinase inhibitors. *First Author: Fadi Haddad, Department of Leukemia, University of Texas MD Anderson, Houston, TX*

Background: Tyrosine kinase inhibitors (TKIs) discontinuation in patients (pts) with CML is increasingly considered. We evaluated the outcome of pts with CML who discontinued TKIs and determined the factors associated with differences in the success rates of TFR. **Methods:** We reviewed data from 284 pts with CML treated with TKIs at our institution between October 1999 and February 2017 and who subsequently discontinued therapy. Major molecular response (MMR) was defined as a *BCR-ABL1/ABL1* transcripts ratio ≤0.1% as determined by real time (RT)-PCR, MR^4 as a ratio ≤0.01% IS, and $MR^{4.5}$ as a ratio ≤0.0032%. TFR failure was defined as the loss of MMR on any single test. We analyzed TFR rates according to duration and depth of response and conducted a multivariate analysis for factors associated with loss of MMR. **Results:** Median age was 63 years (range, 25-93). 199 pts (70%) had electively discontinued their TKI while 70 pts (24%) stopped therapy because of adverse events. 92 pts (32%) had switched ≥1 TKI prior to discontinuation due to drug intolerance or resistance. The median time from the initiation of frontline TKI to discontinuation was 117 months (range, 16-242). The median duration of MR^4 and $MR^{4.5}$ before TKI discontinuation was 74 months (range, 2-207) and 64 months (range, 0-207), respectively. At a median follow-up of 36 months (95% CI, 32-40) after TKI discontinuation, 53 pts (19%) lost MMR, translating into a 5-year TFR rate of 79%. 50 pts (94%) resumed TKI therapy and, among 47 evaluable pts, all but one pt regained MMR, with 41 pts (88%) achieving $MR^{4.5}$. The estimated 5-year TFR rates were 91%, 76% and 70% in pts achieving $MR^{4.5}$ for ≥6 years, between 5 and 6 years, and < 5 years, respectively (P < 0.0001). The estimated 5-year TFR rates were higher with MR^4 and $MR^{4.5}$ ≥5 years, compared with MR^4 < 5 years (87% vs 92% vs 64%; P < 0.0001). Pts who remained on their frontline TKI at the time of discontinuation had a 5-year TFR rate of 82%, compared with 75% and 72% among pts who switched to a second line TKI or beyond because of intolerance or resistance, respectively (P = 0.417). TFR rates did not vary according to the type of frontline TKI used (P = 0.761). By multivariate analysis, only durations in MR^4 or $MR^{4.5}$ ≥5 years before stopping treatment were associated with a lower risk of loss of MMR, with hazard ratios of 0.37 (95% CI, 0.18-0.76; P = 0.007) and 0.20 (95% CI, 0.09-0.45; P < 0.0001), respectively. We evaluated the impact of the frequency of molecular monitoring on the success rate of TFR. The estimated 5-year TFR rate was 79% for pts monitored monthly compared with 85% for pts monitored every 6-8 weeks following discontinuation (P = 0.263). **Conclusions:** Our findings suggest that achieving MR^4 for ≥5 years was associated with a very high probability of maintaining TFR, and that less frequent molecular monitoring could be more cost-effective without any negative impact on outcomes. Research Sponsor: Charif Souki Cancer Research Fund.

7051 **Poster Session**

Comparison of demographics, disease characteristics, and outcomes between African American patients and White patients with myelodysplastic syndrome: A population-based study. *First Author: Arnaud Lesegretain, Harvard Medical School, Boston, MA*

Background: Myelodysplastic syndrome (MDS) consists of a heterogeneous group of clonal myeloid neoplasms, classified as a malignancy since 2001. Previous studies have described inferior outcomes for African Americans (AA) versus Whites (W) in several solid tumors and hematological malignancies, including AML. We performed an analysis of the Survival, Epidemiology, and End Results (SEER) cancer registry to analyze baseline characteristics and various outcomes. **Methods:** Using SEER (18 Registries, 2000-2018, Nov 2020 submission), we included 37,564 patients (pts) with microscopically confirmed MDS, age > = 20, diagnosed between 2000-2013 based on ICO-03 codes. MDS sub-types were grouped into low, intermediate, and high-risk disease. We compared baseline characteristics, mortality rates per attributed cause of death (COD) and overall survival (OS). Multivariate Cox regression and Propensity Score analyses were conducted to reduce effect of confounding due to imbalance in baseline covariates. **Results:** We included 34,543 W (92%) and 3021 AA (8%) pts; There were more males (58%) among W vs AA (49%). At diagnosis the median age was 71 and 76 in AA and W subjects, respectively. Low and high risk MDS comprised 22.8% and 14.5% of cases among AA and 21.5% and 16.3% among W pts, respectively. 66.8% of AA were living in large metropolitan areas vs 60.2% for W pts. mOS was 33 months for AA and 26 months for W; HR for OS comparing W vs AA using a univariate Cox PH model was: 0. 79 (0.76- 0.82), p < 0.001. In a multivariate Cox-PH model, HR for OS after adjusting for sex, age at diagnosis, histology, urban-rural continuum, income group was: 0.90 (95%CI 0.86-0 .94), p < 0.001. HRs after stratified cox PH model and propensity score matching model for age, sex, histology and income group were 0.92 (0.88-0.96), p < 0.001 and 0.93(0.88-0.98), p = 0.01 respectively. Analysis by histology shows statistically significant association between race and OS for refractory anemia and MDS-unclassifiable while not significant for refractory anemia with ringed sideroblasts, refractory anemia with excess blasts and MDS with del(5q). Incidence rate ratio for AA vs W for death attributed to the two most frequent CODs were: MDS/Leukemia: 0.74 (0.69-0.81, p < 0.001); CVD: 1.07 (0.94-1.21, ns). **Conclusions:** In this large study of MDS cases reported to the SEER registry, we observed differences in age, sex, disease subtype, socio-economic factors, mortality rate per attributed COD, survival outcomes between AA and W. The finding of AA having better OS outcomes than W pts is unexpected and needs to be further investigated, specifically the contribution of the less well-defined low-grade risk forms of MDS. Although caution in the interpretation is necessary due to multiple limitations inherent to the SEER dataset, this data does raise intriguing questions for future study. Research Sponsor: None.

7052 **Poster Session**

Anti–PD-1 antibody (sintilimab) plus decitabine as first-line treatment for patients with higher-risk myelodysplastic syndrome (MDS): Preliminary results from a single-arm, open-label, phase II study. *First Author: Jing Wang, Peking University People's Hospital, Peking University Institute of Hematology. National Clinical Research Center for Hematologic Disease, Beijing Key Laboratory of Hematopoietic Stem Cell Transplantation, Beijing, China*

Background: Hypomethylating agents (HMAs) are the preferred treatment for untreated patients (pts) with higher-risk MDS, but the survival of pts after HMAs treatment is poor. It has been demonstrated that the PD-1/PD-L1 expression was upregulated by HMAs in MDS pts, providing a strong rationale for combining HMAs with PD-1 antibody for MDS treatment. Therefore, this single-arm, open-label, clinical trial was performed to evaluate safety and efficacy of Sintilimab plus decitabine for pts with higher-risk MDS (ChiCTR2100044393). **Methods:** Adult pts with higher-risk MDS by the IPSS-R were enrolled. Patients received decitabine 20mg/m^2 intravenously daily for 5 days and sintilimab 200mg IV starting on the first and 22nd day of a cycle every 42 days until unacceptable toxicity, relapse, or progression, for a maximum of 8 cycles. The primary endpoint was overall response rate (CR+PR+mCR). Simon's optimal two-stage design was employed.If five or more pts in stage I (13 pts) achieved ORR, the study would enroll 34 additional pts in stage II (47 pts). Secondary endpoints included safety, and survival outcomes. The relationship between expression levels of immune-checkpoint and efficacy of the combination therapy, as well as other potential biomarkers were also explored via genomic profiling. **Results:** At data cut-off (January 31, 2022), 21 pts were enrolled with a median follow-up time of 5.8 months. The median age of pts was 64 years (range 30-83), and the other characteristics are summarised in Table.The ORR was 62%,with six pts reaching complete response (CR),four pts reaching marrow CR and three pts achieved marrow CR+ hematologic improvement (HI). In addition,four pts reaching HI. The most common grade 3 TEAEs(> 10%) were febrile neutropenia (76.2%) and pulmonary infection (38.1%). No grade 4 TEAEs and treatment-related deaths occurred. A total of 12 pts (57.1%) experienced immune-related adverse event, including rash (28.6%), pneumonia (9.5%), hypothyroidism (9.5%), elevated serum bilirubin (4.8%) and transpeptidase (4.8%), which were all resolved by glucocorticoid. In these 21 pts, the most frequently mutated genes are ASXL1 (28.6%) , RUNX1 (14.3%) and TET2(14.3%). Updated biomarker data will be presented during the ASCO meeting. **Conclusions:** To the best of our knowledge, this is the first study to evaluate the efficacy and safety of sintilimab plus decitabine in pts with untreated higher-risk MDS. The preliminary results demonstrate that the combination therapy is relatively safe with anti-tumor activity. Clinical trial information: ChiCTR2100044393. Research Sponsor: Innovent Biologics.

Pts Characteristic		No. (%)/ Median (Range), n = 21
Male		14 (66.7%)
Laboratory values	Bone marrow blasts (%)	10 (0-18)
	WBC ($\times 10^9$/L)	2.3 (0.6-8.3)
	Hgb (g/dL)	73 (36-125)
	Platelets ($\times 10^9$/L)	37 (6-240)
IPSS-R category	High	8 (38.1%)
	Very High	11 (52.4%)
Cytogenetics	Normal	7 (33.3%)
	Complex	7 (33.3%)

7053 **Poster Session**

Ivosidenib in patients with *IDH1*-mutant relapsed/refractory myelodysplastic syndrome (R/R MDS): Updated enrollment and results of a phase 1 dose-escalation and expansion substudy. *First Author: David Andrew Sallman, Moffitt Cancer Center, Tampa, FL*

Background: Mutations in isocitrate dehydrogenase 1 (*IDH1*) occur in ~3% of patients (pts) with MDS and are associated with increased transformation to acute myeloid leukemia (AML). Ivosidenib (IVO), an oral, potent, targeted inhibitor of the mutant IDH1 (mIDH1) enzyme, is FDA approved for m*IDH1* R/R AML and m*IDH1* newly diagnosed AML in pts ≥75 years old or with comorbidities precluding the use of intensive induction chemotherapy. In the first-in-human study of IVO in pts with m*IDH1* advanced hematologic malignancies (NCT02074839), 12 pts with R/R MDS received IVO 500 mg once daily (QD). Based on encouraging safety and efficacy findings, including an investigator-assessed overall response rate (ORR) of 75%, with median response duration of 21.4 months, the FDA granted Breakthrough Therapy designation to IVO in m*IDH1* R/R MDS and the study was amended to enroll additional pts. We report updated results. **Methods:** This substudy of the single-arm, open-label study of IVO evaluated pts with R/R MDS after documented failure or relapse following prior standard therapy including intensive chemotherapy and hypomethylating agents. Other key eligibility criteria included: high disease burden based on IPSS or IPSS-R risk at baseline; an Eastern Cooperative Oncology Group performance status score of 0–2; and no prior IDH1 inhibitor therapy. Pts received IVO 500 mg QD orally on days 1–28 of 28-day cycles. **Results:** As of 08May2021, 16 pts with R/R MDS were enrolled: 5 (31%) pts remained on treatment and free from leukemic transformation; 11 (69%) had discontinued including 6 for disease progression, 1 for allogeneic stem cell transplantation, and 1 owing to an adverse event (AE) of sepsis (the only fatal AE; reported by investigator as not related to IVO). AEs are summarized in the Table. 2 pts each experienced differentiation syndrome (grade 2) and QTcF prolongation (grade 1 and 2). 7/16 pts achieved complete response (CR, 44%; 95% CI, 20%, 70%), 1 achieved partial response (6%), and 5 achieved marrow CR (31%), resulting in an ORR of 81% (95% CI, 54%, 96%). Hematologic improvement in ≥1 lineages was achieved by 11/16 (69%) pts. The Kaplan-Meier estimate of duration of CR+PR at 12 months was 60%. 3 pts experienced CRs lasting 24.0, 63.7, and 65.4 months, which remain ongoing. 5/7 pts (71%) who were transfusion dependent at baseline became independent of red blood cell or platelet transfusions for 56 or more consecutive days on treatment. Additional translational data are being analyzed. **Conclusions:** In pts with m*IDH1* R/R MDS, IVO monotherapy was tolerable and induced durable remissions and transfusion independence. These findings support the role of IVO as an effective, oral, targeted treatment for pts with m*IDH1* R/R MDS. Clinical trial information: NCT02074839. Research Sponsor: Stephanie Kapsalis.

AE, n (%)	Pts with R/R MDS receiving 500 mg IVO QD, N = 16
Grade ≥3	11 (69)
Treatment-related	8 (50)
Treatment-related grade ≥3	2 (13)
Serious	7 (44)

7054 **Poster Session**

Impact of magrolimab treatment in combination with azacitidine on red blood cells in patients with higher-risk myelodysplastic syndrome (HR-MDS). *First Author: James Yuhtyng Chen, Stanford University School of Medicine, Stanford, CA*

Background: Magrolimab is a monoclonal antibody that blocks CD47, a "don't eat me" signal expressed on cancer cells to escape immune surveillance and macrophage-mediated clearance. Prior preclinical studies have shown that CD47 is critical to RBC homeostasis, with CD47 deficiency decreasing RBC half-life. Fc-mediated opsonization also depletes RBCs, raising concerns for potential on-target anemia from anti-CD47 agents via multiple mechanisms. Notwithstanding, several clinical trials have demonstrated that magrolimab can be safely administered as a monotherapy with initial lower "priming" dose yielding transient anemia with compensatory reticulocytosis, with anemia not observed at subsequent higher maintenance doses. However, the mechanism underlying this observed protection has not been fully defined. Here we describe manageable anemia in patients (pts) with HR-MDS treated with magrolimab in combination with azacitidine (AZA) (NCT03248479) and further investigate these underlying mechanisms in preclinical models. **Methods:** In a multicenter prospective study, CBCs, peripheral blood, and bone marrow (BM) were collected at prespecified timepoints from HR-MDS pts (n = 57) treated with magrolimab in combination with AZA. CBCs were measured, and blood and BM samples were analyzed by flow cytometry for expression of CD47 on RBCs and WBCs. Magrolimab was initially dosed with a priming dose (1mg/kg) followed by an initial weekly maintenance dosing (30mg/kg) before transitioning to every 2 weeks maintenance dosing. AZA 75mg/m^2 was administered on days 1-7 of the 28-day cycle. Preclinical modeling studies were conducted with intact and Fc-deficient anti-mouse CD47 (MIAP410) and anti-human CD47 (magrolimab) antibodies in murine models, including C57BL/6J B-hSIRPA/hCD47 mice. **Results:** Combination treatment of magrolimab with AZA resulted in a tolerable anemia that correlated with rapid, near complete loss of CD47 from RBCs, but not WBCs. The initial 1mg/kg priming dose was sufficient for this CD47 loss, which persisted under subsequent 30mg/kg maintenance doses. Both findings are consistent with prior clinical observations in solid tumor pts with magrolimab monotherapy and lymphoma pts in combination with rituximab. Our preclinical studies with mouse models revealed that the CD47 removal is mechanistically independent of previously described RBC antigen modulation mechanisms and cellular compartments. Instead, this CD47 loss requires anti-CD47 crosslinking between RBCs and non-RBCs. **Conclusions:** Overall, these results support that on-target magrolimab mediated anemia is mitigated by a near complete loss of RBC CD47. HR-MDS patients treated with magrolimab in combination with AZA exhibit a tolerable anemia through priming and maintenance doses. Clinical trial information: NCT03248479. Research Sponsor: Gilead Sciences, Inc.

7055 **Poster Session**

Hyperferritinemia as predictive biomarker of poor clinical outcomes in CMML. *First Author: Luis E. Aguirre, Moffitt Cancer Center, Tampa, FL*

Background: CMML is a heterogenous disease exhibiting features innate to MPN and MDS. Increasing evidence supports a close interplay between systemic inflammation and risk of myeloid malignancies, notably for those with history of infection or autoimmune disease. CMML has been associated with inflammation and end-organ damage related to CKD and CVD. Analysis of gene signatures from CMML-derived monocytes has shown them to be highly proinflammatory. High ferritin may serve as a practical biomarker of disease activity to help identify pts at higher risk of poor outcomes. **Methods:** Retrospective data was collected from a database of CMML pts treated at Moffitt Cancer Center. Pts were stratified in 2 cohorts based on ferritin levels (< 1000 or ≥1000 ng/mL). Hyperferritinemia was defined as ferritin > 1000 as seen at diagnosis or during follow-up. Kaplan–Meier was used to estimate OS. Cox regression was used for multivariate analysis. **Results:** Between August 1995 and October 2020 729 pts with CMML were identified. Median age at diagnosis was 71 (17-95). Out of 571 pts with available ferritin levels 29% (n = 168) developed hyperferritinemia vs 71% (n = 403) who did not. mOS was 32.4 mos (95%CI 30-35 mos). Pts with higher ferritin tended to present with CMML-2 (p = 0.001) and harbor a proliferative phenotype (p = 0.01). They presented with higher marrow cellularity (mean 83%, p = 0.08), PLT (mean 177k, p = 0.038), and lower Hb (mean 9.5, p < 0.05). There was no association with % circulating IMC, monocytes, WBC or ANC at baseline. Hyperferritinemia was associated with more profound fibrosis (p = 0.007), cytopenias (p < 0.05), % peripheral blasts (p < 0.05), RBC and PLT transfusion dependence (p < 0.05). Pts with hyperferritinemia had higher risk disease per IPSS-R, CPSS and all CMML models (p < 0.05); and had higher rates of AML transformation (p < 0.05). Pts were also more likely to require treatment earlier (within 3 yrs of diagnosis) (p < 0.05). ASXL1 (p = 0.002), EZH2 (p = 0.003), and SETBP1 (p = 0.019) mutations were more common among pts with hyperferritinemia. Conversely, TET2 (p = 0.001), CBL (p = 0.028) and SRSF2 (p = 0.003) mutations were less common. mOS for pts with hyperferritinemia was 23.9 mos (95%CI 19.9-27.9 mos), much lower than for those with ferritin < 1000 (mOS 40.5 mos, 95%CI 35.4-45.5 mos) (p < 0.05). In multivariate analysis, hyperferritinemia was a significant independent covariate for OS after adjusting for CPSS, transfusion dependence and disease phenotype (dysplastic vs proliferative) (HR = 0.69; 95%CI 0.53-0.89; p = 0.005). **Conclusions:** Almost 1/3 of pts with CMML will develop hyperferritinemia. This is associated with more aggressive disease and higher rates of AML transformation leading to dismal outcomes. ASXL1, EZH2, and SETBP1 MTs confer a higher risk of hyperferritinemia. Our findings indicate that hyperferritinemia is an independent prognostic biomarker that may serve as a surrogate representative of disease biology and comorbidities in CMML. Research Sponsor: None.

7056 **Poster Session**

Long-term utilization and benefit of luspatercept in patients (pts) with lower-risk myelodysplastic syndromes (LR-MDS) from the MEDALIST trial. *First Author: Pierre Fenaux, Service d'Hématologie Séniors, Hôpital Saint-Louis, Assistance Publique-Hôpitaux de Paris and Université Paris 7, Paris, France*

Background: Luspatercept was previously shown to improve anemia in the phase 3 MEDALIST trial of pts with LR-MDS ineligible, intolerant, or refractory to erythropoiesis-stimulating agents (ESAs). Here, we report the long-term clinical value of luspatercept treatment (Tx) in pts from the MEDALIST study including dosing and rates of progression to acute myeloid leukemia (AML) and high-risk MDS (HR-MDS). **Methods:** Eligible pts were ≥ 18 y of age, had LR-MDS requiring regular red blood cell (RBC) transfusions, and were ineligible/intolerant or refractory to ESAs. Pts were randomized 2:1 to subcutaneous luspatercept or placebo every 3 wk for 24 wk. The primary endpoint was RBC transfusion independence (RBC-TI) ≥ 8 wk during wk 1–24. MEDALIST pts were eligible for enrollment into the long-term follow-up study. Median duration of Tx and cumulative duration of response were determined by Kaplan–Meier (KM) analysis. Total person-years for pts at risk of HR-MDS/AML progression was calculated from LR-MDS diagnosis to HR-MDS/AML diagnosis, or to last HR-MDS/AML follow-up date for pts who did not progress. **Results:** As of January 15, 2021, the median duration of Tx was 11.70 (95% CI, 8.97–16.33) mo for luspatercept pts and 5.52 (95% CI, 5.52–5.59) mo for placebo pts. Of those enrolled in MEDALIST, 106/153 (69.3%) pts receiving luspatercept and 64/76 (84.2%) receiving placebo escalated to the maximum dose of 1.75 mg/kg. During the entire Tx phase, RBC-TI ≥ 8 wk was observed in 74/153 (48.4%) and 12/76 (15.8%) pts in the luspatercept and placebo arms, respectively, with a median cumulative duration of response of 80.7 (95% CI, 53.71–154.14) wk and 21.0 (95% CI, 10.86–NE) wk, respectively. During the entire Tx period, RBC-TI ≥ 16 wk was observed in 48/153 (31.4%) and 6/76 (7.9%) pts in the luspatercept and placebo arms, respectively (Table). Among pts randomized to luspatercept, 13/153 (8.5%) progressed to HR-MDS/AML during the entire Tx period, compared with 5/76 (6.6%) for placebo. The total person-years for pts randomized to luspatercept at risk of progressing to HR-MDS/AML was 401.7 y vs 190.9 y for placebo. **Conclusions:** Pts receiving luspatercept had an extended period of clinical benefit and > 50% of pts continued to receive luspatercept for > 1 y, the majority of whom underwent dose escalations to achieve an optimal response. Pts experienced durable responses with luspatercept, with a median cumulative duration of RBC-TI response of approximately 20 mo. Pts receiving luspatercept also appeared to have a longer time to HR-MDS/AML progression than those receiving placebo. Research Sponsor: None.

Achievement of RBC-TI ≥ 16 wk.

	Luspatercept (N = 153)	Placebo (N = 76)
Number of pts who achieved RBC-TI ≥ 16 wk, n (%)	48 (31.4)	6 (7.9)
95% CI	24.12–39.39	2.95–16.40
Common risk difference in response rate (95% CI), %	23.37 (14.05–32.69)	
Odds ratio (95% CI)	5.90 (2.34–14.90)	
P value	< 0.0001	

7057 **Poster Session**

Therapy related myeloid neoplasms (t-MNs) following PARP inhibitors (PARPi): Real-life experience. *First Author: Vincent Marmouset, Gustave Roussy, Villejuif, France*

Background: PARPi have shown promising results in several cancers, especially breast (BC) and ovarian cancer (OC), but may be associated with an increased risk of t-MNs. A careful monitoring of hematologic toxicity to exclude this risk is necessary. Here we described, in a real-life setting, the management of these adverse effect. **Methods:** First,we described, in a large cancer center, the profile of t-MN patients among OC patients treated with PARPi addressed in hematological consultation for cytopenias. Secondly, we compared t-MN post OC characteristics according to previous exposition to PARPi. Lastly, we described a large national observatory of 69 t-MNs post PARPi to decipher specific characteristics of these t-MNs. **Results:** From 2016 to 2021, among 373 PARPi treated patients for OC, 37 (10%) were explored for cytopenia's leading to 13 (3,5%) t-MNs diagnosis. No differences were seen in terms of age, BRCA1/2 status, type of PARPi, hemoglobin level but patients with t-MNs developed delayed cytopenias post-PARPi initiation (11 months vs to 4 months, p = 0.01), had a longer PARPi exposition (9 months vs 3 months, p = 0.01), lower platelets level (74 G/L vs 173 G/L, p = 0.0005), more cytopenias (2 vs 1, p = 0.0005). 77% of t-MNs patients had a *TP53* mutated t-MNs, 33% of patients w/o t-MNs had *TP53* mutated clonal hematopoiesis. In the last 20 years, 37 patients were addressed for t-MN post OC at our institute, with an increased incidence of 50% during the last 6 years. Compared to t-MN not exposed to PARPi, t-MN-PARPi patients had more *BRCA1/2* predisposition (61.5% vs 0% p = 0.03), their OC tended to be non-progressive (CR/PR/SD = 62.5% vs 38.5%, p = 0.3) and tend to have more *TP53* mutated t-MNs (77% vs 47%, p = 0.1). Median OS for t-MNs post PARPi was poor at 8.2 months (CI95% [2.03-18.7]) but not significantly different form other t-MNs (p = 0.8). We then studied 69 t-MNs-PARPi including 28 AML and 41 MDS in patient with history of OC (75%), BC (9%) or both (16%). Median age was 64 years, 80% received Olaparib, 72.5% had a *BRCA1/2* predisposition. Median time between cancer diagnosis and initiation of PARPi was 44 months and median duration of PARPi treatment was 14 months. History of haematological toxicity secondary to PARPi was reported in 51% of patients. Karyotype was often complex (61%) associated with a high rate of *TP53* mutation (70.5%). Median OS was 9.7 months (CI95%, 5.3-13.9). In multivariate analysis, a longer delay between the end of PARPi treatment and t-NM diagnosis (HR 1.046, p = 0.02), as well Olaparib treatment compared to others PARPi (HR 5.82, p = 0.003 and AML diagnosis (HR 2.485, p = 0.01) were associated with shorter OS. **Conclusions:** We describe in a large series a higher incidence of t-MNs post PARPi than previously reported. Unfavorable cytogenetic and molecular abnormalities associated with these t-MNS explained the poor OS. Early detection is crucial particularly in case of delayed appearance of cytopenias. Research Sponsor: None.

7058 **Poster Session**

Risk-adjusted safety analysis of pacritinib (PAC) in patients (pts) with myelofibrosis (MF). *First Author: Naveen Pemmaraju, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: PAC is a novel JAK2/IRAK1 inhibitor that has shown significant activity in pts with MF, including those with platelet (plt) counts $<50\times10^9$/L. Recently, JAK inhibitors have come under increased scrutiny due to specific, emerging toxicities with drugs in this class. This safety analysis focuses on these toxicities of interest for pts treated with PAC 200 mg BID and best available therapy (BAT), including ruxolitinib (RUX), on the Phase 3 PERSIST-2 and Phase 2 PAC203 studies. Data are presented as risk-adjusted incidences to account for differential time at risk for adverse events (AEs) between arms due to cross-over. **Methods:** Pts treated with PAC 200 mg BID on PERSIST-2 and PAC203, and those treated with BAT on PERSIST-2, were included. Risk-adjusted AEs, representing event rate per 100 patient-years (pt-yrs), were calculated for overall and fatal AEs, bleeding AEs (determined by Standardized Medical Dictionary for Regulatory Activities Query [SMQ]), cardiac AEs (by SMQ), major cardiac events (per major adverse cardiovascular events [MACE] classification), infections, thromboses, and secondary malignancies. **Results:** A total of 160 pts were analyzed as the pooled PAC group (n=106 in PERSIST-2; n=54 in PAC203) and 98 pts in the BAT group (44 on RUX). At baseline, median plt count was 57×10^9/L; 61% had prior JAK2 inhibitor therapy. The rate of AEs was higher on PAC versus BAT, while the rate of fatal AEs was lower (Table). Both bleeding and cardiac events occurred at slightly lower rates on PAC compared to BAT. There were no MACE events on PAC, whereas there were on BAT. Malignant neoplasms occurred at similar rates on PAC and BAT, though rate of non-melanoma skin cancers was lower in pooled PAC (3/100 pt-yrs) versus BAT (7/100 pt-yrs), including RUX (11/100 pt-yrs). Infection occurred more frequently on PAC, though fungal and viral infections occurred less frequently, as did herpes zoster reactivation (pooled PAC: 0/100 pt-yrs vs BAT: 2.4/100 pt-yrs, including RUX: 5.5/100 pt-yrs). Thrombosis occurred at similar rates on PAC and BAT. **Conclusions:** Risk-adjusted analysis demonstrates that the safety profile of PAC 200 mg BID is comparable or superior to BAT, including RUX. PAC 200 mg BID may represent a full-dose therapeutic option for pts with MF, including those with thrombocytopenia. Clinical trial information: NCT02055781; NCT04884191. Research Sponsor: CTI BioPharma.

Risk-adjusted treatment-emergent AEs (TEAEs) in PERSIST-2 and PAC203.

	PERSIST-2			PAC203	Pooled
≥1 TEAE (/100 pt-yrs)	PAC N=106	BAT N=98	BAT=RUX N=44	PAC N=54	PAC N=160
Any TEAE	1390	903	1468	2063	1570
Fatal TEAE	12	22	27	10	12
Bleeding AE	98	129	127	105	100
Cardiac AE	62	81	67	101	73
MACE[1]	0	5	5	0	0
Malignancy (excluding leukemic transformation)	8	7	11	0	5
Infection[2]	124	88	80	103	116
Fungal infection	5	12	6	10	6
Thrombosis[3]	2	2	6	10	4

[1]Includes fatal cardiac events, non-fatal myocardial infarction (MI), non-fatal cerebral infarction. [2]Desginated by System Order Class. [3]Includes arterial and venous thrombosis, thrombotic MI, cerebral infarction.

7059 **Poster Session**

Evaluation of serum vascular endothelial growth factor as a biomarker in Erdheim-Chester disease. *First Author: Anais Roeser, Service de Médecine Interne 2, Hôpital Pitié Salpètrière, Assistance Publique Hôpitaux de Paris (AP-HP), Paris, France*

Background: Erdheim-Chester disease (ECD) is a rare histiocytosis characterized by tissue infiltration of $CD68^+$, $CD1a^-$ histiocytes, derived from cells of the mononuclear phagocyte system harboring recurrent mutations in the MAPK-signaling pathway. Vascular endothelial growth factor-A, also referred as VEGF, is a major regulator of angiogenesis, implicated in cancer pathophysiology. Mutation of the RAS oncogene induce the upregulation of VEGF gene expression. We hypothesized that VEGF could play a role in ECD pathophysiology. We aimed to determine if VEGF was expressed by ECD histiocytes, to assess levels of serum VEGF (sVEGF) in ECD patients, and determine if they were associated with patient's characteristics. **Methods:** We conducted a retrospective study, screening all ECD patients seen in the French National Reference Center for Histiocytoses (Pitié-Salpètrière Hospital) from 2009 to 2019. Patients were included if they had at least one sVEGF determination. Biopsies of patients with extreme sVEGF were centrally reviewed and an immunostaining for VEGF was practiced using 2 different antibodies (F/PU483-UP and VG-1). **Results:** We included 248 patients in the analysis. sVEGF were high (> 500pg/mL) at first determination in 123 patients (53%), and > 1000 pg/mL in 47 (19%). Median sVEGF was 843pg/mL in the high sVEGF group, 288pg/mL in the low sVEGF group. Sex, age, and *BRAF* status were not significantly different between the 2 groups. We analyzed 24 histological samples. Histiocytes had a VEGF staining in all samples analyzed, moderate (grade 2) in 5 and 1 cases and intense (grade 3) in 17 and 22 cases based on F/PU483-UP and VG-1 clone respectively. Control (4 biopsies of reactional sinusal histiocytoses) showed no histiocytic VEGF staining. Patients with high sVEGF had more frequently a vascular involvement (71% vs 48%, p = 0.0004) and a cardiac involvement (58% vs 41%, p = 0.008). Consecutive measurements of sVEGF were available for 183 patients (median interval: 24 months). sVEGF significantly decreased during follow-up (p < 0.0001). Consecutive cardiac MRI were available for 45 patients (median interval: 48 months). All patients had cardiac involvement: 6 achieved complete response, 25 partial response, 12 were stable, and 2 progressed. Mean variation of sVEGF (ΔsVEGF) of patients with complete response, partial response and stable disease were respectively - 591.3, -163.9, - 239.6 pg/mL and were significantly different from patients who progressed (mean ΔsVEGF + 555.5pg/mL). No patients in our cohort received a systemic anti-VEGF therapy for ECD or another indication. **Conclusions:** In our study, sVEGF was high in 53% of ECD patients, and its elevation associated with cardiac and vascular involvements. Variations of sVEGF were associated with responses of cardiac involvement under therapy. VEGF was at least partly produced by ECD histiocytes. sVEGF could help monitor cardiac involvement activity. Research Sponsor: None.

7060 **Poster Session**

A phase 1, open-label, dose-escalation study of selinexor plus ruxolitinib in patients with treatment-naïve myelofibrosis.

First Author: Haris Ali, City of Hope, Duarte, CA

Background: Myelofibrosis (MF) is a myeloproliferative neoplasm characterized by unregulated, clonal proliferation of a hematopoietic stem cells in the bone marrow and is commonly associated with gene mutations in *JAK2, CALR*, or *MPL*. Front-line therapy may include the JAK1/2 inhibitor ruxolitinib (RUX), resulting in spleen volume reductions and improvement in MF-related symptoms. Despite the therapeutic effect of RUX, most patients (pts) eventually progress and thus novel combinations are required to increase responses and delay progression. Selinexor (SEL) is an oral selective inhibitor of nuclear export (SINE) compound, specifically inhibiting exportin-1 (XPO1), and currently approved for treatment of multiple myeloma and diffuse large B-cell lymphoma. Significant activity of SEL in combination with RUX has been shown in preclinical studies, and SEL monotherapy in MF refractory to JAK inhibitors demonstrated robust clinical activity and a tolerable safety profile (NCT03627403). Here, we present the initial results of a phase 1 dose escalation study of the combination SEL and RUX in treatment-naïve MF. **Methods:** The ongoing multicenter, open-label, Phase 1/2 study (NCT04562389) is evaluating the efficacy and safety of SEL plus RUX in JAKi-naïve MF pts. Two dose levels of SEL were evaluated, 40mg and 60mg once-weekly (QW) plus RUX twice daily (BID) as per label in 28-day cycles, using a 3+3 design. All pts received 5-HT3 antagonist for nausea prophylaxis. Primary objectives include safety, maximum tolerated dose (MTD), recommended Phase 2 dose (RP2D), and preliminary efficacy. Secondary objectives include spleen, symptom, and anemia response, and OS. **Results:** As of 31 Jan 2022, 10 pts have been dosed in 2 dose levels (40mg (n = 3), and 60mg (n = 7) SEL QW plus RUX). RUX starting dose was 20 mg in 8 pts, 15 mg in one patient and 10 mg in one patient. The median age was 64 (range 45-76). Seven pts had primary MF and 3 had post-ET MF. DIPSS risk category was int-1 (n = 4), int-2 (n = 4) and high risk (n = 2). No dose limiting toxicities have been reported at either dose levels of SEL. One patient required dose interruption due to dizziness and later discontinued treatment due to new onset of atrial fibrillation and pulmonary hypertension (unrelated to SEL and RUX) after 5 months of therapy. All other pts remain on study. There was no grade 3 neutropenia or thrombocytopenia observed. Hemoglobin level was maintained without any significant worsening. The most common treatment-emergent adverse event was low grade nausea (30%). All pts experienced improvement in their white blood cell count. Four of the first 5 evaluable pts demonstrated ≥35% spleen volume reduction at week 12. **Conclusions:** The combination of SEL and RUX has been well-tolerated and with a manageable side effect profile. No dose limiting toxicities were observed in pts with treatment-naïve MF in cohort 1 of once weekly oral SEL 40 and 60 mg with RUX. Clinical trial information: NCT04562389. Research Sponsor: Karyopharm Therapeutics.

7061 **Poster Session**

Thrombocytopenic myelofibrosis (MF) patients previously treated with a JAK inhibitor in a phase 3 randomized study of momelotinib (MMB) versus danazol (DAN) [MOMENTUM].

First Author: Aaron Thomas Gerds, Cleveland Clinic Taussig Cancer Institute and Case Comprehensive Cancer Center, Cleveland, OH

Background: MMB, an oral JAK1/2 and ACVR1/ALK2 inhibitor, showed clinical activity on MF symptoms, RBC transfusion requirements (anemia), and spleen volume in the SIMPLIFY trials, including in MF patients (pts) with thrombocytopenia. MOMENTUM is a pivotal phase 3 study of symptomatic and anemic MF pts previously treated with a JAK inhibitor (JAKi) testing MMB vs DAN. This analysis evaluated MOMENTUM pts with baseline (BL) platelet counts (PLT) ≤150 x 10^9/L. **Methods:** Eligibility: Primary or post-ET/PV MF; DIPSS high risk, Int-2, or Int-1; MF Symptom Assessment Form Total Symptom Score (MFSAF TSS) ≥10; Hgb <10 g/dL; prior JAKi for ≥90 days, or ≥28 days if RBC transfusions ≥4 units in 8 weeks (wks) or Gr 3/4 thrombocytopenia, anemia, or hematoma; palpable spleen ≥5 cm; PLT ≥25 x 10^9/L. JAKi taper and washout was ≥21 days. Randomization: 2:1 to MMB 200 mg QD plus DAN placebo or DAN 600 mg QD plus MMB placebo for 24 wks. Primary endpoint: TSS response (≥50% reduction from BL) rate at wk 24. Key secondary endpoints, assessed sequentially at wk 24: RBC transfusion independence (TI) rate, splenic response rate (SRR; ≥25% reduction in volume from BL), change from BL in TSS, SRR (≥35% reduction from BL) and rate of zero transfusions since BL. **Results:** 60 (74%) of 81 MMB pts and 25 (58%) of 43 DAN pts with BL PLT ≤150 x 10^9/L completed the 24-week randomized treatment (RT) phase. Median BL TSS were 29 (MMB) and 24 (DAN), Hgb were 7.9 (MMB) and 8.0 (DAN) g/dL, and PLT were 67 x 10^9/L (MMB) and 64 x 10^9/L (DAN). Prior JAKi was ruxolitinib in 124 pts (100%) and fedratinib in 6 pts (5%). Efficacy results are in Table. These results are consistent with the overall ITT analysis set (N=195). Most common Gr ≥3 TEAEs in the RT phase were thrombocytopenia (MMB, 31%; DAN, 16%) and anemia (MMB, 7%; DAN, 14%); Gr ≥3 bleeding events occurred in 9% of MMB and 5% of DAN pts. TEAEs led to study drug discontinuation in 15% of MMB and 19% of DAN pts in RT phase. A trend toward improved OS up to wk 24 was seen with MMB vs DAN [HR (95% CI)=0.490 (0.195, 1.235)]. Additional analyses of pts with BL PLT <100 x 10^9/L (N=100) and BL PLT <50 x 10^9/L (N=31) show similar treatment effects of MMB vs DAN. **Conclusions:** In thrombocytopenic MF pts who were symptomatic and anemic, MMB was superior to DAN for symptom responses, transfusion requirements, and spleen responses and showed comparable safety and favorable survival. MMB may address a critical unmet need in thrombocytopenic MF pts. Clinical trial information: NCT04173494. Research Sponsor: Sierra Oncology, Inc.

Wk 24 Endpoint in Subjects with PLT ≤150x10^9/L	MMB (N=81)	DAN (N=43)	Difference (95% CI)
TSS response rate, %	29.6	11.6	18.0 (0.7, 31.5)
TI rate, %	32.1	18.6	13.5 (-3.9, 28.5)
SRR ≥25, %	39.5	7.0	32.5 (15.3, 45.4)
TSS change from BL*	-10.7	-3.8	-7.0 (-11.7, -2.2)
SRR ≥35, %	22.2	4.7	17.6 (2.3, 29.1)
Zero transfusion rate, %	30.9	11.6	19.2 (2.3, 32.8)

*Least-squares mean from mixed model for repeated measures.

7062 **Poster Session**

Lisocabtagene maraleucel (liso-cel) as second-line (2L) therapy for R/R large B-cell lymphoma (LBCL) in patients (pt) not intended for hematopoietic stem cell transplantation (HSCT): Primary analysis from the phase 2 PILOT study.

First Author: Alison Sehgal, University of Pittsburgh Medical Center, Hillman Cancer Center, Pittsburgh, PA

Background: Pts with R/R LBCL after first-line (1L) treatment (tx) who are unable to undergo high-dose chemotherapy (HDCT) and HSCT have poor outcomes and limited tx options. PILOT (NCT03483103) evaluated liso-cel, an autologous, CD19-directed chimeric antigen receptor (CAR) T cell product, as 2L tx in pts with R/R LBCL not intended for HSCT. **Methods:** Eligible pts were adults with R/R LBCL after 1L tx who were not deemed candidates for HDCT and HSCT by their physician and met ≥ 1 frailty criteria: age ≥ 70 yr, ECOG PS = 2, DLCO ≤ 60%, LVEF < 50%, CrCl < 60 mL/min, or ALT/AST > 2 × ULN. Bridging tx was allowed. Pts received lymphodepletion with cyclophosphamide and fludarabine, followed 2–7 days later by liso-cel at a target dose of 100 × 10^6 CAR^+ T cells. Cytokine release syndrome (CRS) was graded per Lee 2014 criteria and neurological events (NE) per NCI CTCAE, version 4.03. Primary endpoint was ORR per independent review committee (IRC); all pts had ≥ 6 mo follow-up (f/u) from first response. **Results:** Of 74 pts leukapheresed, 61 received liso-cel and 1 received nonconforming product. Common reasons for pre-infusion dropout included death and loss of eligibility (5 each). For liso-cel–treated pts, median age was 74 yr (range, 53–84; 79% ≥ 70 yr) and 69%, 26%, and 5% met 1, 2, and 3 frailty criteria, respectively; 26% had ECOG PS = 2 and 44% had HCT-CI score ≥ 3. After 1L tx, 54% were chemotherapy refractory, 21% relapsed ≤ 12 mo, and 25% relapsed > 12 mo; 51% of pts received bridging chemotherapy. Median (range) on-study f/u was 12.3 mo (1.2–26.5). ORR and CR rate was 80% and 54%, respectively. Median DOR and PFS was 12.1 mo and 9.0 mo, respectively. Median OS has not been reached (Table). Most frequent tx-emergent AEs (TEAE) were neutropenia (51%), fatigue (39%), and CRS (38%), with grade (gr) 3 CRS in 1 pt (2%) and no gr 4/5 CRS. Any-grade NEs were seen in 31%, gr 3 in 5% (n = 3), and no gr 4/5 NEs; 7% received tocilizumab, 3% corticosteroids, and 20% both for tx of CRS/NEs. Overall, gr ≥ 3 TEAEs occurred in 79%, with gr 5 in 2 pts (both due to COVID-19). Two pts (3%) had gr 3/4 infections and 15 (25%) had gr ≥3 neutropenia at Day 29. **Conclusions:** In the PILOT study, liso-cel as 2L tx in pts with LBCL who met ≥ 1 frailty criteria and for whom HSCT was not intended demonstrated substantial and durable overall and complete responses, with no new safety concerns. Clinical trial information: NCT03483103. Research Sponsor: Bristol Myers Squibb.

Efficacy, IRC assessed (Lugano 2014 criteria)	Liso-cel treated (N = 61)
ORR / CR rate, n (%) [95% CI]	49 (80) [68.2–89.4] / 33 (54) [40.8–66.9]
DOR, median (95% CI), mo Median (range) f/u, mo	12.1 (6.2–NR) 15.5 (0–23.0)
DOR for pts achieving CR / PR, median (95% CI), mo	21.7 (12.1–NR) / 2.1 (1.4–3.3)
PFS, median (95% CI), mo Median (range) f/u, mo	9.0 (4.2–NR) 13.0 (0.7–23.9)
OS, median (95% CI), mo Median (range) f/u, mo	NR (17.3–NR) 17.6 (1.2–35.4)
Probability of OS at 1 year (95% CI), %	70.0 (56.1–80.3)

TPS7063 **Poster Session**

An open-label, multicenter, phase 1b/2 study of navtemadlin (KRT-232) in patients with relapsed/refractory acute myeloid leukemia secondary to myeloproliferative neoplasms.

First Author: Raajit Rampal, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Patients with relapsed/refractory (R/R) acute myeloid leukemia (AML) secondary to myeloproliferative neoplasms (MPN) have limited treatment options, resulting in poor prognosis with median overall survival < 6 months (Dunbar 2020). Although conventional AML therapy can induce responses in a subset of patients, it does not prolong survival in AML secondary to MPN (Khan 2017). Navtemadlin is a potent, selective, orally available murine double minute 2 (MDM2) inhibitor that restores p53 activity to drive apoptosis in *TP53* wild-type (*TP53*^{WT}) malignancies. MDM2 is frequently overexpressed in AML with the majority being *TP53*^{WT}, suggesting that MDM2 inhibition may be a rational approach for the treatment of AML secondary to MPN (Rampal 2014; Carvajal 2018). Preclinically, navtemadlin had dose-dependent activity reducing leukemic cell burden and significantly prolonging survival in a murine MPN-blast phase, patient-derived xenograft model (Wang 2021). Evidence of clinical activity of navtemadlin monotherapy in R/R AML was observed among *TP53*^{WT} patients in a Phase 1b dose-escalation study (Erba 2019). In a Phase 2 study of intermediate-high risk R/R myelofibrosis patients, navtemadlin demonstrated clinical activity that correlated with disease-modifying effects (Al-Ali 2020; Vachhani 2021). Together, these studies provide biological and clinical support for evaluating navtemadlin in patients with R/R AML secondary to MPN. **Methods:** The open-label, multicenter Phase 1b/2 KRT-232-104 study (NCT04113616) is evaluating *TP53*^{WT} patients with R/R AML secondary to MPN (myelofibrosis, polycythemia vera, or essential thrombocythemia). Eligible patients are aged ≥18 years with ECOG performance status of 0-2 and adequate hepatic and renal function. Patients must have received ≥1 prior lines of therapy for AML secondary to MPN; prior treatment with a FLT3 or IDH1/IDH2 inhibitor is required if appropriate and available. Patients who have undergone allogeneic or autologous stem cell transplantation within 3 months or have active graft-versus-host disease prior to first study dose will be excluded. Patients (n = 12/arm) will be randomly assigned to receive oral navtemadlin once daily in Arm 1: 360 mg 7 days (D) on/21D off, Arm 2: 360 mg 7D on/21D off in Cycle 1 followed by 240 mg 7D on/21D off in subsequent cycles, or Arm 3: 180 mg 7D on/14D off until disease progression or unacceptable toxicity. The primary endpoint is Recommended Phase 2 Dose of navtemadlin. Secondary endpoints include rates of complete remission (CR; per modified 2017 European LeukemiaNet response criteria), CR with partial hematologic improvement, CR with incomplete hematologic recovery, overall response rate, duration of response, progression-free survival, overall survival, and safety. This trial is ongoing and will enroll patients at 65 global sites. Clinical trial information: NCT04113616. Research Sponsor: Kartos Therapeutics, Inc.

TPS7064 **Poster Session**

COVALENT-101: A phase 1 study of BMF-219, a novel oral irreversible menin inhibitor, in patients with relapsed/refractory (R/R) acute leukemia (AL), diffuse large B-cell lymphoma (DLBCL), and multiple myeloma (MM).

First Author: Farhad Ravandi, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Menin, a protein involved in transcriptional regulation, impacting cell cycle control, apoptosis, and DNA damage repair, plays a direct role in oncogenic signaling in multiple cancers. Inhibition of menin is therefore a novel approach to cancer treatment. Preclinical data of BMF-219, a highly selective, orally bioavailable, small-molecule irreversible inhibitor of menin, show sustained potent abrogation of menin-dependent oncogenic signaling in vitro and in vivo. BMF-219 exhibited a strong anti-proliferative effect on various menin-dependent acute myeloid leukemia (AML) cell lines, DLBCL lines representing Double/Triple Hit Lymphoma (DHL/THL) and Double Expressor Lymphoma (DEL), and MM cell lines with diverse mutational backgrounds. BMF-219 also showed high potency *ex vivo* in patient samples from MLL-rearranged and NPM1-mutant AML, THL and MYC-amplified DLBCL, and bone marrow mononuclear cells from treatment-naive and R/R MM. **Methods:** COVALENT-101 (NCT05153330) is an open-label, multi-cohort, non-randomized, multicenter Phase I study evaluating the safety, tolerability, and clinical activity of escalating doses of once daily oral BMF-219 in patients with R/R AL, DLBCL and MM who have received standard therapy. Utilizing an accelerated titration design, doses of BMF-219 will be escalated in single-subject cohorts independently for each indication until 1 subject experiences either a ≥ Grade 2 related-adverse event or dose limiting toxicity (DLT). At that point, the cohort will switch to a classical "3 + 3" design. Treatment will continue in 28-day cycles until progression or intolerability. Expansion cohorts for each indication will enroll patients to obtain further safety and efficacy data. Patients with R/R AL, R/R DLBCL ≥ 2 but ≤ 5 therapies, and R/R MM who received ≥ 3 therapies and failed or are ineligible for any standard therapies are eligible. Patients must have ECOG PS ≤ 2, and adequate organ function. Key exclusion criteria include known CNS disease involvement, prior menin inhibitor therapy, and clinically significant cardiovascular disease. The primary objective is to determine independently for each cohort/indication the optimal biological dose (OBD)/ recommended Phase 2 dose (RP2D) of BMF-219 oral monotherapy. Key secondary objectives include further evaluation of safety and tolerability, characterization of the pharmacodynamics and pharmacokinetics of BMF-219, and assessment of its antitumor activity based on best overall response rate (ORR), duration of response (DOR), progression-free survival (PFS), and time to progression (TTP) per disease-specific response criteria as assessed by the investigator. Food-effect studies will be performed in DLBCL and MM patients at certain dose levels. The enrollment commenced in January 2022. Clinical trial information: NCT05153330. Research Sponsor: Biomea Fusion, Inc.

TPS7065 **Poster Session**

Tamibarotene in combination with venetoclax and azacitidine in previously untreated adult patients selected for RARA-positive AML who are ineligible for standard induction therapy (SELECT AML-1).

First Author: Eytan Stein, Department of Medicine, Leukemia Service, Memorial Sloan Kettering Cancer Center, New York, NY

Background: RARA-positive (RARA+) AML is a novel genomically defined patient subset with an actionable biological target for treatment with tamibarotene, an oral and selective RARα agonist (McKeown 2017). RARA+ patients can be selected by a blood-based biomarker test, with approximately 30% of newly diagnosed (ND) AML patients being RARA+ (Vigil 2017). As a biologically targeted agent for patients with *RARA* overexpression, tamibarotene has the potential to provide benefit irrespective of mutation or cytogenetic risk classification. In RARA+ ND AML patients ineligible for standard induction therapy, tamibarotene plus azacitidine (aza) led to a CR/CRi rate of 61% and a rapid onset of response (de Botton 2020). Approximately one-third of patients with ND unfit AML do not respond to front-line standard of care venetoclax (ven)/aza (DiNardo 2020). Translational data suggest RARA positivity enriches for monocytic features reported to be associated with ven resistance (Fiore 2020, Pei 2020). This data suggests the RARA biomarker selects for patients who may respond to tamibarotene and may be less likely to respond to ven/aza. Given that tamibarotene plus aza has been generally well tolerated, with no increase in myelosuppression compared to single agent aza (de Botton 2020), it is anticipated that tamibarotene can be administered safely in combination with ven/aza. **Methods:** This is a Phase 2, open-label, multi-center study in the U.S. and France comparing the clinical activity of tamibarotene/ven/aza to ven/aza in treatment-naive RARA+ AML patients ineligible for standard induction chemotherapy. The primary objectives are to characterize the safety of the combination and to compare the CR/CRi rate of tamibarotene/ven/aza vs. ven/aza, with secondary objectives to compare CR rate, CR/CRh rate, duration of response, and time to response. The overall response rate using tamibarotene/ven/aza following ven/aza treatment failure will be explored. Clinical activity will be characterized by ELN criteria (Dohner 2017). This 3-part trial includes a safety lead-in, randomized efficacy study, and salvage arm. Following the safety lead-in, approximately 80 patients will be randomized 1:1 to receive tamibarotene/ven/aza or ven/aza. Response rates and 95% exact binomial confidence intervals will be calculated by treatment group. In the salvage arm, tamibarotene will be added for study patients randomized to ven/aza who experience progressive disease, relapse, or treatment failure. Patients will be treated with aza at 75 mg/m^2 IV/SC daily on days 1-7, ven on days 1-28 per VENCLEXA USPI, followed by tamibarotene at 6 mg twice per day by mouth on days 8-28 of each 28-day cycle. The SELECT AML-1 trial opened in July 2021 with ongoing enrollment. Clinical trial information: NCT04905407. Research Sponsor: Syros Pharmaceuticals.

TPS7066 **Poster Session**

Phase 1/2, open-label, dose-escalation, dose-expansion study of menin inhibitor DSP-5336 in adult patients with acute leukemia with and without mixed-lineage leukemia (*MLL*)-rearrangement (r) or nucleophosmin 1 (*NPM1*) mutation (m).

First Author: Naval Guastad Daver, Department of Leukemia, MD Anderson Cancer Center, Houston, TX

Background: DSP-5336, a menin *MLL* interaction inhibitor, elicited antitumor activity in *MLL*–r or *NPM1m* acute leukemia models *in vitro* and *in vivo*. An open-label, single-arm, phase 1/2 study (NCT04988555) will evaluate the safety and efficacy of DSP-5336 and determine the recommended phase 2 dose (RP2D) in patients with relapsed/refractory (R/R) acute myeloid leukemia (AML) or acute lymphocytic leukemia (ALL). **Methods:** Patients aged ≥18 y with R/R AML, ALL, or acute leukemia of ambiguous lineage after ≥1 line of standard therapy, ECOG PS 0–2, and adequate organ function are eligible. Patients will receive DSP-5336 twice daily for 28 d/cycle. In phase 1, there will be two parallel escalation cohorts: patients who do not receive concomitant azole antifungal medication and patients who receive antifungal azoles (ie, posaconazole, voriconazole, or fluconazole); 21–30 patients will be enrolled during phase 1 into multiple ascending dose levels. Dose escalation will use a Bayesian logistic regression model. Phase 2 will enroll two arms: R/R AML with *MLL*–r and R/R AML with *NPM1m* (10–20 patients/arm). Patients will be treated at the RP2D to evaluate clinical activity and safety. Clinical trial information: NCT04988555. Research Sponsor: Sumitomo Dainippon Pharma Oncology, Inc.

Study endpoints.

Endpoints	Phase 1 (R/R AML or ALL)	Phase 2 (R/R AML with *MLL*–r and/or *NPM1m*)
Primary	Safety DLTs; TEAEs, SAEs; changes in vital signs, PEs, clinical lab values, ECG & ECHO parameters Tolerability Dose interruptions, reductions, and/or discontinuations Biologic efficacy	Clinical Responses CR (MRD–), CR, CRh, CRi, PR, MLFS, CR + CRh, OR (=CR [MRD–] + CR + CRh + CRi + MLFS + PR), DOR, TTR, time to CR, TI, OS, EFS, RFS
Secondary	Pharmacokinetics Plasma DSP-5336 concentration-time profiles and PK parameters Clinical Responses CR (MRD–), CR, CRh, CRi, PR, MLFS, OR (=CR [MRD–] + CR + CRh + CRi + MLFS + PR), time to CR, DOR, TTR, TI, OS, RFS, EFS Cardiac Safety QT interval changes and morphology	Safety DLTs; TEAEs, SAEs; changes in vital signs, PEs, clinical lab values, ECG parameters Tolerability Dose interruptions, reductions, and/or discontinuations
Exploratory	Pharmacodynamics Changes in expression levels of leukemogenesis and myeloid differentiation genes	

Definitions: AE, adverse event; CR, complete response; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; DLT, dose-limiting toxicity; DOR, duration of response; ECG, electrocardiogram; ECHO, echocardiogram; EFS, event-free survival; MLFS, morphologic leukemia-free state; MRD, minimal residual disease; OR, objective response; PE, physical examination; PR, partial response; RFS, relapse-free survival; SAE, serious AE; TEAE, treatment-emergent AE; TI, transfusion independence; TTR, time to response.

TPS7067 **Poster Session**

Lemzoparlimab (lemzo) with venetoclax (ven) and/or azacitidine (aza) in patients (pts) with acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS): A phase 1b dose escalation study.

First Author: Naval Guastad Daver, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Despite treatment advances, pts with AML or higher-risk MDS who are ineligible for standard intensive treatments still have poor survival, highlighting the need for novel therapies. Overexpression of CD47 is common in leukemic stem cells and AML blasts and correlates with poor clinical outcomes. Lemzo is an anti-CD47 antibody with red blood cell–sparing properties. Treatment with ven plus aza has shown favorable safety and efficacy in older/unfit pts with AML and higher-risk MDS. Blocking CD47 is hypothesized to hypersensitize AML cells to the antitumor activity of ven and aza. This study will evaluate the safety and dose-limiting toxicities (DLTs) of lemzo with ven + aza for pts with treatment-naïve AML, as well as lemzo with aza ± ven for treatment-naïve higher-risk MDS. **Methods:** This phase 1b, open-label, dose-escalation study (NCT04912063) is enrolling adults with: (1) treatment-naïve AML with adverse cytogenetic/molecular risk not suitable for induction therapy, with an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) 0–2 (aged ≥75 years) or 0–3 (aged ≥18–74 years) excluding acute promyelocytic leukemia; or (2) treatment-naïve higher-risk MDS (Revised International Prognostic Scoring Score > 3) with < 20% bone marrow blasts, ECOG-PS 0–2, and no immediately planned stem cell transplant. For each 28-day cycle, aza is administered subcutaneously or intravenously (IV) daily for 7 days within the first 9 days (7-0-0 or 5-2-2 schedule); ven is administered orally daily on days 1–28 (AML, following dose ramp-up) or days 1–14 (ven-containing MDS cohorts). Lemzo is administered IV at a schedule that is to be determined in this study. Dose escalation has Bayesian optimal interval design and may be expanded to investigate alternate dosing for lemzo. Dose expansion will initiate at recommended phase 2 dose. Treatment discontinuation criteria are unacceptable toxicity, progressive disease, lack of partial/complete remission or clinical benefit within 6 cycles, or at physician's discretion. Pts who discontinue study treatment without progression will continue with posttreatment follow-up; pts who progress will enter survival follow-up. The primary endpoints are DLTs of lemzo. Secondary endpoints for both cohorts include best overall responses of complete remission, duration of response, event-free survival, and overall survival. Exploratory biomarker endpoints are included. Safety assessments include adverse event (AE, graded per National Cancer Institute Common Terminology Criteria for AEs v5.0) monitoring, physical examinations, vital signs, electrocardiograms, and laboratory tests. Response rates will be analyzed with estimates and 95% confidence intervals based on exact binomial distribution. Time-to-event endpoints will be analyzed using Kaplan–Meier methodology. Clinical trial information: NCT04912063. Research Sponsor: AbbVie.

TPS7068 **Poster Session**

Oral azacitidine plus venetoclax in patients with relapsed/refractory or newly diagnosed acute myeloid leukemia: The phase 1b OMNIVERSE trial. *First Author: Farhad Ravandi, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: For patients (pts) with acute myeloid leukemia (AML) who cannot undergo intensive chemotherapy (IC), lower-intensity treatment (Tx) regimens, including low-dose cytarabine (LDAC) and hypomethylating agents (HMAs; azacitidine [AZA], decitabine), are generally well tolerated but are associated with lower response rates than IC [Vey 2020]. Similarly, the BCL2 inhibitor, venetoclax (VEN), has shown antileukemic activity, although only modest clinical benefit as monotherapy [Konopleva 2016]. VEN + AZA shows synergistic activity in preclinical models, enhancing leukemic cell apoptosis in vitro and anti-tumor activity in vivo [Jin 2020]. In IC-ineligible pts with ND AML, VEN + injectable AZA significantly increased complete remission (CR)/CR with incomplete hematologic recovery (CRi) rates ($P < 0.001$) and prolonged overall survival (OS; $P < 0.001$) vs AZA only [DiNardo 2020]. VEN, in combination with an HMA or LDAC, is approved in the US for Tx of pts with ND AML ≥ 75 years (y) of age or who cannot undergo IC due to comorbidities. Oral-AZA (CC-486) is approved for Tx of pts with newly diagnosed (ND) AML in first CR or CRi after IC who cannot receive curative therapy (eg, HSCT). In the phase 3 QUAZAR AML-001 trial, maintenance Tx with Oral-AZA 300 mg QD for 14 days (d)/28-d Tx cycle improved OS and relapse-free survival vs placebo in older pts in CR/CRi after IC [Wei 2020]. Incorporation of AZA into DNA is S-phase-restricted; thus, extending AZA exposure over a longer duration by using an oral formulation increases the opportunity for cycling tumor cells to incorporate the drug to sustain therapeutic activity [Laille 2015]. Additionally, an all-oral combination regimen allows for outpatient administration to optimize pt convenience and reduce resource utilization. **Methods:** OMNIVERSE (NCT04887857) is an open-label, multicenter, 2-part phase 1b trial. The main goals are to evaluate safety and establish the maximum tolerated dose of Oral-AZA + VEN in pts ≥ 18 y of age with relapsed/refractory AML who are ineligible for further IC (*part 1*), and subsequently, in pts with ND AML ≥ 75 y of age, or pts 18–74 y of age with comorbidities that prevent use of IC or HSCT (*part 2*). Key eligibility criteria include ECOG performance status of 0–2 (ECOG 3 is allowed for pts 18–74 y of age with comorbidities) and unfavorable-risk cytogenetics for pts with ND AML. The Oral-AZA starting dose is 300 mg QD × 14 d/28-d cycle, which can be de-escalated to 200 mg QD × 14 d depending on dose-limiting toxicities; oral VEN 400 mg QD is taken continuously (or 21 d/cycle for dose level –2). A modified toxicity probability interval-2 design is used to evaluate dose levels. Sample size depends on the dose levels utilized (≤ 18 pts/part). Enrollment began in 2021. The trial is ongoing at clinical sites in the United States and Australia. Clinical trial information: NCT04887857. Research Sponsor: Bristol Myers Squibb.

TPS7069 **Poster Session**

Phase 1B/2A safety, pharmacokinetics, and pharmacodynamics study of fosciclopirox alone and in combination with cytarabine in patients with relapsed/refractory acute myeloid leukemia. *First Author: Tara L. Lin, University of Kansas Medical Center, Kansas City, KS*

Background: Fosciclopirox (F) is a γ-secretase inhibitor being developed for the treatment of acute myeloid leukemia (AML). Following intravenous (IV) administration, F is rapidly and completely metabolized to its active metabolite, ciclopirox (CPX). CPX binds to γ-secretase complex proteins Presenilin 1 and Nicastrin, which are essential for Notch activation. In HL60 cells, CPX inhibits Notch 1 and Notch 2 expression, reduces levels of γ-secretase complex proteins Presenilin 1 and Nicastrin, and decreases expression of the downstream Notch target gene Hes-1. Utilizing Notable Labs predictive precision medicine platform, bone marrow (BM) and peripheral blood (PB) samples obtained from 10 AML patients treated with CPX demonstrated significant blast count reductions. **Methods:** Study CPX-POM-003 (NCT04956042) is an open-label Phase 1B/2A, trial designed to characterize the efficacy, safety, and PK/PD of F alone and in combination with cytarabine (ara-C) in patients with relapsed/refractory AML (R/R AML). Eligible patients must be 18 years of age or older with relapsed AML after complete remission or with primary refractory AML refractory to at least two cycles of induction therapy. There will be up to three cohorts of patients, approximately 42 R/R AML patients, evaluated. If disease response to F alone (Cohort 1a) is observed in at least 4 of 14 patients, an additional 14 patients will be enrolled in Cohort 1b. If disease response is not observed following F alone, the study may be terminated or a second cohort, Cohort 2a, may be initiated to evaluate the combination of F + ara-C. If disease response to F + ara-C is observed in at least 4 of 14 patients, an additional 14 patients will be enrolled in Cohort 2b. If response to F + ara-C is not observed in at least 4 of 14 patients, the study will be stopped for futility. F is being administered as 900 mg/m^2 once daily as a 20-minute IV infusion on Days 1 to 5 of each 21-day treatment cycle. Ara-C is administered as 1 gm/m^2 once daily on Days 1 to 5 of each cycle. BM and PB samples are collected prior to and during Cycles 1 (C1) and 2 (C2) for disease response assessment and blast count determination. Additional BM and PB samples are obtained after every two cycles beyond C2 for patients continuing treatment. Disease response is determined based on Döhner et al, *Blood* 2017;129(4)424-447. Next Generation Sequencing (NGS) profiles will be determined prior to and at the end of C1, and thereafter as clinically indicated. Immunohistochemistry will be performed on BM samples to elucidate drug mechanism. *Ex vivo* Drug Sensitivity Screening (DSS) will be performed on BM and PB samples obtained prior to treatment as well as on C1 Days 8 and 21. The steady-state plasma pharmacokinetics of F are being characterized during C1. Enrollment began in October 2022 with four patients enrolled to date. Clinical trial information: NCT04956042. Research Sponsor: CicloMed LLC, Pharmaceutical/Biotech Company.

TPS7070 **Poster Session**

A phase 1 study of CD38-bispecific antibody (XmAb18968) for patients with CD38 expressing relapsed/refractory acute myeloid leukemia and T-cell acute lymphoblastic leukemia. *First Author: Guru Subramanian Guru Murthy, Division of Hematology/Oncology, Medical College of Wisconsin, Milwaukee, WI*

Background: Outcomes of adults with relapsed/refractory T-cell acute lymphoblastic leukemia (T-ALL) and acute myeloid leukemia (AML) have remained poor. CD38 is a transmembrane glycoprotein with several important functions including its role in immune escape of tumor cells [Chillemi A et al. Front Immunol 2017, Furano A et al. J Immunol 1990]. Several studies have demonstrated that CD38 is expressed in T-ALL and AML and is targetable with CD38 blocking agents [Naik J et al. Haematologica 2019, Bride KL et al. Blood 2018, Tembhare et al. J Immunother Cancer 2020]. XmAb18968 is a novel CD38-CD3 bi-specific T-cell engager with Fc domain modified to minimize Fcγ receptor binding and non-selective T-cell activation resulting in reduced cytokine release without compromising target cell killing. We hypothesize that targeting CD38 in relapsed/refractory T-ALL and AML would be safe and feasible using XmAb18968. **Methods:** This is an investigator-sponsored multi-institutional phase I study evaluating the safety and tolerability of XmAb18968. Patients aged 18 years or above with relapsed/refractory T-ALL or AML (including measurable residual disease relapse), CD38 expression ≥ 20% by flow cytometry, and adequate organ function will be eligible. Major exclusion criteria are hematopoietic cell transplantation within 6 months of enrollment, active acute graft-versus-host disease, and acute promyelocytic leukemia. The primary objective is to determine the recommended phase 2 dose (RP2D) and toxicity profile of XmAb18968. The secondary objectives include determination of response rates, duration of response, survival and pharmacokinetics. Exploratory objectives include correlation of responses with genomic profile, characterizing changes in serum cytokines and phenotypic expression of activated T-cells and leukemic cells, correlation of the phenotypic expression with changes in the transcriptome at the single-cell level, proteomics evaluation of cytokine secretion at the single-cell level and correlation of response with N-glycan profiling, quantitative site-occupancy and direct glycopeptide analysis. The study will follow 3+3 design. Dose escalation will proceed in two separate groups: Group A for subjects with T-ALL and Group B for subjects with AML. Patients will be entered sequentially to each dose level [0.8mg cohort, 1mg cohort, 1.3mg cohort, 1.5mg cohort). The observation period for dose-escalation will be 28-days. RP2D will be defined as the highest dose level at which none of the 3 treated subjects, or no more than 1 of the 6 treated subjects' experiences a dose limiting toxicity. A minimum of 24 and a maximum of 60 patients will be enrolled. The study is being conducted at 6 sites in United States and is currently open for enrollment. Clinical trial information: NCT05038644. Research Sponsor: Xencor Inc.

TPS7071 **Poster Session**

Phase 1 study of LP-108 as monotherapy and in combination with azacitidine in patients with relapsed or refractory myelodysplastic syndromes (MDS), chronic myelomonocytic leukemia (CMML), or acute myeloid leukemia (AML). *First Author: Alison R. Walker, The Ohio State University Wexner Medical Center, Columbus, OH*

Background: BCL2 inhibition as a means of targeting intrinsic apoptotic pathways that confer a survival advantage to leukemic blasts has become a key therapeutic strategy for patients with myeloid malignancies. LP-108 is an oral highly potent and selective inhibitor of BCL-2 with comparable or more potent *in vitro* inhibitory activity as compared to the FDA approved oral BCL-2 inhibitor venetoclax. We propose to investigate LP-108 as monotherapy and in combination with azacitidine in patients with relapsed or refractory (r/r) MDS, CMML or AML. **Methods:** The primary objectives of the trial are 1.) To determine the safety, tolerability and determine the maximum tolerated dose (MTD) and the recommended phase 2 dose / optimal biological dose (OBD) of LP-108 as a single agent (Arm 1) and in combination with azacitidine (Arm 2) in patients with relapsed/refractory MDS/CMML/AML; 2.) To characterize the pharmacokinetic profile of LP-108 as monotherapy and in combination with a fixed dose of azacitidine. The secondary objectives of the trial are 1.) To evaluate the objective response rate of LP-108 (monotherapy or combination therapy) in r/r MDS/CMML/AML as well as progression free survival, duration of response and overall survival. In Arm 1 patients will be enrolled according to a 3+3 design with escalating doses of LP-108 for a 28 day cycle (firs table). DLTs will be determined in the first 28 days. In Arm 2 patients will be enrolled according to a 3+3 design with escalating doses of LP-108 in combination with a fixed dose of azacitidine (second table). DLTs will be determined in the first 28 days. DLT for both arms is defined as some ≥ Grade 3 non-hematological toxicities or prolonged myelosuppression. Patients may continue treatment until disease progression, unacceptable toxicity, or per investigator discretion. Patients age ≥ 18 years with r/r MDS with excess or blasts or with high or very-high risk disease per the R-IPSS, or r/r MDS for Arm 2, r/r AML, or frontline older and/or unfit AML for Arm 2, or r/r CMML may enroll. Patients with prior hypomethylating agents or venetoclax exposure may enroll. The blast count at the time of starting therapy must be ≤ 30 x 10^9 cells/L. Hydroxyurea is allowed prior to and during treatment. Ejection fraction ≥ 50% is required. Calculated creatinine clearance shall be ≥ 30 mL/min. Strong CYP3A4 inducers and inhibitors are prohibited. Patients on weak/moderate azole antifungals were allowed to enroll. Enrollment to Arm 1 is complete and there have been no DLTs to date. Enrollment to Arm 2 is pending. Arm 1 Dose Escalation Scheme (LP-108 monotherapy). Clinical trial information: NCT04139434. Research Sponsor: Newave Pharmaceuticals.

Arm 2 dose escalation Scheme (LP-108 and azacitidine).

Cohort	LP-108 Dose
1	100 mg
2	200 mg
3	400 mg
4	600 mg

Cohort	LP-108 Dose	Azacitidine Days 1-7 or days 1-5, 8, 9
1	100 mg	75 mg/m2
2	200 mg	75 mg/m2
3	400 mg	75 mg/m2

TPS7072 **Poster Session**

Emotion and symptom-focused engagement (EASE): A multisite randomized controlled trial of an intervention for individuals with acute leukemia. *First Author: Kyle Fitzgibbon, Princess Margaret Cancer Centre - UHN, Toronto, ON, Canada*

Background: Acute leukemia (AL) is characterized by rapid symptom onset requiring urgent hospitalization and initiation of intensive treatment with high mortality. Despite this, there is scant research on its psychological and physical impacts and even less on interventions to alleviate them [Bryant 2016]. We conducted a longitudinal study showing substantial physical and psychological distress in these patients [Rodin 2013; Zimmermann 2013; Nissim 2013; Nissim 2014; Gheihman 2016; Rodin 2018a; Shaulov 2019]. Despite this distress, we observed a lack of referrals for specialized psychosocial and palliative care. Based on these findings, we developed an integrated psychosocial and early palliative care (symptom control) intervention, Emotion And Symptom-focused Engagement (EASE), for AL [Rodin 2015]. In a subsequent randomized phase II trial of EASE in patients newly diagnosed with AL, we demonstrated its feasibility and found preliminary evidence that it reduces physical and psychological distress compared to usual care [Rodin 2020]. EASE includes: i) an 8-week manualized psychotherapy intervention tailored to AL to prevent and treat psychological symptoms through: supportive counselling and trauma-focused cognitive-behavioural therapy; and emotional assessment and affect modulation; ii) 4-week systematic screening of physical symptoms with automatic referrals to palliative care for the management of moderate to severe symptoms. **Methods:** We are conducting a multi-centre randomized controlled phase III trial of 266 AL patients comparing EASE to usual care in collaboration with the Canadian Cancer Trials Group at Princess Margaret Cancer Centre, Sunnybrook Health Sciences, Kingston Health Sciences and the Ottawa Hospital in Ontario, Canada. Patients are newly diagnosed with acute myeloid leukemia or acute lymphoblastic leukemia and randomized within two weeks of hospital admission for induction chemotherapy with curative intent. Patients randomized to EASE will receive psychological support from a trained mental health clinician for 8 weeks and will be assessed for physical symptoms twice weekly until discharged from hospital. Moderate to severe physical symptoms will trigger a referral to a symptom-control team for symptom management. The symptom-control team consists of a physician and nurse with expertise in symptom control and other professionals as needed. All participants will be assessed for physical symptom severity, psychological distress, quality of life and satisfaction with care at baseline, 4, 8, 12 weeks, 6 and 12 months. Hypotheses will be tested using multilevel modeling (MLM) with maximum likelihood estimation, conducted as intention-to-treat analyses. The DMC last reviewed the trial in April 2021 and suggested that the trial continue as planned. Clinical trial information: NCT04224974. Research Sponsor: Canadian Institutes of Health Research, Other Foundation.

TPS7073 **Poster Session**

A phase II study of CPX-351 in younger patients < 60 years old with secondary acute myeloid leukemia: Trial in progress. *First Author: Mahesh Swaminathan, Roswell Park Comprehensive Cancer Center, Buffalo, NY*

Background: Patients (pts) with secondary acute myeloid leukemia (s-AML) and therapy-related AML (t-AML) have poor long-term outcomes following standard induction 7+3 chemotherapy. CPX-351, a liposomal formulation of cytarabine and daunorubicin fixed at the synergistic ratio of 5:1, is indicated for the treatment of pts with newly diagnosed s-AML and t-AML based on the results of a phase III trial favorably comparing CPX-351 to 7+3. Although the trial only enrolled pts aged 60-75 years (Y), CPX-351 is approved by the United States Food and Drug Administration for all adult pts with t-AML and AML with myelodysplasia-related changes (AML-MRC). In a prior retrospective analysis of CPX-351 in pts <60 Y with s-AML, we noted that the outcomes of these younger pts appeared inferior to those reported in older pts (60-75 Y) in the phase III trial (Przespolewski et al. Blood 2018 p.2677). Therefore, we designed this prospective study to evaluate the efficacy of CPX-351 in pts <60 Y with untreated s-AML and t-AML. **Methods:** In this phase II single-arm multi-institutional study, pts aged 18-59 Y with untreated t-AML or AML-MRC, adequate organ function, and ECOG performance status ≤ 2 are eligible. Pts with active central nervous system disease and infections were excluded. CPX-351 will be dosed at 100 mg/m^2 cytarabine and 44 mg/m^2 daunorubicin on days 1, 3, and 5 during induction. Bone marrow biopsy will be performed between days 14-21 to assess response. If needed, re-induction CPX-351 dose will be 44 mg/m^2 daunorubicin/100 mg/m^2 cytarabine on days 1 and 3. Pts achieving a complete remission (CR) following induction can receive up to 2 cycles of consolidation CPX-351 dosed as cytarabine 65 mg/m^2 and daunorubicin 29 mg/m^2 on days 1 and 3. The primary endpoint of the study is overall response rates defined as CR and CR with incomplete blood count recovery (CRi)) within 45 days of beginning therapy. Secondary endpoints are duration of response, event-free survival, overall survival, rate of allogeneic stem cell transplant, and adverse events. A maximum of 46 pts will be enrolled at 4 U.S. sites with 5-year follow-up from the start of CPX-351.The study is open and has enrolled 4 pts to date. Clinical trial information: NCT04269213. Research Sponsor: U.S. National Institutes of Health.

TPS7074 **Poster Session**

A phase 1b study to evaluate safety, tolerability, pharmacokinetics, and efficacy of SER-155 in adults undergoing hematopoietic stem cell transplantation to reduce the risk of infection and graft versus host disease (NCT04995653). *First Author: Doris M. Ponce, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: In patients undergoing allogeneic hematopoietic stem cell transplantation (HCT), loss of gastrointestinal microbial diversity is associated with risk of bloodstream infections (BSI), acute graft-versus-host disease (aGvHD), and death. SER-155 is a cultivated investigational microbiome therapeutic rationally designed to improve clinical outcomes in patients undergoing HCT by restoring colonization resistance to pathobionts, promoting epithelial barrier integrity, and reducing colonic inflammation. SER-155-001 is a Phase 1b study to evaluate the efficacy, safety, and pharmacokinetics (PK) of SER-155 in adults undergoing HCT. **Methods:**This study will enroll approximately 70 subjects $\geq$ 18 years in an open-label Cohort 1 (n = 10) followed by a double-blind, placebo-controlled Cohort 2 (n = 60) randomized 1:1 to SER-155 or placebo and stratified by conditioning regimen intensity. Exclusion criteria include history of severe colitis of any etiology or active inflammatory bowel disease or total colectomy, transplant using umbilical cord blood or *ex vivo* T-cell therapy, receipt of fecal microbiota transplant or any live microbial therapeutic within 3 months prior to screening, and evidence of relapse or progression of hematologic malignancy (minimal residual disease is allowed). Following screening, subjects in both cohorts will receive 2 treatment courses (before and after HCT), each comprised of microbiome conditioning with oral vancomycin or placebo followed by SER-155 or placebo, and a conditional 3rd treatment course if the subject receives antibiotics (Table). Safety outcomes will be followed through 52 weeks post HCT. The primary endpoint is to evaluate the incidence and severity of adverse events, serious adverse events, and adverse events of special interest. Secondary endpoints include rates of BSI, gastrointestinal infections, aGvHD, febrile neutropenia and overall survival in placebo vs SER-155 arms. Microbiome related endpoints include engraftment of SER-155 bacterial strains in the gastrointestinal tract (PK endpoint) and fecal microbiome diversity, composition and metabolites. Clinical trial information: NCT04995653. Research Sponsor: Seres Therapeutics.

	Microbiome conditioning regimen	Treatment course*
Cohort 1:	Oral vancomycin (125 mg, 4 times daily) for 4 days	2 capsules of SER-155 once daily for 10 days
Cohort 2:	Oral vancomycin (125 mg, 4 times daily)	2 oral capsules of SER-155 once daily for 10 days
	Placebo vancomycin 4 times daily	2 oral capsules placebo once daily for 10 days

*A third course will be administered without microbiome conditioning following completion of antibiotics for subjects who receive 3 days of systemic antibiotics following HCT.

TPS7075 **Poster Session**

A randomized, double-blind, placebo-controlled study of tamibarotene/azacitidine versus placebo/azacitidine in newly diagnosed adult patients selected for RARA+ HR-MDS (SELECT-MDS-1). *First Author: Amy Elizabeth Dezern, Johns Hopkins University, Baltimore, MD*

Background: A novel genomically defined subset of higher-risk MDS (HR-MDS) patients with an actionable target characterized by overexpression of *RARA* has been identified (McKeown 2017). Approximately 30% of HR-MDS patients are RARA-positive (RARA+) by a blood-based biomarker test (Vigil, 2017). Biologically targeted therapy with tamibarotene, an oral selective RARα agonist, has potential to provide clinical benefit for RARA+ HR-MDS patients, irrespective of mutation or cytogenetic risk. Initial clinical data in RARA+ R/R HR-MDS patients treated with tamibarotene showed myeloid differentiation, improved blood counts, and reduced bone marrow blasts, including one patient who achieved marrow complete remission with hematologic improvement (Jurcic 2017). Tamibarotene in combination with azacitidine (aza) showed high complete response rates (CR) with rapid onset of response in RARA+ newly diagnosed (ND) unfit AML patients, including those with low blast count ($\leq$ 30%) AML, and a majority of patients achieved or maintained transfusion independence (de Botton 2020). Tamibarotene/aza was generally well tolerated with no increase in myelosuppression compared to aza alone (de Botton 2020). Historical precedent demonstrating similar clinical outcomes in HR-MDS and AML, particularly low blast count AML (Estey 2021), supports further development of tamibarotene/aza in HR-MDS to improve clinical outcomes of standard of care treatment with hypomethylating agents (HMAs). **Methods:** This Phase 3, multi-center, randomized, double-blind, placebo-controlled study will compare activity of tamibarotene/aza to placebo/aza in RARA+ patients with ND HR-MDS. The primary objective is to characterize and compare the CR rate of tamibarotene/aza vs placebo/aza, with secondary objectives to characterize ORR, EFS, OS, transfusion independence rate, time to and duration of initial and complete responses, and safety. Approximately 190 patients will be randomized 2:1, providing 90% power to detect the difference in CR rates between the experimental and control arms, with a one-sided alpha of 0.025. Patients must be RARA+ based on the investigational biomarker test, ND with HR-MDS by WHO classification (Arber 2016), classified by IPSS-R risk category as very high, high, or intermediate risk with a blast count > 5% at study entry. Patients suitable for transplant at screening, or with prior treatment for MDS with any HMA, chemotherapy or transplant are excluded. Aza will be administered at 75 mg/m^2 IV/SC daily on days 1-7 (or 1-5, 8-9) followed by tamibarotene/placebo at 6 mg BID orally days 8-28 of each 28-day cycle. Response will be assessed per modified IWG MDS criteria (Cheson 2006). The SELECT-MDS-1 trial opened in February 2021, recruitment is ongoing, with sites located in North America, Israel, and Europe. Clinical trial information: NCT04797780. Research Sponsor: Syros Pharmaceuticals.

TPS7076 **Poster Session**

Phase II trial assessing safety and preliminary efficacy of high-dose intravenous ascorbic acid in patients with *TET2*-mutant clonal cytopenias of undetermined significance. *First Author: Zhuoer Xie, Mayo Clinic, Rochester, MN*

Background: Clonal cytopenias of undetermined significance (CCUS) is operationally defined as unexplained persistent cytopenias arising in the context of leukemia-associated somatic driver mutations in hematopoietic stem and progenitor cells, without morphologic evidence for an underlying hematological neoplasm. Patients with *TET2* mutant ($TET2^{MT}$) CCUS have a high probability of progression to myeloid neoplasms, with approximated 10-year cumulative rates of progression being 90%. To date, no FDA-approved treatment for CCUS has been established, and we have shown that these patients can have transfusion burdens akin to patients with myelodysplastic syndrome (MDS) (Li M et al. Blood Adv 2020). Thus there is an urgent and unmet need for therapies for these patients. Intravenous (IV) ascorbic acid (AA) dosed at pharmacologic concentrations could have anti-cancer activity via two mechanisms: (1) hydrogen peroxide-induced oxidative stress and (2) DNA demethylation mediated by TET activation (cofactor for TET1/2/3). TET2, the primary enzyme for catalyzing oxidative reactions, converts 5-methylcytosine to 5-hydroxymethylcytosine, a crucial step leading to iterative DNA demethylation. Our study hypothesis is that IV AA in $TET2^{MT}$ CCUS will restore hematopoiesis and limit clonal progression by stimulating TET2 (the unmutated allele) and TET3 activities. **Methods:** LS1781 (NCT03418038) is an investigator-initiated, prospective, single-arm, single-institution, phase II trial assessing the safety and preliminary efficacy of high dose of IV AA for patients with $TET2^{MT}$ CCUS (harboring ≥1 $TET2^{MT}$ or $TET2^{MT}$ combined with concurrent spliceosome MTs). IV AA (1g/kg, maximum 100g) is given 3 times weekly for 12 weeks through a central line with assessments being carried out before each cycle (4 weeks), at 12 weeks, and one year. The primary endpoint is the hematologic response rates determined by MDS IWG 2018 criteria. Secondary endpoints include safety and side effects. Exploratory endpoints include the impact of AA on $TET2^{MT}$ variant allele fraction, plasma cytokine levels, DNA methylation, and hydroxymethylation (as measured by Infinium MethylationEPIC array), and TET activity. Patients 18 years or older with $TET2^{MT}$ CCUS, and with any of the following laboratory criteria: (1) hemoglobin ≤10g/dL, (2) absolute neutrophil count (ANC) ≤1000/mm^3, (3) platelet count ≤100,000/mm^3 are eligible. Fifteen patients will be enrolled at Mayo Clinic Rochester and the Mayo Clinic Health System. Dose modifications have been established and will be considered based on adverse events. Treatment will be discontinued for disease progression or in the event of ≥Grade 3 adverse events that don't resolve promptly. Enrollment to the trial began in June 2021, with 7 patients enrolled at abstract submission. Clinical trial information: NCT03418038. Research Sponsor: U.S. National Institutes of Health.

TPS7077 **Poster Session**

A phase 1 study of NTX-301, an oral DNMT1 inhibitor, in patients with MDS and AML (trial in progress). *First Author: Pankit Vachhani, University of Alabama at Birmingham, Division of Hematology/Oncology, Department of Medicine, Birmingham, AL*

Background: Patients with relapsed and/or refractory (r/r) myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), and acute myeloid leukemia (AML) who are not candidates for stem-cell transplantation have dismal outcomes. Novel therapies are needed. The nucleoside analogue NTX-301 (5-aza-4'-thio-2'-deoxycytidine or Aza-TdC) is incorporated into DNA, where it engages the active site of DNA methyltransferase I (DNMT1), a maintenance methyltransferase that contributes to the hypermethylation and silencing of tumor suppressor genes. DNMT1 can become trapped in a covalent complex with DNA, thus depleting free enzyme and inhibiting the normal maintenance methylation of CpG sites, resulting in re-activation of tumor suppressor genes. Preclinical data suggest a correlation between NTX-301 activity in leukemia xenograft models and decreased levels of DNMT1. NTX-301 offers an improvement over traditional DNA methyltransferase inhibitors (azacitidine, decitabine) by virtue of a higher incorporation rate into DNA at lower levels of cytotoxicity. **Methods:** This is a phase 1, open-label, multi-center, dose-escalation study to assess the safety, tolerability, and recommended myeloid monotherapy dose of NTX-301 in patients with r/r myeloid neoplasms. Patients ≥ 18 years with r/r higher-risk MDS (intermediate, high, very-high risk by IPSS-R), high-risk CMML (int-2/high by CPSS or CPSS-mol), or AML (marrow blasts ≤ 30% or WBC < 20,000 cells/μL without leukoreduction) are eligible. Other key eligibility criteria: Eastern Cooperative Oncology Group performance status 0–2; adequate cardiac, renal, and liver function; and resolved acute effects of any prior therapy. Successive cohorts of patients will receive escalating doses of NTX-301 starting from 2 mg QD. Each cycle is 21 days in duration (treatment for 5 days/week x 2 weeks and 1 week off). The trial incorporates accelerated titration design for dose level 1 and 2 followed by traditional 3+3 dose escalation design (3-6 patients per cohort) from dose level 3. Intrapatient dose escalation is allowed. NTX-301 treatment will continue until disease progression or unacceptable toxicity, whichever occurs first. Primary endpoints: incidence and severity of adverse events, dose-limiting toxicities (DLTs), maximum tolerated dose (MTD), biologically effective dose (BED). Secondary endpoints: PK parameters of NTX-301, PD assessment through global hypomethylation assay and other markers in blood and marrow, and clinical efficacy [overall response rate (ORR), complete remission (CR), marrow CR (mCR), partial remission (PR), stable disease (SD), hematologic improvement (HI) per mIWG criteria]. After the MTD/BED is identified, the safety and efficacy of NTX-301 will be explored further in selected myeloid malignancies. The study began enrolling patients in January 2021 and is still recruiting. Clinical trial information: NCT04167917. Research Sponsor: Southern Research.

TPS7078 **Poster Session**

Pediatric and young adult leukemia adoptive therapy (PLAT)-08: A phase 1 study of SC-DARIC33 in pediatric and young adults with relapsed or refractory CD33+ AML. *First Author: Todd Michael Cooper, Seattle Children's Hospital, Cancer and Blood Disorders Center, Seattle, WA*

Background: The acute and late effects of acute myeloid leukemia (AML) therapy in children can be devastating, and relapse rates remain high. Targeted therapies are needed to decrease toxicity and improve cure rates. Most AML patients express CD33 on their leukemic blasts. CD33 is a viable target with CD33 targeted therapies approved for AML. CD33 targeted CAR T cell therapies are being developed, but safety and efficacy remain a challenge. Safety concerns include cytokine release syndrome, neurotoxicity and aplasia. Efficacy is limited, with antigen escape and T cell exhaustion proposed as mechanisms of treatment failure. Dimerizing Agent Regulated ImmunoReceptor Complex (DARIC) is a next-generation technology that utilizes a split receptor design separating the antigen binding and intracellular signaling subunits (Leung, 2019). These subunits remain inactive until the administration of rapamycin which allows for dimerization of the subunits, enabling T cell activation when antigen is present. Modulating CAR T cell activation may aid hematopoietic recovery, enhance CAR T cell function and persistence, and mitigate toxicity. We developed a DARIC T cell product, SC-DARIC33, that couples the DARIC technology with a lentiviral construct that incorporates the use of a novel humanized camelid nanobody for targeting the C2 splice isoform within the membrane proximal domain of CD33. **Methods:** Up to 18 patients will be enrolled in this phase 1 study (NCT05105152). Patients must have early first relapse of AML (≤ 6 months from diagnosis), first relapse refractory to at least one reinduction attempt, second or greater relapse, or refractory *de novo* AML. The first 3 patients must be ≥18 years, all patients who meet eligibility criteria must be ≤28 years. The primary objectives of this Phase I study (NCT05105152) are assessment of safety/toxicity and feasibility of manufacturing of SC-DARIC33. Secondary objectives include assessment of efficacy, on/off rate of DARIC expression, engraftment, expansion and persistence of SC-DARIC33. Also, the effect of cessation of rapamycin on activation state of SC-DARIC 33 and on hematopoietic recovery will be evaluated. Subjects receive lymphodepletion prior to a single dose of SC-DARIC33 T cells on Day 0 followed by initiation of rapamycin on Day +2 with the purpose of activating the T cells. Rapamycin continues until Day 21 and bone marrow evaluation occurs on Day 28. Subsequent cycles of rapamycin are allowed for patients who respond. The trial will implement a BOIN design with three possible dose levels (1 x 10^6, 5 x 10^6, and 10 x 10^6 $DARIC^+$ cells/kg) to determine the maximum tolerated dose (MTD). The trial is open for enrollment at Seattle Children's Hospital. Clinical trial information: NCT05105152. Research Sponsor: 270 Bio.

TPS7080 **Poster Session**

Phase II trial of luspatercept with or without hydroxyurea for the treatment of patients with myelodysplastic/myeloproliferative neoplasms with ring sideroblasts and thrombocytosis or unclassifiable with ring sideroblasts. *First Author: Abhishek Avinash Mangaonkar, Division of Hematology, Mayo Clinic, Rochester, MN*

Background: Myelodysplastic syndrome/myeloproliferative neoplasms (MDS/MPN) are classified as a distinct category under the World Health Organization (WHO) classification of myeloid neoplasms. MDS/MPN with RS and thrombocytosis (MDS/MPN-RS-T) and MDS/MPN, unclassifiable with > 15% bone marrow ring sideroblasts (MDS/MPN-U-RS) have similar clinical and pathological characteristics with symptomatic or transfusion-dependent anemia as the predominant morbidity. Luspatercept has been approved in myelodysplastic syndromes with ring sideroblasts (MDS-RS) and MDS/MPN overlap syndromes, based on the phase 3 MEDALIST clinical trial which primarily included MDS-RS patients with an objective erythroid response rate of approximately 40 per cent. In this trial, some MDS-RS patients also experienced an increase in neutrophil and platelet counts. This raises a safety concern for MDS/MPN patients with elevated platelet or WBC counts such as MDS/MPN-RS-T and MDS/MPN-U-RS. Previous studies have shown clinical and biological differences between MDS-RS and MDS/MPN-RS-T, with the latter group at a significantly elevated risk for thrombotic events. Additionally, several MDS/MPN-RS-T patients are on hydroxyurea which may blunt the erythroid response of luspatercept. Therefore, it is imperative to establish the safety and efficacy of luspatercept in this patient group. **Methods:** This is an investigator-initiated, prospective, phase II study of luspatercept in MDS/MPN overlap neoplasms with ring sideroblasts and thrombocytosis or unclassifiable with ring sideroblasts with 2 arms; hydroxyurea-independent (cohort A) and hydroxyurea-dependent (cohort B). Hydroxyurea and/or aspirin use is allowed as per investigator discretion. The primary goal is to study the efficacy and safety of luspatercept in MDS/MPN-RS-T or MDS/MPN-U-RS with symptomatic anemia. The primary endpoint is to assess erythroid response rate as per the 2015 International Working Group MDS/MPN response criteria. Secondary endpoints include response duration, time to acute myeloid leukemia (AML) transformation, thrombosis rate, AML-free and overall survival. Inclusion criteria include newly diagnosed or relapsed/refractory adult patients with WHO-defined diagnosis of MDS/MPN-RS-T or MDS/MPN-U-RS with symptomatic or transfusion-dependent anemia and unlikely to respond (EPO level > 200 IU/L) or intolerant to erythropoiesis stimulating agent (ESA) therapy. Prior therapy with lenalidomide, hypomethylating agents or immunosuppressive therapy is allowed. The overall plan is to enroll 54 patients across the three Mayo Clinic sites, Minnesota, Arizona and Florida. Enrollment to the trial began in January 2022 with 1 patient enrolled at the time of abstract submission. Clinical trial information: NCT05005182. Research Sponsor: BMS.

7500 **Oral Abstract Session**

Glofitamab in patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) and ≥ 2 prior therapies: Pivotal phase II expansion results. *First Author: Michael Dickinson, Peter MacCallum Cancer Centre, Royal Melbourne Hospital and The University of Melbourne, Melbourne, Australia*

Background: Glofitamab is a T-cell engaging bispecific antibody (Ab) with a novel 2:1 configuration that confers bivalency for CD20 (B cells) and monovalency for CD3 (T cells). In a Phase I/II study (NCT03075696), escalating glofitamab doses were highly active and well tolerated in pts with R/R B-cell lymphomas, with obinutuzumab pretreatment (Gpt) and Cycle (C) 1 step-up dosing providing effective CRS mitigation. For the first time, we present pivotal Phase II expansion results in pts with R/R DLBCL and ≥2 prior therapies. **Methods:** All pts had DLBCL (DLBCL NOS, HGBCL, PMBCL, or trFL) and had received ≥2 prior regimens including ≥1 anti-(a) CD20 Ab and ≥1 anthracycline. IV Gpt (1000mg) was given 7 days before the first glofitamab dose. IV glofitamab was then given as step-up doses on Day (D) 1 (2.5mg) and D8 (10mg) of C1 and at the target dose (30mg) on D1 of C2–12 (21-day cycles). The primary endpoint was CR rate (best response during initial treatment) assessed by Independent Review Committee (IRC) using Lugano 2014 criteria. CRS was assessed using ASTCT criteria. **Results:** As of Sep 14, 2021, 107 pts had received ≥1 dose of study treatment (median age: 66 yrs [21–90]; Ann Arbor stage III–IV disease: 74%; IPI score ≥3: 54%; DLBCL NOS: 74%). Median prior therapies was 3 (2–7); 59% had ≥3 prior therapies and 35% had received prior CAR T-cells (CAR-Ts). Most pts were refractory to a prior aCD20 Ab-containing regimen (85%) and to their most recent regimen (85%). Many were refractory to their initial therapy (59%) and to prior CAR-Ts (32%). After a median follow-up of 9 months (0.1–16), ORR and CR rates by IRC were 50.0% and 35.2%, respectively. CR rates were consistent in pts with and without prior CAR-Ts (32% vs 37%). Median time to CR was 42 days (95% CI: 41–48). The majority of CRs (33/38; 87%) were ongoing at data cut. An estimated 84% of complete responders and 61% of responders remained in response at 9 months. At data cut, the projected 12-month OS rate was 48%, and 92% of complete responders were alive. These results are consistent with earlier Phase I data in 100 pts treated with target glofitamab doses ≥10mg (CR rate: 34%; estimated 20-month CR rate in complete responders: 72%). CRS occurred in 68% of pts, was primarily associated with the initial doses, and was mostly Gr 1 (51%) or Gr 2 (12%); Gr 3 (3%) and Gr 4 (2%) events were uncommon. All but 2 CRS events were resolved at data cut. Glofitamab-related neurologic AEs potentially consistent with ICANS occurred in 3 pts (all Gr 1–2). No glofitamab-related Gr 5 (fatal) AEs occurred. Glofitamab-related AEs leading to discontinuation were uncommon (3 pts, 3%). **Conclusions:** Fixed-duration glofitamab induces durable complete remissions and has favorable safety in pts with R/R DLBCL and ≥2 prior therapies, including those with prior exposure to CAR-Ts. Glofitamab is a promising new therapy for pts with heavily pretreated and/or highly refractory DLBCL. Clinical trial information: NCT03075696. Research Sponsor: Third-party medical writing assistance, under the direction of all authors, was provided by Scott Malkin of Ashfield MedComms, an Ashfield Health company, and was funded by F. Hoffmann-La Roche Ltd.

7501 **Oral Abstract Session**

GEMSTONE-201: Preplanned primary analysis of a multicenter, single-arm, phase 2 study of sugemalimab (suge) in patients (pts) with relapsed or refractory extranodal natural killer/T cell lymphoma (R/R ENKTL). *First Author: Huiqiang Huang, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: R/R ENKTL is a rare and aggressive type of non-Hodgkin's lymphoma. Responses to chemotherapy after failure of prior asparaginase-based regimen were not durable with a median OS of < 7 months (mos) and 1-year OS rate of < 20% (Lim et al, Ann Oncol 2017; Bellei et al, Haematologica 2018). The only targeted therapy approved in China for R/R peripheral T cell lymphoma (ENKTL included) showed an ORR of 18.8% and a CR rate of 6.3% (Shi et al, Ann Oncol 2015). Here, we present the primary analysis from GEMSTONE-201, the largest registrational study reported to date to evaluate an anti-PD-L1 mAb in R/R ENKTL. Suge received breakthrough therapy designation from US FDA in 2021 for adult R/R ENKTL pts based on preliminary data of this study. **Methods:** Pts with ECOG PS of 0/1 and histologically confirmed ENKTL who failed prior asparaginase-based regimen were enrolled. Pts accepted suge at 1200 mg Q3W, iv, for up to 24 mos, until progression, death, or withdrawal from study. The primary endpoint was ORR (CR+PR) assessed by independent radiological review committee (IRRC) per Lugano 2014 criteria. Key secondary endpoints included investigator-assessed ORR, CR and PR rate, DoR assessed by IRRC and investigators, and safety. **Results:** As of the data cutoff date, Nov 10, 2021, 80 pts were enrolled and treated (median follow-up of 13.4 mos). Median age was 48 years (range 29-74); 64% were males; 74% had ECOG PS of 1 at baseline; 68% had stage IV disease; about half (49%) received ≥ 2 lines of prior systemic therapy. The median duration of treatment was 5.2 mos (range 0.7-37.4); 23 pts remained on treatment. Among the 78 evaluable pts as per IRRC, ORR was 46.2% (95% CI: 34.8%, 57.8%); 29 (37.2%) pts achieved CR; median DoR was not reached (NR); 12-mo DoR rate was 86%. Investigator's assessments in 79 evaluable pts were consistent with IRRC results, i.e. ORR of 45.6% (95% CI: 34.3%, 57.2%), 24 (30.4%) pts with CR, and median DoR of NR. The 1- and 2-year OS rates were 68.6% and 54.6%, respectively; median OS was NR (range 0.9-37.2^{+} mos). Of all pts, 96% (n = 77) had at least one AE. The most common AEs were pyrexia and WBC decreased (n = 24 each, 30%). Grade ≥ 3 AEs occurred in 31 (39%) pts. Suge-related AEs occurred in 61 (76%) pts and were mostly (60%) Grade 1/2. The most common irAE assessed by sponsor was hypothyroidism (n = 13, 16%). SAEs occurred in 18 (23%) pts; 5 (6%) pts had suge-related SAEs which had all been resolved (1 with sequelae). Fatal AEs occurred in 5 (6%) pts and none were suge-related as assessed by investigators. **Conclusions:** Suge has demonstrated deep and durable anti-tumor activity in R/R ENKTL pts, with a high CR rate and a promising OS benefit trend comparing to historical data. Suge had a well-tolerated safety profile and no new safety signals were detected. Primary analysis indicates that suge could provide a new treatment option to R/R ENKTL pts. Clinical trial information: NCT03595657. Research Sponsor: CStone Pharmaceuticals.

LBA7502 **Oral Abstract Session**

Primary results from the double-blind, placebo-controlled, phase III SHINE study of ibrutinib in combination with bendamustine-rituximab (BR) and R maintenance as a first-line treatment for older patients with mantle cell lymphoma (MCL). *First Author: Michael Wang, The University of Texas MD Anderson Cancer Center, Houston, TX*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

7503 **Oral Abstract Session**

First-line brentuximab vedotin plus chemotherapy to improve overall survival in patients with stage III/IV classical Hodgkin lymphoma: An updated analysis of ECHELON-1. *First Author: Stephen M. Ansell, Mayo Clinic, Rochester, MN*

Background: To date, an overall survival (OS) benefit from upfront treatment for new treatment combinations over existing approaches has rarely been shown in first-line classical Hodgkin lymphoma (cHL). With the introduction of newer active therapies for relapsed/refractory disease, demonstration of improved OS with first-line therapy has been challenging. In ECHELON-1 (NCT01712490), 5-year follow-up analyses supported the long-term progression-free survival (PFS) benefit with first-line brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine (A+AVD) vs doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) in patients (pts) with stage III/IV cHL, independent of interim positron emission tomography status. A+AVD had a manageable long-term safety profile, with numerically fewer second malignancies and a greater number of pregnancies reported vs ABVD (Connors et al, NEJM 2018; Straus et al, Lancet Haematol 2021). We report a prespecified OS analysis after approximately 6 years' follow-up (cut-off, June 1, 2021). **Methods:** Pts were randomized 1:1 to receive up to 6 cycles of A+AVD (n = 664) or ABVD (n = 670) on day 1 and 15 every 28 days. OS was the key secondary endpoint and was an event-driven, pre-specified, alpha-controlled analysis in the intention to treat population. **Results:** At a median follow-up of 73 months, 39 and 64 OS events occurred in A+AVD and ABVD arms, respectively: OS significantly favored A+AVD vs ABVD (HR 0.590; 95% confidence interval [CI] 0.396–0.879; p = 0.009). Estimated 6-year OS rates (95% CI) were 93.9% (91.6–95.5) vs 89.4% (86.6–91.7) with A+AVD vs ABVD, respectively. There was a consistent OS benefit for A+AVD vs ABVD across prespecified subgroups. The 6-year PFS estimate was 82.3% (79.1–85.0) vs 74.5% (70.8–77.7) with A+AVD vs ABVD, respectively (HR 0.678 [95% CI 0.532–0.863]). Overall, A+AVD had a comparable long-term safety profile to ABVD. Treatment-emergent peripheral neuropathy continued to resolve or improve in both arms, with 86% (379/443) and 87% (249/286) of cases in the A+AVD and ABVD arms either completely resolving (72% vs 79%) or improving (14% vs 8%) by last follow-up. Fewer second malignancies were reported in the A+AVD vs ABVD arm (23 vs 32). More female patients reported pregnancy (49 vs 28) or live births (42 vs 19 in females) in the A+AVD vs the ABVD arm; no stillbirths were reported. No new safety signals were identified. **Conclusions:** A+AVD treatment resulted in a statistically significant 41% reduction in the risk of death vs ABVD, with a manageable safety profile consistent with prior reports. These outcomes confirm A+AVD as a preferred option for pts with previously untreated stage III/IV cHL. Clinical trial information: NCT01712490. Research Sponsor: Takeda Development Center Americas, Inc. (TDCA).

7504 **Oral Abstract Session**

Brentuximab vedotin and association with event-free survival (EFS) in children with newly diagnosed high-risk Hodgkin lymphoma (HL): A report from the Children's Oncology Group phase 3 study AHOD1331 (NCT 02166463).

First Author: Sharon M. Castellino, Emory University and Children's Healthcare of Atlanta, Atlanta, GA

Background: The anti-CD30 antibody drug conjugate, Brentuximab vedotin (Bv) is approved for adults with advanced stage HL but its use has not been established in children or adolescents. We compared the efficacy and safety of Bv with doxorubicin, vincristine, etoposide, prednisone and cyclophosphamide (Bv-AVE-PC) to the standard pediatric dose intensive regimen ABVE-PC, inclusive of bleomycin. **Methods:** This multicenter randomized, open-label phase 3 study enrolled patients 2-21 years (yrs) with previously untreated HL, stages IIB + bulk, IIIB, IVA, IVB. Patients were randomized to 5 cycles of either ABVE-PC or Bv-AVE-PC given every 21 days with granulocyte colony-stimulating factor support. Centrally reviewed PET-CT after 2 cycles (PET2) identified slow responding lesions (SRL) defined as Deauville score > 3. Involved site radiotherapy (ISRT) was given to bulky mediastinal adenopathy and SRL. The primary objective was 3-year EFS; events include relapse/progression, second malignant neoplasm (SMN) or death. Final data cutoff was 31 December 2021. **Results:** 600 participants were enrolled across 151 institutions from March 2015 to August 2019; 587 were eligible. Median age was 15.6 yrs (range 3.4-21). Patient and disease characteristics were balanced across study arms. Histology was nodular sclerosing in 76.5%. Stage distribution: 20.6% IIB-bulk; 19.3% IIIB; 28.5% IVA; 31.7% IVB. At a median follow-up of 42.1 mos (0.1-80.9), 3-year EFS (95%CI) by intent-to-treat analyses was 82.5% (77.4, 86.5) with ABVE-PC and 92.1% (88.4, 94.7) with Bv-AVE-PC (HR 0.41 (0.25, 0.67), p = 0.0002). Median time to 1st event was 9.4 months for both arms but the range differs by arm (3.6-57.8 ABVE-PC; 1.3, 25.8 Bv-AVE-PC). Relapse rate was 17% following ABVE-PC and 7% with Bv-AVE-PC. One SMN is noted in each arm: thyroid cancer at 57.8 mos and acute myeloid leukemia at 20.3 mos. 3-year overall survival (95%CI) was 98.5% (96.0, 99.4) for ABVE-PC and 99.3% (97.3, 99.8) for Bv-AVE-PC (p = 0.38). PET2 SRL rates were comparable (ABVE-PC 19% vs. Bv-AVE-PC 18%, p = 0.8). As-treated ISRT receipt did not differ (ABVE-PC 55.7% vs. Bv-AVE-PC 52.7%, p = 0.69). No difference in grade 3/4 adverse events was observed; myelosuppression, reflected in a 32% incidence of > grade 3 febrile neutropenia, did not differ by arm (p = 0.67). Only 19% of patients experienced > grade 2 neuropathy by the Balis pediatric neuropathy scale, with no difference between arms (p = 0.86). **Conclusions:** Brentuximab vedotin with AVE-PC in a dose intensive regimen has superior efficacy to ABVE-PC for pediatric patients with high-risk HL. A 59% risk reduction in EFS was achieved with no increase in toxicity and with fewer patients receiving ISRT compared to prior pediatric trials for high-risk HL. Clinical trial information: 02166463. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

ABSTRACT WITHDRAWN

7507 **Oral Abstract Session**

Racial disparities affecting Black patients with diffuse large B-cell lymphoma.

First Author: Daniel Arthur Ermann, Huntsman Cancer Institute-University of Utah Health Care, Salt Lake City, UT

Background: Diffuse Large B-cell Lymphoma (DLBCL) is the most common subtype of Non-Hodgkin Lymphoma, with the majority of patients (pts) achieving long-term survival due to the curative nature of frontline therapy. However, limited data exists regarding presentation and clinical outcomes for underrepresented minorities. In this study, we aimed to evaluate the influence of racial identity on overall survival (OS) outcomes for DLBCL pts. **Methods:** The National Cancer Database was used to identify DLBCL pts diagnosed from 2004-2018. Demographic and treatment characteristics were compared between racial groups. Kaplan-Meier and Cox regression analyses were used to compare OS between Black and white populations. Multivariate analysis and propensity score matching was performed with adjustment for age, stage, co-morbidity score, median income, and insurance status. **Results:** Of 223,709 DLBCL pts, 87% were white, 8% Black, and 5% other. As compared to white pts at diagnosis, Black pts were younger (mean 56 years [SD ± 16] vs. 66 years [SD ± 15]), more likely to have ≥1 co-morbidity (33% vs. 27%), be HIV-positive (26% vs. 5%), and have both B-symptoms (40% vs. 30%) and stage IV disease (42% vs. 37%) (All p<0.001). In terms of socioeconomic demographics, Black pts were more likely to be uninsured (8% vs. 3%) and be in the lowest median income quartile (43% vs. 15%), but were more likely to receive treatment at academic centers (50% vs. 36%) (all p<0.001). Both Black and white pts had similar IPI scores at diagnosis and were equally likely to receive multi-agent chemotherapy (77% vs. 77%, p<0.001). With a median follow up of 44.9 months, median OS for all treated HIV-negative DLBCL pts was 109 months (range 21-197). Compared to age-matched white pts, Black pts age ≤ 60 had worse median OS (46 vs. 76 months) along with 5- (73% vs. 75%) and 10-year OS (65% vs. 69%) (all p <0.001). Similar results were seen for Black and white pts between the ages of 61-79, but these differences were not demonstrated for pts ≥80 years old (Table). On multivariate analysis, Black race was independently associated with worse OS (HR 1.06, CI 1.01-1.10, p=0.02). Interestingly, the propensity matched analysis demonstrated no significant OS difference between Black and white pts (median 127 vs. 117 months; HR 1.0, CI 0.94-1.06; p=0.90). **Conclusions:** We present the largest study to date examining racial disparities in DLBCL. This data demonstrates that Black patients have significantly shorter OS compared to white patients, which persists on multivariate analysis. However, this disparity in survival became nonsignificant when patients are equally matched on surrogate markers of healthcare access such as insurance status and median income. Further studies into examining these racial differences are warranted to optimize care for all DLBCL patients. Research Sponsor: None.

	Median OS (mo)	5-yr OS (%)	10-yr OS (%)	P
Age ≤60				
W	76	75	69	<.001
B	46	73	65	
Age 61-79				
W	91	78	59	<.001
B	78	75	56	
Age ≥80				
W	34	38	13	0.20
B	38	39	17	

7508 **Oral Abstract Session**

Influence of racial and ethnic identity on overall survival in patients with chronic lymphocytic lymphoma.

First Author: Victoria Vardell, University of Utah, Salt Lake City, UT

Background: Chronic lymphocytic leukemia (CLL) is the most prevalent adult leukemia and results in highly variable clinical outcomes. Epidemiologically, CLL occurs in White ethnicity more frequently and thus, CLL outcomes among underrepresented minorities are not well studied. We sought to examine differences in treatment patterns and survival outcomes based on racial identity of CLL patients and how these have changed over time. **Methods:** The National Cancer Database was used to identify CLL patients diagnosed from 2004-2018. Demographic and treatment characteristics were compared between White, Black, Asian, Hispanic and other minority groups. Kaplan Meier and adjusted Cox regression survival analysis were used to compare overall survival (OS) between races. Survival analysis was repeated by year of diagnosis in Black and White populations. **Results:** Of 97,804 CLL pts identified, 90.7% of patients were White, 7.6% Black (N = 7,391), 2.6% Hispanic (N = 2,487), 0.6% Asian (N = 613), and 1.1% were other. Compared to White pts, Black pts were younger at diagnosis (median age 66 years [interquartile range 61-79] vs. 70 years [range 58-75], more likely to have ≥1 comorbidity (27.9% vs. 21.3%), and be uninsured (6.6% vs. 2.1%) (all p < 0.001). Black pts were more likely than White pts to have CLL directed treatment immediately after diagnosis (35.9% vs 23.6%; p < 0.001). With a median follow-up of 4.3 years, median OS for all CLL patients was 9.0 years (CI 8.9-9.1 years). Black pts had a shorter median OS of 7.0 years (CI 6.7-7.3 years) compared to White pts (9.14 years [CI 9.0-9.3]), p < 0.001), as well as inferior OS at 5-years (61% vs. 69%) and 10-years (36% vs. 46%), p < 0.001. On multivariate analysis adjusted for age and Charlson-Deyo score, Black race was independently associated with shorter OS (HR 1.51 [CI 1.46-1.57], p < 0.001). While OS lengthened with successive year of diagnosis for all races, the relative survival of Black compared to White pts did not improve over the observed time period. Referenced to the White population, Black pts diagnosed between 2004-2006 had a HR of 1.64 (CI 1.52-1.76) for mortality, and those diagnosed between 2016-2018 had a HR of 1.64 (CI 1.44-1.85). **Conclusions:** We present the largest study to date describing racial disparities in CLL. Black pts have significantly shorter OS compared to White pts, which is sustained when adjusted for the higher prevalence of comorbidities in the Black CLL population. Unfortunately, the survival gap between White and Black patients has not improved since 2004, highlighting the need for targeted research directed at improving survival in Black pts with CLL. Research Sponsor: U.S. National Institutes of Health.

	N	Median OS (Years)	95% CI	Adjusted HR	95% CI	P
All CLL	97,804	9.0	(8.9–9.1)			
White	88,680	9.1	(9.0–9.3)		Ref.	
Black	7,391	7.0	(6.7–7.3)	1.51	(1.46–1.57)	< 0.001
Asian	613	*	*	0.91	(0.78–1.10)	0.220
Other	1,120	*	*	0.85	(0.75–0.96)	0.009
Hispanic	6,727	10.4	(9.2–11.5)	1.03	(0.96–1.11)	0.400

* Median not reached.

7509 **Clinical Science Symposium**

A phase 1 study of ADI-001: Anti-CD20 CAR-engineered allogeneic gamma delta (γδ) T cells in adults with B-cell malignancies. *First Author: Sattva Swarup Neelapu, The University of Texas MD Anderson Cancer Center, Department of Lymphoma/Myeloma, Houston, TX*

Background: ADI-001 is a first-in-class allogeneic gamma delta (γδ) CAR T-cell therapy targeting the B-cell antigen CD20. ADI-001 also has both adaptive and innate cytotoxic effector functions to complement CAR targeting, potentially enhancing efficacy and reducing the possibility of tumor escape due to antigen loss. ADI-001 expresses MHC independent γδ T cell receptors, thus lowering the risk of graft versus host disease (GvHD) without the need for gene-editing. **Methods:** This phase 1 trial evaluates ADI-001 in adults with relapsed/refractory advanced B-cell lymphoma. Eligibility criteria included presence of measurable lesions, expression of CD20 and ≥ 2 prior systemic therapies. All patients received conditioning therapy with fludarabine and cyclophosphamide. ADI-001 is administered at 3 flat dose levels (DL; DL1:3E7, DL2:1E8, or DL3:3E8 cells) in a 3 + 3 dose-escalation scheme. Dose-limiting toxicities (DLT) were monitored during the initial 28-days post-treatment. Patients who completed the 28-day DLT period were considered evaluable. Treatment-emergent adverse events were graded by CTCAE v5.0, and immune effector cell toxicity assessment and grading were performed per ASTCT criteria. Objective response rates (ORR) were evaluated by independent radiographic review per Lugano 2014 criteria. **Results:** As of 14 February 2022, eight patients were enrolled and six were evaluable. Of these six patients, 2/6 were female (33%) and the median age was 62 years (range 45-75). The median number of prior therapies was 3.5 (range 2-5) and median IPI score was 3.5 (range 2-4). One patient received prior anti-CD19 CAR T cells therapy with lisocabtagene maraleucel. There were five patients with large B-cell lymphoma and one with mantle cell lymphoma. Among the six evaluable patients, three were treated on DL1 and three on DL2. Most related AEs (78%) were of grade 1/2. There were three AESI: two CRS (one grade 1 and one grade 2) and one grade 1 ICANS, and the only related SAEs were the grade 2 CRS and grade 1 ICANS. There was no reported GvHD and no protocol defined DLT events. At day 28, the ORR based upon PET/CT was 67% (4/6 patients) and the CR rate was 67% (4/6 patients). Both patients with ≥ 3 months post-treatment follow-up remained in CR. Additional data will be presented at the meeting. **Conclusions:** ADI-001 γδ CAR T cells were well tolerated, with a favorable safety profile and encouraging preliminary efficacy. Patients who achieved CR at day 28 appeared to be disease free during further follow-up at month-3. Clinical trial information: NCT04735471. Research Sponsor: Adicet Bio.

7510 **Poster Discussion Session**

Zanubrutinib plus obinutuzumab (ZO) versus obinutuzumab (O) monotherapy in patients (pts) with relapsed or refractory (R/R) follicular lymphoma (FL): Primary analysis of the phase 2 randomized ROSEWOOD trial. *First Author: Pier Luigi Zinzani, Institute of Hematology "Seràgnoli", University of Bologna, Bologna, Italy*

Background: FL is the most common type of indolent non-Hodgkin lymphoma. Approved treatment options are limited for pts with R/R FL. In a phase 1b trial (*Blood Adv.* 2020;4(19):4802-4811), ZO was found to be tolerable and associated with early signal of efficacy. ROSEWOOD (BGB-3111-212) is a phase 2, randomized study designed to assess efficacy and safety of ZO vs O in pts with R/R FL. **Methods:** Pts with R/R FL who received ≥2 lines of therapy, including an anti-CD20 antibody and an alkylating agent, were randomized 2:1 to receive either ZO or O. O was given in both arms on Days 1, 8, and 15 of Cycle 1, Day 1 of Cycles 2-6, and then every 8 weeks up to 20 doses maximum. Z (160 mg twice daily) was given until progressive disease (PD) or unacceptable toxicity; Pts with confirmed PD in the O arm were allowed to crossover to ZO. Primary endpoint was overall response rate (ORR) by independent central review. Secondary endpoints included complete response rate (CRR), duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety. Exploratory endpoint included ORR by investigator after crossover. Primary analysis cutoff was October 8, 2021. **Results:** A total of 217 pts were randomized to ZO (n = 145) or O (n = 72). Median study follow-up was 12.5 mo; median age was 64 yrs. Incidence of high FL International Prognostic Index score was 53% (ZO) and 51% (O). Pts received a median of 3 prior lines of therapy, with 28% (ZO) and 25% (O) of pts receiving > 3 lines. Proportion of pts refractory to rituximab, refractory to the most recent line of therapy, or with PD within 24 mo of initiation of first-line immunochemotherapy was 54%, 32% and 28% with ZO and 50%, 40% and 32% with O, respectively. The study met its primary endpoint: ORR was 68.3% with ZO vs 45.8% with O (p= 0.0017). CRR was 37.2% (ZO) vs 19.4% (O); 18-mo DOR rate was 70.9% (ZO) vs 54.6% (O); and median PFS was 27.4 mo (ZO) vs 11.2 mo (O; hazard ratio [HR], 0.51 [95% CI, 0.32-0.81], p= 0.0040). Median time to new anti-lymphoma therapy or crossover was not evaluable (NE; ZO) vs 12.1 mo (O; HR, 0.37 [95% CI, 0.23-0.60], p< 0.0001). ORR for 29 pts who crossed over to ZO was 24.1%. Median OS was NE; 18-mo OS probability was 85.4% (ZO) vs 72.6% (O). Most common any grade AEs in the ZO arm were thrombocytopenia (34.3%), neutropenia (27.3%), diarrhea (16.1%), fatigue (14.0%), constipation (13.3%), cough (11.9%), pyrexia (11.2%), and dyspnea (10.5%). Grade ≥3 AEs with incidence > 5% with ZO were neutropenia (22.4%) and thrombocytopenia (14.0%); incidence of atrial fibrillation was 0.7% and major bleeding was 1.4%. Incidence of treatment-emergent AEs leading to death was 5.6% (ZO) and 9.9% (O). **Conclusions:** ZO demonstrated superior efficacy to O in treatment of pts with R/R FL. ZO had a favorable benefit-risk profile and represents a potential combination therapy for pts with R/R FL. Clinical trial information: NCT03332017. Research Sponsor: BeiGene USA, Inc.

7511 **Poster Discussion Session**

Efficacy and safety of zandelisib administered by intermittent dosing (ID) in patients with relapsed or refractory (R/R) follicular lymphoma (FL): Primary analysis of the global phase 2 study TIDAL. *First Author: Andrew David Zelenetz, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Zandelisib, a PI3Kδ inhibitor with high target-binding affinity, is administered by intermittent dosing (ID) on days 1-7 of 28-day cycles to potentially enable regulatory T-cell repopulation and lower the risk of immune adverse events (irAEs) seen with continuous PI3Kδ inhibition. In a phase 1b study in 37 patients (pts) with R/R FL, zandelisib daily for two 28-day cycles for tumor debulking then on ID achieved an overall response rate (ORR) of 87% (78% single agent and 95% with rituximab) with < 10% irAEs (Pagel et al. ICML 2021; #113). We conducted the TIDAL study to further evaluate zandelisib in R/R indolent lymphomas (NCT03768505). **Methods:** Eligible pts ≥18 years with FL Grade I-IIIA, progressive disease after ≥2 prior therapies, and no prior PI3K inhibitor, gave consent and received zandelisib 60 mg daily for 2 cycles then on ID. Not reported here are an arm randomizing pts to zandelisib daily continuously, closed to enrollment early, and an actively enrolling arm in R/R marginal zone lymphoma (MZL). The planned FL sample size was 120 pts on ID, with the primary efficacy population (PEP) pre-defined as the first 91 pts treated. The primary efficacy endpoint was ORR by the Lugano criteria in the PEP as assessed by independent review and analyzed after a minimum 6-month follow-up. **Results:** 121 FL pts were enrolled. In the PEP (N = 91), the median number of prior therapies was 3 (range 2-8), 21 pts (23%) had received prior stem cell transplant, 42 (46%) had disease refractory to last therapy, 31 (34%) had tumors ≥5 cm, and 51 (56%) were POD24. Overall response rate was 70.3% (n = 64) (95% CI 59.8-79.5%) and complete response rate was 35.2% (n = 32) (95% CI 25.4-45.9%). Responses occurred early with 87.5% (n = 56) of responses observed at the end of Cycle 2 and 75% (n = 24) of CRs at the end of Cycle 4. The data are still immature to estimate accurately the duration of response (DOR). With a median follow-up of 9.4 months (range 0.8-24) for all 121 pts, 12 pts (9.9%) discontinued therapy due to any drug-related AE. Grade 3 AEs of special interest (AESI) were diarrhea in 6 pts (5%), colitis in 2 (1.7%), rash in 4 (3.3%), stomatitis in 3 (2.5%), and 1 (0.8%) each for AST and ALT elevation, and non-infectious pneumonitis. Grade 3 AESIs primarily (15 of 18, 83%) occurred in cycles 1-3, during daily dosing. **Conclusions:** Zandelisib on ID achieved high ORR and CR rate in heavily pretreated FL pts, and was associated with < 10% of discontinuations due to drug-related AEs and grade 3 AESI, results comparable to the Phase 1b study. Longer follow-up is needed to estimate median DOR. This profile supports evaluation of zandelisib alone and in combination in various B-cell malignancies, both in relapsed disease and earlier lines of therapy. Zandelisib plus rituximab vs chemoimmunotherapy is being studied in the phase 3 trial COASTAL in R/R FL and MZL (NCT 04745832). Clinical trial information: NCT03768505. Research Sponsor: MEI Pharma, Inc.

7512 **Poster Discussion Session**

Subcutaneous rituximab induction followed by short rituximab maintenance to improve progression-free survival in patients with low-tumor burden follicular lymphoma: Final results of FLIRT phase III trial, a LYSA study. *First Author: Guillaume Cartron, CHU de Montpellier, Montpellier, France*

Background: In low–tumor burden follicular lymphoma (FL), maintenance rituximab (MR) has been shown to improve progression-free survival (PFS) when compared with observation. RESORT study (Kahl et al. 2014) clearly showed that Rituximab (R) retreatment strategy provided similar time to treatment failure that maintenance strategy with less rituximab use. It is not known whether short MR using sub-cutaneous (sc) route could improve PFS while reducing R infusions. **Methods:** Patients with the diagnosis of low-tumor burden FL (GELF criteria) within the last 4 months before signing informed consent were randomly assigned to either Iv-Arm : 4-weekly iv infusions of R 375 mg/m^2 or Sc-Arm: one iv infusion of R (D1, 375 mg/m^2) followed by 3 sc infusions of R (1400 mg, on days 8, 15 and 22) followed by Rsc maintenance on months (M) 3, 5, 7 and 9. The primary endpoint was PFS and secondary endpoints included safety, response rates (M3, M12), duration of response (DOR), time to next anti-lymphoma treatment (TTNTL) and overall survival (OS). **Results:** A total of 202 patients were included, 102 in Iv-Arm and 100 in Sc-Arm and constitute the intent to treat population. The median uses of R were 4 infusions (range: 1-4, Iv-Arm) and 8 infusions (range: 2-8, Sc-Arm). With a median follow-up of 50.2 months (95% CI: 48.3-54.5), 4-year PFS was 41.2% (95% CI: 30.6%; 51.6%) in Iv-Arm and 58.1% (95% CI: 47.5%; 67.4%) in Sc-Arm. Median PFS was then 36.1 months (95% IC: 23.9-52.6) in Iv-Arm and 73.8 months (95% CI: 39.4-NA) in Sc-Arm (Fig 1.) (HR: 0.58; 95% CI: 0.39-0.87; P = 0.0076). Patients with at least one AE grade ≥ 3 were 8 (7.8%) and 12 (12.4%) in Iv-Arm and Sc-Arm, respectively. According to Cheson criteria, ORR at M3 were: 83% and 80% including 38% and 29% of CR/CRu, in Iv-Arm and Sc-Arm, respectively. According to Lugano criteria, 36.3% (Iv-Arm; 95% CI: 27.0%. 46.4%) and 59.0% (Sc-Arm; 95% CI: 48.7%; 68.7%) were in CMR at M12. The median DOR was 32.7 months (95% IC: 20.6-49.7) and 70.8 months (36.4-NR) (HR: 0.56; 95% IC: 0.37-0.84) in Iv-Arm and Sc-Arm, respectively. 4-year TTNLT was 54% (95% CI: 42.9%; 63.8%) in Iv-Arm and 61.8% (95% CI: 50.8.6%; 71.0%) in Sc-Arm (HR: 0.81, 95% IC: 0.53-1.24). 4-year TTNLT chemotherapy was 60.8 % (95% CI: 49.6%; 70.3%) in Iv-Arm and 71.4% (95% CI: 60.7%; 79.8%) in Sc-arm (HR: 0.69, 95% IC: 0.42-1.12) (Fig 2.). OS was not different according to treatment arm, 4-year OS was 95.0% (95% CI: 88.5%; 97.9%) in Iv-Arm and 96.7% (95% CI: 89.9%; 98.9%) in Sc-Arm. **Conclusions:** This phase III study met its primary endpoint and demonstrated that Rsc induction followed by a short MRsc improves PFS of patients with low-tumor burden. MRsc did not however improved TTNLT. R in low-tumor burden FL allowed to avoid cytotoxic use in most patients 6 years after treatment initiation. Clinical trial information: NCT02303119. Research Sponsor: LYSA, Pharmaceutical/Biotech Company.

7513 **Poster Discussion Session**

Interim results of a phase II multicenter study with the oral histone deacetylase inhibitor abexinostat in patients with relapsed/refractory follicular lymphoma. *First Author: Lin Gui, National Cancer Center/ National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, Beijing, China*

Background: Follicular lymphoma (FL) is generally considered incurable with patients (pts) often experiencing multiple relapses requiring varying lines of subsequent treatments. Abexinostat (Abx) is a novel potent oral pan- Histone Deacetylase Inhibitor (HDACi) with a pharmacokinetic profile that allows maintenance of sufficient drug concentrations for anti-tumor activity with twice daily (BID) dosing. In prior phase 1/2 studies, Abx was shown to be well-tolerated with significant clinical activity and durable responses in patients with Relapsed/Refractory (R/R) FL. **Methods:** This open label, single arm study is being conducted to assess the efficacy and safety of Abx in pts with R/R FL. Adults with histologically confirmed grade 1, 2 or 3a FL who have previously received at least 2 lines of therapies, and ECOG PS of 0-2 are being recruited. Abx is administered orally at 80 mg BID 4 hours apart in "one week on, one week off" schedule (Days 1 to 7 & 15 to 21 of a 28-day cycle). Pts undergo efficacy assessment by enhanced CT/MRI every 8 weeks for the first 24 weeks, and every 12 weeks thereafter, and PET-CT at weeks 12 and 24 and to confirm a complete response, in accordance with the Lugano 2014 criteria. The primary endpoint is overall response rate (ORR) assessed by independent review committe (IRC), defined as the % of pts who achieve complete response (CR) or partial response (PR). Secondary endpoints include duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety. In a planned interim futility analysis conducted with the first 37 pts, if <12/37 (32%) responded (CR or PR), the study was to be terminated. **Results:** Between June 17, 2020 and Jan 28, 2022, 41 pts received Abx. 37 pts underwent at least one post baseline tumor assessment. Median age was 55 (range 34 – 79), 46% of pts were male, 70% had stage IV disease and 24% had >3 FLIPI-2. Pts had a median of 3 prior lines of therapy (range 2-6), and 22% were refractory to the last prior treatment. As of the data cutoff date on Jan 31, 2022, of 37 pts evaluable for efficacy, the ORR was 70% (26/37 pts), 16% CR (6/37) and the disease control rate was 92% (34/37). The median time to response was 10.8 weeks. The study has met the pre-defined stage I criteria and has entered stage II, aiming to enroll up to 81 evaluable pts. Of 41 pts evaluable for safety, the most common treatment emergent adverse events (TEAEs) (≥ 30%) were thrombocytopenia (85%), diarrhea (61%), neutropenia (54%), leukopenia (49%), asthenia (39%), nausea (37%), and anemia (34%). Grade ≥ 3 TEAEs (≥ 5%) included thrombocytopenia (41%), neutropenia (27%), leukopenia (7%), lymphopenia (7%), prolonged QT (7%), and anemia (5%). One pt discontinued treatment due to AEs. **Conclusions:** Oral Abx demonstrated promising efficacy and was well tolerated in patients with R/R FL. Clinical trial information: NCT03934567. Research Sponsor: Xynomic Pharmaceuticals, Inc.

7514 **Poster Discussion Session**

Real-world outcomes of brentuximab vedotin maintenance after autologous stem cell transplant in relapsed/refractory classical Hodgkin lymphoma: Is less enough? *First Author: Charlotte Wagner, Huntsman Cancer Institute-University of Utah, Salt Lake City, UT*

Background: The AETHERA trial demonstrated improvement in PFS with 16 cycles of brentuximab vedotin (BV) after autologous stem cell transplant (ASCT) in BV-naive patients with high-risk relapsed/refractory classical Hodgkin lymphoma (r/r cHL). However, in real world, patients are rarely able to complete all 16 cycles of BV at full dose. We performed a multicenter retrospective study to assess the impact of cumulative dose on toxicity and 2-year PFS. **Methods:** Patients from 11 institutions across the US who had received at least one cycle of BV maintenance after ASCT for r/r cHL with one of these features were included: primary refractory disease (PRD), extra-nodal disease (END), or relapse < 12 months of diagnosis (RL<12). PFS was compared between the three cohorts based on a total cumulative dose of 28.8 mg/kg (1.8 mg/kg x 16 cycles): C1, those that received >75% (21.7 to 28.8 mg/kg) cumulative dose of BV, C2, those that received between 51% -75% (14.5 to 21.6 mg/kg) dose and C3, those that received ≤ 50% (≤ 14.4 mg/kg) dose. **Results:** Between July 2015-June 2019, 100 patients with a median age of 34 years (19-70) underwent ASCT for r/r cHL. At relapse, 44% had PRD, 47% had RL<12, 39% had END and 45% had received BV as initial (1%) or salvage (44%) therapy. 71% had CR before ASCT and 23% received >1 line of salvage (>1 SLT). There was no difference in baseline characteristics between the cohorts. Thirty-six patients were in C1, 27 in C2, and 37 in C3. Only 14% of patients received full cumulative dose of BV. The median number of cycles completed was 12. Fifty-seven patients discontinued early: 39 for toxicity, 7 for progression, 5 for patient preference, 2 for cost and 4 for other reasons. Six of the patients who stopped early for progression were in C3. Grade ≥3 adverse events for neuropathy, neutropenia, and infections were 16%, 7%, and 5% respectively. There was no difference in severity of neuropathy in patients who had received BV prior to ASCT (p=.37). The median follow up was 3.37 years (.4–6.35). The 2-year PFS was 85% for all subjects, 94% for C1, 84% for C2, and 72% for C3 (p=.079) (Table). Patients in C3 had worse PFS compared to C1 (p=.035); this difference remained significant after adjusting for five other factors. There was no difference in PFS between C1 and C2 (p=.29). **Conclusions:** The majority of patients discontinued BV maintenance early due to toxicity. 2-year PFS was robust regardless of cumulative dose of BV. We conclude that total cumulative dose of 28.8 mg/kg of BV maintenance is not necessary and 51%-75% of total BV dose may still attain a similar PFS advantage. Research Sponsor: None.

Patient cohort	N	2-year PFS (95% CI)	P-value, unadj.	P-value, adj for PRD, CR before ASCT, RL<12, >1 SLT, Prior BV
All	100	0.85 (0.77-0.92)	—	—
C1	36	0.94 (0.87-1.00)	Ref.	Ref
C2	27	0.84 (0.71-1.00)	0.29	0.22
C3	37	0.72 (0.59-0.88)	0.035	0.024

7515 **Poster Discussion Session**

Outcomes of classic Hodgkin lymphoma, relapsed within one year of diagnosis, in the era of novel agents. *First Author: Sanjal Desai, University of Minnesota, Minneapolis, MN*

Background: Primary refractory disease (PRD) and early relapse (ER) are predictors of poor prognosis in classic Hodgkin lymphoma (cHL). In this multicenter retrospective study, we describe outcomes of PRD and ER in pts with relapsed/refractory (R/R) cHL treated with salvage therapy (ST) and autologous stem cell transplant (ASCT). **Methods:** Of 14 sites, adult patients with R/R cHL who received ST and underwent ASCT were enrolled. PRD was defined as progression on frontline chemoimmunotherapy or within 6 months of diagnosis. ER was defined as relapse from 6 months-1 yr of diagnosis. Pts who relapsed >1 yr of diagnosis were called late relapses (LR). Study objectives were Overall response rates (ORR), CR rates, PFS, and OS. **Results:** Of 986 total pts, 160 had PRD, 365 had ER and 461 had LR. Significantly higher number of pts with PRD, but not ER, had bulky disease (41% vs 27%, p<0.01) and B symptoms (53% vs 38%, p<0.001) than LR. Higher proportions of pts with PRD and ER required >1 line of ST (44% vs 30% vs 23%, p<0.001) before ASCT and received BV maintenance (25% vs 24% vs 16%, p<0.05). When adjusted for B symptoms and Bulky disease, PRD and ER had significantly lower ORR (65% vs 76% vs 84%, p<0.001) and CR (37% vs 46% vs 57%, p<0.001) to first ST than LR. Pts with PRD and ER had significantly lower PFS (56.3%, 61.4%, vs 77.6%, p<.0001) and OS (93% vs 89% vs 94%, p=0.01) than LR. In pts with ER, Brentuximab/bendamustine (BBV) and brentuximab vedotin/nivolumab (BV/nivo) had a trend towards higher ORR (92% vs 92% vs 75%) but significantly higher CR (79.2% vs 76% vs 42%, p<0.01) than platinum based chemotherapy (PBC). In pts with PRD, BBV and BV/Nivo had a statistically insignificant trend towards higher ORR and CR than PBC. The table shows 2 yr PFS by type of ST in PRD, ER, LR. There was no difference in PFS by time to relapse in BV/nivo, CPI and miscellaneous agents. BV/Nivo had a significantly higher PFS than PBC in PRD (88% vs 48%, p<0.05) and ER (95% vs 57%, p<0.05). There was no difference in PFS of PBC and other ST in PRD, ER or LR. OS was not significantly associated with type of ST in either group. **Conclusions:** PRD and ER are associated with lower response to ST and survival after ASCT compared to late relapse. In pts with PRD and ER, BV/Nivo has high ORR and CR and leads to significantly higher PFS comparable to pts with late relapse and may be preferable ST regardless of time to relapse. Research Sponsor: None.

Type of ST	PRD % (CI_{95})	ER % (CI_{95})	LR % (CI_{95})	P
PBC (541)	48.2 (34.9–61.5)	57 (51–63)	76 (71–81)	<0.001
BBV (78)	53 (23–83)	63 (46–80)	73 (58–88)	NS
BV/Nivo (60)	89 (78–100)	95 (91–99)	96 (93–99)	NS
BV alone (105)	57 (39–75)	61 (48–74)	78 (69–86)	NS
CPI (24)	78 (60–96)	80 (61–99)	84 (74–94)	NS
Gem (97)	35 (1–70)	54 (40–68)	63 (55–71)	NS
Misc (68)	65 (48–82)	68 (53–83)	70 (62–78)	NS

BV; brentuximab vedotin, CPI; checkpoint inhibitors, Gem; gemcitabine-based therapy, NS; not significant, P; p value, CI_{95}; 95% confidence interval.

7516 **Poster Discussion Session**

Favezelimab (anti–LAG-3) plus pembrolizumab in patients with anti–PD-1–naive relapsed or refractory (R/R) classical Hodgkin lymphoma (cHL): An open-label phase 1/2 study. *First Author: Nathalie A. Johnson, Jewish General Hospital, Montréal, QC, Canada*

Background: PD-1 inhibitors are a standard of care in pts with R/R cHL but new approaches are still needed to deepen and lengthen responses. Dual blockade of PD-1 and LAG-3 has demonstrated antitumor activity in preclinical models. The multicohort phase 1/2 MK-4280-003 study (NCT03598608) evaluated the safety and efficacy of favezelimab (MK-4280), a humanized IgG4 LAG-3 inhibitor, plus pembrolizumab (pembro; a PD-1 inhibitor) in pts with R/R hematologic malignancies. This analysis focused on anti–PD-1–naïve pts with R/R cHL (cohort 1). **Methods:** This study included a safety lead-in phase (part 1) to determine the recommended phase 2 dose (RP2D) followed by a dose-expansion phase (part 2). Eligible pts in cohort 1 must have R/R cHL after autologous stem cell transplantation (ASCT) or be ineligible for ASCT and have had no prior anti–PD-1 therapy. In part 1, patients from all cohorts received pembro IV 200 mg Q3W and favezelimab IV 200 mg or 800 mg Q3W. Dose escalation followed the mTPI design. In part 2, pts received pembro + favezelimab at the established RP2D for up to 35 cycles. Primary end point was safety. Secondary end point was ORR. DOR, PFS, and OS were exploratory end points. **Results:** Only 1 dose-limiting toxicity (DLT; autoimmune hepatitis [grade 4]) was identified among the first 6 pts from all cohorts in part 1 at the favezelimab 200 mg dose; thus, the dose was escalated to 800 mg. No DLTs were observed in the 15 additional pts treated at the 800 mg dose. The RP2D for the combination was defined as 800 mg Q3W + pembro 200 mg Q3W. In cohort 1, 30 pts were enrolled; median age was 40 years, 53% had ECOG PS 0, and 80% had ≤3 prior lines of therapy. After a median follow-up of 13.5 mo, ORR for cohort 1 was 73% (95% CI, 54-88; CR, 7 pts [23%]; PR, 15 pts [50%]). 28 of 30 pts (93%) had reduction from baseline in target lesions. Median DOR was not reached (NR; 95% CI, 0+ to 23+ mo); 6 pts (51%) had response ≥12 mo. Median PFS was 19 mo (95% CI, 8-NR); 12-mo PFS rate was 57%. Median OS was NR (95% CI, NR-NR); 12-mo OS rate was 94%. As of the database cutoff (Nov 1, 2021), 9 of 30 pts had discontinued (3 AEs; 6 PD). Treatment-related AEs (TRAE) occurred in 26 pts (87%); most common (≥10%) were hypothyroidism (27%), fatigue (20%), infusion-related reactions (20%), headache (17%), and arthralgia, hyperthyroidism, myalgia, and nausea (10% each); grade 3 or 4 TRAEs occurred in 6 pts (20%). 10% of pts discontinued due to TRAEs. No treatment-related deaths occurred. **Conclusions:** Favezelimab 800 mg + pembrolizumab 200 mg Q3W demonstrated a tolerable safety profile and effective antitumor activity in pts with anti–PD-1–naïve R/R cHL. Further studies will be useful to compare its activity to that of pembrolizumab alone. Clinical trial information: NCT03598608. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

7517 **Poster Discussion Session**

Outcomes by BCL2 and MYC expression and rearrangements in untreated diffuse large B-cell lymphoma (DLBCL) from the POLARIX trial.

First Author: Franck Morschhauser, Lille University Hospital Center, Lille Cedex, France

Background: Overexpression of BCL2 and MYC, and translocation of *MYC*, *BCL2*, and *BCL6*, are associated with poorer outcomes in patients (pts) with DLBCL (Horn et al. Blood 2013). We previously reported progression-free survival (PFS) from POLARIX in subgroups of pts with DLBCL receiving Pola-R-CHP or R-CHOP, including pts with double expressor lymphoma (DEL; favoring Pola-R-CHP: hazard ratio [HR] 0.64, 95% confidence interval [CI] 0.42–0.97), and double- or triple-hit lymphoma (DHL/THL; favoring R-CHOP: HR 3.81, 95% CI 0.82–17.64) (Tilly et al. NEJM 2022). In this prespecified exploratory analysis, we further analyzed immunohistochemistry (IHC) expression status of BCL2, MYC, and rearrangements (R) of *BCL2*, *BCL6* and *MYC* as independent prognostic markers. We also explored the prognostic impact of DEL within treatment arms. **Methods:** BCL2 and MYC protein expression were assessed by IHC and identified as IHC+ (≥50% [BCL2]/≥40% [MYC]) or IHC−; *MYC*-R, *BCL2*-R, and *BCL6*-R were detected by fluorescence in situ hybridization (Tilly et al. NEJM, 2022). Exploratory multivariate Cox regression models were adjusted for treatment, stratification factors (IPI, bulky disease, geographic region), age >60 years, cell of origin, and biomarker evaluated, as appropriate. **Results:** The prevalence, univariate HR, and 2-year (yr) PFS estimates of BCL2+/MYC+ and *BCL2*-R/*MYC*-R/*BCL6*-R subgroups are presented (Table) except for *BCL6*-R, because all 4 PFS events in this subgroup were with Pola-R-CHP. Multivariate analyses results for Pola-R-CHP vs R-CHOP in pts with BCL2+ (HR 0.60, 95% CI 0.43–0.86) and in pts with MYC+ (HR 0.63, 95% CI 0.45–0.89) were similar to results of univariate analyses. Multivariate analyses of other subgroups were not performed due to the low pt number with *BCL2*-R/*MYC*-R/*BCL6*-R. While pts with DEL treated with Pola-R-CHP had improved PFS vs pts treated with R-CHOP (HR 0.64, 0.42–0.97), the prognostic impact of DEL vs non-DEL was more pronounced with R-CHOP (univariate HR 1.53, 95% CI 1.06–2.21; multivariate HR 1.29, 95% CI 0.88–1.91) vs Pola-R-CHP (univariate HR 1.10, 95% CI 0.72–1.69; multivariate HR 1.42, 95% CI 0.89–2.28). **Conclusions:** Multivariate analyses support the benefit of Pola-R-CHP in pts with BCL2+ and MYC+ DLBCL. The poor prognostic impact associated with DEL appears reduced in Pola-R-CHP- vs R-CHOP-treated pts. Clinical trial information: NCT03274492. Research Sponsor: POLARIX is sponsored by F. Hoffmann-La Roche Ltd and Genentech, Inc. Third-party medical writing assistance, under author direction, was provided by Carla Smith of Ashfield MedComms, and was funded by F. Hoffmann-La Roche Ltd.

	Pola-R-CHP		R-CHOP		
	N, prevalence (%)	2-yr PFS (%)	N, prevalence (%)	2-yr PFS (%)	Univariate PFS HR (95% CI)
BCL2 IHC	359		365		
BCL2+	56	75	55	63	0.65 (0.46–0.92)
BCL2–	44	79	45	80	0.97 (0.60–1.56)
MYC IHC	366		368		
MYC+	64	78	70	69	0.68 (0.48–0.96)
MYC–	36	75	30	74	0.92 (0.57–1.51)
***BCL2*-R**	332		334		
Yes	28	77	23	76	0.90 (0.51–1.59)
No	72	76	77	70	0.78 (0.55–1.09)
***MYC*-R**	331		336		
Yes	12	77	10	71	0.86 (0.36–2.08)
No	88	76	90	71	0.78 (0.57–1.06)
BCL6*-R	38		34		
Yes	26	70	29	100	Not evaluable
No	74	79	71	58	0.46 (0.17–1.26)

**BCL6*-R only tested in pts with *MYC*-R; N=pts with central lab results.

7518 **Poster Discussion Session**

Three-year follow-up of outcomes with KTE-X19 in patients with relapsed/refractory mantle cell lymphoma in ZUMA-2.

First Author: Michael Wang, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Brexucabtagene autoleucel (KTE-X19) is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy approved for the treatment of patients (pts) with relapsed/refractory (R/R) mantle cell lymphoma (MCL). In ZUMA-2, a 93% objective response rate (ORR; 67% complete response [CR] rate) was reported with KTE-X19 in pts with R/R MCL (median follow-up: 12.3 mo; 60 efficacy-evaluable pts; Wang et al. *N Engl J Med*. 2020). Here, we present updated outcomes with 2 years of additional follow-up. **Methods:** Adult pts (≥18 years) with R/R MCL underwent leukapheresis and conditioning chemotherapy followed by a single infusion of KTE-X19. Minimal residual disease (MRD) was an exploratory endpoint (sensitivity 10-5) evaluated in peripheral blood using next-generation sequencing. Updated results are reported for all 68 treated pts. **Results:** After 35.6 mo median follow-up, the ORR (CR + partial response) was 91% (95% CI, 81.8-96.7), with a 68% CR rate (95% CI, 55.2-78.5). The median duration of response (DOR) was 28.2 mo (95% CI, 13.5-47.1), with 25 of 68 treated pts (37%) still in ongoing response (all CR) at data cutoff. Late relapse > 24 mo post-infusion was infrequent (n = 3). The medians for progression-free survival (PFS) and overall survival (OS) were 25.8 mo (95% CI, 9.6-47.6) and 46.6 mo (95% CI, 24.9-not estimable), respectively. MRD was analyzed in 29 pts total; 24 of 29 were MRD-negative at mo 1, and 15 of 19 with available data were MRD-negative at mo 6. At data cutoff, the medians for DOR, PFS, and OS in the 15 MRD-negative pts were all not reached, vs 6.1, 7.1, and 27.0 mo, in the 4 MRD-positive pts, respectively. MRD-negative status at mo 1, 3, and 6 was associated with durable response, with 55%, 71%, and 69% of MRD-negative pts at those timepoints remaining in ongoing CR at data cutoff. Circulating tumor DNA analysis of MRD at mo 3 and 6 was predictive of relapse (AUC 0.80 and 0.75, respectively). No new safety signals were observed. Only 3% of treatment-emergent adverse events (AEs) of interest occurred since the primary report. The most frequent Grade ≥3 AE was neutropenia (1 [1%] Grade 3; 7 [10%] Grade 4). Two pts had KTE-X19-related Grade 3 serious infections: pneumonia and upper respiratory tract infection (n = 1); influenza (n = 1). There were no new cytokine release syndrome AEs and 1 new serious neurologic AE of Grade 3 encephalopathy (13.0 mo post-infusion) that was considered not related to study treatment. Three new Grade 5 AEs occurred, none of which were considered related to study treatment: *Salmonella* bacteremia (24.9 mo post-infusion), myelodysplastic syndrome (25.2 mo post-infusion), and acute myeloid leukemia (37.5 mo post-infusion). **Conclusions:** These data represent the longest follow-up of CAR T-cell therapy in pts with MCL to date and suggest that KTE-X19 induces durable long-term responses with manageable safety and low late relapse potential in R/R MCL. Clinical trial information: NCT02601313. Research Sponsor: Kite, a Gilead Company.

7519 **Poster Discussion Session**

Fixed-duration (FD) ibrutinib (I) + venetoclax (V) for first-line (1L) treatment (tx) of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): Three-year follow-up from the FD cohort of the phase 2 CAPTIVATE study.

First Author: William G. Wierda, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: CAPTIVATE (PCYC-1142) is a multicenter phase 2 study of 1L I+V in CLL. The primary analysis (PA) evaluating FD tx with I+V was previously presented (Ghia et al., ASCO 2021). Here we present 3-y follow-up results from the FD cohort. **Methods:** Patients (pts) aged ≤70 y with previously untreated CLL/SLL received 3 cycles of I then 12 cycles of I+V (I 420 mg/d orally; V ramp-up to 400 mg/d orally). Responses were investigator assessed per iwCLL 2008 criteria. Undetectable minimal residual disease (uMRD; $<10^{-4}$) was measured by 8-color flow cytometry. Serious AEs (SAEs) deemed related to I reported >30 d after last dose of study drug were collected. **Results:** 159 pts were enrolled (median age 60 y), including pts with high-risk features of del(17p)/*TP53* mutation (17%), unmutated IGHV (uIGHV; 56%), and complex karyotype (19%). 147 (92%) and 149 (94%) pts completed tx with I and V, respectively. With 1 y of additional follow-up since PA, median time on study was 39 mo (range 1-41). ORR was 96% and was consistent (96%-97%) in pts with high-risk features (Table).The primary endpoint of complete response (CR) including CR with incomplete bone marrow recovery (CRi) rate in pts without del(17p) (n=136) increased nominally from 56% (95% CI, 48-64) to 58% (95% CI 50-66); in all pts, CR rate increased from 55% (95% CI 48-63) to 57% (95% CI 50-65). In pts achieving CR, 93% had durable responses lasting ≥12 mo post-tx. Of pts with uMRD in peripheral blood at 3 mo post-tx, 66/85 (78%) evaluable pts maintained uMRD through 12-mo post-tx. At 36 mo, PFS was 88% (95% CI 82–92) and OS was 98% (95% CI 94–99); similar rates were seen in pts with high-risk features (Table). All pts are off tx; no new SAEs of any kind have occurred since the PA. Available data on relevant mutations in *BTK*, *PLCγ2*, or *BCL-2* at time of PD will be presented. As of January 2022, 12 pts were retreated with single-agent I after PD (tx duration range 3-29 mo); of evaluated pts, 7/9 had partial responses and 2/9 had stable disease. **Conclusions:** Fixed duration I+V continues to provide deep, durable responses and clinically meaningful PFS, including in pts with high-risk disease features, representing an all-oral, once-daily, chemotherapy-free FD regimen for previously untreated pts with CLL/SLL. With an additional 1 y of follow-up, no OS events or SAEs occurred. Manageable safety profile is unchanged as previously reported. To date, successful single-agent I retreatment responses are observed. Clinical trial information: NCT02910583. Research Sponsor: Pharmacyclics LLC, an AbbVie Company.

Efficacy outcomes	FD Cohort – All treated population N=159	del(17p)/*TP53* n=27	uIGHV n=89
ORR, n (%)	153 (96)	26 (96)	86 (97)
CR, n (%)[a]	91 (57)	15 (56)	57 (64)
36-mo PFS, % (95% CI)	88 (82–92)	80 (58–91)	86 (77–92)
36-mo OS, % (95% CI)	98 (94–99)	96 (76–99)	97 (90–99)

[a]Included 3 pts with CRi.

7520 **Poster Discussion Session**

Phase 1/2 study of zilovertamab and ibrutinib in mantle cell lymphoma (MCL) or chronic lymphocytic leukemia (CLL).

First Author: Hun Ju Lee, The University of Texas MD Anderson Cancer Center, Department of Lymphoma/Myeloma, Houston, TX

Background: Zilovertamab (Zilo) is a humanized monoclonal antibody that inhibits the tumor promoting activity of ROR1 and has demonstrated additive/synergistic activity with many anticancer agents, including ibrutinib (Ibr). **Methods:** Patients (Pts) with relapsed or refractory (RR) MCL or treatment-naïve (TN) or RR CLL were enrolled. In Part 1 (Dose Escalation), multiple doses were examined. Zilo 600 mg IV starting q2wks x3 then q4wks + Ibr qD was selected as the recommended dosing regimen for use in Part 2 (Expansion) and Part 3 (CLL only, Zilo+Ibr vs. Ibr alone). **Results:** As of 18Jan2022 data cutoff, 26 evaluable RR MCL pts, including pts who received prior Ibr (5) or auto-SCT (7), and 34 evaluable CLL pts (12 TN and 22 RR) were enrolled into Parts 1&2. In Part 3, 22 evaluable pts were randomized (2:1) to receive either Zilo+Ibr (15) or Ibr (7). Safety: Treatment-emergent adverse events (TEAEs) (≥30%, N = 84), regardless of relationship, included fatigue (41.7%), contusion (39.3%), and diarrhea (38.1%). Most common (≥5%) Grade ≥3 TEAEs included hypertension (10.7%), pneumonia (7.1%), atrial fibrillation, fatigue, and neutropenia (all 6.0%). Grade ≥3 neutrophil decrease observed in 9.4% or 17.6%, platelet decrease in 12.5% or 2.9%, or hemoglobin decrease in 9.4% or 0% of pts with MCL or CLL, respectively in Parts 1&2. Investigators scored TEAEs as due to Ibr in 78.1% or 85.3%, or to Zilo in 15.6% or 23.5% of pts with MCL or CLL, respectively. Efficacy (MCL): Objective response rate (ORR) was 80.8% (34.6% CR, 46.2% PR). ORR for pts with prior Ibr was 80% (2CR, 2PR) and median duration of response (mDOR) was 13.7 months (M) (95%CI: 11.93, NE). ORR was 100% in pts who had prior SCT+/- CAR-T (5CR, 2PR), and mDOR was 34.1 M (95% CI 13.84, NE). Overall median PFS (mPFS) was 35.9 M (95% CI: 17.3, NE) at median follow-up of 15.0 M. For MCL pts with *TP53* aberrancy (6), Ki67 > 30% (13), ≥ 3 prior lines of therapies (4), blastoid histology (3), bulky disease ≥5 cm (4), intermediate MIPIb (6), or high MIPIb (11), the mPFS (in M) was 17.3 (95% CI: 2.85, NE), Not Reached (NR) (95% CI: 2.85, NE), 35.9 (95% CI: 16.52, NE), NR (min 9.18, max 27.87), 26.6 (95% CI: 0.03, NE), 35.9 (min 8.30, max 35.9) or 16.5 (95% CI: 2.72, NE). Efficacy (CLL): In Parts 1&2 ORR was 91.2% (8.8% CR, 82.3% PR/PR-L), and 8.8% had stable disease (SD). At median follow-up of 31.4 M, mDOR was 33.5 M and mPFS was NR (95% CI: 36.3, NE); the mPFS (in M) for pts with 1, 2, or ≥ 3 prior therapies was NR (min 19.3, max 41.3), NR (min 31.3, max 36.8) or 36.3 (95% CI: 15.7, NE). At median follow-up of 21.1 M in Part 3, mPFS was NR for TN or RR in both Zilo+Ibr and Ibr arms. **Conclusions:** Zilo+Ibr is well-tolerated. Striking responses were observed in MCL pts, with mPFS of 35.9 M (95% CI: 17.3, NE) and CR of 34.6%, which compares favorably to mPFS of 12.8 M (95% CI 8.5, 16.6) and CR of 20% reported for single agent Ibr (Rule 2017). For CLL, ORR and PFS compare very favorably to Ibr monotherapy data (Byrd 2019). Clinical trial information: NCT03088878. Research Sponsor: Oncternal Therapeutics, Inc., Other Foundation.

7521 **Poster Discussion Session**

ASPEN: Long-term follow-up results of a phase 3 randomized trial of zanubrutinib (ZANU) versus ibrutinib (IBR) in patients with Waldenström macroglobulinemia (WM).

First Author: Constantine Si Lun Tam, Peter MacCallum Cancer Centre, Melbourne, Australia

Background: ASPEN is a randomized, open-label, phase 3 study comparing ZANU, a potent and selective Bruton tyrosine kinase inhibitor (BTKi), with the first-generation BTKi IBR in patients with WM. We present data with a median follow-up of 43 months. **Methods:** Patients with *MYD88* mutations were assigned to cohort 1 and randomized 1:1 to receive ZANU 160 mg twice daily or IBR 420 mg once daily. Randomization was stratified by *CXCR4* mutational status and lines of prior therapy (0 vs 1-3 vs > 3). Patients without *MYD88* mutations were assigned to cohort 2 and received ZANU 160 mg twice daily. The primary endpoint was proportion of patients achieving complete response or very good partial response (CR+VGPR). **Results:** A total of 201 patients (ZANU arm, n = 102; IBR arm, n = 99) were enrolled in cohort 1 and 28 patients were enrolled in cohort 2. A larger proportion of patients in the ZANU arm of cohort 1 vs IBR had *CXCR4* mutations by next-generation sequencing (32% vs 20%, or 33 of 98 vs 20 of 92 with data available) and were aged > 75 years (33% vs 22%). Median duration of treatment was 42 months (ZANU) and 41 months (IBR), with 67% and 58% remaining on treatment, respectively. The CR+VGPR rate by investigator was 36% with ZANU vs 22% with IBR (p= 0.02) in cohort 1, and 31% in cohort 2. One patient achieved CR (cohort 2). In patients with wild type or mutant *CXCR4* from cohort 1, CR+VGPR rates with ZANU vs IBR were 45% vs 28% (p= 0.04) and 21% vs 5% (p= 0.15), respectively. Median progression-free survival and overall survival were not yet reached. Rates of atrial fibrillation, diarrhea, hypertension, localized infection, hemorrhage, muscle spasms, pneumonia, and adverse events leading to discontinuation or death were lower with ZANU vs IBR (Table). Exposure-adjusted incidence rates of atrial fibrillation/flutter and hypertension were lower with ZANU vs IBR (0.2 vs 0.8 and 0.5 vs 1.0 persons per 100 person-months, respectively; p< 0.05). Rate of neutropenia was higher and rate of grade ≥3 infection was lower with ZANU vs IBR. Safety outcomes of ZANU were similar between cohorts 1 and 2. **Conclusions:** ASPEN is the largest phase 3 trial with head-to-head BTKi comparison in WM. At a median follow-up of 43 months, ZANU was associated with higher CR+VGPR rate and demonstrated clinically meaningful advantages in long-term safety and tolerability vs IBR. Clinical trial information: NCT03053440. Research Sponsor: BeiGene USA, Inc.

AE (all grade), % of treated patients	Cohort 1 ZANU (n = 101)	Cohort 1 IBR (n = 98)	Cohort 2 ZANU (n = 28)
AE, grade ≥3	74.3	72.4	71.4
AE leading to discontinuation	8.9	19.4	14.3
Atrial fibrillation / flutter[a]	7.9	23.5	7.1
Diarrhea	21.8	34.7	32.1
Hemorrhage[a] / major bleeding[b]	55.4 / 7.9	62.2 / 12.2	39.3 / 7.1
Hypertension[a]	14.9	25.5	10.7
Muscle spasm	10.9	28.6	14.3
Neutropenia[a]	33.7	19.4	21.4
Infection[a] (grade ≥3) / pneumonia	78.2 (20.8) / 5.0	79.6 (27.6) / 18.4	82.1 (32.1) / 14.3

[a]Grouped term.
[b]Includes grade ≥3 hemorrhage and central nervous system bleeding of any grade.

7522 **Poster Session**

Phase 1/2 study of anbalcabtagene autoleucel, novel anti-CD19 CAR-T cell therapy with dual silencing of PD-1 and TIGIT in relapsed or refractory large B-cell lymphoma.

First Author: Won Seog Kim, Samsung Medical Center, Seoul, South Korea

Background: Anbal-cel is a novel 2nd generation autologous CD19 CAR-T cell therapy which has been knock-downed for PD-1 and TIGIT using OVIS platform. Anbal-cel demonstrated the eradication of CD19 positive tumor cells *in vitro* and *in vivo* better than conventional CD19 CAR-T cells. The knock-down of PD-1 and TIGIT at CD19 CAR-T cells exerts the superior T-cell functionality by delaying the exhaustion of CAR-T cells. **Methods:** This phase 1 dose escalation part (NCT04836507) was evaluated the safety and preliminary efficacy in patients with r/r LBCL. Anbal-cel was manufactured at GMP facility with fresh leukapheresis product. Patient was administered as a single intravenous dose at dose level 1 ($2x10^5$ cells/kg), DL2 ($7x10^5$ cells/kg) or DL3 ($2x10^6$ cells/kg). Lymphodepletion with cyclophosphamide (500mg/m^2) and fludarabine (30mg/m^2) was performed for 3 days prior to Anbal-cel infusion. **Results:** As of Jan 17 2022, 9 patients with r/r DLBCL were infused with Anbal-cel; 4pts at DL1, 3pts at DL2 and 2pts at DL2. Median age was 54 (range 26-71); all patients received 2 or more prior lines of therapy and 44% (4/9) received ≥4 prior line of treatment before the study. 78% (7/9) patients were refractory to their last treatment. 67% (6/9) of patients were at IPI 3-4 and 44% (4/9) of patients had bulky disease. No patient experienced DLT during the study. Of the 9 patients, 5 (56%) experienced CRS; 4 (44%) were grade 1 or 2 and one patient experienced grade 3 CRS. Median time to onset of CRS was 7 days (range, 1-16) with median duration of 4 days (range, 0-18). One patient dosed at DL3 experienced grade 2 ICANS, time to onset of ICANS was 7 days and lasted for 13 days. This patient had prior CNS involvement history before the study. Most commonly reported grade 3/4 AEs were neutrophil count decrease (6/9, 67%), anemia (5/9, 56%), thrombocytopenia (2/9, 22%), platelet count decrease (2/9, 22%) and no infection was reported. Complete response rate (CRR) was 78% and complete responses were observed at the lowest dose level and from patients expressing less than 10% CD19 at IHC; 3 complete responses (CR) at DL1, 2 CRs at DL2 & DL3 respectively. Dose-dependent CRC01 expansion was observed; median T_{max} was 15.4, 15.8, 11.0 days at DL1, DL2 & DL3 each; median C_{max} was 18,003, 30,103, 53,688 copies/ug gDNA at DL1, DL2 & DL3 each; median $AUC_{0\text{-}28day}$ was 679,125, 1,110,108, 2,852,235 copies/ug gDNA at DL1, DL2 & DL3 respectively. **Conclusions:** Anbal-cel demonstrated promising efficacy and tolerable safety profile in this dose escalation study. Based on this phase 1 study, phase 2 patient enrollment will be commenced in Mar 2022 to evaluate the response rate, duration of response of CRC01 as well as safety. In addition, various biomarker studies are planned to investigate the differential mode of action of Anbal-cel during phase 2 study. Clinical trial information: NCT04836507. Research Sponsor: Curocell Biotherapeutics.

7523 **Poster Session**

First-line treatment (Tx) with subcutaneous (SC) epcoritamab (epco) + R-CHOP in patients (pts) with high-risk diffuse large B-cell lymphoma (DLBCL): Phase 1/2 data update.

First Author: Lorenzo Falchi, Lymphoma Service, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Outcomes of pts with newly diagnosed DLBCL with high/poor risk according to the revised International Prognostic Index (IPI) treated with immunochemotherapy (IC) remain suboptimal, with a 4-year survival rate of 55% (Sehn et al, *Blood* 2007). SC epco is a well-tolerated bispecific antibody with single-agent activity in the relapsed/refractory (R/R) aggressive B-cell NHL setting. The mechanism of action and safety profile of epco are distinct from IC, and epco is well suited for use in combinations and in earlier lines of therapy. Addition of a novel agent to standard of care IC may overcome the adverse prognosis of high-risk pts. Presented here are updated results of epco + rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in previously untreated DLBCL pts with IPI 3–5 (EPCORE NHL-2 arm 1; NCT04663347). **Methods:** Adults with previously untreated CD20$^+$ DLBCL and IPI ≥3 received SC epco (every week, cycle [C] 1–4; every 3 weeks, C5–6) + R-CHOP for 6 cycles (21 d) followed by single-agent epco every 4 weeks up to 1 y (in cycles of 28 d). To mitigate CRS, epco step-up dosing and corticosteroid prophylaxis were required. Response was assessed by PET-CT with contrast per Lugano 2014 criteria. **Results:** As of Dec 1, 2021, 33 pts (median age, 66 y; range, 19–82) received epco + R-CHOP (epco 24 mg, n = 4; 48 mg, n = 29). Median time from diagnosis to first dose was 25 d (range, 5–70). All pts had IPI ≥3 and ≥24% had double- or triple-hit DLBCL. Median follow-up was 3 mo (range, 0–9.7); median number of total cycles initiated was 5 (1–13). Overall, 94% of pts (31/33) remained on Tx. Tx-emergent adverse events (TEAEs) in ≥30% of pts were neutropenia (48%; febrile neutropenia in 9% of all pts), CRS (45%), infections (42%), anemia (39%), injection-site reactions (36%), nausea (33%), constipation (30%), and pyrexia (30%). No TEAEs led to epco discontinuation. AEs of special interest included CRS (42% grade [G] 1/2, 3% G3) and ICANS (3% G2); 1 pt had tumor lysis syndrome (3% G3). Most CRS events occurred in C1 and resolved after a median of 2 days (1–11); 4 pts with CRS received tocilizumab. No fatal TEAEs were reported. In efficacy-evaluable pts, the overall response rate (ORR) was 96% (24/25); 68% (17/25) had complete metabolic response (CMR). For the 10 pts who received 6 cycles of R-CHOP and had a subsequent response assessment, the ORR and CMR rate were 100% and 90%, respectively. As of the data cutoff, all of these 10 pts remained in response, with the longest duration of response 7.1+ mo and ongoing. Updated data will be presented. **Conclusions:** Epco is the first SC bispecific antibody assessed in combination with standard of care in previously untreated DLBCL. The safety profile of epco + R-CHOP is manageable. CRS events were mostly of low grade and did not lead to Tx discontinuation. ORR and CMR rate were high with no relapses as of the data cutoff date. Clinical trial information: NCT04663347. Research Sponsor: Genmab A/S and AbbVie.

7524 **Poster Session**

Subcutaneous epcoritamab with rituximab + lenalidomide (R^2) in patients (pts) with relapsed or refractory (R/R) follicular lymphoma (FL): Update from phase 1/2 trial.

First Author: Lorenzo Falchi, Lymphoma Service, Memorial Sloan Kettering Cancer Center, New York, NY

Background: R/R FL is associated with poor prognosis and less frequent, shorter responses with each line of treatment (Tx). Although R^2 is an effective regimen in R/R FL with an acceptable safety profile, FL remains incurable; thus, better Tx options are needed. Subcutaneous epcoritamab is a bispecific antibody that simultaneously binds to CD3 on T cells and CD20 on malignant B cells. In the dose-escalation part of the phase 1/2 EPCORE NHL-1 trial, single-agent epcoritamab (0.76–48 mg) resulted in an overall response rate of 90% and a complete response rate of 50% in R/R FL. The distinct mechanisms of action of epcoritamab and R^2 may combine to increase antitumor response, with generally non-overlapping toxicity profiles. We present updated data for epcoritamab with R^2 in R/R FL (EPCORE NHL-2 arm 2; NCT04663347). **Methods:** Adults with R/R CD20$^+$ FL received epcoritamab + R^2 for 12 cycles (C) of 28 d; epcoritamab was administered at 24 or 48 mg in dose escalation and 48 mg in expansion. During C1, step-up epcoritamab dosing and corticosteroids were required to mitigate CRS. Response was assessed by PET-CT. The epcoritamab regimen for these pts was: Q1W, C1–3; Q2W, C4–9; Q4W, C≥10 up to 2 y. **Results:** As of December 1, 2021, 30 pts (median age, 68 y) had received epcoritamab + R^2 (24 mg, n=3; 48 mg, n=27), 21 pts (70%) had stage IV disease, and 20 pts (67%) had FLIPI scores 3–5. Median (range) number of prior lines of therapy was 1 (1–5), 30% had primary refractory disease, and 40% had disease progression within 24 mo after starting first-line Tx (20% within 24 mo after starting immunochemotherapy). At a median (range) follow-up of 5.1 mo (0.8–12.3), 25 pts (83%) remained on Tx; 5 pts discontinued Tx due to progression (n=2), AEs (n=2), or consent withdrawal (n=1). Common Tx-emergent AEs (TEAEs) of any grade (G) included infections (57%), injection-site reactions (50%), constipation (37%), fatigue (37%), and neutropenia (37%). CRS was seen in 15 pts (50%; G1/2 43%, G3 7%), with most events in C1. All CRS events resolved with standard management, including tocilizumab in 3 pts, and 1 pt discontinued Tx due to CRS. One pt experienced G2 ICANS. No fatal TEAEs occurred. Antitumor activity is shown in the Table. As of the data cut, all responders remained in response, with the longest duration of response being 7.0+ mo and ongoing. **Conclusions:** Subcutaneous epcoritamab+ R^2 exhibits promising efficacy, including a high CMR rate, in pts with R/R FL. The safety profile was consistent with prior data, and CRS events were generally low grade and in C1. Updated data with an additional 30 pts will be presented. Clinical trial information: NCT04663347. Research Sponsor: Genmab A/S and AbbVie.

Antitumor activity.

n (%)	Total N=30
Evaluable pts	27
Overall response	27 (100)
Complete metabolic response (CMR)	25 (93)
Partial metabolic response	2 (7)
Stable disease	0
Progressive disease	0

7525 **Poster Session**

SHR2554, an enhancer of zeste homolog 2 (EZH2) inhibitor, in relapsed or refractory (r/r) mature lymphoid neoplasms: A first-in-human phase 1 study. *First Author: Yuqin Song, Key Laboratory of Carcinogenesis and Transitional Research (Ministry of Education), Department of Lymphoma, Peking University Cancer Hospital and Institute, Beijing, China*

Background: Dysregulation of histone methyltransferase EZH2 plays critical roles in lymphomagenesis. Emerging evidence shows that EZH2 also contributes to tumor immune evasion. SHR2554 is an oral, small-molecule inhibitor exhibiting potent selectivity for EZH2. We initiated a first-in-human study to assess SHR2554 across a broad spectrum of lymphoid neoplasms that had relapsed or was refractory to standard systemic therapies, including B-cell lymphomas, T-cell lymphomas, and classical Hodgkin lymphoma (cHL). **Methods:** This multicenter, phase 1 study was composed of 3 parts: dose escalation phase according to mTPI-2 design, dose expansion phase, and clinical expansion phase in selected tumor subtypes. Dose was escalated at 50, 100, 200, and 400 mg BID, and then de-escalated at 300 and 350 mg based on the observed toxicities. Two dose levels (300 and 350 mg) were expanded. Subsequently, follicular lymphoma (FL), peripheral T-cell lymphoma (PTCL), and cHL were selected for clinical expansion at RP2D. Primary endpoints were to assess the safety and determine the MTD and RP2D. Key secondary endpoint included clinical activity at RP2D in different subtypes. **Results:** As of Sep 10, 2021, 113 heavily pretreated pts were enrolled, with 53 (46.9%) having received ≥3 lines of prior systemic therapies. In dose escalation phase, DLTs occurred in 2 of 3 pts at 400 mg and 1 of 6 pts at 350 mg; thus, 350 mg BID was the MTD. Combined with the safety, tolerability, PK/PD, and preliminary efficacy findings observed in dose escalation and expansion phases, RP2D was determined to be 350 mg BID. As of cutoff date, 41 FL, 22 PTCL, and 21 cHL pts who received SHR2445 at 350 mg BID completed at least one post-baseline efficacy assessment. ORR in FL was 58.5% (95% CI 42.1-73.7); majority of responses (66.7%) were still ongoing, and the estimated median DoR was 9.3 mos (95% CI 5.6-NR). *EZH2*^{mut} FL pts showed a slightly higher ORR than *EZH2*^{WT} FL pts (62.5% vs 55.2%). *EZH2* mutations were not detected in pts with PTCL or cHL. ORR in PTCL was 63.6% (95% CI 40.7-82.8); majority of responses (71.4%) were still ongoing, and the estimated median DoR was 7.4 mos (95% CI 2.9-NR). All cHL pts had received prior chemotherapy and anti-PD-1/PD-L1 antibodies. Shrinkage in target lesions was shown in 76.2% of cHL pts; ORR was 19.0% (95% CI 5.4-41.9); majority of responses (75.0%) were still ongoing, and the median DoR had not been reached yet. Grade ≥3 treatment-related AEs occurred in 38 of the 113 pts (33.6%), with the most common being decreased platelet count (17.7%), decreased neutrophil count (8.8%), decreased white blood cell count (8.0%), and anemia (6.2%). **Conclusions:** SHR2554 showed a manageable safety profile and promising anti-tumor activity in pts with r/r lymphomas, supporting further explorations in FL, PTCL, and cHL. Clinical trial information: NCT03603951. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

7526 **Poster Session**

Characterization of CD20 expression loss as a mechanism of resistance to mosunetuzumab in patients with relapsed/refractory B-cell non-Hodgkin lymphomas. *First Author: Stephen J. Schuster, Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA*

Background: Mosunetuzumab (M) is a bispecific antibody targeting CD20 and CD3 that redirects T cells to engage and eliminate malignant B cells being developed for relapsed or refractory (R/R) B-cell non-Hodgkin lymphomas (B-NHL). CD20 is an optimal target, with uniform expression across B-NHL histologies and minimal receptor turnover. We characterized CD20 loss as a potential mechanism of resistance to M in patients (pts) on a Phase I/II trial (NCT02500407) receiving M monotherapy for the treatment (tx) of R/R B-NHL. **Methods:** Pts with R/R B-NHL received M intravenously in 3-week cycles, for eight to 17 cycles depending on tumor response. At baseline (BL), biomarker-evaluable (archival or fresh) biopsies were collected from 293 pts. Biopsies from 62 pts were collected at additional time points during tx with M and/or at disease progression (PD). The proportion of CD20+ and PAX5+ tumor cells was determined by immunohistochemistry (IHC) using dual-staining with anti-CD20 (clone L26, VENTANA) and anti-PAX5 (clone DAK-PAX5, DAKO) antibodies. Expression of *MS4A1,* the gene encoding CD20, was measured by RNA-sequencing (RNA-seq); *MS4A1* mutation profiling was performed by whole exome sequencing (WES). Levels of CD20 expression were assessed relative to response rates. Correlative analyses were performed and assessed centrally (IHC, RNA-seq, and WES) and locally (IHC). **Results:** CD20 levels were consistently high (> 75% CD20+PAX5+ cells) in the majority of BL biopsies and generally comparable across histologies (FL, DLBCL, tFL, MCL, and RT). BL CD20 loss (≤5% CD20+PAX5+ cells) was seen in 16/293 pts (5.5%), more commonly in aggressive NHL, and responses to M were not seen in these pts. Among 62 pts with BL and on-tx/at-PD biopsies, BL CD20 levels were ≤5% in 7/62 pts (11%) (6/7 pts [86%] progressed before completing Cycle 2). CD20 levels were maintained in on-tx biopsies from 23/24 pts (96%). At PD, biopsies showed CD20 loss in 7/26 pts (27%). For five pts with BL, on-tx and at-PD biopsies, all pts maintained CD20 while on-tx and 1/5 pts (20%) had CD20 loss at PD. There was no clear association between CD20 reduction and histology. Data from 185 BL biopsies showed generally concordant levels of CD20 gene and protein expression (r = 0.72). In 10/185 pts (5%), *MS4A1* was expressed without detectable CD20 protein expression; DNA sequencing revealed novel mutations in *MS4A1*, including mutations leading to truncation of the protein. CD20 transmembrane and extra-cellular domain mutations were also observed but do not block CD20 expression. **Conclusions:** In pts with R/R B-NHL treated with M, low BL CD20 expression is associated with lack of response to M. During M tx, loss of tumor cell expression of CD20 is one mechanism of acquired resistance; however, CD20 expression is maintained in most pts with PD, implying alternative mechanisms for acquired M resistance. Clinical trial information: NCT02500407. Research Sponsor: Third-party editorial assistance, under the direction of all authors, was provided by Aisling Lynch, PhD of Ashfield MedComms, an Ashfield Health company, and was funded by F. Hoffmann-La Roche Ltd.

7527 **Poster Session**

Epcoritamab (epco) with gemcitabine + oxaliplatin (GemOx) in patients (pts) with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) ineligible for autologous stem cell transplant (ASCT) induces high response rate even in pts failing CAR T therapy. *First Author: Joshua Brody, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: Pts with R/R DLBCL who fail or are ineligible for ASCT have very poor outcomes with standard palliative chemotherapy. Rituximab + GemOx had a complete response rate of 33% (Cazelles et al, *Leuk Lymphoma* 2021); novel approaches are needed. Epco is a subcutaneously administered bispecific antibody targeting CD3 on T cells and CD20 on B cells. In the EPCORE NHL-1 dose-escalation trial, epco had manageable safety and antitumor activity in heavily pretreated B-cell NHL including DLBCL. EPCORE NHL-2 is a phase 1/2 trial evaluating epco + standard B-cell NHL therapies; shown here are results from arm 5 (NCT04663347). **Methods:** Adults with R/R CD20^{+} DLBCL who failed or were ineligible for ASCT received epco (QW, cycle [C] 1–3; Q2W, C4–9; Q4W, C≥10) and GemOx (Q2W, C1–4) until disease progression or unacceptable toxicity (28 d/C). Step-up epco dosing and prophylactic corticosteroids were required in C1 to mitigate CRS. Response was assessed by PET-CT per Lugano 2014 criteria. **Results:** As of Dec 1, 2021, 27 pts (median age, 71 y; range, 47–87 y) had received epco + GemOx (epco 24 mg, n=3; 48 mg, n=24). Most were stage IV (56%), primary refractory (56%), and refractory to last therapy (70%). Median number of prior therapies was 2 (range, 1–13). Median follow-up was 6.0 mo (range, 1.0–11.1), with treatment (Tx) ongoing in 16 pts (59%). The most common Tx-emergent AEs were CRS (70%), thrombocytopenia (70%), neutropenia (56%), anemia (52%), and infections (52%). CRS events were all grade (G) 1/2, with most cases occurring in C1; all cases resolved. One pt had ICANS (G3); 1 pt had tumor lysis syndrome (G3). Six pts (22%) had G5 AEs; investigator could not rule out contribution of epco in 2 pts: small bowel perforation in pt (72 y) with transformed DLBCL and extensive gastrointestinal involvement (had complete metabolic response [CMR]); acute hepatitis/multiorgan failure in pt (68 y) with transformed DLBCL and liver involvement (had CMR). Of 4 pts with fatal AEs unrelated to epcoritamab by investigator, 2 (87 y) had primary refractory disease and 2 (74 y) had multiple comorbidities. Response is shown in the Table. At the time of data cut, 65% of responders remained in response with the longest duration of response 6.9 mo. All 3 pts with prior CAR T remained on Tx and in response (2 CMR and 1 partial metabolic response [PMR]). **Conclusions:** When considering individual safety profiles of epco or GemOx, no unexpected safety findings were observed for epco + GemOx. In this R/R population with high unmet need, these initial data are encouraging and warrant further clinical evaluation. Clinical trial information: NCT04663347. Research Sponsor: Genmab A/S and AbbVie.

Antitumor activity.

n (%)	Total n=25
Overall response	23 (92)
CMR	15 (60)
PMR	8 (32)
Stable disease	0
Progressive disease	0
No response assessment[a]	2 (8)

[a]Two pts died within 60 d of first dose without assessment.

7528 **Poster Session**

Subcutaneous epcoritamab + R-DHAX/C in patients (pts) with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) eligible for autologous stem cell transplant (ASCT): Preliminary phase 1/2 results. *First Author: Pau Abrisqueta, Vall d'Hebron University Hospital, Barcelona, Spain*

Background: Current standard of care for pts with R/R DLBCL eligible for ASCT includes salvage immunochemotherapy, such as rituximab, dexamethasone, cytarabine, and oxaliplatin or carboplatin (R-DHAX/C), followed by consolidation with high-dose therapy (HDT) and ASCT. However, salvage therapy fails in many pts, and novel treatment (Tx) options are needed to improve response and long-term outcomes. Epcoritamab, a bispecific antibody targeting CD3 on T cells and CD20 on B cells, had a manageable safety profile and meaningful single-agent antitumor activity in pts with heavily pretreated B-cell non-Hodgkin lymphoma (NHL) in the dose-escalation part of the EPCORE NHL-1 trial. Here we present initial results from arm 4 (epcoritamab + R-DHAX/C) of the EPCORE NHL-2 phase 1/2 trial (NCT04663347). **Methods:** Adults with R/R CD20^{+} DLBCL who were eligible for HDT-ASCT were enrolled. Pts received standard R-DHAX/C with subcutaneous epcoritamab (QW, 21-d cycle [C] 1–3). If HDT-ASCT was postponed, pts could continue epcoritamab monotherapy (28-d C: QW, C4; Q2W, C5–9; Q4W, C≥10) until disease progression or unacceptable toxicity. Step-up epcoritamab dosing and corticosteroids were required to mitigate CRS in C1. Response was determined by PET-CT per Lugano criteria. **Results:** As of Jan 26, 2022, 27 pts (median age, 59 y; range, 30–75) had received epcoritamab + R-DHAX/C. Of these, 74% had received 1 prior line of therapy, the remainder (26%) 2–3 prior therapies; 3 pts had prior CAR T. The majority of pts (70%) had primary refractory disease. The most common Tx-emergent adverse events (any grade [G]) were thrombocytopenia (67%), neutropenia (48%; febrile neutropenia, 19% in all pts), infections (37%), nausea (37%), and anemia (33%). Adverse events of special interest were CRS in 8 pts (30%; all G1/2) and ICANS in 1 pt (G2; discontinued epcoritamab, pt with prior CAR T). No clinical tumor lysis syndrome was observed. CRS events occurred early in Tx; median time to resolution was 2 d. Of the 23 evaluable pts, 11 pts underwent ASCT; among these, overall response rate (ORR) was 100% prior to ASCT (82% [9/11] complete metabolic response [CMR]; 18% [2/11] partial metabolic response [PMR]). In 12 pts, HDT-ASCT was postponed/canceled and epcoritamab monotherapy continued; of these, 5 (42%, including 2 with prior CAR T) had CMR and 3 (25%) had PMR. The CMR and PMR rates for the entire evaluable population were 61% (14/23) and 22% (5/23), respectively. **Conclusions:** Subcutaneous epcoritamab in combination with R-DHAX/C in pts with R/R DLBCL had a manageable safety profile. CRS events were of low grade and resolved with standard management. ORR and CMR rate were high. At the time of data cutoff, 70% of pts had either received ASCT or continued epcoritamab Tx in CMR. Clinical trial information: NCT04663347. Research Sponsor: Genmab A/S and AbbVie.

7529 **Poster Session**

Two-year follow-up result of RELIANCE study, a multicenter phase 2 trial of relmacabtagene autoleucel in Chinese patients with relapsed/refractory large B-cell lymphoma. *First Author: Zhitao Ying, Department of Lymphoma, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital & Institute, Beijing, China*

Background: RELIANCE study is the first pivotal CD19 CAR-T study that got IND approval by the authority in China (NCT04089215). Initial findings of this study demonstrated high response rates and low rates of CAR-T–associated toxicity with Relmacabtagene autoleucel (Carteyva, also known as Relma-cel, JWCAR029) treatment in heavily pretreated patients with Relapsed/Refractory (r/r) large B-cell lymphoma (LBCL) (Ying *et al.* Cancer Med, 2020). Here we provide 2-year follow-up result of RELIANCE study. **Methods:** 59 adults (age ≥18 years) with ≥2 prior therapies r/r LBCL were randomized to receive lymphodepletion chemotherapy followed by a single infusion of Carteyva at a dose of 100×10^6 or 150×10^6 CAR+T cells, patients were evaluated for efficacy using Lugano criteria (Cheson 2014), for toxicity using CTCAE v4.03 and for cytokine release syndrome (CRS) using Lee *et al.* criteria (Blood 2014). Primary endpoint was 3-month objective response rate (ORR); key secondary endpoints included complete response rate (CRR) at 3 months, duration of response (DOR), progression-free survival (PFS), overall survival (OS) and treatment-emergent adverse event (TEAE) profile. **Results:** The cutoff date was December 22, 2021. All 59 patients (median age 56.0 years, range 18–75 years) were post-treatment with Carteyva, among of them 26 patients completed trial, 8 patients on study, 25 patients withdrew. Among the modified intent-to-treat (mITT) population of 58 efficacy-evaluable patients, best ORR and CRR was 77.6% and 53.5%, respectively. The median follow-up was 24 months(95% CI 23.9-24.1), median PFS and DOR was 7 months (95% CI 4.76–24.15) and 20.3 months (95% CI 4.86–NA), median OS was NA (95% CI NA–NA). 2-year PFS, DOR and OS rates were 38.3%, 38.1% and 69.0%, respectively. 91.5% patients reported treatment–related TEAEs with 72.9% patients had Grade ≥3, among this, the most common Grade ≥3 AE were neutropenia (42.4%) and leukopenia (22%). CRS and NT of any grade occurred in 47.5% and 20.3% of patients (Grade 3–4 CRS, 5.1%; Grade 3–4 NT, 3.4%). Median onset of CRS and NT was 4 (1–10) days and 8.5 (2–11) days, After Day 90, 6(10.2%) patients reported AEs Grade ≥3, the most common were lymphocytopenia 2(3.4%), neutropenia 2(3.4%) and leukopenia 1(1.7%). Grade ≥ 3 infections occurred in 2(3.4%) patients, which was gastroenteritis and herpes zoster. 17 (28.8%) patients died in this study, 12(20.3%) due to disease progression. **Conclusions:** As the longest follow-up term of CD19+ CAR T cell study in heavily pretreated patients with r/r LBCL in China, Carteyva demonstrated durable responses with a high 2-year OS rate, the median OS not yet reached for responding patients, and a manageable safety profile. These data continue supporting the compelling clinical benefit-risk profile of Carteyva for r/r LBCL patients. Clinical trial information: NCT04089215. Research Sponsor: None.

7530 **Poster Session**

Demographics and treatment outcomes in patients with EBV$^+$ PTLD treated with off-the-shelf EBV-specific CTL under an ongoing expanded access program in Europe: First analyses. *First Author: Sylvain Choquet, Hôpital de la Pitié-Salpêtrière, Paris, France*

Background: Patients undergoing allogeneic hematopoietic cell transplant (HCT) or solid organ transplant (SOT) are at risk of developing Epstein–Barr virus driven post-transplant lymphoproliferative disorder (EBV$^+$ PTLD), a rare hematologic malignancy, which is often aggressive and life-threatening. Patients with relapsed or refractory (r/r) EBV$^+$ PTLD have few treatment options with poor outcomes, demonstrating a clear unmet medical need. Tabelecleucel is an investigational, off-the-shelf, allogeneic EBV-specific T-cell immunotherapy being studied in patients with serious EBV$^+$ diseases (NCT04554914 & NCT03394365) that has demonstrated clinical benefit and favorable safety profile in the treatment of EBV$^+$ PTLD after failure of rituximab (R) ± chemotherapy (Prockop, EBMT 2021, ATC 2021, ASH 2021). **Methods:** Atara Biotherapeutics supports an ongoing expanded access program (EAP) in Europe for patients with EBV$^+$ diseases who have no other treatment options. Here we report demographics, efficacy and safety results of r/r EBV$^+$ PTLD patients following SOT or HCT who presented between Jul 2020 and Nov 2021 and consented to research. **Results:** A total of 48 EAP requests from 9 countries for patients with EBV$^+$ diseases were received. Twenty-two patients from 7 countries consented to this research: 16 EBV$^+$ PTLD and 6 EBV$^+$ non-PTLD. Of the 16 PTLD patients 15 received at least one dose of tabelecleucel. Overall, 9 out of 15 (60%) patients achieved a response as assessed by the treating physician, with 6 complete responses and 3 partial responses. Eight out of nine responses were seen after the first cycle. No adverse events were reported as related to tabelecleucel by the treating physician. **Conclusions:** The successful execution of this European EAP demonstrates the feasibility to deliver an off-the-shelf allogeneic EBV$^+$ T-cell therapy in time-sensitive clinical situations when no other treatment options exist. These data show clinically meaningful outcomes for patients with r/r EBV$^+$PTLD post-SOT or post-HCT treated with tabelecleucel consistent with previously reported favorable safety and efficacy profile (Prockop, ASH 2021). Research Sponsor: Atara Biotherapeutics.

	EBV$^+$ PTLD post HSCT (N=5)	EBV$^+$ PTLD post SOT (N=11)	Total (N=16)
Median age (range)	54 (12-64)	48 (12-65)	48.5 (12-65)
Male	3 (60%)	2 (18%)	5 (31%)
ECOG PS ≥ 2 or Lansky PS ≤ 60	1 (20%)	4 (36%)	5 (31%)
Median prior lines of therapy (range)	2 (1-3)	1 (0-4)	1 (0-4)
Treated and response assessed	4 (80%)	11 (100%)	15 (94%)
Responders*/Treated (%)	3/4 (75%)	6/11 (54.5%)	9/15 (60%)
CR*	3 (75%)	3 (28%)	6 (40%)
PR*	-	3 (28%)	3 (20%)

n (%); * Best overall response. CR, Complete Response; ECOG, Eastern Cooperative Oncology Group; PR, Partial Response; PS, Performance Score.

7531 **Poster Session**

Molecular disease monitoring in patients with relapsed/refractory B-cell non-Hodgkin lymphoma receiving anti-CD19 CAR T-cell therapy. *First Author: Meryl D. Colton, University of Colorado School of Medicine, Aurora, CO*

Background: Chimeric antigen receptor (CAR) T-cell therapy has improved the historically poor outcomes for relapsed and refractory (R/R) B-cell non-Hodgkin's lymphoma (NHL). However, nearly 60% of patients will either fail to respond or relapse after CAR T-cell therapy. Currently, PET/CT scans are used to assess response. Cell-free circulating tumor DNA (ctDNA) is released by tumor cells into the peripheral blood and can be measured for minimal residual disease (MRD) assessment. **Methods:** In this retrospective, IRB approved pilot study, archived lymphoma tissues and ctDNA from peripheral blood samples on day 0, 14, 28, 56, 80, 180, and 365 after CAR T-cell infusion from 10 patients with R/R NHL were collected for next-generation sequencing (NGS) of clonal variable-diversity-joining (VDJ) rearrangements [Adaptive biotechnologies (Seattle, WA)]. Response was assessed by PET/CT on days 30, 60, 90, 180 and 365 and graded according to the Lugano 2014 criteria. The primary endpoint was to determine the feasibility of detecting ctDNA to monitor disease response after anti-CD19 CAR T-cells. The secondary endpoint was to compare the sensitivity/specificity of MRD assessment from ctDNA to PET/CT imaging. **Results:** Nine out of 10 patients with a trackable sequence [median age 69 (range: 56-76); 55.6% male; median LDH 224], were included in this study. Each received tisagenlecleucel CAR T-cell therapy after median two prior treatments (range: 2-4). 7/9 patients had R/R diffuse large B-cell lymphoma (DLBCL), and 2/9 had transformed follicular lymphoma. At a median follow up of 12.7 months (range: 1.5-30 months), four patients were alive. By day 90, three patients (33.3%) achieved a radiographic complete response (CR) whilst six patients (66.6%) had progressive disease (PD). MRD and radiographic response are outlined in the Table. Detectable MRD on day 14 or day 28 had 83% sensitivity and 100% specificity for radiographic progression at any time before one year. For patients with PD, the median (interquartile range) MRD at day 0, 14, and 28 were 17.31 (1.01, 96.84), 9.12 (0.30, 18.8), and 23.77 (8.01, 137.53) copies per milliliter (mL), respectively. For patients with detectable MRD at day 28, mOS and mPFS were 205 and 38 days, respectively. **Conclusions:** Our pilot study demonstrated that monitoring MRD was a sensitive and specific method to detect disease response and relapse. In addition, MRD can be monitored more frequently, thus allowing for earlier detection of relapse. MRD and PET/CT identified progressive disease (PD) or complete response (CR) by day 90 in nine patients (A-I) with R/R NHL post CAR T-cell infusion. Research Sponsor: Novartis.

MRD on day 0-365 is ctDNA (copies per mL).

ID	PET/CT outcome	Day 0	Day 14	Day 28	Day 56	Day 80	Day 180	Day 365
A	CR	0	0	0				
B	CR	0		0			0	0
C	CR	0.14	0	0	0	0		0
D	PD	0	0		0	0		
E	PD	21.97	12.34	137.54				
F	PD	12.64	5.90	23.78				
G	PD	96.84	0.30	1.01		17.49	0.72	
H	PD	1.01	18.85	8.01	66.83			
I	PD	1,599.82	3,767.53	5,427.03				

7532 **Poster Session**

Autologous hematopoietic stem cell transplantation in tandem with anti-CD30 CAR T-cell infusion in relapsed/refractory CD30$^+$ lymphoma. *First Author: Xiuxiu Yang, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China*

Background: Long-term outcome is unfavorable for patients with relapsed/refractory (r/r) classical Hodgkin lymphoma (cHL) who are resistant to salvage chemotherapy, even followed by autologous stem cell transplantation (ASCT). Long-term survival is most likely achieved in patients who are sensitive to salvage therapy and have a complete response (CR) before ASCT, while outcome is poor in patients with residual disease. Although CD30-directed chimeric antigen receptor (CAR30) T-cell therapy induces high response rates in these patients, the duration of response is limited. **Methods:** We conducted an open-label, single-center and single-arm pilot study to explore the safety and efficacy of ASCT in tandem with CAR30 T-cell infusion in r/r CD30$^+$ lymphoma (Chinese Clinical Trial Registry, number ChiCTR 2100053662). Patients will receive BEAM as preconditioning. HSCs are infused at day zero and followed by the infusion of 3rd generation CAR30 T cells in the next week. Between June 1, 2019 to May 1, 2021, 6 patients enrolled, including 5 with cHL and 1 with anaplastic lymphoma kinase-negative anaplastic large cell lymphoma (ALCL). The median age was 24 years. No patient had a prior history of ASCT. Three patients (50.0%) relapsed ≥ 2 times and 3 patients (50.0%) had primary refractory diseases. All had a Deauville score of 4 or 5, and 5 patients (83.3%) had a stable or progressive disease (SD/PD) to previous treatments at enrollment. **Results:** CD34$^+$ cells were infused at day zero with a median dosage of 3.9 (IQR, 3.2-6.1) $\times$ 10^6 /kg and followed by the infusion of CAR30 T cells with a median dosage of 7.6 (IQR, 5.5-9.7) $\times10^6$ /kg at +2 to +6 days. Cytopenias represented the most commonly severe advers events (≥ grade 3). The engraftments of neutrophil or platelet occured at a median time of 13.5 (IQR,12.3-14.0) days or 11.5 (IQR, 11.0-12.8) days, respectively, suggesting rapid multilineage engraftments post-ASCT. Cytokine release syndrome (CRS) was observed in 5 (83.3%) patients, all of which were grade 1. No neurotoxicity or severe infection was observed. At month 3 after HSC infusion, all patients achieved objective responses, including 5 (83.3%) with a CR and 1 with a patial response (PR). With a median follow-up of 18.2 (range, 9.9-32.1) months, the median PFS and OS were not reached. At January 31, 2022, the data-cutoff date, all patients maintained their responses and remained alive without disease relapse or progression. Of note, responses were sustained in all 5 patients who had a SD/PD at enrollment. **Conclusions:** Our work demonstrates tandem administration of ASCT and CAR30 T-cell therapy was well-tolerated and highly active in r/r HL and ALCL, even in PET-positive or chemorefractory patients who were expected to have inferior outcome after ASCT, although further large-scale validation in prospective clinical trial is warranted. Clinical trial information: ChiCTR2100053662. Research Sponsor: National Natural Science Foundation of China.

7534 **Poster Session**

Standard chemotherapy followed by allogeneic or autologous transplantation: The role of allogeneic transplantation in the AATT study. *First Author: Norbert Schmitz, Department of Medicine A, Haematology and Oncology, University Hospital Muenster, Münster, Germany*

Background: Prognosis of relapsed and refractory T-cell lymphoma patients (pts) is devastating. Early results of the AATT study (Autologous or Allogeneic Transplantation in T-cell lymphoma, Schmitz et al. ASCO 2019; NCT00984412) showed that standard chemotherapy followed by allogeneic transplantation (alloSCT) compared to autoSCT did not improve outcome of poor-risk patients. We wanted to investigate the long-term clinical course of AATT patients (pts) focusing on pts receiving alloSCT off study. **Methods:** AATT was a randomized trial comparing alloSCT with autoSCT in younger pts (18-60 yrs) with newly diagnosed PTCL who achieved stable disease or better after 4 courses of CHOEP and 1 course of DHAP. Pts were to receive BEAM/autoSCT or myeloablative conditioning/alloSCT from matched related or unrelated donors for consolidation. Local investigators gave updated detailed reports on all further therapy until last follow up or death in order to report long-term EFS and OS focusing on patients receiving alloSCT off study and after failing autoSCT. **Results:** 103 pts (median age 50 years) randomized to autoSCT (n = 54) or alloSCT (n = 49) formed the full analysis set (FAS), 67 pts (65%) actually received autoSCT (n = 41) or alloSCT (n = 26) (per protocol set, PPS). Median observation time for EFS (OS) was 80 (84) months in the FAS and PPS population. At 7 years EFS and OS were 36% [95%CI: 27% - 46%] and 58% [48-68] for all 103 pts; EFS and OS for patients randomized to autoSCT vs. alloSCT were 34% [22-47] vs. 38% [25-52] and 61% [47-74] vs. 55% [41-69]. For patients actually transplanted 7-year-EFS and -OS were 50% [34-66] vs. 61% [42-80] and 72% [58-86] vs. 61% [42-80]. None of these survival rates differed significantly. TRM was 0/41 (0%) after autoSCT and 8/26 (31%) after alloSCT. Relapse rates were 15/36 (42%) vs. 1/21 (5%) for patients auto- or allografted. Overall, 26/ 50 pts received alloSCT off study because of early relapse/ progression before transplantation or after failing autoSCT. 7-year-OS for these pts is 62% (43-80). Ten of 15 pts relapsing after autoSCT received alloSCT as next therapy. Eight of these pts remain alive 39 – 94 mos after transplantation 5-year-OS of 24 pts who did not receive alloSCT was 17% (2-32). **Conclusions:** Seven-year OS-rates for the FAS- and the PPS cohort are remarkably high (58% and 68%) reflecting the high rate of long-term survivors after alloSCT also in pts with early relapse and after autoSCT. Pts not undergoing alloSCT had a dismal outcome. For T-cell lymphoma pts with early progression/ relapse after first-line therapy or failing autoSCT alloSCT offers cure in a significant portion of pts and should therefore be the preferred option for all transplant-eligible pts. Clinical trial information: NCT00984412. Research Sponsor: BMBF (Bundesminisiterium fuer Bildung und Forschung) (Germany), Other Government Agency.

7535 **Poster Session**

First-in-human phase I study of a ROR1-targeting bispecific T-cell engager (NVG-111) shows evidence of efficacy in patients with relapsed/refractory CLL and MCL. *First Author: Parag Jasani, Royal Free London NHS Foundation Trust, London, United Kingdom*

Background: NVG-111 is a first in class, humanized, tandem scFv ROR1xCD3 bispecific T cell engager that mediates potent killing of ROR1$^+$ tumours by engaging an epitope on the Frizzled domain of ROR1 and redirecting T cell activity via the CD3 binder. **Methods:** This phase I/II study is evaluating NVG-111 in patients with relapsed/refractory (R/R) CLL and MCL who have received ≥2 prior systemic therapies and have achieved a stable, or partial response to the last line of therapy. NVG-111 was delivered as continuous intravenous (cIV) infusion over 21 days per cycle, with each patient typically receiving 3 cycles of treatment. The first 3 single patient cohorts were subjected to accelerated dose titration (ADT) over a range of 0.3-30μg/day. Dose-escalation steps in the subsequent, multi-patient, cohorts were determined using a continuous reassessment method with overdose control. The primary endpoints are safety and determination of MTD/RP2D. Secondary objectives are pharmacokinetics, pharmacodynamics, immunogenicity and anti-tumor activity, assessed by multicolor flow cytometry to quantitate minimal residual disease (MRD4). **Results:** As of January 2022, six patients (all males, median age 60 years) had been enrolled to the study; three into each of the ADT cohorts and the remaining into a 30 μg/day flat dosing cohort. Five patients had CLL, and one had MCL, with all subjects remaining on ibrutinib whilst receiving NVG-111. The most common adverse events were Grade 1 lethargy, headaches, nausea, vomiting and thrombocytopenia. All 3 patients exposed to a flat dose of NVG-111 at 30μg/day suffered Grade 1 cytokine release syndrome (CRS) during week 1 of cycle 1. This did not require tocilizumab or dose interruption except in one patient who developed transient, grade 3 immune effector cell–associated neurotoxicity syndrome-like symptoms (ICANS). CRS or ICANS was not observed in subsequent cycles of treatment at this dose level. Response was observed in all 5 evaluable patients who had completed efficacy assessment after 3 cycles of NVG-111. Amongst these, 2 patients had undetectable MRD in the blood with one being MRD negative in the bone marrow. Dose escalation is ongoing, including exploration of step-up dosing. **Conclusions:** Early data with NVG-111 shows promising efficacy with a predictable and manageable safety profile. Clinical trial information: NCT04763083. Research Sponsor: NovalGen Ltd.

7536 **Poster Session**

Real-world analysis of safety and efficacy of CAR T-cell therapy in patients with lymphoma with decreased renal function. *First Author: Omar Mamlouk, University of Texas MD Anderson Cancer Center, Department of Nephrology, Houston, TX*

Background: Chimeric antigen receptor T-cell therapy (CART) is approved for treatment of relapsed and refractory large B cell lymphoma (r/r LBCL), however eligibility for patients (pts) treated on clinical trials included normal kidney function (NKF). There is a gap in knowledge regarding the safety and efficacy of CART in pts with reduced kidney function (RKF), despite the prevalence of chronic kidney disease in lymphoma pts. **Methods:** This is a single-center retrospective analysis of adult pts with r/r LBCL who received CART between 2017-2021. RKF was defined as estimated glomerular filtration rate (GFR) of < 60 ml/min and NKF defined as GFR ≥ 60 ml/min, at time of lymphodepletion chemotherapy (LDC). Increased length of ICU stay define as > 3 days. Kaplan-Meier method used to estimate the time-to-event endpoints including progression free survival (PFS), and overall survival (OS). **Results:** We identified 210 pts who received CART, of those 169 (80.5%) had NKF and 41(19.5%) had RKF (15-59 ml/min, 27% < 45). Median age of pts was 60 and 63% of RKF pts were older than 60 vs 45% in NKF group (p = 0.03). Median Hematopoietic cell transplantation-specific comorbidity index (HCT-CI) score of pts with RKF was higher than NKF (3 vs. 1, P = 0.004). Pts with RKF had significantly longer ICU length of stay (29.3% vs. 13.6%; p = 0.01). There was no difference in grade 3 hematological toxicity (82.9% vs. 84.5%, p = 0.80) or infection within 30 days of CART (51.2% vs. 37.9%, p = 0.11) between RKF and NKF pts, respectively. CART specific toxicity including grade and frequency of cytokine release syndrome and neurotoxicity was also not related to renal function. After a median follow-up of 22.9 months (95% CI: 21.1-25.6 months), there was no significant difference in PFS and OS when comparing pts with RKF vs. NKF; PFS at 1 year of 31% (19-50%) vs. 33% (26-41%), p = 0.97, and OS at 1 year was 47% (34-67%) vs. 44% (37-57%), p = 0.45, and respectively. However, pts with RKF had a significant increase in non-relapse mortality (NRM) at 3 months (19.5% vs. 8.3%, p = 0.03), and at 6 months (22% vs. 9.5%, p = 0.02), respectively. **Conclusions:** In this retrospective single center study we observed reassuring durable remission rates in pts with r/r LBCL and RKF who received CART, without significantly different PFS or OS. Interestingly our analysis found that increased ICU length of stay and higher rates of NRM early after CART were associated with RKF. While our data shows RKF does not preclude pts from receiving CART for r/r LBCL, it does suggest that patients with RKF may need closer monitoring and multidisciplinary management. Research Sponsor: Cancer Center Support Grant (CCSG).

7537 **Poster Session**

Cost-effectiveness of CD19 chimeric antigen receptor T-cell (CAR-T) therapy versus autologous stem cell transplantation (ASCT) for high-risk diffuse large B-cell lymphoma (DLBCL) in first relapse. *First Author: Amar Harry Kelkar, Dana-Farber Cancer Institute, Boston, MA*

Background: The recently reported ZUMA-7 and TRANSFORM trials demonstrate superior event-free survival among patients with primary refractory or early relapsed DLBCL compared to salvage chemotherapy with ASCT. However, given a cost of >$370,000, it is not known whether second-line CAR-T is cost-effective compared to ASCT. Thus, we developed a state-transition microsimulation model to simulate clinical outcomes and costs associated with therapy for DLBCL patients in first relapse, using ZUMA-7 and TRANSFORM data. **Methods:** The model begins at initiation of second-line therapy comparing salvage chemotherapy with ASCT or CAR-T therapy. We examined a three-year time horizon, including crossover to the alternative strategy therapy in the third line, as well as subsequent lines of therapy, using open-source Amua 0.3.0 software. Base case analysis was performed using 1000 first-order Monte Carlo simulations and probabilistic sensitivity analysis (PSA) was performed with 1000 simulations to test model uncertainty. Conditional probabilities of survival and disease progression were extracted from Kaplan-Meier curves from pivotal clinical trials using the WebPlotDigitizer tool. Costs were estimated from public sources in US Dollars ($) and effects were estimated in quality-adjusted life years (QALY) using published utility values. **Results:** Median overall survival was 15 months (95% confidence interval [CI] 13-19 months) with ASCT and 21 months (95% CI 17-29 months) with CAR-T. The PSA demonstrated costs and effectiveness per patient of $243,581 and 1.06 QALYs with ASCT and $470,150 and 1.22 QALYs with CAR-T with an incremental cost-effectiveness ratio (ICER) of $1,383,320/QALY. Incremental net monetary benefit of CAR-T versus ASCT, based on a willingness-to-pay (WTP) threshold of $200,000/QALY, was -$193,812. The break-even price for CAR-T and all subsequent therapies, based on a one-way sensitivity analysis, was $170,489. **Conclusions:** The model demonstrated improved survival and QALYs for the second-line CAR-T therapy, but was not cost-effective, as the ICER exceeded $1,000,000/QALY, which is higher than most accepted WTP thresholds. A limitation of these early data is that they only assess outcomes over three years. To estimate the full effect of these therapies, we will extrapolate the Kaplan-Meier curves for additional analyses. Clinical outcomes of second-line CAR-T are promising, but prices would need to be considerably lower to enable equitable access and affordability. Research Sponsor: None.

Cost-effectiveness table.

Strategy	Cost	Cost 95% CI	QALY	QALY 95% CI	ICER	Notes
ASCT Strategy	$ 243,581	$221,774-$265,460	1.06	0.90-1.22	—	Baseline
CAR-T Strategy	$ 470,150	$460,764-$480,997	1.22	1.02-1.43	$ 1,383,320/QALY	

7538 **Poster Session**

Acalabrutinib versus rituximab plus idelalisib or bendamustine in relapsed/refractory chronic lymphocytic leukemia: ASCEND results at 4 years of follow-up.

First Author: Wojciech Jurczak, Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland

Background: Acalabrutinib (acala) is a next-generation, highly selective, covalent Bruton tyrosine kinase (BTK) inhibitor approved for patients (pts) with chronic lymphocytic leukemia (CLL). In the primary analysis of ASCEND (median follow-up 16.1 mo), acala showed superior efficacy with an acceptable tolerability profile vs idelalisib (Id) plus rituximab (R) (IdR) or bendamustine (B) plus R (BR) in pts with relapsed/refractory (R/R) CLL (Ghia et al. *J Clin Oncol*. 2020;38:2849-2861). We report the results of the ASCEND study at ~4 years of follow-up. **Methods:** In this multicenter, randomized, open-label, phase 3 study (NCT02970318), pts with R/R CLL received oral (PO) acala 100 mg BID until progression or unacceptable toxicity or investigator's (INV) choice of IdR (Id: 150 mg PO BID until progression or unacceptable toxicity; R: 375 mg/m^2 x1 then 500 mg/m^2 IV [8 total infusions]) or BR (B: 70 mg/m^2 IV; R: 375 mg/m^2 x1 then 500 mg/m^2 IV [6 cycles]). Progression-free survival (PFS), overall survival (OS), overall response rate (ORR), and safety were assessed. **Results:** A total of 310 pts (acala, n=155; IdR, n=119; BR, n=36) were randomized (median age 67 y; del(17p) 15%, unmutated IGHV 74%, Rai stage 3/4 42%). At median follow-up of 46.5 mo (acala) and 45.3 mo (IdR/BR), acala significantly prolonged INV-assessed PFS vs IdR/BR (median not reached [NR] vs 16.8 mo; *P*<0.0001); 42-mo PFS rates were 62% for acala vs 19% for IdR/BR. In pts with del(17p), median PFS was NR (acala) vs 13.8 mo (IdR/BR; *P*<0.0001). In pts with unmutated IGHV, median PFS was NR (acala) vs 16.2 mo (IdR/BR; *P*<0.0001). Median OS was NR in both arms; 42-mo OS rates were 78% (acala) vs 65% (IdR/BR). ORR was 83% (acala) vs 84% (IdR/BR) (ORR + partial response with lymphocytosis: 92% [acala] vs 88% [IdR/BR]). AEs led to drug discontinuation in 23% of acala, 67% of IdR, and 17% of BR pts. Events of clinical interest (acala vs IdR/BR) included all-grade atrial fibrillation/flutter (8% vs 3%), all-grade hypertension (8% vs 5%), all-grade major hemorrhage (3% vs 3%), and grade ≥3 infections (29% vs 29%). **Conclusions:** At ~4 years of follow-up, acala maintained efficacy compared with standard-of-care regimens and a consistent tolerability profile in R/R CLL. Clinical trial information: NCT02970318. Research Sponsor: AstraZeneca.

Treatment exposure and common AEs.

	Acala (n=154)		IdR (n=118)		BR (n=35)	
Median treatment exposure (mo)	44.2		11.5 (Id), 5.5 (R)		5.6 (B), 5.5 (R)	
Common AEs[a], n (%)	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Neutropenia	37 (24)	29 (19)	55 (47)	47 (40)	12 (34)	11 (31)
Headache	36 (23)	1 (1)	7 (6)	0	0	0
Diarrhea	33 (21)	3 (2)	62 (53)	31 (26)	5 (14)	0
Upper respiratory tract infection	31 (20)	3 (2)	20 (17)	4 (3)	4 (11)	1 (3)
Fatigue	19 (12)	2 (1)	10 (8)	1 (1)	8 (23)	1 (3)
Nausea	13 (8)	0	17 (14)	1 (1)	7 (20)	0
Infusion-related reaction	1 (1)	0	9 (8)	2 (2)	8 (23)	1 (3)

[a]Any grade in ≥20% of pts. AE reporting period: up to 30 days after last study drug dose or at disease progression, whichever comes first.

7539 **Poster Session**

Acalabrutinib ± obinutuzumab versus obinutuzumab + chlorambucil in treatment-naïve chronic lymphocytic leukemia: Five-year follow-up of ELEVATE-TN.

First Author: Jeff Porter Sharman, Willamette Valley Cancer Institute and US Oncology Research Center, Eugene, OR

Background: For ELEVATE-TN (NCT02475681), we previously reported superior efficacy of acalabrutinib (A) ± obinutuzumab (O) vs O + chlorambucil (Clb) in patients (pts) with treatment-naive (TN) chronic lymphocytic leukemia (CLL) at 28.3 and 46.9 months (mo) median follow-up. Now, we report results from a 5-y update. **Methods:** Pts were randomized to A+O, A, or O+Clb. Pts who progressed on O+Clb could cross over to A monotherapy. Investigator-assessed (INV) progression-free survival (PFS), INV overall response rate (ORR), overall survival (OS), and safety were evaluated. **Results:** A total of 535 pts (A+O, n=179; A, n=179; O+Clb, n=177) had a median age of 70 y. At a median follow-up of 58.2 mo (range, 0.0–72.0; data cutoff Oct 1, 2021), median PFS was not reached (NR) (hazard ratio [HR]: 0.11) for A+O and A (HR: 0.21) vs 27.8 mo for O+Clb (both *P*<0.0001). Estimated 60-mo PFS rates were 84% (A+O), 72% (A), and 21% (O+Clb). Median OS was NR in any treatment arm, and significantly longer in the A+O vs O+Clb arms (HR: 0.55; *P*=0.0474); estimated 60-mo OS rates were 90% (A+O), 84% (A), and 82% (O+Clb). ORR was significantly higher with A+O (96%; 95% CI 92–98) and A (90%; 85–94) vs O+Clb (83%; 77–88; *P*<0.0001 [A+O], *P*=0.0499 [A]). Complete response (CR)/CR with incomplete hematologic recovery (CRi) rates were higher with A+O (29%/3%) vs O+Clb (13%/1%); 13%/1% had CR/CRi with A; CR increased since the interim analysis (previously 21% [A+O] and 7% [A]). Adverse events (AEs) and treatment exposure are shown in the Table. Treatment is ongoing in 65% (A+O) and 60% (A) of pts; the most common reasons for treatment discontinuation were AEs (17% [A+O], 16% [A], 14% [O+Clb]) and progressive disease (6%, 10%, 2%, respectively). Crossover from O+Clb to A occurred in 72 (41%) patients; 25% of these pts discontinued A (10% due to AEs and 11% due to progressive disease). **Conclusions:** After a 5-y follow-up, efficacy and safety of A+O and A monotherapy were maintained, with significantly longer OS in the A+O arm compared with O+Clb. Clinical trial information: NCT02475681. Research Sponsor: AstraZeneca.

Treatment exposure and TEAEs.

	A+O (n=178)		A (n=179)		O+Clb (n=169)	
	58.1 (A), 5.5 (O)		58.0		5.6 (O), 5.5 (Clb)	
Median treatment exposure (mo)	Any grade	G≥3	Any grade	G≥3	Any grade	G≥3
Common TEAEs (≥30% of pts), n (%)						
Diarrhea	77 (43.3)	10 (5.6)	76 (42.5)	1 (0.6)	36 (21.3)	3 (1.8)
Headache	72 (40.4)	2 (1.1)	70 (39.1)	2 (1.1)	20 (11.8)	0
Arthralgia	60 (33.7)	4 (2.2)	47 (26.3)	2 (1.1)	10 (5.9)	2 (1.2)
Neutropenia	60 (33.7)	55 (30.9)	22 (12.3)	20 (11.2)	77 (45.6)	71 (42.0)
Nausea	44 (24.7)	0	44 (24.6)	0	53 (31.4)	0
Infusion-related reaction	26 (14.6)	5 (2.8)	1 (0.6)	0	69 (40.8)	10 (5.9)
Selected AEs of interest, n (%)						
Bleeding	88 (49.4)	8 (4.5)	78 (43.6)	6 (3.4)	20 (11.8)	0
Hypertension	17 (9.6)	8 (4.5)	16 (8.9)	7 (3.9)	6 (3.6)	5 (3.0)
Atrial fibrillation	11 (6.2)	2 (1.1)	13 (7.3)	2 (1.1)	1 (0.6)	0

TE (treatment-emergent) AE: period from first dose to 30 days after last dose or start of new anticancer therapy, whichever is earlier.

7540 **Poster Session**

Four-year follow-up from a phase 2 study of obinutuzumab, ibrutinib, and venetoclax in CLL.

First Author: Kerry Anne Rogers, Division of Hematology, The Ohio State University, Columbus, OH

Background: Targeted agent combinations for chronic lymphocytic leukemia (CLL) have resulted in safe regimens with improved progression-free survival (PFS) compared to chemoimmunotherapy. The optimal regimen and long-term outcomes remain unknown. We conducted a phase 2 study of obinutuzumab (OBIN), ibrutinib (IBR), and venetoclax (VEN) in relapsed/refractory (RR) and treatment-naïve (TN) CLL patients (pts) and report extended follow up on two previously reported cohorts (RR, TN 1) and a new cohort of identically treated TN pts (TN 2). **Methods:** Pts with TN or RR (≥1 prior treatment) CLL requiring treatment were eligible. Treatment was given for 14 28-day cycles (C). OBIN was started C1, IBR C2, and VEN C3 with standard dose escalation. Response was assessed 2 months (mos) after C14 (EOT) by iwCLL 2008 criteria. Minimal residual disease (MRD) was measured by 10-color flow cytometry with a cutoff of $< 1x10^{-4}$. The primary endpoint was complete remission (CR) with undetectable MRD (uMRD) in blood and bone marrow at EOT. A sample size of 25 pts per cohort achieves 90% power to test the null hypothesis of 10% against 30% with 1-sided α of 10%. The Kaplan-Meier method was used to estimate PFS and overall survival (OS). **Results:** 75 pts were treated in 3 cohorts (Table). Data are as of 1/3/2022. In the TN 2 cohort, the overall response rate (ORR) at EOT was 96% (95% CI: 80-100) and CR with uMRD was 20% (95% CI: 7-41). The ORR for TN 1 and TN 2 combined was 90% (95% CI: 78-97) and CR with uMRD was 24% (95% CI: 13-38). Median follow up was 56 (0-65), 57 (7-63), and 30 (24-35) mos, respectively, for RR, TN 1, and TN 2. There were 3 deaths (RR = 1, TN 1 = 1, TN 2 = 1) and 6 disease progressions (RR = 4, TN 1 = 2, TN 2 = 0). Estimated 48-month PFS for TN 1 and RR cohorts were both 96% (95% CI: 72-99) and OS was 85% (95% CI: 60-95) and 100%, respectively. The estimated 24-month PFS and OS for TN 2 were both 96% (95% CI: 75-99). The most frequent adverse events were neutropenia (95%, 73% grade ≥3), leukopenia (95%, 45% grade ≥3), lymphopenia (93%, 40% grade ≥3), and thrombocytopenia (91%, 28% grade ≥3). The only grade ≥3 non-hematologic toxicity occurring at ≥20% was hypertension (85%, 39% grade ≥3). Atrial fibrillation occurred in 11% of pts. **Conclusions:** At extended follow-up, remissions remain durable after fixed duration OBIN, IBR, and VEN. The efficacy and acceptable safety justify further study and are being compared to IBR and OBIN in 2 phase 3 US cooperative group trials. Clinical trial information: NCT02427451. Research Sponsor: Genentech.

Characteristic, median (range) or n (%)	RR (n = 25)	TN 1 (n = 25)	TN 2 (n = 25)	All (n = 75)
Age in years	58 (42-73)	59 (24-77)	58 (38-74)	58 (24-77)
Women	9 (36)	10 (40)	8 (32)	27 (36)
Prior Therapies	1 (1-3)	-	-	-
High-Risk Modified Rai Stage	-	17 (68)	20 (80)	-
IGHV Unmutated[1]	19 (79)	17 (71)	19 (76)	55 (75)
Complex Karyotype[2]	8 (33)	8 (32)	11 (44)	27 (36)
FISH del(17p)(p13.1)[3]	1 (4)	3 (12)	2(8)	6 (8)

[1]2 missing: 1 TN, 1 RR. [2]1 missing: RR. [3]Hierarchical according to risk. IGHV = Immune Globulin Heavy Chain Gene, FISH = Fluorescence In Situ Hybridization.

7541 **Poster Session**

Preclinical activity of irreversible Menin inhibitor, BMF-219, in chronic lymphocytic leukemia.

First Author: Priyanka Somanath, Biomea Fusion, Inc., Redwood City, CA

Background: Menin is a scaffold protein that drives oncogenic function through transcriptional modulation directed by its various cofactors. A previous report demonstrated that menin regulates a distinct set of gene targets independent of its function with the MLL proteins in hematopoiesis and is essential for B-cell maturation (Li et al.*Blood.*2013;122(12):2039-46.). Chronic Lymphocytic Leukemia (CLL) is a disease of malignant B lymphocytes, for which standard-of-care agents are generally well tolerated; however, CLL patients with certain genetic backgrounds demonstrate inferior outcomes to these regimens. A major driving feature of CLL is overexpression of the anti-apoptotic marker, BCL2. We previously reported the ability of BMF-219, a selective, irreversible menin inhibitor, to downregulate the expression of BCL2 in acute leukemia cells. Additionally, we have reported the synergy of BCL2-targeted agent, venetoclax, with BMF-219 in potent cell killing of diffuse large B-cell lymphoma (DLBCL) preclinical models, prompting our exploration of BMF-219 activity in CLL. Here, we provide the first preclinical evidence for menin as a therapeutic target in CLL, by demonstrating high potency of BMF-219 against a diverse collection of CLL patient specimens. **Methods:** A comprehensive panel of CLL samples isolated from patients with Rai Stage 1 to 3 disease, including relapsed or refractory disease, were cultured *ex vivo* in the presence of BMF-219 or clinical reversible menin inhibitors to assess the antileukemic activity of the compounds. Samples were analyzed for differential gene expression of select targets in response to treatment. **Results:** BMF-219 demonstrated high potency, achieving > 98% cell lethality at 1 μM exposure in all patient samples tested, with IC_{50} values in the range of 0.1 to 0.38 μM. Specimens isolated from patients with clinical profiles of high-risk genetic backgrounds associated with inferior outcomes to standard therapy, such as mutations in TP53 and NOTCH1, and chromosomal aberrations such as del(13q), trisomy 12 and complex karyotype, exhibited high sensitivity to BMF-219 treatment. BMF-219 was also highly effective against patient samples with clinical profiles of resistance to bendamustine, ibrutinib and venetoclax therapy. In comparison, clinical reversible menin inhibitors demonstrated no significant activity across all patient samples tested, with incalculable IC_{50} values and < 15% reduction in cell viability at 1 μM exposure. Expression of select target genes in treated CLL cell lines was explored and will be reported. **Conclusions:** Collectively, our data demonstrate the potent preclinical activity of BMF-219 against CLL patient specimens harboring various mutational and cytogenetic backgrounds, including categories of high-risk. These data highlight the unique potential of irreversible menin inhibition as a novel therapeutic option for patients with CLL. Research Sponsor: None.

7542 **Poster Session**

Racial and socioeconomic disparities among patients with chronic lymphocytic leukemia: Analysis of Surveillance, Epidemiology, and End Results program data. *First Author: Adam Kittai, Division of Hematology, The Ohio State University Comprehensive Cancer Center, Columbus, OH*

Background: Therapy for chronic lymphocytic leukemia (CLL) has changed dramatically over the past 20 years. With the cost of new therapies and rapid practice changes, it is unclear if patients (pts) are benefiting equally from this progress. We assessed Surveillance, Epidemiology, and End Results (SEER) program data to determine how race and socioeconomic status (SES) affect survival for pts with CLL. **Methods:** CLL cases reported to 18 SEER Program registries from 2006 – 2018 were included. Pt characteristics such as age at diagnosis (dx), sex, year (yr) of dx, race, and SES as determined by rural/urban census tract residence (RUCA), and neighborhood (as represented by the Yost Index, a composite measure of 7 variables assessing different aspects of the SES of a census tract) were collected and analyzed. Multivariable cox regression (MVA) was used to determine adjusted odds of survival. Two separate databases were utilized, one which included data to 2018, and another which contained SES data but only had data available to 2016. **Results:** 46,605 cases from 2009 – 2018 were identified without SES data. The median age was 70 yrs, 60% were male, and there was an even distribution of patients diagnosed with CLL annually from 2009 – 2018. Of the cases with race reported, 89.9% were white, 7.3% Black, 2.4% Asian/Pacific islander, and 0.3% American Indian/Alaska Native. After a median follow up of 47 months, the median 3, 5, and 10 yr overall survival (OS) was 79.5%, 69.5%, and 48.8%, respectively. MVA showed Black race (HR 1.5, 95% CI 1.4 – 1.6) as the strongest independent prognostic variable for worse OS controlling for yr of dx, suggesting race was a significant factor in OS in the era of modern therapies. Using the linked RUCA and Yost tertiles for SES, 47,867 cases of CLL from 2006 – 2016 were analyzed. Median age, sex, and race distribution were similar to the prior analysis. MVA showed American Indian/Alaska Native, and Black race as independent prognostic variables for worse OS, and Yost group 2 and 3, representing higher SES, were found to be significant independent prognostic variables for improved OS (Table 1). In this analysis, race remained an independent variable for worse OS after controlling for SES. **Conclusions:** Black race and low SES are prognostic of OS in CLL. Further research is needed to determine whether this is due to access to therapy, quality of care, social determinants of heath, or disease biology. Research Sponsor: None.

MVA for OS by demographic variables.

Variable	HR (95% CI)	Wald P-value
Age*	1.09 (1.08 - 1.09)	<.0001
Male vs. Female	1.33 (1.28 - 1.37)	<.0001
Yr of Dx*	0.99 (0.98 - 1.00)	0.0045
Race vs. White		
American Indian/Alaska Native	1.41 (1.03 - 1.92)	0.03
Asian/Pacific Islander	0.97 (0.86 - 1.09)	0.57
Black	1.33 (1.24 - 1.41)	<.0001
Yost vs. Group 1		
Group 2	0.82 (0.79 - 0.86)	<.0001
Group 3	0.68 (0.65 - 0.71)	<.0001
RUCA Rural vs. Urban	0.97 (0.91 - 1.02)	0.24

*1 year increase.

7543 **Poster Session**

A phase Ib/II study of lisaftoclax (APG-2575), a novel BCL-2 inhibitor (BCL-2i), in patients (pts) with relapsed/refractory chronic lymphocytic leukemia or small lymphocytic lymphoma (R/R CLL/SLL). *First Author: Jianyong Li, Jiangsu Province Hospital, Nanjing, China*

Background: B-cell malignancies evade apoptosis by overexpressing BCL-2 proteins. Approved BCL-2i venetoclax requires a slow dose ramp-up to limit risk of tumor lysis syndrome (TLS) and has been associated with severe neutropenia. Investigational single-agent lisaftoclax is a novel, oral BCL-2i active against hematologic malignancies (HMs), with potentially synergistic antitumor effects when combined with other agents in B-cell malignancies. **Methods:** The aim of this multicenter open-label study was to evaluate dose-limiting toxicity (DLT), maximum tolerated dose (MTD), recommended phase 2 dose (RP2D), efficacy, pharmacokinetics (PK), and pharmacodynamics of lisaftoclax in pts with R/R CLL/SLL (per 2008 iwCLL NCI-WG guidelines). Lisaftoclax was administered orally once daily at 3 dose cohorts (400, 600, or 800 mg) every 28 days, with 15 pts in each cohort. **Results:** As of the data cutoff date of January 25, 2022, 45 pts had been enrolled, with a median (range) age of 58 (38-80) years. DLT and MTD were not observed. The preliminary PK profile showed that exposures increased with lisaftoclax doses from 400 to 800 mg (average half-life: 4.2-6.6 hours). A total of 42 pts experienced any-grade treatment-related adverse events (AEs), including neutropenia (55.6%); anemia (42.2%); decreased leukocyte count (40%); thrombocytopenia (37.8%); lowered lymphocyte count (17.8%); hyperuricemia (31.1%); hypokalemia (24.4%); increased blood bilirubin (22.2%); hypertriglyceridemia (20%); diarrhea (20%); hyperphosphatemia, hypocalcemia, and decreased weight (15.6% each); increased AST (15.6%) and blood LDH (13.3%); pyrexia; and increased ALT and blood creatinine (11.1% each). A total of 28 (62.2%) pts experienced grade ≥ 3 AEs and 13 (28.9%) serious AEs. Of these, 25 (55.6% of total) and 9 (20%) were related to lisaftoclax, and 14 (31.1%) led to treatment discontinuation. One clinical TLS was reported. With a median (range) treatment of 7 (1-17) cycles and median (range) time to response of 1 (1-13) cycles, 1 of 41 evaluable pts with CLL experienced complete response (CR) and 27 with CLL/SLL achieved partial response (PR), for an objective response rate (ORR) of 68.29%. The RP2D of lisaftoclax as monotherapy was determined as 600 mg. **Conclusions:** BCL-2i lisaftoclax was well tolerated up to 800 mg/day. There were no significant new or unmanageable safety findings, and the ORR was 68.29%. Lisaftoclax may offer a treatment alternative for pts with R/R HMs, with a daily ramp-up schedule that may be more convenient and "user friendly." Clinical trial information: NCT04494503. Research Sponsor: Ascentage Pharma Group Corp Ltd (Hong Kong).

7544 **Poster Session**

Survival outcomes in patients with chronic lymphocytic leukemia treated at academic centers. *First Author: Victoria Vardell, University of Utah, Salt Lake City, UT*

Background: Chronic lymphocytic leukemia (CLL), the most prevalent leukemia in western countries, is associated with highly variable clinical outcomes. This study aims to evaluate whether patients with CLL treated at Commission on Cancer accredited academic centers (ACs), which offer high clinical volume, clinical trial access, and postgraduate physician education, have improved survival compared to non-academic centers (NACs). **Methods:** The National Cancer Database (NCDB) was used to identify CLL patients diagnosed between 2004-2018. Demographic and treatment characteristics were compared between center categories with binary logistic regression for odds of receiving CLL treatment at an AC. Survival analysis was completed with Kaplan Meier and multivariate Cox regression, adjusted for the only available disease-related characteristics in the NCDB, age and Charlson-Deyo comorbidity score, to compare overall survival (OS). **Results:** Of the 98,186 patients identified, 33.3% were treated at ACs. Patients treated at ACs were younger than those treated at NACs (median age 67 vs. 71 years, p<0.001). ACs were more likely to treat Black and other minority patients, with Black patients representing 9.7% vs. 6.3% of AC vs NAC patients (p<0.001). ACs were more likely than NACs to treat privately insured (39.1% vs. 30.3%), uninsured (3.2% vs.2.0%) and patients on Medicaid (4.1% vs. 2.9%) (p<0.001), as well as patients from the highest quartiles of income (OR 1.46), and education (OR 1.12), when referenced to lowest quartiles (p<0.001). ACs were more likely to manage patients with surveillance versus NACs (53.7% vs. 45%, p<0.001). With a median follow up of 4.3 years, median OS at ACs was significantly improved when compared to NACs, with a median OS of 11.0 years (CI 10.5-11.3) vs. 8.2 years (CI 8.1-8.3), respectively (p<0.001). Survival benefit was maintained at both 5-years (73% vs. 66%) and 10-years (53% vs. 43%) (both p<0.001). On multivariate analysis adjusted for age and comorbidity, management of CLL patients at ACs was an independent factor for improved OS (HR 0.87, CI 0.85-0.89, p<0.001). **Conclusions:** In this study of a large population of CLL patients, there is significant demographic and socioeconomic variation between CLL patients treated at ACs and NACs. While our study is limited by the available disease and treatment level data available, the improved OS benefit of CLL patients managed at ACs suggests possible differences in treatment and clinical trial availability, and supportive care management. Further investigations into the factors contributing to such disparities would be beneficial to help standardize care and improve outcomes. Research Sponsor: U.S. National Institutes of Health.

		Median OS		Univariate			Adjusted		
	N	(Years)	95% CI	HR	95% CI	P	HR*	95% CI	P
All CLL	98,186	9.0	(8.9-9.1)						
NAC	65,479	8.2	(8.1-8.3)		Ref.			Ref.	
AC	32,707	11.0	(10.5-11.3)	0.73	(0.71-0.75)	<0.001	0.87	(0.85-0.89)	<0.001

*Adjusted for age, Charlson-Deyo comorbidity score.

7545 **Poster Session**

Favezelimab (anti–LAG-3) plus pembrolizumab in patients with relapsed or refractory (R/R) classical Hodgkin lymphoma (cHL) after anti–PD-1 treatment: An open-label phase 1/2 study. *First Author: John Timmerman, UCLA Medical Center, Los Angeles, CA*

Background: PD-1 inhibitors are a standard of care for R/R cHL but optimal therapy after anti–PD-1 therapy failure is yet to be defined. LAG-3/PD-1 coblockade has demonstrated antitumor activity in preclinical models. This multicohort phase 1/2 study (NCT03598608) evaluated the safety and efficacy of favezelimab (MK-4280), a humanized IgG4 LAG-3 inhibitor, plus the PD-1 inhibitor pembrolizumab (pembro) in pts with R/R hematologic malignancies. Cohort 2 focused on pts with R/R cHL refractory to anti–PD-1 therapy. **Methods:** This study included a safety lead-in phase (part 1) to determine recommended phase 2 dose (RP2D) followed by a dose-expansion phase (part 2). Eligible pts in cohort 2 had R/R cHL, relapsed after or were ineligible for autologous stem cell transplantation (ASCT), and progressed after ≥2 doses of anti–PD-1 therapy (within 12 weeks of last dose). In part 1, pts from all cohorts received pembro IV 200 mg Q3W and favezelimab IV 200 mg or 800 mg Q3W. Dose-finding based on occurrence of dose-limiting toxicities (DLT) was determined using an mTPI design. In part 2, pts received pembro + favezelimab at the established RP2D for up to 35 cycles. Primary end point was safety. Secondary end point was ORR. DOR, PFS, and OS were exploratory. **Results:** Only 1 DLT (autoimmune hepatitis [grade 4]) was observed among the first 6 pts from all cohorts in part 1 at the favezelimab 200 mg dose; thus, the dose was escalated to 800 mg. No DLTs were observed in 15 additional pts at the 800 mg dose. Favezelimab RP2D was defined as 800 mg Q3W + pembro 200 mg Q3W. In cohort 2, 33 pts were enrolled; median age was 37 yrs, 64% had ECOG PS 0, and 94% had ≥4 prior lines of therapy. After a median follow-up of 16.5 mo, ORR for pts receiving favezelimab 800 mg (n = 29) was 31% (95% CI, 15-51; CR, 2 [7%]; PR, 7 [24%]); 66% of responders had an anti–PD-1–based regimen as most recent line of therapy at study entry. 23 of 29 pts (79%) had reduction from baseline in target lesions. Median DOR for pts who received favezelimab 800 mg was not reached (NR; 95% CI, 0+ to 14+ mo). For all pts in cohort 2, median PFS was 9 mo (95% CI, 5-15); 12-mo PFS rate was 39%. Median OS was 26 mo (95% CI, 26-NR); 12-mo OS rate was 91%. At database cutoff (Nov 1, 2021), 20 pts discontinued treatment (7 AEs, 11 PD/clinical progression, 2, withdrawal/physician decision). TRAEs occurred in 28 pts (85%); most common (> 10%) were hypothyroidism (18%), nausea and fatigue (15% each), and arthralgia and diarrhea (12% each); grade 3 or 4 TRAEs occurred in 6 pts (18%); 18% discontinued treatment due to TRAEs. No treatment-related deaths occurred. **Conclusions:** Favezelimab 800 mg + pembro 200 mg Q3W showed a tolerable safety profile and effective antitumor activity in heavily pretreated pts with R/R cHL whose disease had progressed after anti–PD-1 therapy, suggesting that the combination may reinduce a response in these pts. Clinical trial information: NCT03598608. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

7546 **Poster Session**

Polatuzumab vedotin with dose-adjusted etoposide, cyclophosphamide, doxorubicin, and rituximab (Pola-DA-EPCH-R) for upfront treatment of aggressive B-cell non-Hodgkin lymphomas. *First Author: Ryan C Lynch, University of Washington/Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: The phase 3 POLARIX trial demonstrated the superiority of polatuzumab vedotin (Pola) over vincristine in the R-CHOP regimen for large B-cell lymphomas. However, it is unknown if Pola can be safely incorporated into intensified regimens typically utilized for the highest risk histologies. To address this question, we conducted a prospective trial (NCT04231877) evaluating Pola with dose adjusted etoposide, cyclophosphamide, doxorubicin, and rituximab (Pola-DA-EPCH-R). **Methods:** This is a single center, open label, investigator-initiated clinical trial of 6 cycles of Pola-DA-EPCH-R in aggressive large B-cell lymphomas where DA-EPOCH-R is considered standard (eg. HGBCL, PMBCL, and select DLBCL-NOS). Pola is given at 1.8 mg/kg on day 1 without intra-patient dose escalation. All other components of the regimen including escalation of chemotherapy dosing based on neutrophil and platelet nadirs from the previous cycle are given according to Dunleavy et al NEJM 2013. The primary objective is to estimate the safety of Pola-DA-EPCH-R as measured by the rate of dose-limiting toxicities (DLTs) in the first 2 cycles with pre-specified suspension rules if the lower limit of an 80% confidence interval cannot exclude a DLT rate of > 20%. Efficacy, survival, and correlative analyses will also be performed. **Results:** 18 patients enrolled on study and as of Feb 15, 2022, 3 patients remain on study treatment. Median age was 64 years (range 41-74). With only 3 DLTs, the study met its primary endpoint for safety. Five SAEs were observed, including one grade 5 sepsis/typhlitis (during cycle 1), 3 episodes of febrile neutropenia, and a grade 3 perforation of a colonic diverticula which required a treatment delay of 12 days before completing all expected study therapy. Other grade 3+ non-heme AEs in more than one pt. include hyperglycemia (17%), oral mucositis (17%), incidental asymptomatic pulmonary embolism (17%), abdominal pain (11%), and hypokalemia (11%). Grade 1 peripheral sensory neuropathy was uncommon (22%), no grade 2+ neuropathy was observed. One patient required a decrease in Pola dosing due to a platelet nadir at dose level 1. Among those with at least 2 cycles of treatment, 94% were able to increase chemotherapy to at least dose level 2 (Table). Post cycle 2 interim overall response rate (ORR) and complete response (CR) rate was 88% and 24%, respectively. EOT ORR and CR was 93% and 71%, respectively, with one PD. Updated data will be presented at the meeting. **Conclusions:** Using Pola at 1.8 mg/kg to replace vincristine in the DA-EPOCH-R regimen appears feasible and met its primary safety endpoint. These data support the further evaluation and use of this approach in histologies where the potential benefit of both an intensified regimen and Pola may be desired. Clinical trial information: NCT04231877. Research Sponsor: Genentech.

Maximum DL achieved	n (%)
DL1	2 (11%)
DL2	7 (39%)
DL3	4 (22%)
DL4	3 (17%)
DL5	2 (11%)

7547 **Poster Session**

Phase 1 dose escalation study of MH048, a novel and non-covalent BTK inhibitor in patients with relapsed or refractory B-cell malignancies. *First Author: Guoqing Cao, Minghui Pharmaceutical (Shanghai) LTD, Shanghai, China*

Background: Despite impressive clinical response of covalent Bruton's tyrosine kinase (BTK) inhibitors in multiple B cell malignancies, treatment failure often occurs through drug resistance most commonly due to BTK cysteine-481 (C481) mutation or intolerance due to off-target toxicities. We evaluated the safety, pharmacokinetics (PK) and preliminary antitumor efficacy of MH048, an orally bioavailable, potent, and reversible inhibitor of both wild type and C481S-mutant BTK, in selected patients with relapsed or refractory (R/R) B-cell malignancies. **Methods:** Eligible patients with R/R B-cell malignancies were enrolled in a Phase 1, multicenter, open-label, dose escalation study. The primary objectives were to assess the safety and tolerability of MH048, and to determine the maximal tolerated dose (MTD) and the recommended dose for expansion. The secondary objectives were to assess the PK profile and preliminary evidence of anti-tumor activity. **Results:** Twelve patients were treated with MH048 across six dose levels (5 mg, 15 mg, 45 mg, 90 mg, 135 mg, 200 mg QD) in fast state. No dose-limiting toxicities were observed and the MTD was not reached. The most common drug-related TEAEs (Any grade) that occurred in > 2 patients were platelet count decrease (n=5), anemia (n=4), neutrophil count decrease (n=4), lipase increase (n=3), and white blood cell count decrease (n=3). Drug-related grade 3 TEAEs included platelet count decrease, neutrophil count decrease, lipase increase, and hypertension (one patient for each). Plasma exposure of MH048 and its active metabolite (M3) increased in a dose-proportional manner from 5 to 200 mg dose levels. Sign of efficacy was observed starting from 15 mg. Among eleven efficacy-evaluable patients (one patient in 200 mg cohort is yet to be evaluated), one complete response (CR) and four partial responses (PRs) were achieved in ≥90 mg cohorts, including patients with MZL (n=1, CR), MCL (n=2), SLL (n=1) and DLBCL (n=1). Of the two MCL patients with PRs, one was heavily pretreated including ibrutinib prior to the enrollment. The recommended doses for expansion were selected as 135 and 200 mg. **Conclusions:** MH048 was well-tolerated and efficacy in heavily pre-treated patients with B-cell malignancies was observed. Pharmacokinetics studies suggest once-daily dosing. The dose expansion study is ongoing at 135 and 200 mg QD for CLL and MCL patients. Clinical trial information: NCT04689308. Research Sponsor: Minghui Pharmaceutical.

7548 **Poster Session**

Clinical and patient (pt)-reported outcomes (PROs) in a phase 3, randomized, open-label study evaluating axicabtagene ciloleucel (axi-cel) versus standard-of-care (SOC) therapy in elderly pts with relapsed/refractory (R/R) large B-cell lymphoma (LBCL; ZUMA-7). *First Author: Jason Westin, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Elderly pts with R/R LBCL are at risk of inferior outcomes, increased toxicity, and inability to tolerate second-line (2L) SOC treatment (Tx) (Di M, et al. *Oncologist.* 2021). Further 2L SOC Tx is often associated with poor health-related quality of life (QoL) (Lin V, et al. *J Clin Oncol.* 2020;38:e20070). In the pivotal Phase 3 ZUMA-7 study, we assessed outcomes, including PROs, of 2L axi-cel (an autologous anti-CD19 CAR T-cell therapy) versus SOC in elderly pts with R/R LBCL. **Methods:** Pts aged ≥65 y were assessed in a planned subgroup analysis. Pts with ECOG PS 0-1 and R/R LBCL ≤12 mo after 1L chemoimmunotherapy (CIT) were randomized 1:1 to axi-cel or SOC (2-3 cycles of platinum-based CIT; pts with partial or complete response [CR] proceeded to HDT-ASCT). PRO instruments, including the EORTC QLQ-C30 (Global Health [GH] and Physical Functioning [PF]) and the EQ-5D-5L VAS, were administered at timepoints including baseline (BL; prior to Tx), Day (D) 50, D100, D150, and Month (M) 9, then every 3 mo up to 24 mo or time of event-free survival event (EFS), whichever occurred first. The QoL analysis set included all pts who had a BL PRO and ≥1 completed measure at D50, D100, or D150. A clinically meaningful change was defined as 10 points for each EORTC QLQ-C30 score, 7 points for EQ-5D-5L VAS score. **Results:** As of 03/18/2021, 51 and 58 elderly pts were randomized to the axi-cel and SOC arms, respectively, with median ages (range) of 70 y (65-80) and 69 y (65-81). At BL, more axi-cel versus SOC pts had high-risk features, including 2L age-adjusted IPI 2-3 (53% vs 31%) and elevated LDH (61% vs 41%). EFS was superior with axi-cel versus SOC (HR, 0.276, P< 0.0001), with higher CR rates (75% vs 33%). Grade ≥3 Tx-emergent adverse events (AEs) occurred in 94% and 82% of axi-cel and SOC pts, respectively, and Grade 5 Tx-related AEs occurred in 0 and 1 pt. In the QoL analysis set comprising 46 axi-cel and 42 SOC pts, there were statistically significant and clinically meaningful differences in mean change of scores from BL at D100 favoring axi-cel for EORTC QLQ-C30 GH (P<0.0001) and PF (P=0.0019) and EQ-5D-5L VAS (P<0.0001). For all 3 domains, scores also favored (P<0.05) axi-cel over SOC at D150. The mean estimated scores numerically returned to or exceeded BL scores earlier in the axi-cel arm (by D150) but never equaled or exceed BL scores by M15 in the SOC arm. **Conclusions:** Axi-cel demonstrated superiority over 2L SOC in pts ≥65 y with significantly improved EFS and a manageable safety profile. Compared with SOC, axi-cel also showed meaningful improvement in QoL over SOC, measured by multiple validated PRO instruments, with suggested faster recovery to pre-Tx QoL. The superior clinical outcomes and pt experience with axi-cel over SOC should help inform Tx choices in 2L R/R LBCL for pts ≥65 y. Clinical trial information: NCT03391466. Research Sponsor: Kite, a Gilead Compnay.

7549 **Poster Session**

Acalabrutinib in patients with relapsed/refractory (R/R) marginal zone lymphoma (MZL): Results of a phase 2, multicenter, open-label trial. *First Author: L Elizabeth Budde, City of Hope National Medical Center, Duarte, CA*

Background: MZL is a rare indolent B-cell malignancy considered incurable at recurrent stage. Bruton tyrosine kinase (BTK) inhibitors have produced durable responses in patients (pts) with R/R MZL. Acalabrutinib (acala) is a potent next-generation BTK inhibitor with high selectivity for BTK. We report data for acala monotherapy from the R/R MZL cohort (phase 2) of a phase 1b/2 clinical trial (NCT02180711). **Methods:** Pts with histologically confirmed MZL, ECOG performance status ≤2, and ≥1 prior therapy (including ≥1 CD20-directed regimen) received oral acala 100 mg twice daily until disease progression or unacceptable toxicity ± R. The primary objective was overall response rate (ORR; Lugano criteria as assessed by the investigator). Secondary objectives were duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety. Data were analyzed descriptively (no formal hypothesis testing). **Results:** Forty-two pts received acala (median age 69 y [range 42–84]; median 2 prior systemic regimens [range 1–4]). MZL subtypes were extranodal (43%), nodal (31%), and splenic (26%). At data cutoff (Oct 15, 2021), median follow-up duration was 10.7 mo (range 0.4–42.8). Sixteen (38%) pts discontinued acala, most commonly due to disease progression (26%). Among pts evaluable for response (n = 37; 3 pts had not reached the first assessment timepoint and 2 pts exited the study without response assessment), ORR was 54% (95% CI 37%–71%) with 6 complete (16%) and 14 partial (38%) responses; 17 (46%) pts had stable disease. ORRs in extranodal, nodal, and splenic subtypes were 65%, 44%, and 45%, respectively. Median time to initial response was 3.0 mo; median DOR was 19.3 mo (95% CI 8.4–not estimable). Median PFS was 27.4 mo with a 12-mo PFS rate of 66%. Four pts died (disease progression, n = 2; transformation to diffuse large B-cell lymphoma after stopping treatment, n = 1; adverse event [AE], n = 1 [septic shock unrelated to treatment]); median OS was not reached. Treatment was well tolerated with most AEs being grade 1 or 2. Sixteen pts (38%) had grade ≥3 AEs, most commonly (in ≥2 pts) anemia, dyspnea, neutrophil count decrease (n = 3 each), fatigue, thrombocytopenia, and neutropenia (n = 2 each). AEs led to treatment discontinuation in 2 pts (grade 3 hypotension and grade 1 myalgia). Among AEs of clinical interest, hypertension was reported in 2 pts (both grade 2); no cases of atrial fibrillation/flutter or major hemorrhage were reported. **Conclusions:** These early results indicate that acala is efficacious and well tolerated in pts with R/R MZL. The AE profile is consistent with the known safety profile of acala. Clinical trial information: NCT02180711. Research Sponsor: AstraZeneca.

7550 **Poster Session**

Impact of bone marrow involvement in patients with peripheral T-cell lymphoma undergoing autologous stem cell transplant. *First Author: Robert Stuver, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Nodal-based T-cell lymphomas (PTCL) are treated with induction therapy and consideration for autotransplant (autoSCT) in first remission. The impact of bone marrow (BM) involvement at diagnosis and at autoSCT is unclear. **Methods:** We performed a retrospective review of consecutive patients with PTCL-NOS, AITL, and ALCL who received autoSCT in first remission at Memorial Sloan Kettering Cancer Center from 1997-2021. For BM involvement at baseline, patients were classified as positive (≥5% by histology), any involvement (by histology and/or at least 1 high-sensitivity [HS] assay, referring to flow or clonal TCR gene rearrangement), or negative (no involvement by histology and at least 1 negative HS assay). Patients with no baseline BM biopsy were excluded. At end of therapy (EOT, after induction but prior to autoSCT), BM involvement was considered positive (≥5% by histology), minimal residual disease positive (MRD+, no histological involvement but at least 1 positive HS assay), and MRD- (no histological involvement and at least 1 negative HS assay). Patients with no EOT BM but negative baseline BM were included as a separate cohort. Patients with no baseline BM and no EOT BM were excluded, as were those with baseline BM involvement and no EOT BM. The Kaplan-Meier method was used to estimate survival and compared using log-rank tests. **Results:** A total of 135 patients were included. Median follow-up after autoSCT for survivors was 56 months. The 5-year PFS/OS for the entire cohort was 45% and 65%, respectively. By histology, 5-year PFS/OS for PTCL-NOS (N = 27), AITL (N = 78), ALK+ (N = 8) and ALK- (N = 21) ALCL was 36%, 37%, 75%, 74% (p = 0.005), and 51%, 59%, 100%, 85% (p = 0.01). Among those with adequate baseline BM evaluation (N = 98), 31 were positive, 52 had any involvement, and 44 were negative. Five-year PFS and OS in the positive, any involvement, and negative groups was 46%, 42%, 44% (p = 0.82), and 63%, 61%, 74% (p = 0.27). Of those with adequate EOT BM evaluation (N = 72), 1 was positive, 17 were MRD+, and 43 were MRD-; 32 patients had no EOT BM but negative baseline BM. Five-year PFS and OS by the EOT positive, MRD+, MRD-, and no EOT BM but negative baseline groups was 0%, 37%, 45%, 45% (p = 0.86), and 0%, 92%, 59%, 71% (p = 0.39). Of the 17 patients with MRD+ EOT BM, 14 (82%) had AITL. Two-year PFS/OS in the AITL only cohort by EOT BM was 0%, 54%, 48%, 33%, and 0%, 90%, 75%, 72%, for the positive, MRD+, MRD-, and no EOT BM but negative baseline groups (PFS: p = 0.4; OS: p = 0.3). **Conclusions:** In patients treated with upfront induction and autoSCT in first remission, neither BM involvement at diagnosis nor the presence of MRD at the time of autoSCT resulted in worse survival outcomes compared to those with no BM involvement. For patients with PTCL-NOS, AITL, or ALCL in first remission, baseline BM involvement or pre-autoSCT BM MRD+ should not dissuade use of autoSCT consolidation. Research Sponsor: None.

7551 **Poster Session**

Initial safety run-in results of the phase III POLARGO trial: Polatuzumab vedotin plus rituximab, gemcitabine, and oxaliplatin in patients (pts) with relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL). *First Author: Matthew J. Matasar, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Transplant-ineligible pts with R/R DLBCL have a poor prognosis (Gisselbrecht C, et al. Br J Haematol 2018). Several treatment options are available including platinum-based chemotherapies such as oxaliplatin plus rituximab and gemcitabine (R-GemOx). Adding polatuzumab vedotin to R-GemOx (Pola-R-GemOx) may improve outcomes for pts with a continued unmet medical need. The safety of polatuzumab vedotin and platinum-based therapy combinations must be considered as both are associated with neuropathy. POLARGO (NCT04182204; MO40598) is a Phase III, multicenter, open-label, randomized trial evaluating the safety and efficacy of Pola-R-GemOx vs R-GemOx in pts with R/R DLBCL. **Methods:** Results from the safety run-in stage of POLARGO are presented. The primary endpoint is the safety and tolerability of polatuzumab vedotin (1.8 mg/kg) + R-GemOx (R, 375 mg/m^2; Gem, 1000 mg/m^2; Ox, 100 mg/m^2) given every 21 days for up to 8 cycles. Safety was assessed by the incidence, nature, and severity of adverse events (AEs; NCI CTCAE v5.0), with a focus on peripheral neuropathy (PN). Dose interruptions and reductions were used to assess tolerability. Granulocyte-colony stimulating factor was given as primary prophylaxis with each cycle (C) of therapy; anti-infective prophylaxis for pneumocystis and herpes virus was mandatory. **Results:** As of October 26, 2021, 15 pts were enrolled and 11 (73%) pts received ≥4 cycles of Pola-R-GemOx. Median age was 76 (range 47–87) years, 10 (67%) pts had an IPI score of 3–5, 7 (47%) had ≥2 prior therapy lines, and 8 (53%) were refractory to last treatment. Grade (Gr) 3–4 AEs were reported in 5 (33%) pts: thrombocytopenia (20%) and neutropenia (13%) were the most common. Two (13%) pts had serious AEs (Gr 3 febrile neutropenia and Gr 3 infection [n = 1 each]). There were no Gr 5 AEs or AEs leading to drug discontinuation. Eight (53%) pts had Gr 1 or 2 PN; there were no cases of Gr >3 PN. Three (20%) pts had drug interruptions due to PN. Two (13%) pts had a dose reduction of polatuzumab vedotin and oxaliplatin due to PN at C5 and C8, respectively; one pt (7%) had a dose reduction of polatuzumab vedotin due to Gr 4 thrombocytopenia at C2. End-of-treatment (EOT) objective response rate was 40% (95% CI: 16–68) and complete response rate was 27% (95% CI: 8–55); 7 (47%) pts had progressive disease at EOT. Ten (67%) pts received subsequent therapies following Pola-R-GemOx, including CAR-T cell therapy (n = 3) and stem-cell transplant (n = 1). **Conclusions:** In the safety run-in stage, Pola-R-GemOx was safe and tolerable. PN was manageable with dose interruptions and reductions; no cases of Gr ≥3 PN were observed. The toxicity of this combination did not compromise delivery of subsequent treatments. POLARGO is currently enrolling pts to receive Pola-R-GemOx vs R-GemOx; results will be presented at a future meeting. Clinical trial information: NCT04182204. Research Sponsor: POLARGO is sponsored by F. Hoffmann-La Roche Ltd and Genentech, Inc. Third-party editorial assistance, under author direction, was provided by Cheryl Wright and Stephanie Cumberworth of Ashfield MedComms, and was funded by F. Hoffmann--La Roche Ltd.

7552 **Poster Session**

Tislelizumab, a PD-1 inhibitor for relapsed/refractory mature T/NK-cell neoplasms: Results from a phase 2 study. *First Author: Emmanuel Bachy, Hematology Department, Lyon Sud Hospital and Claude Bernard University Lyon 1, Lyon, France*

Background: Effective treatment choices for patients (pts) with relapsed/refractory (R/R) mature T/NK-cell neoplasms after failure of standard therapies are limited. Tislelizumab (TIS), a humanized anti-PD-1 mAb, demonstrated outstanding efficacy and favorable safety in pts with R/R classical Hodgkin lymphoma or solid tumors. We present safety and efficacy of the phase 2 study of TIS in pts with R/R mature T/NK-cell neoplasms. **Methods:** Pts were enrolled into 3 cohorts stratified by the type of T/NK-cell neoplasm to receive TIS 200 mg intravenously every 3 weeks until disease progression or intolerable toxicity. Eligible pts had ≥1 prior systemic therapy, disease progression during/after most recent therapy completion or refractory disease, ECOG ≤2, and life expectancy ≥6 mo. Primary endpoint was investigator-assessed overall response rate (ORR). Secondary endpoints included duration of response (DoR), complete response (CR) rate, progression-free survival (PFS), overall survival (OS) in cohorts 1 and 2, and safety. **Results:** 77 pts were treated. Cohort 1: R/R extranodal NK/T-cell lymphoma (n = 22); cohort 2: R/R mature T-cell neoplasms (n = 44; 21 peripheral T-cell lymphoma not otherwise specified; 11 angioimmunoblastic T-cell lymphoma; 12 anaplastic large cell lymphoma); cohort 3: R/R cutaneous T-cell lymphomas (CTCL; stage ≥1B; n = 11; 8 mycosis fungoides and 3 Sézary syndrome). Of all pts, 76.6% had advanced-stage disease, 51.9% had refractory disease, and 49.4% had ≥3 prior systemic regimens. Median treatment cycles for cohorts 1, 2, and 3 were 5 (range, 1-37), 4.5 (range, 1-38), and 17 (range, 3-25), respectively. Cohort 3 had promising efficacy (median follow-up [FU] 16.6 mo): ORR 45.5%; CR 9.1%; median DoR 11.3 mo (95% CI: 2.76-11.30); median PFS 16.8 mo; median OS not reached (NR). Modest efficacy was reported in cohort 1 (median FU 8.4 mo): ORR 31.8%; CR 18.2%; median DoR NR (95% CI: 2.66-not estimable [NE]); median PFS 2.7 mo; median OS 8.8 mo and also in cohort 2 (median FU 9.3 mo): ORR 20.5%; CR 9.1%; median DoR 8.2 mo (95% CI: 2.50-NE); median PFS 2.7 mo; median OS 13.3 mo. Most frequent adverse events (AEs) were pyrexia (32.5%), anemia (18.2%), arthralgia (18.2%), and diarrhea (15.6%); most frequent grade ≥3 AEs were anemia (7.8%), pneumonia (6.5%), and neutropenia (5.2%). Any grade immune-mediated AEs occurred in 22 (28.6%) pts, most frequently hypothyroidism (10.4%), hyperglycemia (5.2%), and rash (5.2%); and grade ≥3 in 4 (5.2%) pts (blood creatine phosphokinase increased, hepatitis, hypothyroidism, rash, and urticaria [1 pt each]). No treatment-related AEs led to death. **Conclusions:** TIS was well tolerated, achieving modest efficacy in R/R mature T/NK-cell neoplasms, with some long-lasting remissions particularly in CTCL. Further studies are warranted to determine the biologic features associated with response and explore optimal combination therapies. Clinical trial information: NCT03493451. Research Sponsor: BeiGene USA, Inc.

7553 **Poster Session**

Long-term outcomes and circulating tumor DNA analysis from a phase I/II study of lenalidomide and obinutuzumab with CHOP for newly diagnosed diffuse large B-cell lymphoma. *First Author: Hua-Jay Jeffery Cherng, MD Anderson Hematology/Oncology Fellowship, Houston, TX*

Background: Diffuse large B-cell lymphoma (DLBCL) can be cured with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (RCHOP), but a third of patients (pts) experience treatment failure. Randomized trials comparing RCHOP with modified regimens, including replacing R with obinutuzumab (O, CD20 antibody, Vitolo JCO 2017) and adding lenalidomide (L) to RCHOP (Nowakowski JCO 2021), have not significantly improved outcomes. The combination of L and O may have synergy via an enhanced NK-cell mediated antibody dependent cellular cytotoxicity. We hypothesized combining L and O with CHOP (LOCHOP) would be an effective and well tolerated treatment of DLBCL. **Methods:** In this single center phase Ib/II study (NCT02529852) pts with untreated CD20+ DLBCL received 6 cycles of CHOP with O 1000mg IV on days (D) 1, 8, and 15 during cycle 1 and D1 during cycles 2-6, and L 15 mg orally on D1-14 of each cycle. Growth factor and thromboembolism prophylaxis were mandated. The primary objectives were to determine the maximum tolerated dose (MTD) of L and efficacy of LOCHOP. Plasma samples were collected for circulating tumor DNA (ctDNA) analysis. **Results:** Fifty-three pts were enrolled, 6 in phase Ib and 47 in phase II. No dose limiting toxicities were experienced in phase Ib at an MTD of 15 mg of L. Median age was 62 years, 35 (66%) pts had stage III/IV disease, 12 (23%) an IPI > 2, and 26 (49%) and 22 (42%) were germinal center (GC) and non-GC subtype (5 not classified) by Hans algorithm. At end of therapy, 50 pts were evaluable, overall response: 49 (98%), complete response: 45 (90%). Median follow up was 4.5 years and 4-year progression free and overall survival rates were 87.4% and 91.3%. No characteristics were associated with differences in outcomes. Any grade and grade 3-4 adverse events (AEs) were experienced by 100% and 70% of pts. Grade 3-4 AEs included neutropenia (38%), thrombocytopenia (17%), fatigue (13%), neutropenic fever (13%), and infection (9%). Four (8%) pts developed venous thromboembolism. At study entry, 31/33 (94%) profiled pts had detectable ctDNA with CAPP-Seq, 24% had high ctDNA (> log 2.5 hGe/ml) and 24/31 (77%) were evaluable by LymphGen classifier: molecular subtypes included EZB (5, 21%), ST2 (5, 21%), MCD (4, 17%), and other (9, 38%). All 5 EZB and 4/5 ST2 pts were GC subtype while 2/4 MCD pts were non-GC (1 GC, 1 not classified). With LOCHOP, 13/18 (72%) and 11/15 (73%) pts achieved early and major molecular response (Kurtz JCO 2018). By PhasED-Seq (Kurtz Nat Biotechnol 2021), 16/18 (89%) had no detectable ctDNA after ≥5 cycles. **Conclusions:** LOCHOP demonstrates high efficacy and tolerability in newly diagnosed DLBCL, leading to a high rate of undetectable minimal residual disease by ctDNA. Noninvasive molecular subtyping is feasible as a supplement to tissue diagnosis and should be incorporated in future studies aiming to improve on RCHOP. Clinical trial information: NCT02529852. Research Sponsor: Celgene/BMS and Genentech.

7554 **Poster Session**

Treatment patterns and real-world effectiveness of rituximab maintenance in older patients with mantle cell lymphoma: A population-based analyses. *First Author: Mengyang Di, Yale University School of Medicine, New Haven, CT*

Background: In the clinical trial setting, rituximab maintenance (RM) improved survival of older adults with mantle cell lymphoma (MCL) compared to maintenance interferon following RCHOP. However, given the considerable shift away from the use of RCHOP for MCL, real-world effectiveness of RM is now uncertain for MCL in older adults. We used SEER-Medicare, a large population-based data set, to evaluate MCL treatment patterns and assess effectiveness of RM following standard chemoimmunotherapy in older patients. **Methods:** We selected adults ≥66 years old, diagnosed with MCL 2007-2017, with continuous Medicare A/B/D coverage, who received MCL therapy. We captured 1st and 2nd line regimens, defining RM as rituximab (R) given as a single agent after R-based multi-agent induction regimen, with treatment gap ≤200 days (d) prior, for ≥2 consecutive doses and lasting ≥ 28d. We examined the benefits of RM in patients who received bendamustine-R (BR) or RCHOP as 1st line with no consolidative stem cell transplant (SCT). We limited our control group to those who survived ≥ 200d (if no 2nd line given) or had a gap ≥ 200d between completion of induction and initiation of 2nd line treatment to reduce potential immortal time bias. We used propensity score matching (PSM) based on age, sex, race, marital status, Medicaid dual coverage, residence, poverty, frailty, comorbidities, year of diagnosis, extranodal disease, stage, 1st line regimen, and duration of 1st line therapy. We used Cox regression model to compare all-cause mortality (AM) and reported hazard ratio (HR) with 95% confidence interval (CI). We conducted competing risk analysis for mortality from MCL (MFM; competing event [CE]: non-lymphoma mortality [NLM]) and initiation of 2nd line therapy (CE: AM), respectively, reporting sub-HR (sHR). **Results:** Of 1579 older adults treated for MCL, BR (37%) and RCHOP (17%) were the most common 1st line regimens. Among those receiving BR/RCHOP, 44% received RM. Only 3% received SCT. Use of RCHOP decreased substantially over time (2007: 31%, 2017: 5%, *P* for time trend<0.001), with an increase for BR (2007:1%, 2017: 41%, *P*<0.001). We included 386 patients who received either RCHOP (83) or BR (303) (post-PSM; median age: 75, 67% men, 95% White) to examine effectiveness of RM, and all covariates were well balanced. Compared to patients not receiving RM, AM (HR: 0.59, 95% CI: 0.42-0.84), MFM (sHR: 0.53, 95% CI: 0.35-0.81) and initiation of 2nd line therapy (sHR: 0.60, 95% CI: 0.44-0.82) were all significantly lower in patients receiving RM. NLM was similar between RM and non-RM groups, suggesting that PSM worked well. **Conclusions:** Our population-based real-world analyses showed significant benefits of RM in survival and disease control among older patients with MCL who did not receive SCT, despite the shift from RCHOP to BR as 1st line induction regimen. Research Sponsor: None.

7555 **Poster Session**

Quality-adjusted time without symptoms or toxicities (Q-TWiST) analysis of ZUMA-7, a randomized controlled trial of axicabtagene ciloleucel versus standard of care for second-line large B-cell lymphoma. *First Author: Marie José Kersten, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands*

Background: Quality of life (QoL) post cancer therapy is increasingly important. We conducted a Q-TWiST analysis to compare the quality-adjusted survival of axicabtagene ciloleucel (axi-cel, a chimeric antigen receptor T-cell therapy) versus standard of care (SOC) among relapsed/refractory (R/R) large B-cell lymphoma (LBCL) patients enrolled in ZUMA-7 (NCT03391466), a Phase 3, randomized, open-label, multicenter study. ZUMA-7 met its primary endpoint of event-free survival; events were defined as death, progression, or new lymphoma therapy. **Methods:** Overall survival (OS) in the intention-to-treat (ITT) cohort was partitioned into 3 mutually exclusive health states as measured through a median follow-up duration of 23.5 months (m): time with grade 3/4 adverse events (AE) before an event (TOX); time without symptoms from events or toxicity (TWiST); and time after event (REL). Q-TWiST was calculated as the average time spent in each state, weighted by state-specific QoL utility (u, ranging from 0 to 1), assuming a base case u(TOX)=0.5, u(REL)=0.5, u(TWiST)=1. Threshold analyses assessed the mean Q-TWiST differences between axi-cel and SOC by varying u(TOX) and u(REL) from 0 to 1. Relative gains for axi-cel (axi-cel Q-TWiST gain divided by mean SOC OS) ≥15% were considered "clearly clinically important" using published norms. Nonparametric bootstrap 95% confidence intervals (CI) were computed. Subgroup analyses were performed for relapse status and age. Sensitivity analyses varying the follow-up duration from 3 to 37.7m were explored. **Results:** For the ITT cohort (n=359), mean time spent in TOX and TWiST was significantly longer for the axi-cel cohort compared to SOC, and mean time spent in REL was significantly shorter for axi-cel (Table). Using the base case, quality-adjusted survival was significantly longer for axi-cel by 3.7m, representing a 21.9% relative gain. In threshold analyses, the difference in Q-TWiST ranged from 1.2m (u(TOX)=0, u(REL)=1) to 6.2m (u(TOX)=1, u(REL)=0) in favor of axi-cel. Q-TWiST gains favored axi-cel across all subgroup analyses. Q-TWiST gains from axi-cel increased with longer follow-up. **Conclusions:** Axi-cel was associated with statistically significant and "clearly clinically important" gains in quality-adjusted OS vs. SOC in R/R LBCL, regardless of the relative decline in QoL associated with treatment toxicity, disease progression, or additional cancer treatment. Research Sponsor: Kite Pharma.

Mean (95% CI) months in health states and Q-TWiST, over 23.5m of follow-up.

State	Axi-cel	SOC	Difference (Axi-cel − SOC)
TOX	1.16 (0.83, 1.48)	0.74 (0.51, 0.94)	0.42 (0.04, 0.82)
TWiST	11.18 (9.73, 12.61)	5.39 (4.21, 6.56)	5.79 (4.07, 7.62)
REL	6.02 (4.9, 7.15)	10.66 (9.42, 11.93)	-4.64 (-6.39, -3.09)
Q-TWiST	14.8 (13.6, 15.9)	11.1 (10, 12.1)	3.7 (2.3, 5.2)

7556 **Poster Session**

In-field recurrences in relapsed/refractory (R/R) B-cell non-Hodgkin lymphoma (NHL) bridged with radiation prior to CD19 chimeric antigen receptor T-cell therapy (CART). *First Author: Omran Saifi, Mayo Clinic Department of Radiation Oncology, Jacksonville, FL*

Background: The majority of R/R NHL progressions after CART involve pre-existing sites, suggesting a promising role for bridging radiotherapy (bRT). We assessed the local control rate of disease sites bridged with radiotherapy prior to CART and identified predictors of in-field recurrence. **Methods:** We retrospectively reviewed 35 patients with aggressive B-cell NHL who received bRT between leukapheresis and CART infusion between 2018 and 2021 at a multi-site single institution. bRT local control rate (LC), calculated based on the total number of irradiated sites, was defined from bRT end date. Progression-free survival (PFS) and overall-survival (OS) were defined from the date of CART infusion. In-field recurrence was defined as disease relapse occurring within the radiation planning target volume. Kaplan-Meier plots and cox regression modeling were used to estimate the desired output. **Results:** Median age of the cohort at time of CART infusion was 59 (range 19-73). The median equivalent 2 Gy dose (EQD2) administered was 23.3 Gy (range 4-41 Gy). The median time from end of bRT to CART infusion was 14 days (range 6-42). Five (14%) patients also received bridging chemotherapy with bRT. Among the 34 evaluable patients, 30 (88%) achieved an objective response (59% complete response and 29% partial response). At a median follow-up of 12 months, 1-year PFS was 48% and 1-year OS was 72%. No progression occurred beyond 240 days. On review of treatment plans and pre-treatment PET/CT scans, 59 sites were identified that received bRT prior to CART infusion. The median size and SUVmax of the irradiated sites were 8.7cm (range 1.5-22) and 13 (range 4-46), respectively. Of the 59 irradiated sites, 8 sites (13.6%) in 7 patients had in-field local recurrence, translating to 1-year LC of 84%. No in-field recurrence occurred beyond 180 days. Moreover, no local recurrence occurred in patients who received radiation to all known sites of active disease to EQD2> 30 Gy (n = 4 patients); these patients remained in remission except for 1 who experienced progression outside the bRT field. On univariate analysis, triple hit lymphoma (THL) (OR 22.8, 95% CI: 3.8-138.3; p < 0.001), tumor size (OR 1.25, 95% CI: 1.1-1.4; p < 0.001), specifically ≥ 9cm (OR 9.4, CI: 1.2-77.3; p = 0.036) and SUVmax (OR 1.1, CI: 1.02-1.15; p = 0.008), specifically ≥ 20 (OR 5.6, CI: 1.3-23.7; p = 0.018), were significantly associated with increased risk of in-field recurrence. On multivariate analysis, THL (OR 32.9, CI: 3.2-336.0; p = 0.03) and tumor size (OR 1.3, CI: 1.1-1.6; p = 0.01) retained significant association with in-field recurrence. **Conclusions:** Bridging radiotherapy prior to CART provides excellent and durable in-field local control for R/R B-cell NHL. Patients with triple hit histology and bulky disease are likely at higher risk of in-field recurrence and may benefit from higher doses of bRT. Research Sponsor: None.

7558 **Poster Session**

Asia subpopulation analysis from the phase III POLARIX trial. *First Author: Yuqin Song, Key Laboratory of Carcinogenesis and Transitional Research (Ministry of Education), Department of Lymphoma, Peking University Cancer Hospital and Institute, Beijing, China*

Background: In the pivotal Phase III POLARIX trial, Pola-R-CHP demonstrated significantly improved progression-free survival (PFS) compared with R-CHOP, with a similar safety profile in patients with previously untreated DLBCL (Tilly et al. 2022). An Asia subpopulation analysis was included as part of the trial design; patients enrolled in Asia were analyzed for the purpose of registration in China of POLARIX (NCT03274492). **Methods:** Patients from mainland China, Hong Kong, Japan, South Korea, and Taiwan (enrolled during the global phase), and from the China extension cohort were included in the Asia subpopulation. POLARIX methods were previously described (Tilly et al. 2022). Briefly, patients with untreated DLBCL were randomized 1:1 using the same stratification factors to receive six cycles of Pola-R-CHP or R-CHOP, plus two cycles of rituximab alone. The purpose of this analysis was to evaluate consistency of PFS (defined as ≥50% risk reduction in PFS) in the Asia subpopulation with the global population. **Results:** Overall, 281 patients (intent-to-treat population; 150, 85, 31 and 15 patients in mainland China, Japan, South Korea and Taiwan, respectively) were analyzed (141 received Pola-R-CHP and 140 received R-CHOP); 160 patients from the global population and 121 from the China extension cohort. Median age was 63 (range 19–79) years, and most patients had an International Prognostic Index of 3–5 (61.9%). At the data cut-off of June 28, 2021, (median follow-up of 24.2 months) PFS was superior with Pola-R-CHP vs R-CHOP (hazard ratio [HR] 0.64; 95% confidence interval [CI]: 0.40–1.03) and met the consistency definition with the global population. The 2-year PFS rate was 74.2% (95% CI: 65.7–82.7) with Pola-R-CHP vs 66.5% (95% CI: 57.3–75.6) with R-CHOP. Other key efficacy results were similar to the global study results (Table). The safety profile was generally comparable for Pola-R-CHP vs R-CHOP, including rates of grade 3–4 adverse events (AEs; 72.9% vs 66.2%), serious AEs (32.9% vs 32.4%), grade 5 AEs (1.4% vs 0.7%), AEs leading to discontinuation of any study treatment (5.0% vs 7.2%), and incidence of peripheral neuropathy (all grades, 44.3% vs 50.4%), respectively. Key efficacy results. CR, complete response. **Conclusions:** The results from the Asia subpopulation of POLARIX were consistent with the global study, with a clinically meaningful improvement in PFS (risk of disease progression, relapse or death reduced by 36%) following treatment with Pola-R-CHP vs R-CHOP, and a comparable safety profile in Asian patients with previously untreated DLBCL. Clinical trial information: NCT03274492. Research Sponsor: POLARIX is sponsored by F. Hoffmann-La Roche Ltd and Genentech, Inc. Third-party editorial assistance, under author direction, was provided by Tracey McManus of Ashfield MedComms, and was funded by F. Hoffmann-La Roche Ltd.

Outcome	Pola-R-CHP (n=141)	R-CHOP (n=140)
Progression-free survival, number of events (%)	30 (21.3)	40 (28.6)
HR (95% CI)	0.64 (0.40–1.03)	
Event-free survival, number of events (%)	30 (21.3)	41 (29.3)
HR (95% CI)	0.62 (0.38–1.00)	
PET-CT CR (independent review) at end of treatment, n (%)	116 (82.3)	109 (77.9)
Overall survival, number of events (%)	10 (7.1)	15 (10.7)
HR (95% CI)	0.64 (0.29–1.42)	

7559 **Poster Session**

Brentuximab vedotin in combination with lenalidomide and rituximab in patients with relapsed/refractory diffuse large B-cell lymphoma: Safety and efficacy results from the safety run-in period of the phase 3 ECHELON-3 study. *First Author: Nancy L. Bartlett, Washington University School of Medicine, St. Louis, MO*

Background: Patients (pts) with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) who relapse after or are ineligible for hematopoietic stem cell transplant (HSCT) or chimeric antigen receptor T cell (CAR-T) therapy generally have poor outcomes. Preclinical data provide the rationale for combining brentuximab vedotin (BV), lenalidomide (len), and rituximab for the treatment of R/R DLBCL. BV+len showed promising clinical activity in a Phase 1 trial with a 57% overall response rate (ORR), 10.2-month median progression-free survival, and 14.3-month overall survival (Ward 2021). We report the results of the open-label safety run-in that was conducted prior to the randomized portion of the study. **Methods:** ECHELON-3 (NCT04404283) is a randomized, double-blind, placebo-controlled, active-comparator, multicenter Phase 3 study. Prior to randomization, an open-label safety run-in was conducted; pts received BV (1.2 mg/kg) and rituximab (375 mg/m^2) both q3w, and len 20 mg qd. Pts must have received ≥2 prior lines of therapy and be previously treated with or were ineligible for HSCT or CAR-T, ECOG score ≤2, and PET-avid, bidimensional measurable disease (> 1.5 cm by CT). Pts with negligible CD30 expression (< 1%) were eligible. Response was assessed by the investigator according to the Lugano Classification Revised Staging System (Cheson 2014). **Results:** 10 pts with R/R DLBCL were enrolled. Median age was 70.5 years, 7 pts were male, and all had an ECOG ≤1. Median prior lines of therapy was 3 (range, 2 to 6); no pts received prior HSCT and 6 pts received prior CAR-T. At a median follow-up of 6.9 months (range, 2.3 to 14.1), the most common treatment emergent adverse events (TEAE) were fatigue (n = 5), anemia (n = 4) and constipation (n = 4). Grade ≥3 events were experienced by 8 pts, most commonly anemia and pneumonia (n = 3 each), and neutropenia and thrombocytopenia (n = 2 each). Serious adverse events were observed in 7 pts. Seven pts each had BV and rituximab dose modifications, and 6 pts had a len dose modification. The most common reasons for any dose modification were anemia (n = 3), neutropenia, peripheral neuropathy, or pneumonia (n = 2 each). 4 pts discontinued treatment due to an AE, 2 of which were treatment related (n = 1 each of Grade 2 fatigue; Grade 3 anemia). There was 1 death due to a TEAE that was not treatment related. The ORR (best response) was 70%, including 4 pts with a complete metabolic response, 2 pts with a partial metabolic response, and 3 pts with progressive disease. Responses were seen in both CD30 (+) and (-) pts, as well as in 4 pts who received prior CAR-T. **Conclusions:** This novel triplet regimen appears active in R/R DLBCL with an acceptable safety profile. The randomized portion of the study is currently enrolling. Clinical trial information: NCT04404283. Research Sponsor: Seagen Inc.

7560 **Poster Session**

Subgroup analysis in RE-MIND2, an observational, retrospective cohort study of tafasitamab plus lenalidomide versus systemic therapies in patients with relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL). *First Author: Grzegorz S. Nowakowski, Division of Hematology, Mayo Clinic, Rochester, MN*

Background: Tafasitamab (tafa) + lenalidomide (LEN) demonstrated efficacy in adult patients (pts) with R/R DLBCL ineligible for autologous stem-cell transplant in the pivotal Phase II study L-MIND (NCT02399085) and received accelerated approval in the United States in 2020 and conditional marketing authorization in Europe and Canada in 2021 in this setting. RE-MIND2 (NCT04697160), an observational, retrospective cohort study, compared pt outcomes from L-MIND with matched pt cohorts treated with other NCCN/ESMO recommended therapies. **Methods:** Methodology for RE-MIND2 has been presented previously. Hypothesis-generating analyses were conducted for pt subgroups of number of extranodal sites (ENS) (0–1 vs ≥2) and elevated lactate dehydrogenase (LDH) (yes vs no) in matched cohorts of pts receiving tafa + LEN vs systemic therapies pooled (STP), polatuzumab vedotin + bendamustine + rituximab (pola-BR), rituximab + LEN (R2), and CD19 CAR-T therapies (CAR-T). The primary endpoint was overall survival (OS). **Results:** Of 3,454 pts enrolled, 961, 106, 106, and 149 were treated with STP, pola-BR, R2, and CAR-T, resulting in 76, 24, 33, and 37 matched pairs for pts receiving tafa + LEN, respectively. Hazard ratios (HR) for OS show a trend toward favoring tafa + LEN in most pt subgroups (Table). Conclusion: These analyses suggest that tafa + LEN may be associated with improved OS vs selected systemic therapies for certain pts with high-risk disease and may further inform physicians' treatment choices for pts with R/R DLBCL. These analyses are not powered for statistical comparison; small sample sizes in some subgroups result in wide confidence intervals (CI) and so results must be interpreted with caution. Data for other treatment cohorts, pt subgroups, and endpoints will be presented. Funding: MorphoSys AG. Clinical trial information: NCT04697160. Research Sponsor: MorphoSys AG.

OS for subgroups for tafa + LEN vs STP, pola-BR, R2, and CAR-T.

	Tafa + LEN vs STP N/N* HR (95% CI)	Tafa + LEN vs pola-BR N/N* HR (95% CI)	Tafa + LEN vs R2 N/N* HR (95% CI)	Tafa + LEN vs CAR-T N/N* HR (95% CI)
Overall	76/76 0.553 (0.358–0.855) p=0.0068†	24/24 0.441 (0.203–0.956) p=0.0340†	33/33 0.435 (0.224–0.847) p=0.0122†	37/37 0.953 (0.475–1.913) p=0.8929†
Number of ENS	52/38	18/11	20/17	23/23
0–1	0.476 (0.27–0.85)	0.573 (0.20–1.65)	0.491 (0.19–1.28)	0.717 (0.28–1.85)
≥2	24/31 0.803 (0.40–1.61)	6/12 0.524 (0.14–2.02)	13/13 0.478 (0.17–1.34)	14/14 1.459 (0.52–4.11)
Elevated LDH	35/32	10/4	13/8	18/15
No	0.448 (0.21–0.96)	0.388 (0.08–1.79)	0.664 (0.15– 3.01)	0.371 (0.12–1.15)
Yes	41/44 0.627 (0.37–1.07)	14/18 0.585 (0.24–1.41)	20/22 0.420 (0.19–0.94)	19/21 1.663 (0.66–4.19)

N/N*, number of pts in the tafa + LEN and observational cohorts, respectively. †Log-rank test. HR estimated using Cox proportional hazard model with observational cohort as reference.

7561 **Poster Session**

Analysis of peripheral neuropathy (PN) using clinician- and patient-reported outcomes (ClinRO and PRO) in the POLARIX study. *First Author: Marek Trneny, Charles University General Hospital, Prague, Czech Republic*

Background: PN is an identified risk of anti-microtubule agents, including polatuzumab vedotin and vincristine. POLARIX (NCT03274492), a Phase III randomized, double-blind, placebo-controlled study comparing Pola-R-CHP with R-CHOP, demonstrated improved progression-free survival (PFS) with Pola-R-CHP (Tilly et al. NEJM 2022). Here, we evaluate the impact of Pola-R-CHP vs R-CHOP on PN using ClinRO and PRO data. **Methods:** Patients with previously untreated diffuse large B-cell lymphoma (DLBCL) received Pola-R-CHP or R-CHOP. ClinRO data were based on PN grading according to the NCI CTCAE v4.0. PRO data were generated from assessment of patient-reported PN symptoms at baseline and Day 1 of each cycle using the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group – Neurotoxicity (FACT-GOG/NTX) subscale, ranging from 0–44, with higher scores representing lower levels of PN (minimal clinically important difference: 1.38–3.68 [Cheng et al. Health Qual Life Outcomes 2020]). **Results:** At baseline, ClinRO and PRO symptom scores showed low PN burden (Table). Overall incidence of PN was comparable between treatment arms (Pola-R-CHP: 52.9%; R-CHOP: 53.9%); most events were grade 1, and incidence of grade 2 (Pola-R-CHP: 12.2%; R-CHOP: 15.5%) and grade 3 (Pola-R-CHP: 1.6%; R-CHOP: 1.1%) events were comparable between treatment arms. FACT-GOG/NTX survey completion was high in both arms (96% at baseline; >80% at other timepoints). When evaluated by cycle, ClinRO and PRO demonstrated that more patients experienced earlier onset PN with R-CHOP than with Pola-R-CHP (Table), with ~10% more R-CHOP- than Pola-R-CHP-treated patients having clinician-reported PN in Cycle (C) 2–5, and a ~+1-point difference (i.e. fewer symptoms) in PRO symptom scores in C3–6 with Pola-R-CHP vs R-CHOP; by C8+, and during follow up, rates and symptoms of PN were similar. PN symptoms resulted in fewer dose reductions (3.9% vs 8.2%) and drug discontinuations (0.7% vs 2.1%) with Pola-R-CHP vs R-CHOP. Duration of PN was similar for both treatments. **Conclusions:** In the POLARIX study, Pola-R-CHP did not result in different rates or severity of PN vs R-CHOP. According to ClinRO and PRO data, PN occurred later following initial exposure to Pola-R-CHP than to R-CHOP, and there were fewer dose modifications with Pola-R-CHP than with R-CHOP. Overall, the risk of PN was manageable. Clinical trial information: NCT03274492. Research Sponsor: POLARIX is sponsored by F. Hoffmann-La Roche Ltd. Third-party medical writing assistance, under the direction of the authors, was provided by Carla Smith of Ashfield MedComms, an Ashfield Health company, and was funded by F. Hoffmann-La Roche Ltd.

	Clinician-reported PN NCI CTCAE v4.0 (all grades, %)		Patient-reported PN FACT-GOG/NTX[a]	
	Pola-R-CHP (n=435)	R-CHOP (n=438)	Pola-R-CHP (n=413)	R-CHOP (n=412)
Baseline (Day 1, Cycle 1)	4.1	7.1	39.81[a]	39.49[a]
Treatment cycle (Day 1 of each)	9.9	19.6	0.22	0.01
2				
3	15.6	26.3	0.17	-0.76
4	24.1	36.5	-0.48	-1.51
5	29.4	40.9	-0.98	-2.15
6	37.0	45.2	-1.96	-2.89
7	40.9	44.7	-2.71	-3.51
8	41.6	41.8	-2.53	-2.50

[a]Adjusted mean changes except baseline (mean score).

7562 **Poster Session**

Methylated DNA markers in early detection of lymphoma: Discovery, validation, and clinical pilot. *First Author: Thomas E. Witzig, Division of Hematology, Mayo Clinic, Rochester, MN*

Background: Lymphoma is the 6th most common cancer and a top 10 cause of cancer deaths. To date, there are no blood test approaches to population screening, and accurate surveillance markers are limited. Methylated DNA markers (MDMs) are broadly informative for early detection of cancer but have not been extensively studied for lymphomas. We sought to discover and validate MDMs in DNA extracted from lymphoma tissue, then test these MDMs in archival blood plasma specimens. **Methods:** Reduced representation bisulfite sequencing (RRBS) was performed on DNA extracted from a discovery set of frozen tissues of classic Hodgkin lymphoma (CHL, n=24), non-Hodgkin lymphoma (NHL, n=78: T-cell-TCL (8); diffuse large B-cell-DLBCL (18); follicular-FL (12); mantle cell-MCL (20); marginal zone-MZL (15)), and lymphoma cell line samples (27); controls included benign lymph node (n=11) and healthy donor buffy coat (n=30). 30 MDMs were ranked by fold-change and AUC and used to design methylation-specific PCR assays for biological validation on independent DNA samples extracted from FFPE tissue from 13 normal lymph node and 63 lymphoma samples and 36 buffy coats from healthy patients. Target enrichment long-probe quantitative-amplified signal assays were developed for 16 MDMs and then assayed in plasma-extracted, bisulfite-converted DNA samples from 390 independent treatment-naïve lymphoma patients (100 CHL and 290 NHL:100 DLBCL, 73 FL, 41 MCL, 41 MZL, 35 TCL), and 210 controls without cancer. Lymphoma plasma samples and 159 controls were provided by the Lymphoma SPORE (CA97274); 51 controls came from a 7-county population archive. Classification of lymphoma cases vs controls was modeled with random forest method and cross-validated across 500 bootstrap samples of each dataset. **Results:** For MDMs tested in DNA from independent biological validation samples, cross-validated random forest models identified 60/63 cases (95% sensitivity) and 12/13 normal controls (92% specificity). In plasmas, a panel of 16 MDMs (*ZNF503, VWA5B1, HOXA9_5195, GABRG3, ITGA5, MAX_chr17_793, BNC1_2407, CDK20, MAX_chr4_184, TPBG, DNAH14, SYT2, CACNG8, FAM110B, and NRN1*) detected 78% (95% CI, 74-82%) of lymphoma cases at 90% specificity. Excluding MZL and TCL, sensitivity increased to 84% (80-88%) including 26/49 (53% (38-67%)) of stage I and 59/71 (83% (71-90%)) of stage II cases. **Conclusions:** MDMs show promise to detect lymphoma. These markers could be evaluated as part of multicancer early detection testing and could also be evaluated as response markers to treatment and subsequent surveillance. Research Sponsor: Exact Sciences (Madison WI), U.S. National Institutes of Health.

Plasma MDM sensitivity (%, 95% CI) by lymphoma subtype and stage at 90% specificity.

By Lymphoma Type	DLBCL	FL	CHL	MCL	MZL	TCL
	80 (71–87)	82 (71–90)	89 (81–94)	88 (74–96)	61 (45–76)	43 (26–61)
By Stage	I	II	III	IV	Unk	
Overall	46 (34–59)	82 (71–90)	95 (86–99)	87 (81–92)	62 (42–79)	
Excluding MZL and TCL	53 (938–67)	83 (72–91)	96 (88–100)	92 (85–96)	86 (42–100)	

7563 **Poster Session**

A phase I/II study of golidocitinib, a selective JAK1 inhibitor, in refractory or relapsed peripheral T-cell lymphoma. *First Author: Won Seog Kim, Samsung Medical Center, Seoul, South Korea*

Background: Peripheral T cell lymphoma (PTCL) is a group of heterogeneous T cell lymphomas. Patients who relapse from or are refractory to 1st line therapy face dismal prognosis. The response rates to commonly used 2nd line agents such as histone deacetylase inhibitors are below 30%. Immunotherapies, such as anti-PD1 antibodies, may induce hyperprogression in certain PTCL subtypes. Hence, r/r PTCL patients urgently need better therapies. Preclinical data shows JAK/STAT pathway may mediate the pathogenesis of PTCL, making it a promising target. Golidocitinib (DZD4205) is an orally available, potent, JAK1 specific inhibitor, demonstrating profound anti-tumor activities in T lymphoma cells *in vitro* and tumor xenograft *in vivo*. Here we report the preliminary data from an ongoing phase I/II study (NCT04105010) of Golidocitinib in r/r PTCL. **Methods:** The study included two parts: Part A (dose escalation) and Part B (dose expansion). In Part A, patients with r/r PTCL were enrolled and received Golidocitinib at different doses (150 mg or 250 mg, QD) to determine the recommended phase II dose (RP2D). Evaluation of safety and efficacy were performed by investigators per CTCAE and Lugano criteria, respectively. Part B is a single-arm, pivotal study, where patients with r/r PTCL will receive Golidocitinib at the RP2D till disease progression or intolerance. **Results:** As of May 31, 2021, a total of 51 patients enrolled in Part A and received Golidocitinib at 150 mg (n = 35) or 250 mg (n = 16). Patient characteristics: median age (range): 61.0 years (29-79); median prior systemic therapies (range): 2 lines (1-8). Ten patients (19.6%) had undergone hematopoietic stem cell transplantation. Fifteen patients (29.4%) had bone marrow involvement at baseline. Histological subtypes included PTCL-NOS (41.2%), AITL (39.2%), ALCL ALK- (7.8%), NKTCL (7.8%), and MEITL (3.9%). At the data cut-off (DCO), 49 patients completed at least one post-treatment Lugano assessment, of whom 21 (42.9%) achieved tumor response, including 11 complete responses (CRs, 22.4%) and 10 partial responses (20.4%). Tumor response was observed in various subtypes, including AITL (13/20), PTCL-NOS (5/19), ALCL ALK- (2/4) and NKTCL (1/4). At the DCO, the median duration of response (DoR) was not reached, and the longest DoR was > 14 months. Forty-eight patients (94.1%) experienced treatment emergent adverse events (TEAEs), of whom 30 (58.8%) experienced ≥ grade 3 TEAEs. Per investigators' assessment, 20 patients (39.2%) experienced ≥ grade 3 TEAEs possibly related to the drug. The most common (≥ 10%) ≥ grade 3 TEAEs were neutropenia (29.4%), thrombocytopenia (15.7%) and pneumonia (11.8%). The majority of TEAEs were reversible or clinically manageable with dose modifications. **Conclusions:** Golidocitinib shows good safety and promising anti-tumor efficacy in r/r PTCL, indicating its potential as a therapeutic option for this unmet medical need. Clinical trial information: NCT04105010. Research Sponsor: Dizal Pharmaceutical Co., Ltd.

LBA7564 **Poster Session**

Results of the DIAL study (NCI 10089), a randomized phase 2 trial of varlilumab combined with nivolumab in patients with relapsed/refractory aggressive B-cell non-Hodgkin lymphoma (r/r B-NHL). *First Author: Jose Caetano Villasboas, Division of Hematology, Mayo Clinic, Rochester, MN*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

7565 **Poster Session**

Association of pretreatment (preTx) tumor characteristics and clinical outcomes following second-line (2L) axicabtagene ciloleucel (axi-cel) versus standard of care (SOC) in patients (pts) with relapsed/refractory (R/R) large B-cell lymphoma (LBCL). *First Author: Frederick L. Locke, Moffitt Cancer Center, Tampa, FL*

Background: The Phase 3 randomized ZUMA-7 trial in 2L R/R LBCL showed axi-cel superiority to SOC (salvage chemotherapy and HDT-ASCT) in event-free survival (EFS; hazard ratio [HR], 0.398; *P*< .0001; Locke et al. *N Eng J Med.* 2021). We report results of exploratory analyses of tumor characteristics, including preTx tumor burden (TB), tissue hypoxia-related lactate dehydrogenase (LDH) level, and tumor microenvironment (TME). **Methods:** TB was calculated as the sum of product diameters of ≤6 reference lesions (Locke et al. *Blood Adv.* 2020). Serum LDH was assessed. PreTx tumor samples were assessed for RNA expression by the NanoString IO 360™ panel and prespecified immune contexture indexes related to T-cell involvement (Immunosign 15 [IS15] and 21 [IS21]; Galon et al. ASCO 2020. #3022). ZUMA-1 data were used for comparison to 3L R/R LBCL. CD19 protein expression was assessed by immunohistochemistry (H-score). Associations between biomarkers and clinical outcomes were assessed using descriptive statistics (*P*< .05 was significant). **Results:** Axi-cel EFS was superior to SOC for both high and low TB (HR, 0.29 and 0.49, respectively; *P*< .001 for both) and elevated and nonelevated LDH (HR, 0.32 and 0.5, respectively; *P*< .001 for both). EFS in axi-cel pts was not associated with preTx TB (HR, 1.01 [95% CI, 0.88-1.16]; *P*= .89) or LDH (HR, 0.98 [95% CI, 0.74-1.29]; *P*= .86), but was worse in SOC pts with higher preTx TB (HR, 1.17 [95% CI, 1.03-1.32]; *P*= .01) or higher LDH (HR, 1.29 [95% CI, 1.02-1.63], *P* =.03). PreTx TB was lower in SOC pts with ongoing response vs nonresponders and pts who relapsed (*P*= .07), but not in axi-cel pts (*P*= .99). Non-germinal center B-cell (GCB) cell-of-origin subtypes is a poor prognostic factor for EFS in SOC (EFS was significantly worse in SOC pts with non-GCB vs GCB; HR, 1.82 [95% CI, 1.12-2.96]; *P*= .02) but not in axi-cel. In IO360 analysis, gene expression of B-cell lineage antigens (CD19, CD20, BCMA) and markers highly expressed by tumor cells (CD45RA, IRF8, BTLA) positively associated with objective and durable responses to axi-cel. While axi-cel remained superior to SOC with high (> median) or low CD19 expression level, the probability of an ongoing response increased with a higher CD19 H-score. PreTx TME IS15 and IS21 scores were generally higher in 2L vs 3L. **Conclusions:** Axi-cel was superior to SOC in all subgroup analyses, including higher TB and LDH. Durable responses with axi-cel were greatest in tumors with prominent B-cell features, but were superior to SOC regardless of these features. Axi-cel intervention in 2L is supported by durable response rates not impacted by high TB, as seen in 3L axi-cel or 2L SOC. Higher preTx immune involvement in 2L vs 3L tumors suggests high TB may be overcome with axi-cel in patients with a more favorable immune contexture. Clinical trial information: NCT03391466. Research Sponsor: Kite, A Gilead Company.

7566 **Poster Session**

Bendamustine rituximab (BR) versus ibrutinib (Ibr) as primary therapy for Waldenström macroglobulinemia (WM): An international collaborative study. *First Author: Jithma P. Abeykoon, Mayo Clinic, Division of Hematology, Rochester, MN*

Background: Parenteral limited-duration BR chemoimmunotherapy and continuous orally administered Ibr, a Bruton tyrosine kinase inhibitor, dominate the treatment landscape of WM, a rare B cell lymphoma. No trials have assessed the comparative effectiveness of these 2 vastly different approaches. We conducted a multiinstitutional, international, collaborative study to compare BR and single-agent Ibr in patients (pts) with treatment naïve (TN) WM. **Methods:** Data from 347 pts with active TN WM, seen between 2011 and 2021 in the US and Europe, were analyzed. The pts on rituximab maintenance were excluded. The modified IWWM-6 criteria (based on IgM alone) were used for response assessment. All time-to-event analyses were performed from the frontline therapy initiation, using the Kaplan-Meier method. **Results:** The median age of the pts treated with BR (n=208) and Ibr (n=139) was 66 (range 40-86) years (y) and 69 (39-97) y, respectively, (p=0.005). With a median follow up of 4.2 y (95% CI 3.8-4.5), the 4-y progression free survival (PFS) was 73% in each group, p=0.6, and 4-y overall survival (OS) was 94% (95% CI 91-98) in the BR group versus (*v*) 82% (95% CI 75-90) in the Ibr group, p=0.01. In a bivariate analysis adjusting for age and the treatment type, only age emerged as a predictor for OS (HR 7.2, p=0.0001). Therefore, a 1:1 age-matched analysis of 246 pts who received Ibr (n=123) or BR (n=123) was performed. Pts with a known *MYD88*^{WT} status who had received Ibr and their age matched controls on BR were excluded. The international prognostic scoring system (IPSS) WM was comparable between the 2 groups (Table**).** A higher proportion of pts on BR attained very good partial or deeper response (≥VGPR) as the best response in comparison to the pts on Ibr (Table). The 4-y PFS for the BR and Ibr groups was similar [72% (95% CI 63-82) *v* 78% (95% CI 70-87), p=0.14] and 4-y OS was 95% (95% CI 91-99) with BR *v* 86% (95% CI 80-93) with Ibr (p=0.3). Premature discontinuation, during active treatment, due to adverse effects (AEs) or lack of response was noted in 13% and 33% of pts on BR and Ibr, respectively. A detailed assessment of the AEs will be presented at the meeting. **Conclusions:** Both BR and Ibr lead to comparable outcomes in pts with TN WM, although deeper responses are attained with BR. These findings require confirmation in prospective studies. For pts who harbor *MYD88*^{L265P} mutation, selection between the 2 approaches should be dictated by their potential toxicities, pt comorbidities, pt/clinician preference (parenteral fixed-duration *v* continuous oral) and access to therapies. Research Sponsor: None.

	BR	Ibr	p
Follow up, median, 95%CI, y	4.5 (3.7-4.9)	4.5 (4-4.7)	0.7
Age, median, range, y	68 (40-86)	68 (39-86)	0.9
IPSS%			0.63
Low	11	17	
Intermediate	33	33	
High	56	48	
Cycles, median (range)	6 (1-6) >4 cycles, 77%	42 (0.3-98)	
Overall response rate %	94	94	0.91
Major response rate %	92	83	0.05
Complete response %	20	2	<0.001
≥VGPR %	50	33	0.009

Visit meetings.asco.org and search by abstract for the full list of abstract authors and their disclosure information.

7567 **Poster Session**

Axicabtagene ciloleucel (axi-cel) in combination with rituximab (Rtx) for the treatment (Tx) of refractory large B-cell lymphoma (R-LBCL): Outcomes of the phase 2 ZUMA-14 study. *First Author: Paolo Strati, The University of Texas MD Anderson Cancer Center, Department of Lymphoma/Myeloma, Houston, TX*

Background: Despite the success of axi-cel, ≈60% of patients (pts) have no response or relapse within ~2 y after Tx (Jacobson C, et al. ASH 2021. #1764), highlighting the need for more therapeutic strategies. In preclinical studies, Rtx augmented CD19 CAR T-cell function and increased tumor reduction and survival in murine models via synergistic targeting with CAR T-cells (Mihara K, et al. *Br J Haematol*. 2010). Here, we report outcomes of ZUMA-14, a Phase 2, multicenter study of axi-cel in combination with Rtx in pts with R-LBCL after ≥2 lines of systemic therapy. **Methods:** Eligible pts were ≥18 y with R/R LBCL. Pts received one Rtx dose (375 mg/m^2) on Day -5, a conditioning regimen of cyclophosphamide and fludarabine on Days -5, -4, and -3, and a single axi-cel infusion of 2×10^6 CAR T cells/kg on Day 0. Starting on Day 21 post–axi-cel infusion, pts received 1 Rtx dose every 28 d for up to 5 doses. The primary endpoint was investigator-assessed complete response (CR) rate. Secondary endpoints included objective response rate (ORR), duration of response (DOR), progression-free survival (PFS), overall survival (OS), safety, and biomarker assessments. The analysis reported here occurred after all treated pts had ≥12 mo of follow-up. **Results:** As of 12/2/21, 27 pts were enrolled, and 26 received axi-cel and ≥1 Rtx dose (15 pts received all 6 Rtx doses); 1 pt discontinued Tx due to an adverse event (AE). Median age was 63 y (range, 38-82), 54% of pts were male, 81% had stage III/IV disease, 62% had extranodal disease, 38% had elevated LDH, and 85% had an aaIPI ≥1 (35% aaIPI 2). The CR rate was 65% (95% CI, 44-83), and the ORR was 88% (95% CI, 70-98). With a median follow-up of 17 mo, 65% of the pts had ongoing response, with 57% ongoing in CR. Medians for DOR, PFS and OS were not reached. The estimated DOR and PFS rates at 12 mo were 64% and 56%, respectively. The estimated 12 mo OS rate was 76%, and 6 pts (23%) died of progressive disease. Most pts (92%) experienced Grade ≥3 AEs. Grade ≥3 cytopenias were reported in 85% of pts, with 38% ongoing on Day 30. Grade ≥3 neurologic events (NEs) occurred in 4 pts (15%), and there was no Grade ≥3 cytokine release syndrome (CRS). Median times to onset of CRS and NEs were 4 d (range, 1-7) and 6 d (range, 3-32), respectively, with median durations of 5 d (range, 2-15) and 7 d (range, 1-39). No pts experienced myelodysplastic syndrome. Median peak CAR T-cell levels were comparable to the ZUMA-1 pharmacokinetic profile. Immune-modulating cytokines, including granzyme B, IL-6, CXCL10, IFN-g and IL-2, were induced in pts following axi-cel and Rtx infusion and were more prominently elevated in responders vs non-responders. Peak Rtx levels were also elevated in responders vs non-responders. **Conclusions:** Results from ZUMA-14 demonstrated that axi-cel in combination with Rtx elicited a high CR rate with no new safety signals detected in pts with R-LBCL. Clinical trial information: NCT04002401. Research Sponsor: Kite, A Gilead Company.

7568 **Poster Session**

Cost effectiveness of polatuzumab vedotin in combination with chemoimmunotherapy (Pola-R-CHP) in previously untreated diffuse large B-cell lymphoma. *First Author: Swetha Kambhampati, City of Hope, Duarte, CA*

Background: In patients with treatment naive diffuse large B-cell lymphoma (DLBCL), the POLARIX study demonstrated a 6.5% improvement in the 2-year (yr) progression-free survival (PFS) with no difference in overall survival or safety using polatuzumab vedotin + R-CHP compared to standard RCHOP. We evaluated the cost effectiveness of pola-R-CHP for DLBCL. **Methods:** We modeled a hypothetical cohort of US adults (mean age, 58 yrs) with treatment naïve DLBCL by developing a Markov model with a 1-month cycle and 20-yr horizon. The cost-effectiveness of two strategies were directly compared (pola-R-CHP, RCHOP) using a range of plausible long-term outcomes. A patient with DLBCL in remission after treatment could develop subsequent progression or relapse, death, or alternative toxicity. Progression rates and overall survival were estimated from POLARIX study. Outcome measures were reported in incremental cost-effectiveness ratios (ICERs), with a willingness-to-pay (WTP) threshold of $150,000/quality-adjusted life-yr (QALY). **Results:** Assuming a 5-yr PFS of 69.6% with pola-R-CHP and 62.6% with RCHOP, pola-R-CHP was more effective (0.81 incremental QALYs) but more costly ($66,218) and was cost-effective at a WTP of 150,000 (ICER $82,220/QALY). Its cost effectiveness was highly dependent on the 5-yr PFS of pola-R-CHP with it no longer being cost effective if the 5-yr PFS was < 65%. One way sensitivity analysis demonstrated that pola-R-CHP is cost effective up to a cost of $270,506 at a WTP of $150,000. Probabilistic sensitivity analysis was derived from performing 10,000 Monte-Carlo model iterations and demonstrated that pola-R-CHP was the cost-effective strategy in 61.3% of iterations with RCHOP being cost-effective in 38.6% of iterations at a WTP of $150,000. **Conclusions:** If the absolute benefit in PFS is maintained over time, frontline pola-R-CHP for treatment of DLBCL would be cost effective at its current cost when compared to RCHOP at a WTP of $150,000/QALY. However, its cost effectiveness is highly sensitive to changes in long-term PFS and the cost of pola-R-CHP. If pola-R-CHP is adopted as frontline therapy for the 29,108 incident cases of DLBCL annually in the US, this will lead to an additional 1.8 billion dollars in healthcare expenditures. This highlights the importance of decreasing the cost of pola-R-CHP and identifying sub-populations that derive the highest benefit from it. Research Sponsor: None.

Cost-effectiveness of Pola-R-CHP (compared to R-CHOP).

Treatment	Clinical Outcomes				Cost-Effectiveness				
	2-yr OS	2-yr PFS	5-yr OS	5-yr PFS	QALYs	Incr QALY	Cost	Incr Cost	ICER
R-CHOP	88.4%	70.2%	77.7%	62.6%	12.55	–	350566	–	
Pola-R-CHP	88.6%	76.6%	81.8%	69.6%	13.35	0.81	416785	66,218	82,220
5-yr PFS with Pola-R-CHP									
60%					12.73	0.17	$504,319	$137,815	904,429
65%					12.97	0.42	$432,198	$141,632	194,347
70%					13.35	0.81	$416,785	$61,076	82,220
75%					14.58	2.03	$402,283	$51,717	24,397

7569 **Poster Session**

Prospective evaluation of the prognostic value of circulating tumor DNA in patients with follicular lymphoma: A pilot study. *First Author: Ismael Fernández-Miranda, Instituto de Investigación Sanitaria Puerta de Hierro-Segovia de Arana, Hospital Universitario Puerta de Hierro-Majadahonda, Majadahonda, Spain*

Background: Follicular lymphoma (FL) is the most frequently occurring indolent non-Hodgkin lymphoma, with generally favorable outcomes but a variable clinical course. Around 20% of patients suffer progression of disease within 24 months (POD24) of chemoimmunotherapy. In this prospective study, we examined the prognostic value of circulating tumor DNA (ctDNA), before and during treatment, to predict response and POD24 in FL patients. **Methods:** We collected 110 plasma samples from 39 patients diagnosed with FL, prospectively enrolled in 8 Spanish hospitals and treated with Chemotherapy-Rituximab regimen from April 2017 to November 2020 with a median follow-up of 41 months (m). Samples were collected before treatment (basal), mid-treatment (3m), at the end of treatment (EOT) (6m) and relapse or follow-up. We performed targeted deep sequencing in cell-free DNA and paired genomic DNA from 30 formalin-fixed paraffin-embedded tumoral (FFPET) samples with the same gene panel. **Results:** Before treatment, ctDNA levels, measured as haploid genome equivalents per milliliter of plasma (hGE/mL), were detected in 17/30 patients. Basal ctDNA levels were higher in patients without complete response (CR) than in CR patients [18 *vs* 14 $\log_2$(hGE/mL); Mann-Whitney P = 0.007] and in patients with POD24 compared to those not-POD24 [18 *vs* 13 $\log_2$(hGE/mL); P = 0.005]. None of the 13 patients with zero basal ctDNA levels, experienced POD24. Patients with at least one mutation detected in basal ctDNA had an inferior 24-months PFS than patients without alterations (64 *vs* 100%, log-rank test P = 0.027). In addition, basal ctDNA levels were detected in one patient with low FLIPI, but partial response and POD24, and by contrast, no ctDNA was detected in another patient with CR and no progression event but high FLIPI. From the alterations detected in FFPET samples, 66% were also identified in basal ctDNA. No alterations were detected in basal ctDNA from 7 patients with CR and 3 patients with watch-and-wait strategy. Dynamic analysis showed that ctDNA levels decreased after treatment for every patient (3 mo), but the reduction at EOT was higher in patients achieving CR than in non-CR patients (12 *vs* 3 log-reduction) and in not-POD24 patients compared to those with POD24 (10 *vs* 8). Furthermore, patients with at least one mutation detected in ctDNA at EOT had a shorter 24-months PFS than those without alterations (50 *vs* 90%). The sensitivity to detect alterations in ctDNA at EOT was 94% in patients not achieving a CR and no mutation was detected in patients with CR. **Conclusions:** In a real-life, prospective-based population, we showed that pre-treatment and dynamic molecular response measured by ctDNA, could be useful to stratify patients and predict response to treatment and early relapse in FL patients. Research Sponsor: Gilead (GLD18/00019), AECC, CAM (PEJ-CAM & S2017/BMD-3778), AES-ISCIII-MINECO (PI17/00272 & PI20/00591.

7570 **Poster Session**

The utility of the novel optimized HLH inflammatory (OHI) index for predicting the risk for mortality and causes of death in lymphoma. *First Author: Adi Zoref Lorenz, Division of immunobiology, Cincinnati Children's Hospital Medical Center and Meir Medical Center, Sackler School of Medicine, Tel Aviv, Israel*

Background: Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening inflammatory syndrome that may complicate hematologic malignancies (HM). We recently developed a simplified diagnostic and prognostic index termed the 'optimized HLH inflammatory' (OHI) index comprising the combined elevation of sCD25 (> 3,900 U/mL) and serum ferritin (> 1,000 ng/mL), which in HM patients both identifies HLH and predicts mortality more accurately than conventional criteria for HLH. In this study, we examined whether mortality in our cohort is directly related to progressive malignancy vs. HLH-associated causes in OHI+ and OHI- patients. **Methods:** We performed a multicenter, retrospective study of patients with newly diagnosed lymphoma from Israel, the USA, and Japan for whom sCD25 and ferritin levels were measured either as routine surveillance or during investigation for HLH and classified patients by their OHI status. The International Prognostic Index, International Prognostic Score, and Follicular Lymphoma International Prognostic Index were used to estimate the predicted prognosis of T/B cell non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma, and follicular lymphoma, respectively. Predicted five-year overall survival was calculated based on the relevant prognostic index and was compared between OHI+ and OHI- patients using the unpaired t-test. The actual survival at five years/last follow-up was recorded, as was the cause of death. The odds ratios (ORs) for observed vs. predicted mortality, and for HLH- vs. malignancy-related death were calculated using the Chi-square test. **Results:** 100 lymphoma patients were studied: 65% with B cell NHL, 18% with natural killer/ T cell lymphoma, 17% with Hodgkin's lymphoma; 37 were OHI+, and 63 were OHI-. The disease-relevant international prognostic index-predicted five-year survival did not differ between OHI + and OHI- patients (a mean of 58% n OHI+ and 57% in OHI- p = 0.62). However, the observed five-year survival in OHI+ patients was lower (12%) than predicted, reflecting a mortality incidence that was four times higher than predicted by the relevant prognostic score (OR 3.9; CI 1.3-12.1). By contrast, OHI- patients had better survival (79%) than predicted by their prognostic scores (OR 0.15; CI 0.07-0.34). More than half of the OHI+ patients died from non-malignant causes (39% multi-organ dysfunction or HLH, 18% infection), while most OHI- patients (92%) died from progressive malignancy. The likelihood of dying from multi-organ dysfunction or HLH was 26 times higher in OHI+ vs. OHI- patients (OR 26.2; CI 4.1-286.7). **Conclusions:** OHI index status strongly correlated with mortality in patients with lymphoma within our cohort, and death in OHI+ patients was largely due to causes other than progressive malignancy. The OHI index appears to identify a harmful inflammatory state and deserves further prospective study. Research Sponsor: U.S. National Institutes of Health.

7571 **Oral Abstract Session**

Real-world outcomes of axicabtagene ciloleucel (Axi-cel) for the treatment of large B-cell lymphoma (LBCL) by race and ethnicity. *First Author: Frederick L. Locke, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

Background: In clinical trials of CAR T-cell therapies and real-world studies published to date, there is a paucity of data on outcomes by race and ethnicity. Here, we examined outcomes by race and ethnicity among LBCL pts who received axi-cel in the real-world setting. **Methods:** A total of 1389 pts with LBCL were identified from a non-interventional post-authorization safety study with pts receiving commercial axi-cel between 10/2017 and 08/2020. Race (African American or Asian vs White) and ethnicity (Hispanic vs non-Hispanic) were self-reported by pts. Pts with rescinded consent, enrolled in trials, having prior non-HCT cellular therapy, primary CNS lymphoma, unknown comorbidity or data in query were excluded. Median follow-up was 12.7 mo. Outcomes included ORR, CR rate, DOR, PFS and OS, grade ≥ 3 CRS (Lee 2014 criteria) and ICANS (ASTCT consensus grade). ORR and CR were evaluated in pts with ≥ 180 days of follow-up. Kaplan-Meier estimates were calculated for PFS and OS. Multivariable analyses comparing race and ethnicity were conducted via logistic and Cox regression. **Results:** Among all, 1127 (81%) were White, 70 (5%) African American and 81 (6%) Asian; 152 (11%) were Hispanic including 104 White, 2 Black, and 1 Asian Hispanic. African Americans, compared to White, were younger (median age 55.5 vs 62.8 years), more likely to have pulmonary impairment (41% vs 28%) and tended to have longer time from diagnosis (≥ 12 mo 71% vs 59%). Hispanic pts were younger (median age 58.5 vs 62.6 years) than non-Hispanic pts. ORR was 74% (CR 57%, 12-mo PFS and OS 48% and 63%) for White, 57% (CR 45%, 12-mo PFS and OS 36% and 62%) for African American, 67% (CR 53%, 12-mo PFS and OS 55% and 65%) for Asian and 73% (CR 55%, 12-mo PFS and OS 50% and 65%) for Hispanic pts. Grade ≥ 3 CRS and ICANS occurred in 7% and 18% of African American, 10% and 19% of Asian, and 8% and 27% of White pts, respectively. Hispanic pts had lower rates of grade ≥ 3 CRS and ICANS (4% and 15%) vs non-Hispanic (9% and 27%). African American race was associated with inferior ORR (OR 0.40; 95% CI, 0.24-0.69) and CR rate (OR 0.55; 95% CI 0.32-0.93) vs White. Asian pts had favorable DOR compared to both White (HR 0.46; 95% CI 0.24-0.87) and African American (HR 0.39; 95% CI 0.17-0.88). No statistical differences were found in OS and PFS across races, nor in any efficacy outcome between Hispanic and non-Hispanic pts. Asian (OR 0.52; 95% CI 0.29-0.96 vs White) and Hispanic pts (OR 0.51; 95% CI 0.31-0.85 vs non-Hispanic) had lower risk of grade ≥ 3 ICANS. **Conclusions:** Overall, axi-cel showed favorable OS, PFS and safety profile regardless of race and ethnicity in the real-world setting. No notable differences in outcomes were observed for Hispanic or Asian pts. Lower response rates in African American pts noted here warrant further investigation including any underrepresentation not explained by a lower incidence rate for DLBCL (SEER), access to care, and disease burden. Research Sponsor: Kite, a Gilead Company, Other Government Agency.

7572 **Poster Session**

Updated interim analysis of the randomized phase 1b/3 study of tazemetostat in combination with lenalidomide and rituximab in patients with relapsed/refractory follicular lymphoma. *First Author: Connie Lee Batlevi, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Tazemetostat (TAZ), an enhancer of zeste homolog 2 (EZH2) inhibitor, showed antitumor activity as monotherapy in patients with relapsed or refractory (R/R) follicular lymphoma (FL) who received ≥2 prior lines of therapy. In clinical studies in patients with R/R FL, lenalidomide and rituximab (R^2) demonstrated an objective response rate (ORR) of 73%–78% and median progression-free survival (PFS) of 36–39 months. This global, multicenter phase 1b/3 study is designed to determine the recommended phase 3 dose (RP3D), efficacy, and safety of TAZ + R^2 in patients with R/R FL after ≥1 prior therapy. We report an updated interim analysis of the phase 1b safety run-in where we assess the clinical activity and pharmacokinetics (PK) of TAZ when administered with R^2 in patients with R/R FL. **Methods:** Phase 1b evaluated TAZ at 3 dose levels (400, 600, and 800 mg orally twice daily) in 28-day cycles with standard-dose R^2 (NCT04224493). In addition to PK and safety, preliminary efficacy analysis was performed on the response-evaluable population, including best overall response, PFS, and duration of response (DOR) per investigator assessment according to Lugano 2014 response criteria. **Results:** As of January 22, 2022, 43 patients were enrolled and receiving TAZ + R^2 (400 [n = 4], 600 [n = 18], and 800 mg [n = 21]). These patients had a median age of 67 years (range, 39–83) and received a median of 1 prior therapy (range, 1–4). Overall, 15/43 (34.9%) patients were refractory to rituximab, 10/39 (25.6%) had POD24, and 6/41 (14.6%) had mutant-type *EZH2*. Median duration of treatment exposure was 32.0 weeks (range, 4.1–68.1). Mean C_{max} and AUC_{0-t} of TAZ 800 mg + R^2 at steady state were similar to those found for TAZ as monotherapy. PK of TAZ was not altered by concomitant administration of daily oral lenalidomide 20 mg, and PK of lenalidomide was not altered by concomitant administration of TAZ. No dose-limiting toxicities were observed in phase 1b, and no new safety signals were identified as of the January 2022 data cutoff. Serious treatment-emergent adverse events (TEAEs) were observed in 14 (32.6%) patients. Grade 3–4 TEAEs were observed in 24 (55.8%) patients; the most common grade 3–4 TEAE was neutrophil count decrease (n = 13; 30.2%). Of 38 patients evaluable for tumor assessment, 19 (50.0%) had a complete response, 17 (44.7%) had a partial response, and 2 (5.3%) had stable disease. ORR was 94.7% (n = 36). With a median follow-up of 5.8 months, median PFS and DOR were not reached and appeared to be similar, regardless of mutation status. **Conclusions:** TAZ + R^2 combination demonstrates consistent and unaltered PK for TAZ and lenalidomide as well as a favorable safety profile and efficacy trend. The 2-arm randomized phase 3 portion will further explore the efficacy and safety of TAZ RP3D 800 mg + R^2 in ≈500 patients with R/R FL. Clinical trial information: NCT04224493. Research Sponsor: Epizyme, Inc.

7573 **Poster Session**

Therapy for patients with POD24 follicular lymphoma: Treatment patterns and outcomes from the Lymphoma Epidemiology of Outcomes (LEO) Consortium. *First Author: Carla Casulo, University of Rochester Medical Center-James P. Wilmot Cancer Center, Rochester, NY*

Background: While most patients (pts) with follicular lymphoma (FL) usually have favorable outcomes, those with refractory disease after first-line anti-CD20 based immunochemotherapy (IC), or progression within 24 months of diagnosis (POD24) have higher risk of premature death. There are no standard approaches for treating this vulnerable group and studies testing novel agents are ongoing in this setting. We sought to investigate clinical practice treatment choices and efficacy for pts with POD24 that align with eligibility criteria for the randomized SWOG1608 which compares IC with novel agents in this population. **Methods:** This was a multicenter observational cohort study from the LEO Consortium. Eligible pts had grade 1-3a FL diagnosed between 1/1/2002 and 2/1/2019, and initiated therapy after POD24 to first-line bendamustine or CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) based IC. Observation, radiotherapy, or rituximab monotherapy were permitted prior to IC and pts with transformation prior to the subsequent therapy after IC were excluded as per S1608. Outcomes of interest were overall and complete response rate (ORR/CR), progression-free survival (PFS), and overall survival (OS). **Results:** We identified 196 eligible pts with early progression to IC (39% antiCD20 Benda; 61% antiCD20 CHOP) who received subsequent therapy. Median age at post IC treatment was 57 years, 78% grade 1-2 FL. Treatments for pts with POD24 included CHOP- or Benda-based in 31%, salvage/hematopoietic stem cell transplant (HSCT) in 27%, novel therapies in 10% (including phosphatidylinositol 3-kinase inhibitors), antiCD20 monotherapy in 9%, and lenalidomide-based treatment in 8% (table); 21% of pts were treated on clinical trials. Across all treatments, ORR (CR) was 63% (37%) (95% CI: 55-70). At a median follow up of 6.2 years, 2 year PFS was 22% (95% CI: 17%-29%) and 5 year OS was 71% (95% CI: 65-79). Outcomes by regimen are shown in the table. **Conclusions:** Pts with FL experiencing POD24 following first-line IC are treated heterogeneously, with many pts still receiving IC as subsequent therapy. Despite modest CR rates and low 2-year PFS, 5-year OS appear to be improving compared to historical outcomes. This supports the ongoing need to investigate novel treatments in this population. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

Post POD24 therapy (%)	ORR (95%CI)/CR %	2 yr PFS % (95%CI)	5 yr OS %
HSCT (27)	59 (44-72)/40	23 (14-37)	67 (56-81)
CHOP +/- Anti CD20 (18)	58 (39-75)/29	20 (10-40)	66 (51-86)
Benda +/- AntiCD20 (13)	85 (61-96)/55	27 (14-51)	83 (70-100)
Novel therapy (10)	50 (29-71)/17	10 (3-37)	84 (65-100)
AntiCD20 monotherapy (9)	59 (34-81)/35	38 (20-69)	73 (53-100)
Lenalidomide based (8)	73 (45-91)/53	27 (12-65)	75 (54-100)
Other chemo (7)	77 (46-94)/23	8 (1-54)	76 (55-81)
Radioimmunotherapy (6)	50 (24-76)/30	18 (5-64)	46 (22-93)
Non systemic (2)	100 (6-100)/100	33 (7-100)	100 (100-100)

7574 **Poster Session**

A phase II, multicenter, single-arm study of parsaclisib, a PI3Kδ inhibitor, in relapsed or refractory follicular lymphoma in China: Updated data from the study. *First Author: Zhong Zheng, Shanghai Institute of Hematology, State Key Laboratory of Medical Genomics, National Research Center for Translational Medicine at Shanghai, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China*

Background: For Follicular lymphoma (FL) patients (pts) of 3rd or higher line, treatment options are limited. Parsaclisib is a potent, highly-selective, next-generation PI3Kδ inhibitor. Initial safety and efficacy data were previously presented (Zhong Zheng et al. ASH 2021; NCT04298879). Here, we report safety, efficacy and survival data of the multicenter, open-label phase 2 study of parsaclisib in 3rd or higher line FL pts in China. **Methods:** Key eligibility included, age ≥ 18 years, histologically confirmed FL grade 1, 2, or 3a, ≥ 2 prior systemic therapies, ECOG PS ≤ 2, and ineligible for hematopoietic stem cell transplantation (HSCT). Pts received parsaclisib 20 mg once daily (QD) for 8 weeks followed by 2.5 mg QD, till disease progression (PD), unacceptable toxicity, death or withdrawn consent. Prophylaxis for Pneumocystis jirovecii pneumonia (PJP) was required. Primary endpoint was objective response rate (ORR) evaluated by an Independent Review Committee (IRC) according to Lugano 2014 criteria, secondary endpoints included: duration of response (DOR), PFS, OS, and safety and tolerability. **Results:** As of the data cutoff date (Dec 12, 2021), 61 pts (median age: 50yr; male [n = 35, 57.4%]) were enrolled. Forty-eight pts remained on treatment and 13 pts had discontinued study treatment mainly due to PD (n = 11). With a median follow-up time 9.5 months (range 6.0-19.7months), the median duration of treatment was 251.0 days (range: 23.0-589.0 days). All 61 pts were evaluable for response, the ORR and complete response rate (CRR) were 86.9% (n = 53, 95% CI: 75.8-94.2%) and 31.1% (n = 19, 95% CI: 19.9-43.3%), respectively. The median time to response (TTR) was 8.0 weeks (95% CI: 7.9-8.0%), and the median DOR was not reached (95% CI: 9.2 months-NC), and 43 of 53 pts with CR or PR still retained CR or PR. As data cutoff, eleven (17.9%) pts had disease progression, the median PFS was not achieved. Three pts died data as data cutoff, the median OS was not achieved. Among the 61 treated pts, 48 (95.1%) pts experienced at least 1 treatment-emergent adverse events (TEAEs), with the most common TEAEs being neutrophil count decreased (49.2%), white blood cell count decreased (32.8%). Twenty-seven patients (44.3%) experienced grade ≥ 3 TEAEs, the most common grade ≥ 3 TEAEs was neutrophil count decreased (n = 10, 16.4%). **Conclusions:** Parsaclisib demonstrated promising efficacy, and acceptable safety profile. These results suggest that parsaclisib could benefit 3rd or higher line Follicular lymphoma patients. Clinical trial information: NCT04298879. Research Sponsor: Innovent Biologics Inc.

7575 **Poster Session**

Open-label, dose-escalation, and expansion trial of CA-4948 in combination with ibrutinib in patients with relapsed or refractory hematologic malignancies.

First Author: Erel Joffe, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

Background: CA-4948 is a novel oral inhibitor of interleukin-1 receptor-associated kinase 4 (IRAK4), which is essential for toll-like receptor (TLR) and interleukin-1 receptor (IL-1R) signaling in B cell proliferation. IRAK4 forms a Myddosome complex with MYD88 adaptor protein and drives overactivation of nuclear factor-kappa B (NF-κB), causing inflammation and tumor growth. CA-4948 has been reported to be well tolerated and active as monotherapy in heavily pretreated patients with relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL). Preclinical studies demonstrated that tumor resistance and survival via IRAK4 activation could be delayed or reversed. CA-4948 crossed the blood-brain barrier in a murine PDX model of pCNS lymphoma, resulting in tumor response and prolonged survival. In combination with Bruton tyrosine kinase (BTK) inhibitors, CA-4948 showed *in vivo* synergy in B-cell NHL. Here we will present an update on the preliminary efficacy data of CA-4948+ibrutinib in R/R hematologic malignancies. **Methods:** This is an ongoing open-label trial (NCT03328078) of CA-4948 as monotherapy and in combination with ibrutinib. Part A1 (completed) dose escalation of CA-4948 as monotherapy; the recommended phase 2 dose (RP2D) is 300 mg BID with continuous oral dosing. Part A2 (dose escalation in combination with ibrutinib), and Part B (a basket design of 4 expansion cohorts of CA-4948 and ibrutinib: BTK-naïve MZL, DLBCL, or PCNSL and NHL with adaptive resistance to ibrutinib). The primary endpoints of Parts A1 and A2 include safety, tolerability, and RP2D. The primary endpoints of Part B include CR or ORR, with key secondary endpoints of DOR, DCR, PFS and OS following treatment of CA-4948 at dose levels of 200 (DL1) or 300 mg BID (DL2) with ibrutinib at full prescribed dose. **Results:** As of December 7th, 2021, 35 heavily pretreated NHL patients have received CA-4948 monotherapy (median age 66 years, range 50-87), of which six patients have been on CA-4948 for approximately 1 year or longer, suggesting CA-4948 has a long-term acceptable safety and tolerability profile at RP2D (dose level of 300 mg BID). In Part A2, 10 patients are treated with CA-4948+ibrutinib (median age 65 years, range 56-82). Median number of prior lines of anti-cancer therapies is 3 (range 1-8). No DLTs were observed at 200 or 300 mg dose levels to date. The preliminary efficacy data of seven evaluable patients with combination therapy showed 1 CR (MCL), 2 PR (MCL and MZL), 3 SD, and 1 PD, 3 of whom had failed prior ibrutinib. The preliminary data indicate the combination therapy may overcome ibrutinib resistance. **Conclusions:** CA-4948 as a monotherapy and in combination with ibrutinib is well tolerated with an acceptable long term safety profile and promising efficacy. Part A2 is transitioning to Part B basket cohorts of MZL, ABC-DLBCL, PCNSL and NHL with adaptive resistance to ibrutinib. Clinical trial information: 03328078. Research Sponsor: Curis.

7576 **Poster Session**

DLBCL cell of origin typing and whole transcriptome analysis using single slides with HTG EdgeSeq.

First Author: Matthew Loya, Genmab US, Inc., Plainsboro, NJ

Background: Diffuse large B-cell Lymphoma (DLBCL) is a highly heterogenous disease. Gene microarrays were initially used to classify DLBCL into germinal center B-cell-like (GCB) or activated B-cell-like (ABC) Cell of Origin (COO) subtypes. ABC is associated with shorter overall survival. In newly diagnosed patients, COO classification by RNA profiling is a validated prognostic. A simpler immunohistochemical (IHC) staining of CD10, MUM1 and BCL6 is a proxy used in clinical practice in lieu of transcriptomics due to its expense, complexity and tissue requirements. Recent advances in the HTG EdgeSeq platform allow genome-scale profiling with minimal tissue. We successfully applied this novel technology to perform simultaneous COO classification, immune cell enrichment and tumor pathway analysis using a single FFPE slide. **Methods:** Accuracy of the HTG EdgeSeq panel (19,000 genes) was assessed in a head-to-head comparison with RNAseq using FFPE tumor samples (n = 8). DLBCL resections and core needle biopsies were commercially sourced and COO typed using Han's algorithm into GCB or non-GCB (n = 65). Tumor locations included: lymphoid organs, gastrointestinal tract, testes, and the pleural cavity. EdgeSeq was performed on single slides with an average tissue area of 40mm^2. Transcriptomic COO classification was performed using a linear combination of genes as described in Wright et al., *PNAS* 2003, substituting HTG platform-specific weights. Validated COO gene sets from literature and commercial diagnostic assays were tested. Immune cell gene signature enrichment analysis was performed using xCell (Aran et al., *Genome Biol* 2017); pathway analysis was performed with GSEA (Subramanian et al., *PNAS* 2005). **Results:** Gene expression levels estimated from whole transcriptome EdgeSeq on single slides were highly correlated to whole transcriptome RNAseq. Differential expression analysis of GCB vs non-GCB showed that key prognostic genes were detectable and enriched in the expected subtypes. Using these pre-established signatures, subtyping accuracy was ~93% on the training set and 89% on the test set. Immune cell enrichment analysis identified class-switched memory B-cells as more prevalent in non-GCB subjects. This is consistent with emerging evidence that memory B-cells are the primary source of ABC DLBCL and not plasma cells (Venturutti & Melnick, *Blood* 2020). Pathway analysis identified genes regulated by the oncogene ic transcription factor *MYC* were enriched in non-GCB samples; *MYC* protein was found to be overexpressed in ABC in a large study (Hu et al., Blood 2013). **Conclusions:** Combined COO typing and whole transcriptome analysis from a single slide efficiently uses precious patient tissue. Longitudinal core needle sampling may yield insights into tumor evolution and therapeutic mechanisms of action across the DLBCL treatment landscape. Research Sponsor: Genmab A/S.

7577 **Poster Session**

Impact of sex on outcomes in patients with hairy cell leukemia (HCL): An HCL Patient Data Registry (PDR) analysis.

First Author: Narendranath Epperla, The Ohio State University, Columbus, OH

Background: HCL is a rare indolent leukemia that is more common in men, with a 4:1 male predominance. To date, no studies have characterized the potential difference in outcomes of HCL between male and female patients. Hence, we sought to evaluate the outcomes of female HCL patients using the HCL-PDR. **Methods:** The HCL Foundation sponsored the development of HCL-PDR to characterize the clinical features and outcomes of this rare leukemia. HCL-PDR is an international multicenter PDR that includes patient, disease and treatment information abstracted from medical records. Adult patients enrolled in the HCL-PDR were included in the study. Female patients with HCL were the study population, with males as the comparator. The primary endpoint was the time to next treatment (TTNT) in females compared to males. Secondary endpoints included response rates (RR) and predictors of TTNT. Responses were categorized as: complete response (CR) including CR/CRu (CR unconfirmed)/HR (hematologic response), and partial response (PR), which included PR/PRu (PR unconfirmed)/pHR (partial HR). CRu was defined as no disease in bone marrow (BM) without available blood counts and HR as blood counts meeting criteria for HR, but no available BM. Cox proportional hazard models were used to estimate the hazard ratios for TTNT risk. **Results:** 357 patients were included: 265 males and 92 females. Table shows baseline characteristics stratified by sex. Among the patients who had disease status assessed after first treatment (n=224, males 169 and females 55), there was no significant difference in RR. However, females had significantly longer median TTNT (17.6 years) relative to males (8 years, HR 0.54, 95% CI 0.32-0.91, p=0.02) that remained significant after adjusting for other variables (RR and BRAF mutation) in multivariable analysis (HR 0.32, 95% CI 0.11-0.97, p=0.04). Factors predictive of longer TTNT include female sex and CR (HR.0.26, 95% CI 0.11-0.57, p=0.001). **Conclusions:** This is the first study to date reporting the clinical characteristics and outcomes in female HCL patients. The significantly longer TTNT in females compared to males may be related to factors such as underlying molecular features or hormonal influences. This finding needs to be explored further. Research Sponsor: HCL Foundation.

	n=357		
	Males (n=265)%	**Females (n=92)%**	**p-value**
Mean age at dx	52	51	0.49
Caucasians	233 (98)	84 (97)	0.67
Never smoker	153 (73)	57 (77)	0.69
HCL type			
cHCL	249 (94)	88 (96)	0.46
vHCL	12 (5)	2 (2)	
Atypical HCL	3 (1)	2 (2)	
BRAF V600E mutated	117 (87)	39 (87)	0.14
Disease status after first treatment, n=224	**Males (n=169)%**	**Females (n=55)%**	
Treatment			
Cladribine	106 (63)	31 (56)	0.14
Pentostatin	29 (17)	9 (16)	
Cladribine+Rituximab	20 (12)	10 (18)	
Vemurafenib	4 (2)	1 (2)	
Others	10 (6)	4 (8)	
RR			
CR/CRu/HR	139 (82)	46 (84)	0.99
PR/PRu/pHR	26 (15)	8 (15)	
SD	4 (2)	1 (2)	

7578 **Poster Session**

Phase I study of the anti-BTLA antibody icatolimab as a single agent or in combination with toripalimab in relapsed/refractory lymphomas.

First Author: Jun Ma, Department of Hematology & Oncology, Harbin Institute of Hematology & Oncology, Harbin, China

Background: The B- and T-lymphocyte attenuator (BTLA) is an inhibitory receptor expressed on B, T and NK cells. Using PBMC derived from melanoma patients, co-blockade of the BTLA and PD-1 pathways improved antigen specific T cell response compared to either blockade alone. Icatolimab (JS004 or TAB004) is a humanized IgG4 monoclonal antibody with a hinge mutation (S228P) that binds BTLA and blocks its interaction with its ligand HVEM. In this first-in-human study, we report the preliminary safety and anti-tumor activity of icatolimab as a single agent or in combination with toripalimab (anti-PD-1) in patients with relapsed /refractory (R/R) lymphoma. **Methods:** Eligible patients with R/R lymphoma were enrolled in this open-label, multicenter study (NCT04477772). Icatolimab was administered as a monotherapy at escalating doses of 1, 3 and 10 mg/kg intravenously Q3W and followed by 3 mg/kg and 200 mg monotherapy dose expansion until disease progression or intolerable toxicity. During combination dose escalation, patients received ascending doses of icatolimab (100mg and 200mg) plus toripalimab (240mg). Dose-limiting toxicity (DLT) was evaluated by a safety monitoring committee. Study objectives included safety, pharmacokinetics, and efficacy. **Results:** A total of 31 patients were enrolled, including 9 in the monotherapy dose escalation, 16 in the monotherapy dose expansion and 6 in the combination dose escalation. The lymphoma subtypes included 15 Hodgkin's lymphoma and 16 non-Hodgkin's lymphoma. The median age was 40 (range 21-70) years with 20 (64.5%) male patients. The median prior line of therapy was 4 with 19 (61.3%) received prior anti-PD-1/L1 therapy. By the cutoff date of January 31 2022, the median follow-up was 22.7 weeks. No DLT was observed in either monotherapy or combination dose escalation. Twenty-nine (93.5%) patients experienced treatment emergent adverse event (TEAE), with 6 (19.4%) experienced grade 3 or above TEAEs. The most common TEAEs were anemia (29.0%) and fever (22.6%). Four treatment-related adverse events led to discontinuation of the study drug. 10 (40.0%) and 6 (100%) patients experienced immune related AE in the monotherapy and combination subgroups respectively, but all were grade 1 or 2. Among 22 evaluable patients receiving monotherapy, 1 PR (follicular lymphoma) and 7 SD were observed per Lugano criteria. By the cutoff date, among 5 evaluable patients receiving the combination (all progressed upon prior anti-PD-1 therapy), 2 PR (ORR 40%) and 1 SD were observed. BTLA receptor was fully occupied in all doses evaluated. The mean half-life of icatolimab was 13.3 days. Biomarker analysis indicated HVEM positivity was associated with favorable response. **Conclusions:** Icatolimab alone or in combination with toripalimab were well tolerated in all doses evaluated and showed preliminary clinical efficacy in patients with R/R lymphoma. Clinical trial information: NCT04477772. Research Sponsor: Shanghai Junshi Biosciences Co., LTD.

TPS7579 **Poster Session**

KITE-363: A phase 1 study of an autologous anti-CD19/CD20 chimeric antigen receptor (CAR) T-cell therapy in patients with relapsed/refractory (R/R) B-cell lymphoma (BCL). *First Author: Loretta J. Nastoupil, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: One mechanism by which B-cell tumors can resist the effects of CD19-targeted CAR T-cell therapy is through CD19 antigen escape (Neelapu et al. ASH 2019). Recent analyses in large B-cell lymphoma (LBCL) demonstrated that approximately one-third to two-thirds of relapses after infusion of CAR T-cell therapy were CD19 negative (Plaks et al. *Blood.* 2021; Spiegel, Dahiya et al. *Blood.* 2021; Spiegel et al. *Nat Med.* 2021). KITE-363 is an autologous CAR T cell transduced with a bicistronic vector with resultant expression of a CD19 CAR with a CD28 costimulatory domain and a CD20 CAR with a 41BB costimulatory domain. In preclinical studies, KITE-363 recognized and eliminated tumor cells expressing CD19 and/or CD20. KITE-363 CAR T-cell therapy has the potential to rescue CD19-negative relapsing patients with BCL as well as prevent CD19 antigen escape by minimizing selective pressure through upfront therapeutic dual targeting. This Phase 1, first-in-human, open-label, multicenter study (NCT04989803) will evaluate the safety and preliminary efficacy of KITE-363 in patients with R/R BCL. **Methods:** The Phase 1 design includes a 3+3 dose-escalation portion (1A), with 5 planned CAR T-cell levels, and a dose expansion portion (1B). Patients may receive optional corticosteroid bridging therapy following leukapheresis. Patients will then receive conditioning chemotherapy (cyclophosphamide and fludarabine) on Day –5 to Day –3 followed by KITE-363 infusion on Day 0. The primary endpoint for Phase 1A is the incidence of adverse events defined as dose-limiting toxicities. The primary endpoint for Phase 1B is investigator-assessed objective response rate per Lugano criteria (Cheson et al. *J Clin Oncol.* 2014). Secondary endpoints include complete response rate, time to next treatment, duration of response, progression-free survival, overall survival, safety, and levels of CAR T cells in blood and cytokines in serum. Eligible adult patients have histologically confirmed BCL, including LBCL, indolent non-Hodgkin lymphoma, nodular lymphocyte-predominant Hodgkin lymphoma (HL), and BCL, unclassifiable (with features intermediate between diffuse LBCL and classical HL), that is R/R after ≥2 lines of therapy (patients with LBCL may have primary refractory disease). Other key inclusion criteria are adequate bone marrow and organ function and ECOG performance status 0–1. Key exclusion criteria are central nervous system (CNS) involvement from lymphoma, active infection including hepatitis B and C, and clinically significant CNS disorder. This study is currently open and accruing patients. Clinical trial information: NCT04989803. Research Sponsor: Kite, a Gilead Company.

TPS7580 **Poster Session**

CRC-403: A phase 1/2 study of bbT369, a dual targeting CAR T-cell drug product with a gene edit, in relapsed and/or refractory B-cell non-Hodgkin lymphoma (NHL). *First Author: Frederick L. Locke, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

Background: Although CD19 directed CAR T cell therapies have improved outcomes for non-Hodgkin's lymphoma (NHL) patients, only about 30-40% of 3L+ patients obtain long term remission after this treatment (Neelapu et al. 2017; Schuster et al. 2019). bbT369, a next generation, dual targeted (CD79a/CD20), gene edited (CBLB gene knock out) autologous CAR T cell therapy was devised to overcome hypothesized mechanisms of CD19 CAR T cell treatment failure including loss/downregulation of target antigen, loss of co-stimulation pathways on tumor cells, exhaustion of CAR T cells, and CAR T cell dysfunction due to an immunosuppressive microenvironment (Shah and Fry 2019). bbT369 uses an OR gated design to limit antigen escape and contains split costimulatory domains (CD28 and 41BB) to enhance T cell activation. **Methods:** CRC-403 (NCT05169489) is a non-randomized, open label, multi-site phase 1/2 study enrolling relapsed and/or refractory B cell non-Hodgkin's lymphoma (NHL), including diffuse large B cell lymphoma (DLBCL), high-grade B cell lymphoma (HGBCL), primary mediastinal (thymic) large B cell lymphoma (PMBCL), follicular lymphoma (FL) 3b, and DLBCL transformed from FL (tFL). Patients must have relapsed after ASCT or at least 2 prior lines of therapy. Patients with tFL must be relapsed after receipt of ASCT or at least 2 prior therapies after documentation of transformation. Patients with previous exposure to non-investigational CD19 directed CAR T cell therapy who did not experience disease progression within 6 weeks of initial CAR T cell infusion are eligible for enrollment. Approximately 50 patients will be enrolled in the phase 1 portion. The primary endpoints of the phase 1 portion are determination of the MTD, determination of recommended phase 2 dose (RP2D) and safety. Secondary endpoints include overall response rate, complete response rate, time to response and time to next anti-lymphoma treatment. Exploratory endpoints include DOR, PFS, OS, CAR+ T cell expansion and correlations between clinical response and T cell phenotype or antigen expression on tumor cells. The starting dose of bbT369 will be $50x10^6$ CAR+ T cells and a BOIN design will be used for dose escalation/de-escalation decisions during the study. Upon establishment of the RP2D, the phase 2 portion will begin enrollment. Clinical trial information: NCT05169489. Research Sponsor: 2seventy bio.

TPS7581 **Poster Session**

A first-in-human phase 1 trial of NX-2127, a first-in-class oral BTK degrader with IMiD-like activity, in patients with relapsed and refractory B-cell malignancies. *First Author: Anthony Mato, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Bruton's tyrosine kinase inhibitors (BTKi) have received regulatory approvals and are standard of care for patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), and WaldenstrÖm macroglobulinemia (WM). However, BTKi-resistant disease remains a clinical challenge with limited options for subsequent therapy. Immunomodulatory drugs (IMiDs, e.g., lenalidomide) are approved as monotherapy for follicular lymphoma (FL), MZL, and MCL, in combination with other therapies for diffuse large B-cell lymphoma (DLBCL) and have shown synergy with BTK-targeted therapy. Dual activity of BTK protein degradation with IMiD-like activity offers a unique approach to overcome known resistance to BTKi. NX-2127 is an oral small molecule that induces BTK degradation via recruitment of cereblon, an adaptor protein of the E3 ubiquitin ligase complex. NX-2127 has shown preclinical activity similar to IMiDs by catalyzing the ubiquitination of Ikaros (IKZF1) and Aiolos (IKZF3), ultimately leading to increased T-cell activation. NX-2127 was shown to degrade both wild-type (WT) and C481-mutated (ibrutinib-resistant) BTK protein in vitro. Robust BTK degradation was also shown in non-human primate studies. Further, NX-2127 demonstrates potent tumor growth inhibition in BTK-dependent mouse xenograft tumor models expressing either WT or ibrutinib-resistant C481S BTK-mutant protein. This dual activity of BTK degradation and IMiD-like activity offers a promising treatment for patients who have failed prior therapy. **Methods:** NX-2127-001 is a first-in-human, dose escalation (Phase 1a) and cohort expansion (Phase 1b) study designed to evaluate the safety, tolerability, and preliminary efficacy of NX-2127 in adult patients with relapsed/refractory B-cell malignancies with once daily oral dosing. Dose escalation will proceed using a modified Fibonacci design with 1 patient per cohort, proceeding to a standard 3 + 3 design based on protocol specified criteria. There will be up to 5 expansion cohorts in Phase 1b enrolling patients with CLL/SLL, DLBCL, FL, MCL, MZL, and WM. Key eligibility criteria include >2 two prior lines of therapy (>1 prior for WM); measurable disease; and an Eastern Cooperative Oncology Group performance status of 0 or 1. Approximately 130 patients (30 in Phase 1a, 100 in Phase 1b) will be enrolled and treated until disease progression or unacceptable toxicity. The primary objectives are to evaluate safety and tolerability and to determine the maximum tolerated dose (Phase 1a), and to evaluate the early clinical activity of NX-2127 in expansion cohorts (Phase 1b). The Phase 1a part of this study is currently enrolling in the United States. Clinical trial information: NCT04830137. Research Sponsor: Nurix Therapeutics.

TPS7582 **Poster Session**

A first-in-human phase 1 study of oral LOXO-338, a selective BCL2 inhibitor, in patients with advanced hematologic malignancies (trial in progress). *First Author: Lindsey Elizabeth Roeker, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: B-cell lymphoma 2 (BCL2) is a key regulator of apoptosis and provides protection from cell death in many hematologic malignancies. LOXO-338 is an orally bioavailable small molecule inhibitor of BCL2, developed to achieve selectivity over BCL-xL and thus avoid dose-limiting thrombocytopenia associated with BCL-xL inhibition. In preclinical studies, LOXO-338 showed a favorable pharmacological profile, selectively inhibited BCL2, and was well-tolerated *in vivo*. LOXO-338 also demonstrated dose-dependent tumor growth inhibition in various murine xenograft models and showed improved efficacy in combination with pirtobrutinib, a highly selective, non-covalent (reversible) BTK inhibitor (Brandhuber et al. *Cancer Res* 2021 81 (13 Suppl) 1258). **Methods:** LOXO-BCL-20001 is a global open-label, first-in-human phase 1 study of oral LOXO-338 in patients (pts) with advanced hematologic malignancies who have received prior therapy. The study will be conducted in 2 parts. Part 1 will evaluate LOXO-338 as monotherapy and will explore different dosing strategies. Part 2 will evaluate LOXO-338 in combination with pirtobrutinib. Part 1 dose escalation will follow an i3+3 design. Each cycle will be 28 days. Eligible pts include those with CLL/SLL, mantle cell lymphoma, and Waldenström macroglobulinemia (WM) who received standard therapy. Pts with other B-cell non-Hodgkin lymphomas (NHL) who received standard therapy, are not candidates for available therapy, or have no options with proven benefit are also eligible. Pts with active or suspected Richter transformation, transformed low grade lymphoma, Burkitt or Burkitt-like lymphoma, and multiple myeloma are also eligible. Pts with AL amyloidosis are eligible in monotherapy dose expansion; all other pts are eligible in both monotherapy and combination dose expansion. Pts must not have progressed while receiving prior BCL2 inhibitor; those with WM or AL amyloidosis must not have received a prior BCL2 inhibitor. Key exclusion criteria include history of CNS involvement, stem cell transplant or CAR-T therapy <60 days, concurrent anticancer therapy, and clinically significant cardiovascular disease. Primary objective is to determine the recommended phase 2 dose of oral LOXO-338 in pts who were previously treated for CLL/SLL and other B-cell NHL, administered alone or in combination with pirtobrutinib. Determining anti-tumor activity in pts with WM and AL amyloidosis is an additional primary objective of part 1 monotherapy. Secondary objectives include determining the safety profile, PK, and preliminary efficacy of LOXO-338 administered alone and in combination with pirtobrutinib. Antitumor activity will be evaluated based on overall response rate (ORR), progression-free survival (PFS), time to progression (TTP) and duration of response (DOR) according to disease-specific response criteria. Clinical trial information: NCT05024045. Research Sponsor: Loxo Oncology at Lilly.

TPS7583 **Poster Session**

inMIND: A phase 3 study of tafasitamab plus lenalidomide and rituximab versus placebo plus lenalidomide and rituximab for relapsed/refractory follicular or marginal zone lymphoma. *First Author: Laurie Helen Sehn, BC Cancer Centre for Lymphoid Cancer and University of British Columbia, Vancouver, BC, Canada*

Background: Most patients with the indolent non-Hodgkin lymphoma (NHL) subtypes follicular (FL) or marginal zone (MZL) respond to first-line treatment but relapse is common, and there is no single standard treatment for patients (pts) with relapsed/refractory (R/R) FL or MZL. Tafasitamab (TAFA) is an Fc-engineered humanized monoclonal antibody (mAb) against CD19 which is broadly expressed in FL and MZL, and regulates B-cell proliferation via B-cell receptor signaling. In preclinical studies, TAFA has shown activity against NHL cell lines in combination with rituximab (anti-CD20 mAb) and lenalidomide (LEN). Monotherapy with TAFA has shown promising clinical activity in a phase 2a study in pts with R/R NHL (NCT01685008), with an ORR of 29% (n/N = 10/34) in pts with FL and 33% (n/N = 3/9) in pts with MZL. In an ongoing phase 2, single-arm study (L-MIND, NCT02399085), TAFA + LEN followed by TAFA alone demonstrated an ORR of 57.5% (n/N = 46/80) in pts with R/R diffuse large B-cell lymphoma (FDA approved indication). These preclinical and clinical observations from phase 2 trials suggest a potential clinical benefit of TAFA + LEN and rituximab for pts with R/R FL or MZL. **Methods:** This phase 3 double-blind, placebo-controlled, randomized study is designed to investigate whether TAFA + LEN and rituximab provides improved clinical benefit compared with LEN and rituximab in pts with R/R FL or R/R MZL. Pts will be randomized 1:1 to receive TAFA (12 mg/kg IV on days 1, 8, 15, and 22 of a 28-day cycle [cycles 1–3], then days 1 and 15 [cycles 4–12]) + LEN (20 mg PO QD, days 1–21/cycle for 12 cycles) and rituximab (375 mg/m^2 IV on days 1, 8, 15, and 22 of cycle 1, then day 1 of cycles 2–5), or placebo (0.9% saline solution IV) + LEN and rituximab. Stratified randomization will be performed separately for pts with R/R FL and R/R MZL. The primary study endpoint is PFS (investigator assessed [INV] by Lugano 2014 criteria) for pts with FL. Key secondary endpoints are PFS (INV) in overall population (FL and MZL), PET-CR rate (INV) at end of treatment (90 days after last treatment) and OS in pts with FL. Inclusion criteria include age ≥18 y, histologically confirmed FL (grade 1, 2, or 3a) or MZL (nodal, splenic, or extranodal), documented R/R disease, ≥1 prior systemic anti-CD20 therapy (including pts with anti-CD20 refractory disease), ECOG PS ≤2, adequate systemic organ function, and high tumor burden (per GELF criteria). Exclusion criteria include prior rituximab + LEN treatment, history of radiotherapy for other diseases (≥25% of bone marrow), nonhematologic malignancy, congestive heart failure (LVEF < 50%), active systemic infection, known CNS lymphoma, or severe immunocompromised state. inMIND (NCT04680052, EudraCT2020-004407-13) is currently enrolling pts; planned enrollment is 528 pts with R/R FL and 60–90 pts with R/R MZL across North America, Europe, and Asia Pacific. Clinical trial information: NCT04680052 / EudraCT2020-004407-13. Research Sponsor: Incyte Corporation, Wilmington, DE, USA.

TPS7584 **Poster Session**

Sequential pembrolizumab (pembro) and chemotherapy (chemo) in newly diagnosed, early unfavorable, or advanced-stage classical Hodgkin lymphoma (cHL): The phase 2 KEYNOTE-C11 study. *First Author: Jane N. Winter, Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL*

Background: PD-1 and PD-L1 inhibitors are standard of care therapies for relapsed/refractory cHL. A recent study of the anti–PD-1 antibody pembro followed by conventional chemotherapy has shown clinical benefit in the first-line setting for cHL (Allen PB et al. *Blood* 2020;137[10]:1318-1326). KEYNOTE-C11 (NCT05008224) is an open-label phase 2 study that is evaluating safety and efficacy of sequential pembro monotherapy and chemo followed by pembro consolidation in newly diagnosed early unfavorable or advanced-stage cHL. **Methods:** Eligible patients (pts) are adults with newly diagnosed and histologically confirmed early unfavorable (Ann Arbor stage I/II plus ≥1 NCCN unfavorable risk factor) or advanced-stage (Ann Arbor stage III/IV) cHL. Pts must have measurable disease per Lugano 2014 criteria and have not received prior radiation therapy, chemotherapy, immunotherapy, or other systemic therapy for cHL. All pts will receive pembro 200 mg IV Q3W for 3 cycles followed by PET to determine response. After pembro induction, all pts will receive 2 cycles of doxorubicin, vinblastine and dacarbazine (AVD day 1 and day 15 Q4W) and undergo another PET assessment (PET3). Pts with negative findings on PET3 (≤3 on the FDG-PET 5-point scale) will receive 2-4 additional cycles of AVD, depending on stage and bulk of disease; those with nonbulky early unfavorable disease will receive 2 cycles, and all others will receive 4 cycles. Pts with positive findings on PET 3 (≥4 on the FDG-PET 5-point scale) and aged < 60 years will transition to 2-4 cycles of escalated therapy with bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone, depending on bulk and stage of disease; those with nonbulky early unfavorable disease will receive 2 cycles, and all others will receive 4 cycles. Pts aged ≥60 years will continue to receive AVD for 4 cycles. All pts will then receive 4 cycles of pembro 400 mg Q6W as consolidation therapy. Treatment will continue until disease progression, unacceptable toxicity, investigator's decision, or maximum duration of treatment is reached. Adverse events will be graded per CTCAE version 5.0. Primary end point is complete response (CR) by BICR per Lugano 2014 response criteria. Secondary end points include CR by investigator review per Lugano 2014 response criteria, rate of PET negativity by BICR according to the FDG-PET 5-point scale, duration of CR by BICR per Lugano 2014 response criteria, and safety and tolerability. Exploratory end points include 2-year modified PFS by BICR per Lugano 2014 response criteria and OS. Efficacy and safety will be evaluated in all pts who received ≥1 dose of pembrolizumab. CR rate with 95% CI will be reported per the Clopper-Pearson exact binomial method. Duration of CR, PFS, and OS will be estimated using the Kaplan-Meier method. Planned enrolment is 140 pts. Clinical trial information: NCT05008224. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

TPS7585 **Poster Session**

KEYNOTE B68: Open-label phase 2 study of the efficacy and safety of pembrolizumab administered every six weeks in patients with relapsed or refractory classical Hodgkin lymphoma or primary mediastinal B-cell lymphoma. *First Author: Philippe Armand, Dana-Farber Cancer Institute, Boston, MA*

Background: Classical Hodgkin lymphoma (cHL) and primary mediastinal B-cell lymphoma (PMBCL) frequently harbor amplifications at 9p24.1, leading to overexpression of PD-L1 and PD-L2, suggesting a genetically driven vulnerability to programmed death 1 (PD-1) blockade. The PD-1 inhibitor pembrolizumab, dosed at 200 mg every 3 weeks (Q3W), demonstrated strong antitumor activity and acceptable safety that led to approvals for adult and pediatric patients with relapsed or refractory (R/R) cHL and R/R PMBCL. Efficacy, safety, and pharmacokinetic (PK) results from studies in solid tumors have since led to accelerated approval for the pembrolizumab 400 mg Q6W regimen for all indications in adults; however, further efficacy and safety data are needed for hematologic indications. The open-label, single-arm, multisite, global, phase 2 KEYNOTE-B68 study (NCT04875195) evaluates the safety, efficacy, and PK profile of pembrolizumab 400 mg Q6W in patients with R/R cHL or PMBCL. **Methods:** Patients must have histologically confirmed R/R cHL (cohort 1) or R/R PMBCL (cohort 2) per WHO classification and radiographically measurable disease per the Lugano 2014 classification criteria and must not have previously received treatment with anti–PD-1 therapy. Eligible patients must have failed to respond to or relapsed after receiving an autologous stem cell transplant (ASCT) or must be ineligible for ASCT and must have failed to respond or relapsed after ≥1 (cHL) or ≥2 (PMBCL) prior lines of therapy; patients with PMBCL must have received ≥1 line of therapy containing rituximab. Approximately 60 patients will be enrolled. They will receive pembrolizumab 400 mg IV Q6W for up to 18 cycles. Disease assessments will occur Q12W by investigator per the Lugano 2014 response criteria. Local radiographic assessments will be collected by computed tomography Q12W and by positron emission tomography at weeks 12 and 24 and to confirm complete response. Adverse events will be monitored and assessed by investigators throughout the study, and their severity will be graded per NCI Common Terminology Criteria for Adverse Events, version 5.0 guidelines. Patients who receive an allogeneic SCT within 2 years of the last dose of study treatment will be monitored for 18 months after SCT for events of clinical interest. The primary end point (assessed per cohort) is objective response rate by investigator per the Lugano 2014 classification criteria. Secondary end points (assessed per cohort) include duration of response by investigator assessment, characterization of the PK profile and immunogenicity for pembrolizumab 400 mg Q6W, and safety. Exploratory end points assessed per cohort include overall survival, progression-free survival per the Lugano 2014 criteria, and molecular biomarker analyses. Clinical trial information: NCT04875195. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

TPS7586 **Poster Session**

A novel microbial-derived peptide therapeutic vaccine (EO2463) as monotherapy and in combination with lenalidomide and rituximab, for treatment of patients with indolent non-Hodgkin lymphoma (SIDNEY). *First Author: Pier Luigi Zinzani, Institute of Hematology "L. e A. Seràgnoli", University of Bologna, Bologna, Italy*

Background: EO2463 is a therapeutic vaccine designed to activate existing commensal bacteria-specific memory T cells that cross-react with B cell markers in order to drive anti-tumor immune activity against B-cell malignancies. The four microbial-derived, synthetically produced peptides contained in EO2463 (OMP72, OMP64, OMP65, and OMP66), correspond to cytotoxic CD8 T cell HLA-A2 restricted epitopes, and exhibit molecular mimicry with the B cell markers CD20, CD22, CD37, and CD268 (BAFF-receptor), respectively. In pre-clinical models, these peptides can generate strong immune responses and specifically stimulate cross-reactive cytotoxic CD8 T cells to recognize the chosen B cell targets. EO2463 also contains a CD4 helper peptide referred to as universal cancer peptide 2, derived from the human telomerase reverse transcriptase catalytic subunit. The present study is a first-in-human clinical trial of this microbiome-derived peptide therapeutic cancer vaccine approach in patients with follicular lymphoma (FL) and marginal zone lymphoma (MZL). **Methods:** This four-cohort phase 1/2 trial will investigate EO2463 monotherapy, and combinations of EO2463/lenalidomide (EL), EO2463/rituximab (ER), and EO2463/lenalidomide/rituximab (ER^2), for treatment of patients with FL and MZL. Cohort 1 is a safety lead-in dose-finding in patients with relapsed/refractory (RR) disease, with a 3-by-3 design to establish the recommended phase 2 dose (RP2D) for EO2463 monotherapy and to confirm the safety of the RP2D for combination schedules of EL, and ER^2. After the recommended EO2463 monotherapy dose is established, cohorts 2, 3, and 4 will open to accrual. Cohort 2 will investigate EO2463 monotherapy in patients with newly diagnosed FL/MZL who are not in need of treatment; cohort 3 will investigate EO2463 monotherapy, followed by ER in patients with limited tumor burden who need treatment, and cohort 4 will further investigate EL, followed by ER^2 in the RR setting. EO2463 will be administered SC 4 times at 2-week intervals, followed by continued booster administrations every 4 weeks for 9 (Cohorts 2 and 3) or 12 (Cohorts 1 and 4) months. Inclusion/exclusion criteria, and the design and schedule of the intense immune and safety monitoring will be presented. The safety lead-in dose-finding is currently ongoing, and no safety concerns have been observed thus far. Clinical trial information: NCT04669171. Research Sponsor: Enterome.

TPS7587 **Poster Session**

Frontline treatment of follicular lymphoma with atezolizumab and obinutuzumab, with and without radiotherapy (The FLUORO study). *First Author: Eliza Anne Hawkes, Austin Health, Heidelberg, Australia*

Background: Follicular lymphoma (FL) is the commonest indolent lymphoma, comprising 20% of non-Hodgkin Lymphoma, with approximately 80% of patients (pts) requiring therapy. At present, advanced stage is incurable; most pts require >1 treatment. Overall response rates (ORR) to standard chemoimmunotherapy (bendamustine or CHOP with rituximab or obinutuzumab) approximate 85% with considerable toxicity (grade 3-5 in 69-75%) (Hiddemann 2018). With the FL population predominantly >65 years, 10-year median survival and need for further therapy, efficacious treatments with low toxicity are desirable. PD1/PDL1 axis inhibitors are active in FL. A phase I study of obinutuzumab (O) + atezolizumab (A) induced 57% ORR in pts with rituximab-refractory FL (Palomba 2017). Our phase II '1st FLOR' study, combining nivolumab + rituximab in treatment naïve FL yielded 92% ORR, (54% Complete Response, CR). Toxicity profiles compared favourably with conventional chemotherapy: 41% grade 3-5 events (Hawkes 2021). FL is sensitive to low dose radiotherapy (RT), with abscopal effects reported, and potential to improve treatment efficacy with minimal additional toxicity when combined with PD1/PDL1 inhibitors (Sharabi 2015). This investigator initiated, multicentre single-arm phase II PET-adapted trial aims to assess the response of O + A +/- RT for treatment-naïve FL, reducing treatment-related toxicity using a chemotherapy-free, multi-modality, synergistic regimen. **Methods:** Eligible pts are >18 years, ECOG 0-2 with untreated, biopsy proven, grade 1-3A stage II-IV FL. Exclusions are significant compressive symptoms, autoimmune disease, pneumonitis and treatment urgency. All pts receive 6 cycles (q21 days) of O 1000mg + A 1200mg (plus O given on days 8 & 15 of cycle 1). Interim PET-CT is performed post cycle 2. Pts with less than CR will undergo RT (4Gy) to residual disease after cycle 3. At end of induction, responding patients will receive maintenance O (up to 12 cycles, 1000mg Q8W). Pts with significant progression will be taken off study. Total follow-up is 2 years post treatment. Primary endpoint is CR rate following 6 x O&A +/- RT. Secondary endpoints include ORR, PFS, OS and adverse events. PET centres are ARTnet accredited with central analysis. An extensive exploratory biomarker substudy is planned. Sample size is 46 according to a Simon's 2-stage design. If ≥5 positive responses (CR +/- PR) without prohibitive toxicity are seen in the first 15 pts, 31 further pts will be recruited**.**The trial has currently enrolled 7 pts from 4 Australian sites. Clinical trial information: NCT04962126. Research Sponsor: Roche Australia, Victorian Comprehensive Cancer Center.

TPS7588 **Poster Session**

CELESTIMO: A phase III trial evaluating the efficacy and safety of mosunetuzumab plus lenalidomide versus rituximab plus lenalidomide in patients with relapsed or refractory follicular lymphoma who have received ≥ 1 line of systemic therapy. *First Author: Loretta J. Nastoupil, Emory University, Atlanta, GA*

Background: Despite significant progress with first-line immunochemotherapy, most patients with follicular lymphoma (FL) will eventually relapse with increasing refractoriness and decreasing duration of response to subsequent therapy lines (Rivas-Delgado et al. 2019). Mosunetuzumab (M) is a CD20xCD3 bispecific antibody that engages and redirects T-cells to eliminate malignant B cells (Sun et al. 2015). In an ongoing, pivotal Phase I/II trial of M monotherapy, patients with relapsed/refractory (R/R) FL who have received ≥2 prior treatment lines achieve deep and durable responses (NCT02500407; Budde et al. ASH 2021). Preliminary data from a Phase Ib study have suggested favorable safety and promising activity of M in combination with lenalidomide (Len), a potent immunomodulatory agent that has shown additive/synergistic activity with an anti-CD20 antibody in R/R indolent lymphoma (Leonard et al. 2019), in patients with R/R FL who have received ≥1 prior therapy (NCT04246086; Morschhauser et al. ASH 2021). The chemotherapy-free M-Len combination may represent a promising outpatient therapy option for future management of patients with R/R FL. The randomized, multicenter Phase III study has been initiated. **Methods:** CELESTIMO (NCT04712097) is a randomized, multicenter, open-label Phase III study evaluating the efficacy and safety of M-Len versus rituximab plus Len (R-Len) in patients with previously treated R/R FL. Patients must have histologically documented CD20+ FL (Grades 1–3a) requiring systemic therapy and have received ≥1 prior line of systemic therapy. Patients are randomized (1:1) to receive M-Len (M intravenously [IV] on Days [D] 1, 8 and 15 of Cycle [C] 1 [21-day cycle] and D1 of C2–12 [28-day cycles], plus Len orally [PO] on D1–21 of C2–12) or R-Len (R IV on D1, 8, 15 and 22 of C1 then on D1 of C3, 5, 7, 9, and 11, plus Len PO on D1–21 of C1–12 [all 28-day cycles]), and stratified by disease progression within 24 months of initial treatment (yes/no), number of prior lines of therapy (1 versus ≥2), and refractoriness to anti-CD20 therapy (refractory/non-refractory). The primary endpoint is progression-free survival (PFS) assessed by independent review committee; secondary endpoints include investigator-assessed PFS, complete and objective response, overall survival, and safety. Biomarkers predictive of response to M-Len and R-Len will also be investigated as exploratory endpoints. The study started recruitment in 2021 and plans to enroll ~400 patients from approximately 16 countries and 150 sites globally. Clinical trial information: NCT04712097. Research Sponsor: Sponsored by F. Hoffmann-La Roche Ltd. Third-party medical writing assistance was provided by Helen Cathro, PhD, on behalf of Ashfield MedComms, an Ashfield Health company, and was funded by F. Hoffmann-La Roche Ltd.

TPS7589 **Poster Session**

Brentuximab vedotin and nivolumab alone and then combined with rituximab, cyclophosphamide, doxorubicin, and prednisone for frontline therapy of patients with primary mediastinal large B-cell lymphoma. *First Author: Raphael Eric Steiner, The University of Texas MD Anderson Cancer Center, Department of Lymphoma/Myeloma, Houston, TX*

Background: Primary mediastinal large B-cell lymphoma (PMBL) is a rare and distinct subtype of diffuse large B-cell lymphoma and affects primarily young adults. PMBL has a unique genomic profile that has similarities to classic Hodgkin lymphoma with CD30 expression and genomic alterations in the programmed T-cell death-ligand 1 (PD-L1) locus 9p24.1. The trial CheckMate-436, including relapsed/refractory PMBL patients treated with nivolumab (antibody that binds to immune checkpoint PD-1) and brentuximab vedotin ((BV) anti-CD30 antibody-drug conjugate) showed an overall response rate (ORR) of 73% and complete response rate (CRR) of 43% (Zinzani et al. JCO 2019). Although most PMBL patients can be cured with frontline chemoimmunotherapy with or without radiotherapy, the outcome of patients having rr-PMBL treated with intensive regimens is generally unfavorable. The discovery of new frontline regimens to decrease chemoresistance and toxicities represents an urgent unmet clinical need for PMBL patients. **Methods:** We are conducting a phase II, open-label, single-center clinical trial combining BV-Nivolumab alone and then combined with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP) for patients with previously untreated PMBL Patients 18 years or older with previously untreated PMBL, stage I to stage IV disease are eligible. However, patients with an urgent need for cytoreductive treatment will be excluded. Patients will receive BV 1.8 mg/Kg IV and Nivolumab 240 mg flat dose IV day 1 for cycles 1 and 2, in a 21-day cycle. During cycles 3 and 4, R-CHP will be added to BV-Nivolumab. Patients who have achieved complete response (CR) at PET/CT before cycle 5 will receive 2 more cycles of BV-Nivolumab+R-CHP (cycle 5 and 6) and BV-Nivolumab only for cycles 7 and 8. In case of CR on PET/CT after cycle 8, therapy will be considered completed. Patients in PR on PET/CT before cycle 5 will receive 4 more cycles of BV-Nivolumab+R-CHP (cycles 5-8). The primary endpoint is CRR at the end of therapy (EOT). The maximum sample size for the PMBL cohort is 40 patients, with a target CRR at EOT of 70%. The null hypothesis is that the true CRR at EOT is 50%, and the alternative hypothesis is that the true CRR at EOT is 70%. The Simon's optimal two-stage design controls the one-sided type I error rate at 0.06 and yields the power of 0.8. The secondary endpoints will include the response rate of BV-Nivolumab+R-CHP at the end of the immune lead-in, landmark survival outcomes, the safety of the combination, and patient-reported outcome. Exploratory analyses include assessing molecular response by sequencing cell-free DNA and Multiplexed ion beam imaging to analyze the tumor microenvironment. The trial is actively accruing at MD Anderson Cancer Center, and 2 out of 40 patients have been enrolled. Clinical trial information: NCT04745949. Research Sponsor: Seagen, Pharmaceutical/Biotech Company.

TPS7590 **Poster Session**

frontMIND: A phase III, randomized, double-blind study of tafasitamab + lenalidomide + R-CHOP versus R-CHOP alone for newly diagnosed high-intermediate and high-risk diffuse large B-cell lymphoma. *First Author: Umberto Vitolo, Candiolo Cancer Institute, Torino, Italy*

Background: Up to 40% of patients relapse or are refractory (R/R) to R-CHOP, the current standard of care for diffuse large B-cell lymphoma (DLBCL), indicating an unmet need, particularly in patients with high-intermediate and high-risk disease (IPI 3–5). POLARIX (NCT03274492) evaluated a modified regimen substituting polatuzumab vedotin for vincristine (pola-R-CHP), demonstrating modest improvement in PFS with no OS benefit between treatment arms. The addition of lenalidomide (LEN) to R-CHOP improved both PFS and OS in the ECOG-ACRIN E1412 trial but not in the Phase III ROBUST study, in which a lower dose of LEN was used, despite a positive trend toward 2-year PFS in a subgroup analysis. The chemo-free immunotherapy tafasitamab + LEN has received accelerated approval in the United States (2020), and conditional marketing authorization in Europe and Canada (2021) in adult patients with R/R DLBCL ineligible for ASCT based on L-MIND (NCT02399085). The primary analysis of First-MIND (NCT04134936), a Phase Ib randomized safety study of R-CHOP + tafasitamab ± LEN in patients with previously untreated and newly diagnosed DLBCL, demonstrated that adding tafasitamab + LEN does not impair dosing and scheduling of R-CHOP, with toxicities similar to those expected with R-CHOP alone (ASH 2021; #3556). frontMIND (NCT04824092) will investigate the efficacy and safety of R-CHOP + tafasitamab + LEN vs R-CHOP alone in previously untreated patients with high-intermediate and high-risk DLBCL. **Methods:** frontMIND is a Phase III, multicenter, randomized, double-blind, placebo-controlled study. Approximately 880 patients are planned to be randomized at ~350 centers in North and South America, Europe, and Asia-Pacific. Eligible patients aged 18–80 years with previously untreated local biopsy-proven, CD20+ DLBCL with IPI score 3–5 (age-adjusted IPI 2–3 if ≤60 years), and ECOG PS 0–2 will be enrolled. Patients with transformed lymphoma (except double or triple hit lymphoma) are excluded. Patients will be randomized 1:1 to receive six 21-day (D) cycles of either R-CHOP + tafasitamab (12 mg/kg intravenously, D 1, 8, and 15) + LEN (25 mg orally, D1–10) or R-CHOP + tafasitamab and LEN placebos. Patients will be followed for up to 5 years after the end of treatment. The primary endpoint is investigator-assessed PFS. Secondary endpoints include investigator-assessed event-free survival, OS, safety, and tafasitamab serum concentration (trough and C_{max} levels). Sensitivity and specificity of minimal residual disease for early detection of disease progression is an exploratory endpoint; further MRD parameters may also be investigated. The study is funded by MorphoSys AG and conducted with the scientific support of members of the Fondazione Italiana Linfomi and the German Lymphoma Alliance. Clinical trial information: NCT04824092. Research Sponsor: MorphoSys AG.

TPS7591 **Poster Session**

Phase 3 randomized study of loncastuximab tesirine in combination with rituximab (Lonca-R) versus immunochemotherapy in patients with R/R DLBCL (LOTIS-5). *First Author: Mehdi Hamadani, BMT & Cellular Therapy Program, Medical College of Wisconsin, Milwaukee, WI*

Background: Patients (pts) with refractory or relapsed (R/R) diffuse large B-cell lymphoma (DLBCL) have poor outcomes with standard treatment. Loncastuximab tesirine (loncastuximab tesirine-lpyl; Lonca), an antibody-drug conjugate (ADC) comprising a humanized anti-CD19 monoclonal antibody conjugated to a pyrrolobenzodiazepine dimer toxin, is approved in R/R DLBCL based on data from the phase 2 LOTIS-2 trial (Caimi et al. *Lancet Oncol* 2021). Rituximab (R) is part of standard immunochemotherapy for DLBCL, both as frontline therapy and in subsequent treatments. Preclinical evidence suggests that the addition of rituximab to anti-CD19 ADC therapy may result in prolonged tumor control (Ryan et al. *Blood* 2017). LOTIS-5 aims to evaluate Lonca-R vs. standard immunochemotherapy of R + gemcitabine + oxaliplatin (R-GemOx) in pts with R/R DLBCL. **Methods:** This is a phase 3 randomized open-label, two-part, two-arm multicenter study of Lonca-R in pts with R/R DLBCL (NCT04384484). A review of safety data from the nonrandomized safety run-in (Part 1), comparing the safety of Lonca-R to previous Lonca safety data, was completed in January 2022. The trial is now continuing to the randomized phase (Part 2). In Part 2, approximately 330 pts will be randomized 1:1 to receive Lonca-R or R-GemOx. The primary objective of the study is to evaluate the efficacy of Lonca-R versus R-GemOx. The primary endpoint is progression-free survival by independent central review (ICR). Secondary endpoints include overall survival, overall response rate (by ICR using 2014 Lugano classification), complete response rate by ICR, duration of response by ICR, frequency and severity of adverse events, changes from baseline in safety laboratory and clinical variables, concentration and pharmacokinetic parameters of Lonca (conjugated and total antibody and unconjugated warhead), immunogenicity, and changes in patient-reported outcomes. The time to event endpoints will be analyzed based on the intent-to-treat population using a stratified log-rank test. The dosing regimen for Lonca-R: Lonca at 0.15 mg/kg + rituximab at 375 mg/m^2 every 3 weeks (Q3W) for 2 cycles and then Lonca at 0.075 mg/kg + rituximab at 375 mg/m^2 Q3W for up to 6 cycles. The dose regimen of R-GemOx: rituximab at 375 mg/m^2, gemcitabine at 1000 mg/m^2 Gem, and oxaliplatin at 100 mg/m^2 every 2 weeks for up to 8 cycles. Key inclusion criteria include age ≥18 years, pathologic diagnosis of DLBCL (including pts with DLBCL transformed from indolent lymphoma) or high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements, ≥1 line of prior systemic therapy, not being a candidate for stem cell transplantation, and measurable disease per the 2014 Lugano classification. The randomized part of LOTIS-5 commenced in January 2022, and recruitment is ongoing. Funding: ADC Therapeutics SA; medical writing: CiTRUS Health Group. Clinical trial information: NCT04384484. Research Sponsor: ADC Therapeutics.

TPS7592 **Poster Session**

Open-label, active-control, phase 2/3 study of zilovertamab vedotin plus standard of care in patients with relapsed or refractory diffuse large B-cell lymphoma. *First Author: Patrick Wayne Cobb, St. Vincent Healthcare Cancer Centers of Montana, Billings, MT*

Background: Consensus treatment guidelines are unavailable for patients with diffuse large B-cell lymphoma (DLBCL) whose disease progresses after first-line therapy. The receptor tyrosine kinase-like orphan receptor 1 (ROR1) is a transmembrane protein that is overexpressed in multiple cancers, including hematological malignancies. Zilovertamab vedotin (ZV; MK-2140, previously known as VLS-101), an antibody-drug conjugate comprising a humanized IgG1 monoclonal antibody, a proteolytically cleavable linker, and the antimicrotubule cytotoxic agent monomethyl auristatin E, targets ROR1 and has shown promising efficacy and tolerability in hematological malignancies, including DLBCL. This 2-part (part 1, dose confirmation; part 2, dose expansion), open-label, randomized, active-control, phase 2/3 study (NCT05139017) will assess safety and efficacy of ZV + standard of care in patients with relapsed/refractory (R/R) DLBCL. **Methods:** Eligible adult patients must have histologically confirmed DLBCL per WHO classification, ineligible for or have failed autologous stem cell transplantation and chimeric antigen receptor T cell therapy, R/R DLBCL after ≥1 line of prior therapy (cohort A) or ≥2 lines of prior therapy (cohort B), measurable disease per Lugano 2014 criteria, and Eastern Cooperative Oncology Group performance status ≤2. Approximately 420 patients will be enrolled in the study (cohort A, n = 230; cohort B, n = 190). In the part 1 dose confirmation phase, 30 patients from cohort A will receive ZV (at increasing doses: 1.5, 1.75, 2.0, 2.25, and 2.5 mg/kg; starting at 1.75 mg/kg) plus gemcitabine-oxaliplatin + rituximab (R-GemOx) to establish the recommended phase 2 dose using the mTPI design. A safety run-in phase of part 2 will include 30 patients from cohort B and will receive ZV + bendamustine and rituximab (BR). Approximately 360 patients will be included in the part 2 dose expansion phase (cohort A, n = 200; cohort B, n = 160). Patients from cohort A will be randomly assigned 1:1 to 6 cycles of either ZV + R-GemOx or R-GemOx. Patients from cohort B will be randomly assigned 1:1 to 6 cycles of either ZV + BR or BR. Disease response assessments by CT and PET scans will occur every 12 weeks until disease progression or study discontinuation. Adverse events (AEs) will be monitored throughout the study and graded per NCI CTCAE version 5.0. In part 1, the primary end point is safety, including DLTs, AEs, and discontinuation due to AEs. The primary end point for cohorts A and B in the dose expansion phase of part 2 will be progression-free survival by blinded independent central review per Lugano 2014 criteria. Key secondary end points in the dose expansion phase of part 2 for both cohorts include objective response rate (including complete response and partial response) and duration of response, both per Lugano 2014 criteria and overall survival. Clinical trial information: NCT05139017. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

TPS7593 **Poster Session**

Alliance A059102: A randomized phase II U.S. intergroup study of CHO(E)P versus CC-486-CHO(E)P versus duvelisib-CHO(E)P in previously untreated, CD30-negative, peripheral T-cell lymphomas. *First Author: Neha Mehta-Shah, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: While PTCL is treated for curative intent, 5-year (yr) overall survival (OS) remains 20-25% with CHOP based therapy. For pts <60 yrs old, the addition of etoposide to CHOP has been associated with improved outcomes. Brentuximab vedotin in combination with chemotherapy demonstrated an OS benefit in PTCL with CD30 >10% by immunohistochemistry, and most significantly improved outcomes in anaplastic large cell lymphoma. This served as proof of principle that biomarker driven therapy can lead to improved outcomes in this rare disease (Horwitz et al Lancet 2019). Duvelisib is a gamma delta PI3 kinase inhibitor with a 50% overall response rate in PTCL and a trend toward a higher response rate in PTCL with a T-follicular helper (TFH) phenotype (Brammer et al. Blood 2021). Azacitidine is a hypomethylating agent that has shown a 75% overall response rate (ORR) in PTCL with TFH phenotype. CC-486, oral azacitidine, has been safely combined with CHOP and showed a 75% ORR with a higher ORR in PTCL with TFH phenotype (Ruan et al. Blood 2021). **Methods:** A051902 is a 3 arm randomized phase II US intergroup study in previously untreated PTCL with CD30 expression <10% comparing standard chemotherapy (CHOP or CHOEP) to CHOP/CHOEP with duvelisib 25mg PO BID or CHOP/CHOEP with azacitidine 300mg PO. Pts will be stratified by age (>60, ≤60) and TFH phenotype. Pts over age 60 will receive CHOP and those ≤60 will receive CHOEP. Prior to the randomized study, there is a safety lead-in study for the first 12 pts combining duvelisib 15mg BID with CHOP/CHOEP. The primary endpoint of the phase II study is complete remission (CR) rate by the Lugano 2014 criteria. The phase II study is powered for a 25% improvement in CR rate (45% vs 70%) in an experimental arm compared to CHOP/CHOEP with a 90% power and type I error rate of 10%. The phase II will enroll 159 pts (53 per arm). Key eligibility: 1. untreated PTCL (nodal T-cell lymphoma with TFH phenotype, follicular T-cell lymphoma, PTCL-NOS, angioimmunoblastic T-cell lymphoma, enteropathy associated T-cell lymphoma, monomorphic epitheliotropic intestinal T-cell lymphoma) with CD30 expression <10%, 2. Stage I-IV, PS 0-2. Pts with transformed mycosis fungoides or anaplastic large cell lymphoma are excluded. Standard CHOP and CHOEP are administered every 21 days with growth factor support. Azacitadine 300mg will be taken on days -6 to -1 prior to cycle 1 and then on days 8 to 21 for cycles 1-5. Duvelisib 25mg BID will be taken continuously. Correlative studies include evaluation of TFH phenotype (by immunohistochemistry, gene expression profiling and DNA sequencing) and cell free DNA evaluation to predict outcomes as well as patient reported outcomes. The study was activated 7/30/2021 and the safety lead-in portion is currently enrolling. Support: U10CA180821, U10CA180882. Clinical trial information: NCT04803201. Research Sponsor: U.S. National Institutes of Health.

TPS7594 **Poster Session**

A phase I study of duvelisib in combination with oral azacitidine (CC-486) in relapsed lymphoid malignancies. *First Author: Hayder Saeed, Univ of Kentucky, Lexington, KY*

Background: Phosphoinositide 3-kinase (PI3K) inhibitors have shown promising activity in lymphoid malignancies such as mature T cell lymphoma, diffuse large B cell lymphoma, and mantle cell lymphoma. Duvelisib's PI3K-δ and PI3K-γ activity in T cell lymphoma is promising as a single agent (Horwitz, Koch et al. 2018). While the safety profile can generally be managed, certain autoimmune adverse events may limit its adaptation in clinical practice. Azacitidine, a pyrimidine nucleoside analog of cytidine, is active in T cell lymphoma (Saillard, Guermouche et al. 2017) as well as in DLBCL (Martin, Bartlett et al. 2018). Hypomethylators could enhance the activity of PI3K inhibitors through increasing PTEN expression (Spangle, Roberts et al. 2017), and upregulation of tumor suppressor genes (Zuo, Liu et al. 2011). Duvelisib's immune mediated adverse events may be related to shifts in T cell differentiation towards Th17 phenotype and decreases in T reg differentiation that found to be more pronounced in patients with higher immune related toxicity (Gadi, Kasar et al. 2019). Studies have shown that T regs can be induced from Cd4+CD25- T cells using DNA methyltransferase inhibition with azacitidine (Fagone, Mazzon et al. 2018). Thus, the intermittent administration of azacytidine can potentially restore the balance by increasing T regs to decrease the autoimmune toxicity while maintaining Th17 phenotype that enhances tumor killing as shown in myelodysplastic syndrome (Jia, Yang et al. 2020). **Methods:** This is a 3+3 phase I dose escalation study designed to determine the maximum tolerated dose (MTD) of CC-486 in combination with duvelisib in patients with lymphoid malignancies. The MTD is defined as the highest dose with an observed incidence of dose limiting toxicity (DLT) in no more than one out of six patients treated at a particular dose level. Secondary endpoints include best overall response, disease control rate and duration of response. Exploratory end points will be biomarker driven with focus on the composition of different T cell compartments during the administration of the combination. Efficacy biomarkers will include measuring the phosphorylation of AKT in peripheral CD3+ T cells. Oral duvelisib will be given continuously with the dose escalation maintained during the first 2 cycles while CC-486 schedule will be 14 days on/14 days off. The first cohort of patients are enrolled, and are in the DLT testing period. Clinical trial information: NCT05065866. Research Sponsor: SecuraBio, BMS.

TPS7595 **Poster Session**

TTI-622-01: A phase 1a/1b dose-escalation and expansion trial of TTI-622 in patients with advanced hematologic malignancies, including diffuse large B-cell lymphoma (DLBCL). *First Author: Krish Patel, Swedish Cancer Institute, Seattle, WA*

Background: CD47 is an innate immune checkpoint that binds signal regulatory protein alpha (SIRPα) and delivers a "don't eat me" signal to suppress macrophage phagocytosis. Overexpression of CD47 on cancer cells serves as a mechanism of immune surveillance evasion, and is associated with poor prognosis in both hematologic and solid malignancies. TTI-622 is a fusion protein consisting of the CD47-binding domain of human SIRPα linked to the Fc region of human IgG4. It is designed to enhance phagocytosis and antitumor activity by preventing CD47 from delivering its inhibitory signal as well as generating a moderate pro-phagocytic signal via IgG4 Fc. Importantly, unlike many CD47-blocking agents, TTI-622 does not bind to human red blood cells. Preclinical studies demonstrate that TTI-622 induces macrophage-mediated phagocytosis of different malignant cell lines, including DLBCL cells, decreases tumor growth and improves survival in a DLBCL xenograft tumor model. Anti-CD47 antibody enhances rituximab stimulated macrophage-mediated phagocytosis of non-GCB DLBCL cell lines (Bouwstra et al, Cancer Immunol Res. 2019). The ongoing phase 1a part of this study has been previously described. Here we describe 2 cohorts within the phase 1b part of the study that are intended to determine the safety and preliminary efficacy of TTI-622 when given in combination with anti-CD20 targeting agent in patients with CD20+ relapsed/refractory (RR) DLBCL. **Methods:** TTI-622-01 is a multi-center Phase 1a/1b study. Phase 1a was designed to determine the MTD, pharmacokinetics (PK), pharmacodynamics, and preliminary antitumor activity of QW, Q2W, and Q3W single-agent TTI-622 in R/R lymphoma using a 3+3 dose escalation schema. Phase 1b, ongoing, will determine the safety, recommended dose and preliminary efficacy of TTI-622 in combination with select approved anticancer treatments for patients with hematological malignancies including, but not limited to anti-CD20 therapy in patients with CD20+ RR DLBCL. Secondary objectives are to further characterize safety, PK and immunogenicity of TTI-622 when combined with approved therapies. Patients will be enrolled in 2 cohorts exploring different doses of TTI-622 in combination with anti-CD20 therapy. Cohorts will open in a staggered manner. In each cohort 3 patients will be dosed and followed for 28 days before expanding enrolment to additional 27 patients per cohort. Key eligibility criteria include: age ≥18 years; relapsed and/or refractory disease after ≥1 prior line of therapy; not eligible for or have progressed after high dose chemotherapy (HDT)/auto-SCT; ≥1 site of measurable disease (Lugano 2014 classification); ECOG PS ≤2; adequate organ functions, no known CNS involvement; no prior anti-CD47 or anti-SIRPα therapy. Patient recruitment is planned or ongoing at 40 sites worldwide. Clinical trial information: NCT03530683. Research Sponsor: Trillium Therapeutics Inc., which was acquired by Pfizer, Inc. in November 2021.

TPS7596 **Poster Session**

Trial in progress: A phase 1b study evaluating the safety, tolerability, and preliminary anti-tumor activity of NT-I7 (efineptakin alfa), a long-acting human IL-7, post-tisagenlecleucel in subjects with relapsed/refractory large B-cell lymphoma. *First Author: Armin Ghobadi, Washington University School of Medicine, St. Louis, MO*

Background: CD19-directed chimeric antigen receptor T-cell (CAR-T) therapy with tisagenlecleucel (Kymriah) is standard of care (SOC) for patients with relapsed/refractory large B-cell lymphoma (r/r LBCL). CAR-T expansion is a strong predictor of response to this therapy. NT-I7 (efineptakin alfa) is a first in-class, long-acting human IL-7 previously shown clinically in solid tumor studies to increase the number and functionality of T-cells in peripheral blood and within tumors. In a $CD19^+$ lymphoma xenograft mouse model that received anti-CD19 universal CAR-T infusion, NT-I7 treatment prolonged survival and enhanced CAR-T gene expression of functional markers, proliferation, persistence, and tumor killing. We hypothesize that NT-I7 administration after tisagenlecleucel SOC for subjects with r/r LBCL may increase expansion and persistence of CAR-T, leading to increased tumor response rate and improved clinical outcomes without safety concerns. **Methods:** This phase 1b study consists of a dose-escalation phase followed by a dose expansion. In dose escalation, subjects receive tisagenlecleucel infusion on Day 0 and a single dose of NT-I7 on Day 21, at 7 dose levels (DLs 1-7): 60, 120, 240, 360, 480, 600, and 720 μg/kg. DLs 1 and 2 will enroll 1 subject each, followed by a 3+3 design for the remaining DLs. Up to 42 subjects will be enrolled for the dose-escalation phase and up to 15 subjects in the dose-expansion phase, treated at the recommended phase 2 dose (RP2D). Eligible subjects are ≥18 years of age with biopsy-proven diagnosis of r/r LBCL after ≥2 lines of systemic therapy, including diffuse LBCL (DLBCL) not otherwise specified (NOS), high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. Subjects must be eligible for tisagenlecleucel as SOC. Subjects who have received prior CD19-directed therapy are ineligible. Primary objectives are to evaluate safety and tolerability and determine the maximum tolerated dose (MTD) and/or RP2D for NT-I7 with this regimen. Secondary objectives are to explore the anti-tumor activity of this regimen for r/r LBCL. The effect of NT-I7 after tisagenlecleucel infusion on the safety profile regarding Grade ≥3 Cytokine Release Syndrome (CRS) and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) will also be evaluated. Exploratory objectives are to assess pharmacokinetic parameters of tisagenlecleucel with NT-I7 administration, and correlative studies will evaluate the effects of this regimen not limited only to the expansion of lymphocytes and serum cytokines. As of January 3, 2022, 2 subjects have received NT-I7 in the dose-escalation phase at DL1 and DL2. Clinical trial information: NCT05075603. Research Sponsor: NeoImmuneTech.

8001 **Oral Abstract Session**

ATLAS: A phase 3 randomized trial of carfilzomib, lenalidomide, and dexamethasone versus lenalidomide alone after stem-cell transplant for multiple myeloma. *First Author: Dominik Dytfeld, Poznań University of Medical Sciences, Poznan, Poland*

Background: Treatment following autologous stem cell transplantation (ASCT) for multiple myeloma (MM) remains an area of active investigation. We have shown that extended post-ASCT treatment with carfilzomib, lenalidomide, and dexamethasone (KRd) after KRd induction improved the depth and duration of response (Jasielec et al, Blood 2020), suggesting a benefit of post-ASCT KRd therapy. Here we directly compare that strategy to standard lenalidomide (R) maintenance. **Methods:** This international open-label phase 3 randomized trial recruited newly-diagnosed MM patients (pts) who received any induction therapy for up to 12 months (mo) followed by single ASCT and achievement of at least stable disease within 100 days afterward. Pts were randomized to receive either KRd or R, stratified by post-transplant response (≥VGPR vs < VGPR) and cytogenetic risk [standard risk (SR) vs high [HR: presence of t(4;14), t(14;16), or del(17p)]. Pts randomized to KRd received carfilzomib 36 mg/m^2 on days (D) 1,2,8,9,15,16 for 4 cycles (C) then D1,2,15,16 starting C5; R 25 mg D1-21, and dexamethasone 20 mg D1,8,15,22 in 28-day cycles. KRd pts with SR who reached IMWG-defined MRD-negativity after C6 de-escalated therapy to R alone after C8 (KRd- > R); the rest continued KRd through C36 followed by R alone until progression. Pts randomized to R received lenalidomide 10 mg C1-3 and then 15 mg daily. The primary objective was to compare progression free survival (PFS) rate between the two arms. Based on historical PFS rates, a sample size of 180 Pts was calculated to provide 85% power with 2-sided alpha 0.05. **Results:** 180 pts were enrolled (R n = 87; KRd n = 93) through 10/21/20; data cutoff was 12/31/21. Pt characteristics in the KRd and R arms were balanced for median age (58 vs 59 yrs), >VGPR (88% vs 92%), and HR (23% vs 21%). After 6 cycles, 47% pts in the KRd arm and 29% in the R arm achieved MRD-negativity (p = 0.017). 34 KRd pts eligible for de-escalation converted to R alone after C8 and were analyzed on the KRd arm per intention-to-treat. At median follow-up of 33.8 mo, 23 pts (25%) on the KRd arm and 38 pts (44%) on the R arm progressed; estimated median PFS was 59.0 mo for KRd vs 41.4 mo for R (Hazard Ratio 0.56, logrank p = 0.026). At cutoff, 90% of KRd and 87% of R pts were alive; no deaths were treatment-related. All-grade toxicities were generally comparable between arms. The most common grade 3+ AEs and those of special interest were neutropenia (KRd 47%; R 59%), thrombocytopenia (KRd 13%; R 7%), infections (KRd 15%; R 6%), cardiovascular toxicities (KRd 4%, R 5%), and secondary malignancies (KRd 2, R 2). **Conclusions:** This is the first randomized phase 3 trial demonstrating superior PFS with extended post-transplant KRd therapy compared to R maintenance. Therefore, MRD/risk-adapted post-ASCT extended KRd treatment may represent a new standard of care. Clinical trial information: NCT02659293. Research Sponsor: Amgen, Pharmaceutical/Biotech Company.

8002 **Oral Abstract Session**

Daratumumab carfilzomib lenalidomide and dexamethasone as induction therapy in high-risk, transplant-eligible patients with newly diagnosed myeloma: Results of the phase 2 study IFM 2018-04. *First Author: Cyrille Touzeau, University Hospital Hôtel-Dieu, Nantes, France*

Background: High-risk (HR) cytogenetic is associated with poor outcome in transplant eligible (TE) newly diagnosed myeloma multiple myeloma (NDMM). The triplet combination carfilzomib lenalidomide and dexamethasone (KRD) plus transplantation demonstrated high efficacy with favorable safety profile in TE-NDMM patients (FORTE). The addition of daratumumab (Dara) to frontline therapy also improved response rate and progression free-survival in TE-NDMM patients (CASSIOPEIA, GRIFFIN). Double transplant also improved outcome of HR TE NDMM patients (EMN02, STAMINA). The phase 2 trial 2018-04 from the Intergroupe Francophone du Myelome (IFM) is evaluating an intensive strategy with Dara-KRD induction and consolidation plus double transplant in HR TE NDMM (NCT03606577). **Methods:** HR MM was defined by the presence of del17p, t(4;14) and/or t(14;16). Stategy includes Dara-KRD induction (6 cycles), autologous stem cell transplantation (ASCT), Dara-KRD consolidation (4 cycles), second ASCT, Dara-lenalidomide maintenance. The primary endpoint was the feasibility of this intensive strategy. Here, we report efficacy and safety analysis of Dara-KRD induction. **Results:** Fifty patients with previously untreated NDMM were included from july 2019 to march 2021 in 11 IFM centers Median age was 57 (range 38 -65). ISS stage 3 was present in 12 (24%) patients. Based on inclusion criteria, all patients had HR cytogenetic, including 17p deletion (n = 20, 40%), t(4;14) (n = 26, 52%) or t(14;16) (n = 10,20%). Forty-six patients completed Dara-KRD induction. Two patients discontinued treatment due to severe adverse event (COVID-19 infection, n = 1 ; drug-induced hepatitis, n = 1) and 2 patients discontinued treatment due to disease progression. Grade 3-4 treatment related adverse event (> 5% of patients) were neutropenia (38%), anemia (14%), thrombocytopenia (8%), infection (6%), renal insufficiency (6%) and deep-vein thrombosis (6%). Two patients (6%) experienced stem-cell collection failure. Overall response rate was 96%, including 92 % > very good partial response. Among 37 (/46) evaluable patients post induction, Minimal Residual Disease negativity rate (NGS, 10-^{5}) was 62%. **Conclusions:** Dara-KRD as induction prior ASCT is safe and allows deep responses in TE NDMM patients with high-risk cytogenetic profile. IFM 2018-04 study is ongoing and longer follow-up is needed to evaluate safety and efficacy of the overall strategy with Dara-KRD induction and consolidation plus double transplant in this subset of HR patients. Clinical trial information: NCT03606577. Research Sponsor: Celgene/BMS, Amgen, Janssen.

8003 **Oral Abstract Session**

Phase 1 study of CART-ddBCMA in relapsed or refractory multiple myeloma. *First Author: Matthew J. Frigault, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: Chimeric Antigen Receptor (CAR) T cell therapies targeting B-cell maturation antigen (BCMA) have demonstrated benefit in patients (pts) with relapsed and/or refractory Multiple Myeloma (RRMM). CART-ddBCMA is an autologous anti-BCMA CAR T cell therapy that utilizes a novel, synthetic binding domain, called a D-Domain, instead of a typical scFv binder. The objective of this first-in-human trial is to assess the safety and efficacy of CART-ddBCMA. **Methods:** This is a Phase 1, multi-center, open label, dose escalation trial for pts with RRMM who have received ≥3 prior regimens or are triple-refractory. After apheresis, bridging therapy is allowed during manufacturing. Pts receive fludarabine and cyclophosphamide (30/300 mg/m^2/day) days -5 to -3 and CART-ddBCMA infusion on day 0. Dose escalation was performed at 100 (DL1) and 300 (DL2) x 10^6 (± 20%) CAR+T cells, followed by expansion of DL1. The primary endpoint is incidence of adverse events (AEs), including dose-limiting toxicities (DLTs). Additional endpoints are depth and duration of response (IMWG Criteria), minimal residual disease (MRD, clonoSEQ), progression-free (PFS) and overall survival (OS). Pts with 1- and 3-months follow-up were eligible for safety and efficacy analysis, respectively. **Results:** As of January 25, 2022, 25 pts received CART-ddBCMA, with median age 66 (range: 44-76), after a median of 5 prior lines of therapy (3-16), including 10 (40%) with extramedullary disease (EMD). Median follow-up was 9.8 (2-23.7) months. Overall, 25 pts (19 DL1; 6 DL2) were evaluable for safety and 24 (18 DL1; 6 DL2) for efficacy analysis. All pts experienced CRS, but only 1 pt (in DL2) had grade (gr) 3 CRS. All other CRS cases were gr ≤2, with no cases of gr ≥3 CRS in DL1. Four pts experienced ICANS (2, gr ≤2; 2, gr 3), with 1 gr 3 case in each of DL1 (5%) and DL2 (17%). Standard management resulted in resolution of CRS/ICANS within 30 days in all cases without sequelae. The ORR = 100%, sCR/CR rate = 67%, and ≥VGPR rate = 88%. Conversion to CR/sCR has occurred with longer follow-up, as late as month 9 in this trial. At time of data-cut 5 pts in DL1 with PR/VGPR have < 9 months follow-up, with 4 (of 4 evaluable) negative at ≥10^{-5} for MRD. Overall, 17 of 20 (85%) evaluable pts have achieved best MRD response of ≥10^{-5}. In the dose escalation pts (i.e., those with longest follow-up, n = 12), the ORR and CR/sCR rate was 100% and 75%, respectively, despite 58% (7/12) EMD in this group. Of the first 6 pts dosed in DL1, 4 (67%) continue in ongoing sCR beyond 18 months, including 3 with EMD. Median duration of response, PFS and OS were not evaluable at the time of data-cut because 19 of 24 evaluable pts (79%) remain in ongoing response. **Conclusions:** CART-ddBCMA administration, to date, has demonstrated clinical activity, including 100% ORR with rates of CR/sCR and ≥VGPR of 67% and 88%, respectively. Durable responses beyond 18 months have been observed, including in pts with EMD. Clinical trial information: NCT04155749. Research Sponsor: Arcellx.

8004 **Oral Abstract Session**

Phase I open-label single arm study of GPRC5D CAR T-cells (OriCAR-017) in patients with relapsed/refractory multiple myeloma (POLARIS). *First Author: He Huang, Department of Hematology, The First Affliated Hospital, Zhejiang University, Hangzhou, China*

Background: GPRC5D, a type-C 7-pass transmembrane receptor protein, is predominantly expressed on malignant plasma cells from MM patients. The autologous GPRC5D-directed CAR-T cell (OriCAR-017), owning to an additional proprietary Ori element, is the 2nd generation CAR-T cell with improvement in expansion and durability. **Methods:** The primary objective of this study was to evaluate safety and tolerability of OriCAR-017. Key enrolment criteria included measurable MM adults, R/R or intolerant to established therapies. Patient received lymphodepleting chemotherapy with fludarabine 30mg/m^2/d and cyclophosphamide 300mg/m^2/d for 3 days followed by a single infusion of OriCAR-017. The trial followed 3+3 design with 1×10^6/kg, 3×10^6/kg and 6×10^6/kg CAR$^+$ T cells cohorts. **Results:** Eleven patients were enrolled and underwent apheresis during June 9, 2021 and January 31, 2022. 9pts have completed infusion and 8pts available for efficacy and safety evaluation, the 9th pt completed infusion at January 23, 2022. 2 pts were suspended infusion due to rapid disease progression. Of the 9 infused pts , median age 65 years (range41-71) and a median of 6 (range3-17) prior therapy lines; 3 (33.0%)/1 (11.0%) triple-class/penta-drug exposed; 2 (22.0%)/1 (11.0%) triple-class/penta-drug refractory; 4 (44.0%) prior BCMA CART therapy. Five out of 6pts had high-risk cytogenetic profiles including 2pts with del(17p). No dose-limiting toxicities occurred. The most common TEAEs were neutropenia (G3/4 100%), thrombocytopenia (G3/4 100%), leukopenia (G3/4 100%), lymphopenia (G3/4 100%) and anemia (G3/4 87.5%). All pts experienced CRS with 7pts in G1, 1pt in G2. All CRSs were rapidly relieved after conventional intervention(tocilizumab and steroids). The median onset time was 3 days (range0-8), median duration 6 days (range5-8). No neurologic toxicities were reported. No nail disorders were reported. 8pts avaliable for efficacy evaluation, median follow up time was 109.5 days (range32-195 days). A 100.0% ORR were observed with 3pts CR/sCR, 2pts VGPR, 3pts PR. Three out of 4pts with prior BCMA CAR-T therapy were available for efficacy evaluation-1sCR, 1VGPR, 1PR. After infusion, 8pts were MRD negative in the bone marrow by flow cytometry (10^{-5}) at day 28, 5pts continued at month 3 and 1pt at month 6. Robust OriCAR-017 expansion in peripheral blood by using qPCR for 8pts, median peak was 507,463.6copies/ml (range152093.7 – 1121996.9), median time to peak expansion was 10 days (range7-14). **Conclusions:** In this phase I study, OriCAR-017 was showed safe and impressive efficacy in RRMM patients. Majority of AEs were transient and manageable. 100% ORR and 100% MRD negative rate, along with favorable safety support OriCAR-017 to be a competitive therapy for RRMM. Furthermore, patients who had relapsed from BCMA CAR-T therapy may still benefit from OriCAR-017. Clinical trial information: NCT05016778. Research Sponsor: Oricell Therapeutics Co., Ltd.

8005 **Oral Abstract Session**

Updated results of a multicenter first-in-human study of BCMA/CD19 dual-targeting fast CAR-T GC012F for patients with relapsed/refractory multiple myeloma (RRMM). *First Author: Juan Du, Changzheng Hospital, Shanghai, China*

Background: GC012F is a B cell maturation antigen (BCMA)/CD19 dual-targeting CAR-T developed on the novel FasT CAR-T platform with overnight manufacturing and designed to improve depth of response and efficacy. Data was presented at ASCO and EHA 2021 for initial 19 pts. We present updated data for study (NCT04236011; NCT04182581) with longer follow up and 9 additional pts treated (n = 28) in 3 different dose levels. **Methods:** From October 2019 to November 2021, 28 heavily pretreated RRMM pts (age 27-76) median of 5 prior lines (range 2-9) were treated on a single-arm, open label, multicenter Investigator Initiated Trial receiving a single infusion of GC012F. 89.3% (25/28) were high risk (HR- mSMART), 8 pts had EM disease, 3 had never achieved a CR including after transplant, 1 pts presented with plasma cell leukemia, 24/28 pts were refractory to last therapy, 3 pts primary refractory. 9/28 pts had received prior anti-CD38, 27/28 pts prior IMiDs. 26/28 pts were refractory to PI, 26/28 pts to IMiDs. After lymphodepletion over 2-3 days (30 mg/m^2/d, 300mg/ m^2/d Flu/Cy) GC012F was administered as single infusion at 3 dose levels: 1x10^5/kg (DL1) n = 2, 2x10^5/kg (DL2) n = 10 and 3x10^5/kg (DL3) n = 16. **Results:** As of Jan 26th 2022, 28 pts - median follow-up (f/u) 6.3 mths (1.8-29.9) - had been evaluated for response. Overall response rate (ORR) in DL1 was 100% (2/2)- DL 2 -80% (8/10) DL 3 -93.8% (15/16) with 27 pts MRD negative by flow cytometry (sensitivity 10^{-4}-10^{-6}). 100% of MRD assessable pts (27/27) achieved MRD negativity. One patient out of 28 could not get assessed. At d28, 21/24 assessable patients were MRD negative (81.5%), 4/28 pts could not get d28 MRD assessment f/u due to COVID-19 restrictions however were assessed at a later timepoint. To date best response is MRD- sCR in 21/28 patients(75.0%) across all dose levels. Some pts after short f/u show responses that are still deepening. Cytokine Release Syndrome (CRS) was mostly low grade: gr 0 n = 3 (10.7%), gr 1-2 n = 23 (82.1%), gr 3 n = 2 (7.1%) – no gr 4/5 CRS and no ICANs were observed (Graded by ASBMT criteria). Median duration of CRS was 3 d (1-8 d). PK results showed no difference amongst dose levels DL1 to DL3. Overall, CAR-T median Tmax was 10 d (range 8-14 d), median peak copy number (Cmax) was 97009 (16,011-374,346) copies /μg DNA with long duration of persistence of up to d793 (data cut-off). CAR-T geometric mean $AUC_{0\text{-}28}$ for DL1, DL2 and DL3 were 468863, 631540 and 581620 copies/μg DNA$\times$day, respectively. Pts continue to be monitored for safety and efficacy including DOR. **Conclusions:** BCMA-CD19 dual FasT CAR-T GC012F continues to provide deep and durable responses with a favorable safety profile in additional RRMM pts across all dose levels demonstrating a very high MRD negativity rate including in pts refractory to anti-CD38, PI and IMIDs. GC012F is currently being studied in earlier lines of therapy as well as additional indications. Clinical trial information: NCT04236011; NCT04182581. Research Sponsor: Gracellbiotechnologies.

8006 **Oral Abstract Session**

Initial safety results for MagnetisMM-3: A phase 2 trial of elranatamab, a B-cell maturation antigen (BCMA)-CD3 bispecific antibody, in patients (pts) with relapsed/refractory (R/R) multiple myeloma (MM). *First Author: Alexander M. Lesokhin, Division of Hematology and Oncology, Memorial Sloan Kettering Cancer Center/Weill Cornell Medical College, New York, NY*

Background: Elranatamab (PF-06863135) is a humanized bispecific antibody that targets both BCMA-expressing MM cells and CD3-expressing T cells. MagnetisMM-3 (NCT04649359) is an open-label, multicenter, non-randomized, phase 2 study to evaluate the safety and efficacy of elranatamab monotherapy in pts with R/R MM. Initial safety results are presented. **Methods:** MagnetisMM-3 enrolled pts who are refractory to at least 1 proteasome inhibitor, 1 immunomodulatory drug, and 1 anti-CD38 antibody. Pts were assigned to 1 of 2 independent, parallel cohorts: those naïve to BCMA-directed therapies (Cohort A) and those with previous exposure to BCMA-directed antibody-drug conjugates or CAR-T cells (Cohort B). Pts received subcutaneous elranatamab 76 mg QW on a 28-d cycle with a 2-step-up priming dose regimen administered during the first week. Dose modifications were permitted for toxicity. Treatment-emergent adverse events (TEAEs) were graded by CTCAE (v5.0), and cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) by ASTCT criteria. **Results:** As of the data cutoff on Dec 31, 2021, 60 pts in Cohort A had received ≥1 dose of elranatamab; the last pt's first dose was ~2 months prior to the cutoff. Median age was 69.0 y (range, 44–89), 48.3% were male, 63.3% were white, 18.3% were Asian and 11.7% were Black/African American. At baseline, 60.0% of pts had an ECOG performance status 1–2 and pts had received a median of 5 (range, 2–12) prior therapies. Median duration of elranatamab treatment was 9.57 wks (range, 0.1–46.1); median relative dose intensity was 87.4% (range, 23.1–101.4). TEAEs were reported in 100% (Grade [G] 3/4, 75.0%) of pts. Most common (≥30%) hematologic TEAEs were neutropenia (36.7% [G3/4, 35.0%]), anemia (36.7% [G3/4, 30.0%]) and thrombocytopenia (30.0% [G3/4, 21.7%]). Among pts who received the 2-step-up priming regimen (n = 56), CRS and ICANS, respectively, were reported in 58.9% (G3/4, 0%) and 3.6% (G3/4: 0%); of those pts, 57.6% (n = 19/33) and 100% (n = 2/2) received tocilizumab and/or steroids. Most common (≥30%) non-hematologic TEAE, other than CRS/ICANS, was fatigue (31.7% [G3/4, 3.3%]). Infections were reported in 46.7% (G3/4: 18.3%) of pts; most frequently reported were upper respiratory tract infections (11.7% [G3/4: 0%]). Discontinuations due to adverse events were reported in 5.0% of pts. No pts permanently discontinued treatment due to CRS or ICANS. There were 10 deaths; causes were MM progression (n = 8), septic shock (n = 1) and unknown (n = 1). Data will be updated at the time of presentation to include ~90 pts. **Conclusions:** Preliminary results of MagnetisMM-3 in pts with R/R MM and no prior BCMA-targeted treatment suggest that 76 mg QW elranatamab with a 2-step-up priming regimen is well tolerated, with no G ≥3 CRS or ICANS observed. Clinical trial information: NCT04649359. Research Sponsor: Pfizer.

8007 **Oral Abstract Session**

Teclistamab, a B-cell maturation antigen (BCMA) x CD3 bispecific antibody, in patients with relapsed/refractory multiple myeloma (RRMM): Updated efficacy and safety results from MajesTEC-1. *First Author: Ajay K. Nooka, Emory University, Winship Cancer Institute, Atlanta, GA*

Background: The BCMA $\times$ CD3 bispecific antibody teclistamab (tec; JNJ-64007957) redirects CD3+ T cells to mediate T-cell activation and subsequent lysis of BCMA-expressing myeloma cells. The multicohort, open-label, phase 1/2 MajesTEC-1 study is investigating safety/efficacy of tec in patients (pts) with RRMM who previously received ≥3 lines of therapy (LOT). In phase 1, the recommended phase 2 dose (RP2D) of tec was identified as a weekly subcutaneous dose of 1.5 mg/kg preceded by step-up doses of 0.06 and 0.3 mg/kg. Initial results from pts treated with the tec RP2D in phase 1/2 (no prior exposure to an anti–BCMA-targeted treatment), demonstrated that tec was well tolerated with encouraging efficacy. Here we present updated results from pts treated at the RP2D, including additional pts and longer follow-up. **Methods:** Eligible pts were aged ≥18 years, had documented MM (per IMWG criteria), and had received ≥3 prior LOT including a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 antibody. Prior BCMA-targeted therapy was not permitted in Phase 1. Pts received tec at the RP2D. The primary endpoint was overall response rate (assessed per IMWG 2016 criteria). Adverse events (AEs) were graded per CTCAE v4.03 (cytokine release syndrome [CRS] and ICANS graded per ASTCT guidelines). Data cutoffs for safety and efficacy (N = 165) were Sep 7 and Nov 9, 2021, respectively. **Results:** Median pt age was 64 y (range 33–84); 58% were male, and median prior LOT was 5 (range 2–14); 100% were triple-class exposed, 70% were penta-drug exposed, 78% were triple-class refractory, and 30% were penta-drug refractory. ORR was 64% (95% CI 56–72), with a complete response or better achieved in 30% of pts. Responses were durable and deepened over time; median duration of response (DOR) was not reached. The 12-mo DOR rate was 66% (95% CI 49–79). The majority of pts who responded to treatment in the first cycle had a reduction in soluble BCMA. The most common hematologic AEs were neutropenia (65%; grade 3/4: 57%), anemia (50%; grade 3/4: 35%), thrombocytopenia (38%; grade 3/4: 21%), and lymphopenia (34%; grade 3/4: 32%). Infections occurred in 104 pts (63%; grade 3/4: 35%). The most common nonhematologic AE was CRS (72%; grade 3: 0.6%; no grade 4/5); median time to CRS onset (range) was 2 days (1–6) and median duration was 2 days (1–9). Five pts (3%) reported a total of 9 ICANS events (all grade 1/2; 7 were concurrent with CRS; all resolved). There were no treatment-related deaths. No pts required a teclistamab dose reduction due to AEs. **Conclusions:** Current data with ~9 months of follow-up reaffirm the deep and durable responses that have been observed with tec in pts with highly refractory MM, with no new safety signals. Additional data with longer follow-up, including subgroup analyses and PFS, will be presented. Clinical trial information: NCT04557098. Research Sponsor: Janssen Research & Development, LLC.

8008 **Oral Abstract Session**

Major risk factors associated with severe COVID-19 outcomes in patients with multiple myeloma: Report from the National COVID-19 Cohort Collaborative (N3C). *First Author: Amit Kumar Mitra, Department of Drug Discovery and Development, Harrison College of Pharmacy, Auburn University, Auburn, AL*

Background: Patients with multiple myeloma (MM), an age-dependent neoplasm of antibody-producing plasma cells, have compromised immune systems due to multiple factors that may increase the risk of severe COVID-19. The NCATS' National COVID Cohort Collaborative (N3C) is a centralized data resource representing the largest multi-center cohort of ~12M COVID-19 cases and controls nationwide. In this study, we aim to analyze risk factors associated with COVID-19 severity and death in MM patients using the N3C database. **Methods:** Our cohort included MM patients within the N3C registry diagnosed with COVID-19 based on positive PCR or antigen tests or ICD-10–CM. The outcomes of interest include all-cause mortality (including discharge to hospice) during the index encounter, and clinical indicators of severity (hospitalization/ED visit, use of mechanical ventilation, or extracorporeal membrane oxygenation/ECMO). **Results:** As of 09/10/2021, the N3C registry included 690371 cancer patients, out of which 17791 were MM patients (4707 were COVID-19+). The mean age at diagnosis was 65.9yrs, 57.6% were >65yo, 46.4% were females, and 21.8% were Blacks. 25.6% had a Charlson Comorbidity Index (CCI) score of ≥2. 55.6% required an inpatient or ED visit, and 3.65% required invasive ventilation. 11.4% developed acute kidney injury during hospitalization. Multivariate logistic regression analysis showed histories of pulmonary disease (OR 2.2; 95%CI: 1.7-2.8), renal disease (OR 1.8; 95%CI: 1.4-2.4), and black race (p<0.001) were associated with higher risk of severity. Interestingly, smoking status was significantly associated with a lower risk of severity (OR 0.7; 95%CI: 0.5-0.9). Further, protective association was also observed between COVID-19 severity and blood or marrow transplant (BMT) (OR 0.52; 95%CI: 0.4-0.7), daratumumab therapy (OR 0.64; 95%CI: 0.42-0.99) and COVID-19 vaccination (OR 0.28; 95%CI: 0.18-0.44). IMiDs were associated increase in the risk of COVID-19 severity (OR 2.1; 95%CI: 1.6-2.7). 2.3% of N3C-myeloma COVID-19+ patients died within the first 10 days, while 4.95% died within 30 days of COVID-19 hospitalization. Overall, the survival probability was 90.5% across the course of the study. Multivariate cox proportional hazard model showed that CCI score ≥2 (HR 4.4; 95%CI: 2.2-8.8), hypertension (HR 1.6; 95%CI: 1.02-2.4), IMiD (HR 2.6; 95%CI: 1.8-3.8) and proteasome inhibitor (HR 1.6; 95%CI: 1.1-2.5) therapy were associated with worse survival. COVID-19 vaccination (HR 0.195; 95%CI: 0.09-0.45) and BMT (HR 0.65; 95%CI: 0.4-0.995) were associated with lower risk of death. **Conclusions:** We have identified previously unpublished potential risk factors for COVID-19 severity and death in MM as well as validated some published ones. To the best of our knowledge, this is the largest nationwide study on multiple myeloma patients with COVID-19. Research Sponsor: None.

8009 **Clinical Science Symposium**

Phase II study of umbilical cord blood–derived natural killer (CB-NK) cells with elotuzumab, lenalidomide, and high-dose melphalan followed by autologous stem cell transplantation (ASCT) for patients with high-risk multiple myeloma (HRMM). *First Author: Samer Ali Srour, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Despite the introduction of several novel agents over the past decade, patients with HRMM continue to have relatively poor outcomes. In a first-in-human study, we previously showed the feasibility of using CB-NK cells up to a dose of 1 x 10^8 cells/kg in MM patients undergoing high-dose melphalan (200 mg/m^2; Mel200) plus lenalidomide and ASCT (NCT01729091). Lenalidomide enhances NK cell function and antibody-mediated cell toxicity against tumor targets. Our preclinical data showed that *ex vivo* expanded NK cells demonstrated higher elotuzumab-mediated cytotoxicity against myeloma targets than non-expanded cells, and the addition of elotuzumab to lenalidomide augmented the CB-NK cell ADCC against MM1.S myeloma targets. Hence, we aimed from this expansion part of the phase 2 clinical trial to determine the efficacy of CB-NK cells combined with elotuzumab/lenalidomide for HRMM undergoing ASCT. **Methods:** Patients with HRMM, ages 18-75 years, were eligible. HRMM defined as: disease relapse within 18 months of ASCT; fluorescence in situ hybridization (FISH) showing t(4:14), t(14:16), t(14:20), deletion (del) 17/17p or gain (amp) 1q; del(13) by conventional cytogenetic analysis; high-risk signatures as determined by the GEP-70 or EMC-92 gene expression profiles. With day 0 defined as day of stem cell infusion, treatment consisted of IV elotuzumab 10 mg/kg (days -15 and -8), oral lenalidomide 10 mg (days -8 to -2 prior to ASCT), Mel200 on day -7, and CB-NK cells on day -5. The primary endpoints were best response rate (≥VGPR) and minimal residual disease (MRD) at 3 months after ASCT, as defined per the IMWG criteria. MRD was tested by using 8-color multiparametric flow cytometry validated to a sensitivity level of 0.001% (1 cell in 100,000). **Results:** Thirty patients, with a median age of 63 (range, 40-72) years, were enrolled between 03/2018 and 01/2021. 97% had R-ISS stages 2/3, 40% had ≥2 high-risk genetic abnormalities, and 23% had del TP53. Most (80%) received induction therapy with bortezomib or carfilzomib + lenalidomide + dexamethasone, 1 patient had prior ASCT, and 4 received >1 prior line of therapy. Before ASCT, 73% had VGPR or better (40% in CR/sCR) and 40% had negative MRD. At 3 months after transplant, 97% achieved ≥VGPR (76%, CR/sCR) and 75% had negative MRD. At median follow-up of 26 (range, 12-44) months, only 4 patients progressed (3 had positive MRD after ASCT). The 2-year PFS and OS rates were 83% and 97%, respectively. No unexpected serious adverse effects attributable to NK cells were noted. **Conclusions:** CB-derived expanded NK cells plus elotuzumab/lenalidomide combined with Mel200 and ASCT results in excellent and durable hematologic and MRD responses in HRMM patients. Furthermore, PFS and OS rates compare favorably to published outcomes for HRMM patients. Clinical trial information: NCT01729091. Research Sponsor: Moonshot Program, Pharmaceutical/Biotech Company.

8000 **Oral Abstract Session**

Ixazomib and daratumumab without dexamethasone (I-Dara) in elderly frail RRMM patients: A multicenter phase 2 study (IFM 2018-02) of the Intergroupe Francophone du Myélome (IFM). *First Author: Xavier Leleu, Centre Hospitalier Universitaire de Poitiers, Poitiers, France*

Background: Frail patients with multiple myeloma have an inferior outcome, especially in the relapse setting. This adverse prognosis is mainly related to a high discontinuation rate due to treatment (Tx) related adverse events. The aim of this phase 2 study is to evaluate efficacy and tolerability of Ixazomib-Daratumumab (I-Dara) without Dexamethasone in elderly frail patients with relapsed myeloma (RRMM) (NCT03757221). **Methods:** Ixa-Dara naïve RRMM patients received oral Ixazomib (4 mg: days 1, 8, 15), IV Daratumumab (16 mg/kg; days 1, 8, 15, 22, cycles 1-2; days 1, 15, cycles 3-6; days 1, cycles 7+) and IV Methylprednisolone before Daratumumab (100 mg at day 1, 8, cycle 1 and then 60 mg). They were enrolled after 1 or 2 prior therapy if their frailty score was ≥ 2 by IMWG score. The primary endpoint was ≥ very good partial response rate (VGPR) at one year. Secondary endpoints included ORR, PFS, OS & toxicity according to NCI-CTCAE version 5. **Results:** Sixty-three patients were screened and 55 enrolled between 03/2018 and 09/2021. Patient were at first (n = 36) or second relapse (n = 19). Thirty-three patients (60%) were previously exposed to bortezomib, 37 (67%) were previously exposed to lenalidomide (Len) and 20 (36 %) were refractory to Len. Median age was 82 (72-93). All patients had a frailty score ≥2 and 13 (24 %) had a 3 or 4 frailty score. In 41 patients ISS at diagnosis was stage I (n = 11), II (n = 18) or III (n = 12). Seventeen (36%) patients harbored high-risk (HR) cytogenetic, including t(4;14) (n = 8) or del17p (n = 10). The median duration of Tx among 28 pts with ongoing Tx was 10 months [5-32] at data cutoff (February, 2)]. The median duration of Tx among 27 pts who stopped Tx was 6 months [0-18]: 18 had progressive disease. Nine patients died during the study: Daratumumab-related bronchospasm (D1C1); Ixazomib-related overdose (C2); sepsis (n = 4), progressive disease (n = 3). Regarding toxicity, 27 pts had a ≥grade 3 AE (49%). The most common grade 3-4 toxicities were thrombocytopenia (n = 9), other cytopenias (n = 4), infection (n = 8), hypertension (n = 3) and gastrointestinal disorders (n = 3). Fourteen out of 28 were SAE including 5 infections, 1 bronchospasm, 1 acute respiratory failure and 2 ixazomib overdoses. Overall response rate, including minimal response, was 86 % with a ≥VGPR rate of 32 % in the whole group. In Len refractory patients the ORR was 82 % and ≥VGPR 41%, in HR cytogenetic patients ORR was 85 % and ≥VGPR 46%. With a median follow-up of 11.6 months median PFS is 16 months and median OS NR (76% estimated at one year). **Conclusions:** In this elderly frail population Ixa-Dara is a feasible combination with favorable efficacy profile even in Len refractory and HR cytogenetic patients. Early toxicity remains a concern in this population eventhough more manageable with Dara SC. Clinical trial information: NCT03757221. Research Sponsor: Janssen and Takeda companies.

8011 **Poster Discussion Session**

Daratumumab (DARA) + lenalidomide, bortezomib, and dexamethasone (RVd) in transplant-eligible newly diagnosed multiple myeloma (NDMM): A post hoc analysis of sustained minimal residual disease (MRD) negativity from GRIFFIN. *First Author: Cesar Rodriguez, Wake Forest University School of Medicine, Winston-Salem, NC*

Background: In the primary analysis of the phase 2 randomized GRIFFIN study, DARA + RVd (D-RVd) improved the stringent complete response (sCR) rate by end of consolidation for transplant-eligible NDMM (42.4% vs 32.0%; 1-sided $P = 0.068$). With longer follow-up (median, 38.6 mo), D-RVd vs RVd improved MRD-negativity (10^{-5}) rates in clinically relevant subgroups (ISS stage III, 71% vs 36%; high cytogenetic risk, 44% vs 29% [del17p, t(4;14), or t(14;16)]; revised high cytogenetic risk, 55% vs 32% [del17p, t(4;14), t(14;16), t(14;20), or gain 1q]). Here we present a post hoc analysis of sustained MRD negativity (median follow-up, 38.6 mo) in the same subgroups and in patients (pts) with ≥CR. **Methods**: Transplant-eligible NDMM pts were randomized 1:1 to 4 D-RVd/RVd induction cycles, ASCT, 2 D-RVd/RVd consolidation cycles, and 2 years of maintenance therapy with lenalidomide (R) ± DARA. For induction/consolidation (21-day cycles), pts received R (25 mg PO Days [D] 1-14), V (1.3 mg/m^2 SC D1, 4, 8, 11), and d (40 mg PO weekly) ± DARA (16 mg/kg IV D1, 8, 15 of Cycles 1-4 and D1 of Cycles 5-6). In maintenance (28-day cycles), pts received R (10 mg PO D1-21; if tolerated, 15 mg in Cycles 10+) ± DARA (16 mg/kg IV Q8W/Q4W or 1800 mg SC per protocol amendments). The primary endpoint was sCR rate by end of consolidation. **Results**: The following features were balanced among randomized pts (D-RVd, n = 104; RVd, n = 103): high cytogenetic risk (16; 14), revised high cytogenetic risk (42; 37), gain 1q (34; 28), and ISS stage III (14; 14). Sustained MRD-negativity rates at 10^{-5} lasting ≥6 and ≥12 months were higher for D-RVd vs RVd among all high-risk subgroups (Table). D-RVd was superior to RVd for rates of sustained MRD negativity lasting ≥12 months for pts with ≥CR (53.7% vs 20.3%) and sCR (59.1% vs 17.4%; Table). Among all pts with sustained MRD negativity, only 1 D-RVd pt subsequently had disease progression, and 1 RVd pt died. Additional data on MRD at 10^{-6} and PFS will be presented. **Conclusions**: MRD data in GRIFFIN show that the addition of DARA to RVd induction/consolidation and R maintenance may lead to durable MRD-negativity (10^{-5}) rates in pts with transplant-eligible NDMM with high cytogenetic risk, ISS stage III, and those who achieve ≥CR or sCR, however larger studies are needed. Clinical trial information: NCT02874742. Research Sponsor: Janssen Oncology, AFT (https://acknowledgments.alliancefound.org).

Sustained MRD negativity (10^{-5} by NGS), n/N (%)	D-RVd ≥6 mo	D-RVd ≥12 mo	RVd ≥6 mo	RVd ≥12 mo
Overall (ITT)	50/104 (48.1)	46/104 (44.2)	15/103 (14.6)	13/103 (12.6)
High cytogenetic risk	4/16 (25.0)	3/16 (18.8)	2/14 (14.3)	2/14 (14.3)
Revised high cytogenetic risk	15/42 (35.7)	14/42 (33.3)	7/37 (18.9)	6/37 (16.2)
Gain 1q	14/34 (41.2)	13/34 (38.2)	5/28 (17.9)	4/28 (14.3)
ISS stage III	7/14 (50.0)	6/14 (42.9)	2/14 (14.3)	2/14 (14.3)
≥CR	48/82 (58.5)	44/82 (53.7)	14/59 (23.7)	12/59 (20.3)
sCR	43/66 (65.2)	39/66 (59.1)	10/46 (21.7)	8/46 (17.4)

8012 **Poster Discussion Session**

A phase II study of daratumumab with weekly carfilzomib, pomalidomide, and dexamethasone in relapsed and refractory multiple myeloma. *First Author: Andrew J Yee, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA*

Background: Daratumumab (dara), carfilzomib (K), pomalidomide (P), and dexamethasone (d) are established in relapsed multiple myeloma (MM) with activity in 3-drug combinations including: dara Kd; dara Pd; and KPd. The paradigm in relapsed/refractory disease is moving towards more intensive and well-tolerated combinations to achieve deeper and more durable responses while ensuring tolerability. Quadruplet regimens are now becoming standard in newly diagnosed MM, and we explored a 4-drug regimen in relapsed disease. Preliminary results of a phase 2 study of dara KPd with a twice/week schedule of K showed an ORR of 86% in pts with a median of 1 prior line (Jasielec et al., ASH 2020). Here we report an ongoing study of dara with *weekly* KPd (dara wKPd) to improve the accessibility of this regimen. **Methods:** This phase 2 study (NCT04176718) will enroll up to 43 pts with relapsed/refractory MM who have received at least 1 prior therapy, including both lenalidomide and a proteasome inhibitor. Prior therapy with dara, K, or P was permitted except for K and P given together as last line of therapy. Dara wKPd was given on a 28-day schedule. Dara was given according to the dara Pd schedule. An initial cohort received dara 16 mg/kg iv (with first dose split over two days); the trial was amended to dara 1800 mg sc. K 56 mg/m^2 iv was given weekly on days 1, 8, 15; for C1D1, dose was 20 mg/m^2. P 4 mg was given po on days 1-21. Dex 40 mg was given weekly with the dose split over two days. Treatment was until progression or unacceptable toxicity. The primary endpoints are overall response and the safety profile of dara wKPd. Secondary endpoints include PFS. **Results:** At time of data cutoff, 24 pts were enrolled; median age was 65 (range 42-73), and median number of prior regimens was 2 (range 1-3). All pts were refractory to their last line of therapy and had prior lenalidomide and bortezomib. Additional prior therapies included: pomalidomide (54%), carfilzomib (13%), ixazomib (46%), cyclophosphamide (4%), auto SCT (29%). High risk FISH was present (out of 24 pts): del 17p (13%); t(14;16) (8%); gain of 1q (46%). Median follow up was 8.4 months. 2 pts came off study due to neutropenia leading to delay in treatment. Grade 3-4 hematologic AEs included neutropenia (46%) and thrombocytopenia (25%). There was 1 episode of febrile neutropenia. Common non hematologic AEs (all; grade 3-4) included fatigue (42%; 0%); dyspnea (38%; 4%); increase in ALT/AST (29%; 8%); insomnia (21%; 0%); neuropathy (17%; 0%). 22 pts were evaluable for response, with an overall response rate of 95% (PR 23%, VPGR 68%, CR 5%). Median PFS at 12 months was 86.2% (95% CI, 70%-100%). **Conclusions:** Dara wKPd shows some of the highest response rates (95%) reported to date in relapsed/refractory MM. This likely reflects the incorporation of 4 active drugs in 1 regimen and builds on the efficacy of dara-based triplet regimens, with manageable toxicity and convenience of weekly K. Clinical trial information: NCT04176718. Research Sponsor: Amgen, Janssen.

8013 **Poster Discussion Session**

Efficacy and safety of teclistamab (tec), a B-cell maturation antigen (BCMA) x CD3 bispecific antibody, in patients (pts) with relapsed/refractory multiple myeloma (RRMM) after exposure to other BCMA-targeted agents. *First Author: Cyrille Touzeau, University Hospital Hôtel-Dieu, Nantes, France*

Background: Tec (JNJ-64007957) is a BCMA x CD3 bispecific antibody (Ab) that redirects CD3+ T cells to mediate T-cell activation and subsequent lysis of BCMA-expressing myeloma cells. MajesTEC-1 is a multicohort, open-label phase 1/2 study of tec in pts with RRMM who previously received ≥3 prior lines of therapy (LOT). Results from a pooled analysis of phase 1 and phase 2 cohort A (median follow-up 7.8 mo) demonstrated an overall response rate (ORR) of 62.0% in pts with no prior anti-BCMA treatment (tx). We present initial results from cohort C, in which pts had prior exposure to an anti-BCMA tx. **Methods:** Eligible pts (age ≥18 y) had documented MM per IMWG criteria and had received ≥3 prior LOT including a PI, an IMiD, an anti-CD38 Ab, and an anti-BCMA tx (chimeric antigen receptor T [CAR-T] or Ab drug conjugate [ADC]). Pts were enrolled into a Simon's stage design, receiving weekly subcutaneous tec 1.5 mg/kg preceded by step-up doses of 0.06 and 0.3 mg/kg. Primary endpoint was ORR (per IMWG 2016 criteria). AEs were graded per CTCAE v4.03; cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS) were graded per ASTCT guidelines. **Results:** As of Sep 7, 2021, 38 pts in cohort C received tec (63% male; median age 63.5 y [range 32–82]; median prior LOT 6 [range 3–14]). 32 (84%) pts were refractory to last LOT; 25 (66%) were refractory to an anti-BCMA tx. Of 25 pts evaluated for efficacy, 16 (64%) had prior ADC, 11 (44%) prior CAR-T (2 pts received both). With median follow-up of 6.9 mo (range 0.7–8.7), ORR was 40% (95% CI 21–61). 5 pts (20%) achieved a complete response or better. The ORR (95% CI) was 38% (15–65) in ADC-exposed pts and 45% (17–77) in CAR-T–exposed pts. Most responses occurred rapidly; 7/25 pts had responses that deepened over time. Median time (range) to first and best response was 1.2 mo (0.2–4.9) and 2.1 mo (1.1–5.7), respectively. Median duration of response was not reached. The safety profile was comparable with that observed in BMCA tx-naive pts, with no new safety concerns. 16 pts (42%; grade 3/4 26%) had infections. Most common AEs (n = 38) were CRS (63%; all grade 1/2; median [range] time to CRS onset: 3 d [2–6], duration of CRS: 2 d [1–4]), neutropenia (55%; grade 3/4 50%), thrombocytopenia (42%; grade 3/4 29%), anemia (39%; grade 3/4 29%), and lymphopenia (40%; grade 3/4 37%). One pt had grade 3 ICANS that resolved with supportive care; pt remains on tx. No pts developed anti-tec Abs. Baseline BCMA expression was comparable with that observed in BCMA tx-naive pts. Updated efficacy and safety data will be presented for 40 pts. **Conclusions:** Initial results of serial targeting of BCMA with tec following ADC or CAR-T tx suggest a promising ORR with responses occurring early and deepening over time. A well-tolerated safety profile was observed in pts previously treated with anti-BCMA tx. Clinical trial information: NCT04557098. Research Sponsor: Janssen Research & Development, LLC.

8014 **Poster Discussion Session**

Elranatamab, a BCMA-targeted T-cell redirecting immunotherapy, for patients with relapsed or refractory multiple myeloma: Updated results from MagnetisMM-1. *First Author: Andrzej J. Jakubowiak, Department of Medicine, University of Chicago Medical Center, Chicago, IL*

Background: Elranatamab (PF-06863135) is a bispecific molecule that activates and redirects the T-cell mediated immune response against multiple myeloma (MM), a plasma cell dyscrasia characterized by expression of B-cell maturation antigen (BCMA). MagnetisMM-1 (NCT03269136), the ongoing Phase 1 first-in-human study for elranatamab, was designed to characterize safety, pharmacokinetics (PK), pharmacodynamics, and efficacy for patients (pts) with relapsed or refractory MM. **Methods:** Elranatamab was given subcutaneously (SC) at doses from 80 to 1000μg/kg either weekly or every 2 weeks (Q2W). Treatment-emergent adverse events (TEAEs) were graded by Common Terminology Criteria for Adverse Events (v4.03) and cytokine release syndrome (CRS) by American Society for Transplantation and Cellular Therapy criteria. PK, cytokine and soluble BCMA profiling, and lymphocyte subset analyses were performed. Response was assessed by International Myeloma Working Group (IMWG) criteria. Minimal residual disease (MRD) was assessed by next generation sequencing at a sensitivity of 1×10^{-5} in accordance with IMWG criteria. **Results:** A total of 55 pts received single-agent elranatamab SC at a dose ≥215μg/kg as of 1-Nov-2021. Median age was 64 (range 42-80) years, and 27% of pts were Black/African American or Asian. Median number of prior regimens was 6 (range 2-15), 91% were triple-class refractory, 56% had prior stem cell transplantation, 27% had high cytogenetic risk, and 22% received prior BCMA-targeted therapy. The most common TEAEs regardless of causality included CRS, neutropenia, anemia, injection site reaction, and lymphopenia. With pre-medication and a single priming dose (600μg/kg or 44mg), the overall incidence of CRS at the recommended dose (1000μg/kg or 76mg) was 67% and limited to Grade 1 (33%) or Grade 2 (33%), with no events Grade 3 or higher. Exposure was dose dependent and Q2W dosing achieved exposure associated with anti-myeloma efficacy. Cytokine increases occurred with the first dose and were reduced by pre-medication. Soluble BCMA decreased with disease response, elranatamab therapy was associated with increased peripheral T cell proliferation, and median time to response was 36 days (range 7-73). With a median follow-up of 8.1 months (range 0.3-21) and including only IMWG confirmed responses, 31% of pts achieved complete response or better and the overall response rate was 64% (95% CI 50-75%). For responders (n = 35), median duration of response was not yet reached, but the probability of being event-free at 6 months was 91% (95% CI 73-97%). Single-agent elranatamab induces durable clinical and molecular responses, and updated data including MRD assessment will be presented. **Conclusions:** Elranatamab shows a manageable safety profile and achieves durable clinical and molecular responses for pts with relapsed or refractory MM. Clinical trial information: NCT03269136. Research Sponsor: This study was sponsored by Pfizer.

8015 **Poster Discussion Session**

Efficacy and safety of talquetamab, a G protein-coupled receptor family C group 5 member D x CD3 bispecific antibody, in patients with relapsed/refractory multiple myeloma (RRMM): Updated results from MonumenTAL-1. *First Author: Monique C. Minnema, University Medical Center Utrecht, Utrecht, Netherlands*

Background: G protein-coupled receptor family C group 5 member D (GPRC5D), which has limited expression in normal human tissue but is highly expressed on malignant plasma cells, is a promising target for multiple myeloma (MM) immunotherapy. Talquetamab (JNJ-64407564) is a first-in-class, bispecific IgG4 antibody that binds to both GPRC5D and CD3 receptors, mediating T-cell–activated lysis of GPRC5D+ MM cells. Here we report updated results with additional patients (pts) and longer follow-up from MonumenTAL-1, a phase 1 trial of talquetamab in RRMM (NCT03399799). **Methods:** Eligible pts had RRMM or were intolerant to standard therapies; prior B-cell maturation antigen-directed therapies were permitted. The primary objectives were to identify the recommended phase 2 doses (RP2Ds) (part 1) and assess talquetamab safety and tolerability at the RP2Ds (part 2). Collective safety, efficacy, PK, and PD data supported 2 RP2Ds for talquetamab: 405 μg/kg SC QW (n = 30) and 800 μg/kg SC Q2W (n = 44). Step-up dosing was used to mitigate against severe cytokine release syndrome (CRS); required premedications were limited to step-up doses and the first full dose of talquetamab. Adverse events (AEs) were graded by CTCAE v4.03 with CRS events graded per Lee et al 2014 criteria. Investigators assessed responses per International Myeloma Working Group criteria. **Results:** As of Jan 17, 2022, pts in the 405 μg/kg/800 μg/kg groups, respectively, received a median of 6 /5 prior lines of therapy, 100%/98% were triple-class (TC) exposed, 77%/75% were TC refractory. Median follow-up (range) was 11.7 (1.0–21.2)/4.2 (0.7–13.7) months. Most AEs were grade 1 or 2. The most common AEs were cytopenias and CRS. Cytopenias (including neutropenia [67%/36%; grade 3/4: 53%/23%]) were reversible, mostly confined to step-up and cycle 1–2 doses, and generally resolved within 1 week. Infections occurred in 47%/34% (grade 3/4: 7%/9%) of pts. CRS (77%/80%; grade 3: 3%/0%) mostly occurred during step-up dosing. Skin-related and nail disorder AEs occurred in 83%/75% of pts (most commonly skin exfoliation: 37%/39% [all grade 1 and 2]). Dysgeusia (63%/57%) was generally mild and managed with dose adjustments. The overall response rates in response-evaluable pts were 70% (21/30 pts)/64% (28/44 pts); very good partial response or better rate: 57%/52%; median time to first confirmed response (range): 0.9 (0.2–3.8)/1.2 (0.3–6.8) months. Median duration of response will be reported. No pts died due to drug-related AEs. The PK and PD profiles of both RP2Ds appear comparable. **Conclusions:** These data show that both RP2Ds of talquetamab have comparable safety, efficacy, and pharmacokinetic profiles and confirm talquetamab as a novel, first-in-class therapy with highly promising efficacy in a heavily pretreated RRMM pt population. Clinical trial information: NCT03399799. Research Sponsor: Janssen Research & Development, LLC.

8016 **Poster Discussion Session**

Comparative efficacy of teclistamab (tec) versus current treatments (tx) in real-world clinical practice in the prospective LocoMMotion study in patients (pts) with triple-class exposed (TCE) relapsed/refractory multiple myeloma (RRMM). *First Author: Niels W.C.J. van de Donk, Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, Netherlands*

Background: Pts with TCE RRMM who have been exposed to ≥3 lines of therapy (LOT) have a poor prognosis and limited tx options. Tec is a B-cell maturation antigen × CD3 bispecific antibody being evaluated in MajesTEC-1 (NCT04557098), a single-arm, phase 1/2 study in pts with RRMM who were TCE to an immunomodulatory drug, a proteasome inhibitor, and an anti-CD38 antibody and received ≥3 LOT. Since MajesTEC-1 lacks a control arm, we assessed the comparative efficacy of tec vs tx currently used in real-world clinical practice (RWCP) by creating an external real-world control arm from LocoMMotion (NCT04035226), a prospective study of RWCP efficacy and safety outcomes in pts with TCE RRMM who received ≥3 LOT. **Methods:** An external control arm for MajesTEC-1 was created from pts in LocoMMotion (248 pts, clinical cutoff May 21, 2021) who met MajesTEC-1 eligibility criteria. Individual pt-level data from MajesTEC-1 were included from 150 pts treated with tec (1.5 mg/kg weekly) at a clinical cutoff of Sep 7, 2021. Inverse probability of tx weighting with average tx effect on the treated was used to adjust for imbalances in baseline covariates of prognostic significance (refractory status, International Staging System stage, time to progression on prior LOT, extramedullary disease, number of prior LOT, time since diagnosis, average duration of prior LOT, age, hemoglobin, lactate dehydrogenase, creatinine clearance, Eastern Cooperative Oncology Group performance status, gender, type of MM, and prior transplant). Comparative efficacy of tec vs RWCP was estimated for overall response rate (ORR), very good partial response (VGPR) rate, complete response or better (≥CR) rate, duration of response (DOR), progression-free survival (PFS), and overall survival (OS). For binary endpoints (ORR, VGPR rate, and ≥CR rate), relative effect of tec vs RWCP was estimated with an odds ratio, transformed into a response-rate ratio (RR) and 95% confidence interval (CI), derived from weighted logistic regression. A weighted Cox proportional hazards model was used to compute hazard ratios (HRs) and 95% CIs for time-to-event endpoints (DOR, PFS, and OS). **Results:** Baseline characteristics were well balanced between the 2 cohorts after reweighting the external RWCP cohort. Pts treated with tec had improved outcomes vs tx used in RWCP: ORR (RR 2.31; 95% CI 1.75–2.87; $P<0.0001$), VGPR rate (RR 5.54; 95% CI 3.38–7.70; $P<0.0001$), ≥CR rate (RR 91.50; 95% CI 12.66–661.43; $P<0.0001$), DOR (HR 0.17; 95% CI 0.08–0.36; $P<0.0001$), PFS (HR 0.47; 95% CI 0.34–0.67; $P<0.0001$), and OS (HR 0.69; 95% CI 0.46–1.05; $P=0.08$). **Conclusions:** Tec showed significantly improved efficacy over RWCP for almost all outcomes, highlighting its potential as a highly effective tx option for pts with TCE RRMM who have been exposed to ≥3 LOT. Research Sponsor: Janssen Global Services, LLC.

8017 **Poster Discussion Session**

Safety and clinical activity of belantamab mafodotin with lenalidomide plus dexamethasone in patients with relapsed/refractory multiple myeloma (RRMM): DREAMM-6 arm-A interim analysis. *First Author: Hang Quach, University of Melbourne, St. Vincent's Hospital Melbourne, Melbourne, VIC, Australia*

Background: Belantamab mafodotin (belamaf; BLENREP) is a B-cell maturation antigen-targeting antibody–drug conjugate approved for patients (pts) with RRMM as monotherapy at 2.5 mg/kg Q3W. Preclinical data demonstrate synergy between belamaf and lenalidomide (Len), suggesting added benefit when combined with standard of care such as Len + dexamethasone (Dex). DREAMM-6 (NCT03544281) Arm A is evaluating belamaf in combination with LenDex in pts with RRMM. **Methods:** This ongoing, two-part, two-arm, open-label study included pts with RMMM previously treated with ≥1 line of therapy (LOT). Pts received 4 belamaf doses/schedules (1.9 mg/kg Q8W or Q4W; 2.5 mg/kg Q4W or Q4W SPLIT dose [50% on Days (D)1, 8] IV) in combination with Len (20 mg PO D1–21) and Dex (20 mg PO/IV D1, 8, 15, 22). Primary objectives were safety (including treatment-related [TR]AEs related to the combination belamaf and LenDex), tolerability, and efficacy (including overall response rate [ORR] defined as ≥partial response). **Results:** As of this interim analysis (data cut: July 23, 2021), 45 pts received ≥1 dose (12 at 1.9 mg/kg Q8W; 4 at 1.9 mg/kg Q4W; 16 at 2.5 mg/kg Q4W; 13 at 2.5 mg/kg Q4W SPLIT). Across cohorts, the median age was 68 y (range: 36–80). Thirteen pts (29%) had high-risk cytogenetics and 6 (13%) had extramedullary disease. Median prior LOT was 3 (range: 1–11) and 26 (58%) had prior Len treatment. The median duration of follow-up and ORR ranged across cohorts (Table). The median duration of response was only reached in the 1.9 mg/kg Q4W cohort (11.1 mo [95% CI: 3.7–not reached [NR]). At the time of data cut, median progression-free survival was not reached in the 1.9 mg/kg Q8W or 2.5 mg/kg Q4W cohorts. Gr ≥3 TRAEs occurred in 42–85%. Gr ≥3 keratopathy occurred in 0 pts in 1.9 mg/kg Q8W, 1 pt (25%) in 1.9 mg/kg Q4W, 8 pts (50%) in 2.5 mg/kg Q4W, and 6 pts (46%) in 2.5 mg/kg Q4W SPLIT cohorts. **Conclusions:** Belamaf + LenDex had a tolerable safety profile, with no new safety signals identified in pts with RRMM. AEs, including keratopathy, were common but manageable with dose modifications. Encouraging clinical activity is observed with this combination in pts with RRMM. Follow-up/correlative studies are ongoing. Funding: GSK (Study 207497); drug linker technology licensed from Seagen Inc.; mAb produced using POTELLIGENT Technology licensed from BioWa. Clinical trial information: NCT03544281. Research Sponsor: GlaxoSmithKline.

Follow-up, ORR, and safety.

n, (%), unless specified	Belamaf 1.9 mg/kg Q8W + LenDex n=12	Belamaf 1.9 mg/kg Q4W + LenDex n=4	Belamaf 2.5 mg/kg Q4W + LenDex n=16	Belamaf 2.5 mg/kg Q4W SPLIT + LenDex n=13
Duration of follow-up, median, mo	3.4	17.4	16.2	12.0
ORR	5 (42)	3 (75)	10 (63)	9 (69)
≥Very good partial response	2 (17)	2 (50)	8 (50)	5 (38)
Gr ≥3 TRAEs	5 (42)	2 (50)	13 (81)	11 (85)
AEs leading to dose interruption/delay	11 (92)	3 (75)	13 (81)	12 (92)
Serious TRAEs	2 (17)	0	3* (19)	3 (23)

*Includes 1 fatal serious TRAE (febrile neutropenia).

8018 **Poster Discussion Session**

Safety and clinical activity of belantamab mafodotin with pembrolizumab in patients with relapsed/refractory multiple myeloma (RRMM): DREAMM-4 Study. *First Author: Attaya Suvannasankha, Indiana University Simon Cancer Center and Roudebush VAMC, Indianapolis, IN*

Background: Belantamab mafodotin (belamaf; BLENREP), a B-cell maturation antigen (BCMA) targeted antibody–drug conjugate approved for adult patients with RRMM, has a multimodal mechanism that eliminates myeloma cells via direct cytotoxicity and a systemic anti-tumor immune response, which may be augmented by an immune checkpoint inhibitor. DREAMM-4 (NCT03848845) assessed safety and clinical activity of belamaf with pembrolizumab (pembro) in RRMM. **Methods:** This was a Phase I/II, single-arm, open-label study of adults with RRMM after ≥3 lines of therapy (LOT, including anti-CD38 monoclonal antibody, proteasome inhibitor, and immunomodulator). Part 1 established the dose of belamaf 2.5 mg/kg with pembro 200 mg, both IV Q3W up to 35 cycles, for the Part 2 expansion. Primary efficacy endpoint was investigator-assessed overall response rate (ORR, ≥partial response [PR] per IMWG criteria by investigator). Secondary endpoints included duration of response (DoR), progression-free survival (PFS), adverse events (AEs) per NCI-CTCAE v4.03, and pharmacokinetics (PK). **Results:** This primary analysis of all treated pts (as of Oct 18, 2021) included 34 pts (6 in Part 1 and 28 in Part 2). In both parts, median prior LOT was 5 (range 3–13); 10 pts (29%) had high-risk cytogenetics and 9 (26%) had extramedullary disease. ORR was 47%, with most responses (10/16 pts) ≥ very good PR (VGPR, Table). Median follow-up was 14.7 months (mo); median (95% CI) DoR was 8.0 (2.1–not reached) mo; median PFS was 3.4 (1.4–5.6) mo. Most pts had ≥1 AE (any grade [Gr]: 97%; Gr ≥3: 74%) and treatment-related AE (TRAE, any Gr: 97%; Gr ≥3: 65%). Most common (≥35%) AEs were keratopathy (any Gr: 76%; Gr ≥3: 38%), vision blurred (any Gr: 38%; Gr ≥3: 0%), and thrombocytopenia (any Gr: 35%; Gr ≥3: 29%). AEs led to dose delays (65%) and dose reductions (32%), but not discontinuation. Nine pts had a serious AE (SAE); 4 pts had ≥1 SAE related to study treatment. Two pts had immune-related AEs of Gr 1 (gout and autoimmune hypothyroidism). Preliminary PK and soluble BCMA data were consistent with single-agent belamaf therapy. **Conclusions:** Belamaf + pembro demonstrated a favorable ORR compared with single-agent belamaf in heavily pre-treated RRMM. No new TRAEs were identified; AE frequency and severity were similar to single-agent belamaf. Correlative biomarker studies are ongoing. Clinical trial information: NCT03848845. Research Sponsor: GSK (205207), Pharmaceutical/Biotech Company.

Response, n (%)	Belamaf 2.5 mg/kg + pembro 200 mg Q3W Part 2 (N=28)	Belamaf 2.5 mg/kg + pembro 200 mg Q3W Parts 1 and 2 (N=34)
ORR, n (%) [95% CI]	12 (43) [25.4–62.8]; p=0.4490	16 (47) [29.8–64.9]
≥VGPR, n (%) [95% CI]	7 (25) [10.7–44.9]	10 (29) [15.1–47.5]
sCR	0	0
CR	2 (7)	4 (12)
VGPR	5 (18)	6 (18)
PR	5 (18)	6 (18)
SD	6 (21)	8 (24)
PD	8 (29)	8 (24)
NE	2 (7)	2 (6)

CR, complete response; NE, not evaluable; PD, progressive disease; sCR, stringent CR; SD, stable disease.

8019 **Poster Discussion Session**

Synergistic effects of low-dose belantamab mafodotin in combination with a gamma-secretase inhibitor (nirogacestat) in patients with relapsed/refractory multiple myeloma (RRMM): DREAMM-5 study. *First Author: Sagar Lonial, Emory University, Winship Cancer Institute, Atlanta, GA*

Background: Preclinical data demonstrate that nirogacestat, a gamma-secretase inhibitor, may increase cell-surface levels of a B-cell maturation antigen (BCMA) and reduce soluble BCMA levels, which could enhance anti-BCMA agent activity in multiple myeloma. In the DREAMM-5 (NCT04126200) Phase I/II platform trial belantamab mafodotin (belamaf; BLENREP), a BCMA-targeting antibody-drug conjugate, is being evaluated in combination with nirogacestat to determine if the combination can result in similar efficacy and an improved ocular safety profile compared to the currently approved belamaf schedule (single agent dose 2.5 mg/kg Q3W) in patients with RRMM which showed a 31% overall response rate (ORR) and 44.5% Gr3/4 keratopathy (BLENREP US prescribing information). **Methods:** This cohort within the DREAMM-5 nirogacestat combination sub-study has a sequential dose-exploration (DE) phase evaluating 0.95 mg/kg Q3W belamaf with 100 mg BID nirogacestat continuously, followed by a randomized cohort expansion (CE) comparing the combination to a belamaf 2.5 mg/kg Q3W arm. **Results:** Preliminary results from the 10 patients (pts) in the DE cohort with low-dose belamaf + nirogacestat are presented in this abstract. Pts had a median (range) of 4.5 (3–10) prior lines of therapy. At time of data cut-off (Nov 15, 2021), pts received a median (range) of 7 cycles (1–26). The ORR was 60% (n=6/10) and 20% (n=2) achieved a very good partial response (Table). The key emergent adverse events (AEs) included ocular events (n=7 [70%]; ≥Grade [Gr] 3, n=2 [20%] of which Gr 3 keratopathy was reported in 1 pt [10%]), diarrhea (n=7 [70%]; Gr 3, n=1 [10%]) and hypophosphatemia (n=7 [70%]; Gr 3, n=1, [10%]). There were 2 Grade 5 AEs, neither of which were related to study treatment. No pt permanently discontinued study due to treatment related AEs. **Conclusions:** Encouraging clinical activity and a manageable safety profile is observed with low dose belamaf (0.95 mg/kg Q3W) + nirogacestat (100 mg BID continuously) in pts with RRMM. This ongoing sub-study is actively recruiting patients and will continue to evaluate belamaf + nirogacestat efficacy and safety. Updated results will be reported at the congress. Funding: GSK (208887); drug linker technology licensed from Seagen Inc.; mAb produced using POTELLIGENT Technology licensed from BioWa. Clinical trial information: NCT04126200. Research Sponsor: GSK 208887.

Response and safety.

	DE Cohort N=10n (%)
Overall response rate	6 (60)
Very good partial response	2 (20)
Partial response	4 (40)
AEs (Gr ≥3)	8 (80)
Diarrhea	Gr 1/2: 6 (60)Gr 3: 1 (10)
Hypophosphatemia	Gr 1/2: 6 (60)Gr 3: 1 (10)
Ocular events[a]	Gr 1/2: 5 (50) Gr 3: 2 (20)
Keratopathy	Gr 1/2: 1 (10)Gr 3: 1 (10)

[a]CTCAE5 (based on visual acuity and ocular symptoms and reported by investigators).

8020 **Poster Discussion Session**

Biological correlative analyses and updated clinical data of ciltacabtagene autoleucel (cilta-cel), a BCMA-directed CAR-T cell therapy, in lenalidomide (len)-refractory patients (pts) with progressive multiple myeloma (MM) after 1–3 prior lines of therapy (LOT): CARTITUDE-2, cohort A. *First Author: Hermann Einsele, Universitätsklinikum Würzburg, Medizinische Klinik und Poliklinik II, Würzburg, Germany*

Background: Cohort A of the multicohort phase 2 CARTITUDE-2 (NCT04133636) study is evaluating cilta-cel safety and efficacy in pts with MM who received 1–3 prior LOT and were len-refractory – a difficult-to-treat population with poor prognosis. We present updated results. **Methods:** Pts had progressive MM after 1–3 prior LOT, including a PI and IMiD, were len-refractory, and had no prior exposure to BCMA-targeting agents. A single cilta-cel infusion (target dose 0.75×10^6 CAR+ viable T cells/kg) was given post lymphodepletion. Safety and efficacy were assessed, and the primary endpoint was MRD negativity at 10^{-5}. Management strategies were implemented to minimize risk of movement/neurocognitive AEs (MNTs). Pharmacokinetic (PK) analyses (C_{max} and T_{max} of CAR+ T-cell transgene levels in blood) are being conducted, as well as analyses of levels of CRS-related cytokines (eg, IL-6) over time, peak levels of cytokines by response and CRS, association of cytokine levels with ICANS, and CAR+ T cell CD4/CD8 ratio by response, CRS, and ICANS. **Results:** As of January 2022 (median follow-up [MFU] 17.1 mo [range 3.3–23.1]), 20 pts (65% male; median age 60 y [range 38–75]) received cilta-cel. Pts received a median of 2 (range 1–3) prior LOT, and a median of 3.5 y (range 0.7–8.0) since MM diagnosis. 95% were refractory to last LOT, and 40% were triple-class refractory. ORR was 95%, 90% achieved CR or better, and 95% had ≥VGPR. Median times to first and best response were 1.0 mo (range 0.7–3.3) and 2.6 mo (range 0.9–13.6), respectively. 16 pts were MRD-evaluable, all of whom achieved MRD negativity at 10^{-5}. Median DOR was not reached and 12-mo event-free rate was 79%. The 12-mo PFS rate was 75%. Median time to onset of CRS was 7 d (range 5–9) and occurred in 95% of pts (gr 3/4: 10%), with median duration of 3 d (range 2–12). Neurotoxicity occurred in 30% of pts (5 gr 1/2; 1 gr 3/4). 3 pts (15%) had ICANS (all gr 1/2); 1 pt had gr 2 facial paralysis. No MNTs were seen. 1 death occurred due to COVID-19 (assessed as tx-related by the investigator), 2 due to progressive disease, and 1 due to sepsis (not related to tx). Preliminary PK analyses indicate that peak expansion of CAR-T cells occurred at d 10.5 (range 8.7–42.9) and median persistence was 153.5 d (range 57.1–336.8). **Conclusions:** At a longer MFU of 17.1 mo, a single cilta-cel infusion led to deepening and durable responses in pts with MM who had 1–3 prior LOT and were len-refractory. Follow-up is ongoing. Updated and in-depth PK, cytokine, and CAR-T subset analyses and clinical correlation will be presented and provide novel insights into biological correlates of efficacy and safety in this pt population. This pt population is being further evaluated in the CARTITUDE-4 study (NCT04181827), which has concluded enrollment. Clinical trial information: NCT04133636. Research Sponsor: Janssen Research & Development, LLC, Pharmaceutical/Biotech Company.

8021 **Poster Discussion Session**

Correlative analysis to define patient profiles associated with manufacturing and clinical endpoints in relapsed/refractory multiple myeloma (RRMM) patients treated with idecabtagene vicleucel (ide-cel; bb2121), an anti-BCMA CAR T cell therapy.

First Author: Julie Rytlewski, Bristol Myers Squibb, Princeton, NJ

Background: The anti-BCMA autologous CAR T cell therapy ide-cel has achieved deep and durable responses in RRMM patients (Munshi, N Engl J Med 2021). Prior studies have described the correlation between patient characteristics and clinical outcomes from CD19 CAR T cell therapy (Finney, J Clin Invest 2019; Fraietta, Nat Med 2018). We sought to define patient profiles correlated with manufacturing and clinical endpoints in RRMM patients treated with ide-cel in clinical trials using unsupervised clustering and multivariate machine learning across multiple key variable domains. **Methods:** Clinical and manufacturing data were harmonized across 164 RRMM patients treated with ide-cel in KarMMa (NCT03361748) and KarMMa-2 cohort 1 (NCT03601078). Based on individual multivariate importance, 10 selected peripheral blood mononuclear cell (PBMC), drug product (DP), and in-process cell growth variables were used to define patient clusters. Random forest classifiers were generated to identify patient characteristics associated with manufacturing and clinical endpoints. Wilcoxon rank sum and Kruskal-Wallis tests were used to compare 2 and 3+ categorical groups; Cox proportional hazards were used to compare groups with time-to-event data. **Results:** Using an unsupervised method, 4 patient clusters were identified that represented 10%, 57%, 15%, and 18%, respectively, of the total 164 patients. Cluster 4 was the most favorable and was characterized by a higher frequency of T cells in PBMCs; increased T-cell size during manufacturing; higher DP T-cell transduction, potency, and vector copy number; and ultimately a > 3-fold higher CAR T cell yield compared with the least favorable cluster 1. Cluster 2 contained most patients and was associated with intermediate manufacturing endpoints. Patients in cluster 4 had a higher complete response rate, longer progression-free survival, and were defined by lower tumor burden, higher absolute lymphocyte count (ALC), and longer washout period after alkylator treatment, among others (Table). **Conclusions:** The current study identified patient profiles in RRMM using accessible laboratory or medical history data that correlated with longitudinal outcomes. These findings may inform patients likely to achieve improved outcomes with CAR T cell therapy. Clinical trial information: NCT03361748. Research Sponsor: 2seventy bio, formerly bluebird bio, Pharmaceutical/Biotech Company.

Select patient variables across clusters.

Variable Median [Q1-Q3]	Cluster 1 n = 17	Cluster 2 n = 94	Cluster 3 n = 24	Cluster 4 n = 29
Monoclonal protein (g/L)†	12.08 [8.07-21.33]	10.73 [5.50-21.51]	7.36 [4.95-13.38]	7.00 [4.65-11.07]
ALC (10^9/L)†	0.50 [0.29-0.78]	0.85 [0.54-1.36]	0.67 [0.49-0.86]	0.91 [0.62-1.26]
Patients with alkylator exposure within 6 months*(%)	47	31	29	24

†Assessment at screening timepoint *Time of last exposure is measured relative to date of apheresis.

8022 **Poster Session**

Prognostic value of early bone marrow MRD status in CAR-T therapy for myeloma.

First Author: Radhika Bansal, Division of Hematology, Mayo Clinic, Rochester, MN

Background: Bone marrow (BM) assessment of minimal residual disease (MRD) is being considered as a surrogate endpoint in clinical trials and is prognostic for survival in multiple myeloma (MM). Timing of BM assessment is variable across Chimeric Antigen Receptor T cell (CART) therapy trials and differs from standard of care practice. BM myeloma cell clearance can be detected by month 1 post CART, even before serum immunofixation becomes negative. BM is still hypocellular at month 1, thus prognostic value of MRD negative (MRDneg) at this timepoint is unclear. We examined impact of Day 30 MRD status in patients (pts) who received CART at Mayo Clinic. **Methods:** Medical records were reviewed retrospectively for MM pts who received CART between 8/2016 and 6/2021. PFS and OS were plotted by Kaplan-Meier method. **Results:** Sixty MM pts received CART and had BM biopsy at month 1. Median age was 62 yrs, 53% were male, and 78% were BM MRDneg by flow cytometry. Baseline demographics were similar between MRDneg and MRD+ (Table). Overall, 85% (40/47) who were month 1 BM MRDneg had i/u FLC<normal. Patients who achieved CR/sCR had higher rates of BM MRDneg (100% vs 61%, p<0.001) and i/u FLC< normal (89% vs 58%, p<0.001). At month 1, 24/60 (40%) pts had hypocellular BM. Serial BM samples at month 3 (n=35), 6 (n=28) and 12 (n=23) showed MRDneg rate of 93% (25/27), 56% (9/16) 58% (7/12), respectively. . Rate of hypocellularity was 54% (19/35), 32% (9/28) and 30% (7/23), respectively. Among the MRDneg/hypocellular pts at month 1, hypocellular BM was seen in 8/11 (73%) pts at month 3 and 2/4 (50%) pts at month 6 and 12. Compared to MRD+, pts who had BM MRDneg at months1 had longer PFS (Table). PFS was not statistically significantly different between pts who had BM MRDneg and were either hypocellular or not. MRDneg pts with i/u FLC<normal at months1 had better median PFS compared to those who did not. (MRD+:2.9 months (1.2-NR). MRDneg/FLC>normal: 4.9 months (2.3-NR). vs MRDneg/FLC<normal:17.9 months (11.8-NR), p<0.0001). **Conclusions:** Hypocellular BM is common in the 3 months post CART. Regardless of BM cellularity, BM MRDneg at month 1 correlates with deep response and prolonged PFS. Majority of BM MRDneg pts at month 1 also had FLC<normal. BM MRDneg status and FLC normalization were associated with longer survival. Our data support the continued evaluation of BM early post CART infusion as a prognostic tool. Research Sponsor: None.

Patient demographics and outcomes.

Variable	All pts (N=60)	MRDneg (N=47)	MRD+ (N=13)	P- Value
High risk cytogenetics, n(%)	28 (70)*	21 (70)	7 (70)	1.0
ISS Stage II/III, n (%)	14 (31)	11 (31)	3 (30)	0.9
Bridging therapy, n (%)	46 (77)	39 (83)	7 (54)	0.03
Plasmacytoma, n(%)	16 (27)	14 (30)	2 (15)	0.3
Cytokine release syndrome, all grade, n (%)	45 (75)	36 (77)	9 (69)	0.6
ICANS, all grade, n(%)	13 (22)	11 (23)	2 (15)	0.5
FLC depletion, n(%)	43 (72)	40 (85)	3 (23)	<0.001
Best response- CR/sCR, n(%)	27 (45)	27 (57)	0 (0)	<0.001
Progression free survival (95% CI)	10.4 (6.0-17.9)	17.5 (10.4-NR)	2.9(1.2-NR)	<0.0001

8023 **Poster Session**

Association of socioeconomic status with adherence to oral agents in patients with multiple myeloma.

First Author: Wilbur Rutter, CVS Health, Lincoln, RI

Background: The introduction of novel oral immunomodulatory drugs has improved the overall survival rates of patients with multiple myeloma (MM). Poor adherence to oral therapies may lead to drug resistance, poor response to treatment and other downstream effects. It is unknown if socioeconomic status (SES) mediates adherence to oral MM agents. **Methods:** This is a retrospective review of newly diagnosed adult patients with MM with drug coverage through a large pharmacy benefit manager (PBM) who received oral MM agents between September 1, 2016 and September 1, 2020. Patients were excluded if they were not eligible for PBM benefits for the 6 months prior to or the 12 months after the index date and if they had a stem cell transplant based on a proxy signal. Adherence was defined as an annual medication possession ratio between 0.8 and 1.2. An SES composite index was developed using ZIP code level factors in a K-means clustering algorithm. Multivariable logistic regression for adherence was conducted using the SES-index and controlled for other patient-specific demographics. **Results:** In total, 6,602 patients were enrolled in the study, of which, 4,211 (64.5%) were defined as adherent. There were significant unadjusted differences in age (67.89 vs 64.06, p<0.00001), ZIP code-based SES index (p=0.00049), census region (p<0.00001) and insurance plan type (p<0.00001). Results from multivariable logistic regression are shown in table. Patients residing in Very Low SES ZIP codes were significantly less likely to be adherent to oral MM agents compared to those residing in Very High SES locations. Odds of adherence increased as patient's age increased. Increasing polypharmacy was negatively associated with oral MM agent adherence. **Conclusions:** Aside from patients residing in Very Low SES ZIP codes, ZIP code-based SES measures were not associated with worse adherence. Other mediating factors include younger age and number of co-prescribed medications. Further investigations of adherence to oral MM agents with clinically relevant outcomes are warranted. Research Sponsor: None.

Variable	OR (95% CI)	p-value
Zip code SES composite index		
Very Low	0.75 (0.56–1)	0.048
Low	0.81 (0.62–1.07)	0.14
Medium	0.85 (0.64–1.12)	0.24
High	0.9 (0.68–1.19)	0.47
Very High	*(reference)*	-
Age		
< 50	0.79 (0.64–0.97)	0.022
50–64	*(reference)*	-
65–84	1.71 (1.5–1.94)	< 0.00001
≥85	2.11 (1.58–2.83)	0.00001
Polypharmacy		
None (<10)	*(reference)*	-
Mild (10–13)	0.66 (0.57–0.76)	< 0.00001
Moderate (14–18)	0.46 (0.4–0.53)	< 0.00001
Extreme (≥19)	0.34 (0.29–0.39)	< 0.00001

8024 **Poster Session**

Pomalidomide, bortezomib, and dexamethasone in lenalidomide-pretreated multiple myeloma: A subanalysis of OPTIMISMM by frailty.

First Author: Albert Oriol Rocafiguera, Hematology Department, Institut Català d'Oncologia, Carretera de Canyet s/n, Barcelona, Spain

Background: Patients (pts) with multiple myeloma (MM) are likely to be older adults, and advanced age is associated with lower survival rates, in part due to comorbidities and frailty. Results from the phase 3 OPTIMISMM trial (NCT01734928) demonstrated that pomalidomide (P) in combination with bortezomib + dexamethasone (Vd) significantly improved progression-free survival (PFS) in lenalidomide (LEN)-pretreated pts with relapsed/refractory MM (RRMM) vs Vd, irrespective of age and Eastern Cooperative Oncology Group performance status (ECOG PS). Here, we report results from a post hoc analysis assessing outcomes of PVd vs Vd in pts with RRMM by frailty status. **Methods:** Pts with MM and 1–3 prior lines of therapy (including a LEN-containing regimen) who had been randomized 1:1 to PVd or Vd were assessed for frailty. Frailty scores were calculated using age (≤ 75 yr = 0; 76–80 yr = 1; > 80 yr = 2), the Charlson Comorbidity Index (≤ 1 = 0; > 1 = 1) and ECOG PS (0 = 0; 1 = 1; ≥ 2 = 2). Pts were classified as non-frail (NF; combined score: 0 or 1) or frail (F; combined score: ≥ 2). PFS, overall response rate (ORR), and safety outcomes were assessed by treatment group and frailty status. **Results:** In the intent-to-treat population (N = 559) (data cutoff Oct 26, 2017), 93/281 (33.1%) pts who received PVd and 93/278 (33.5%) who received Vd were frail. Baseline characteristics were similar between treatment groups within each frailty subgroup. Median PFS was longer with PVd vs Vd in NF ($P = 0.001$) and F ($P = 0.006$) subgroups (Table). ORR was higher with PVd vs Vd in NF ($P < 0.001$) and F ($P < 0.001$) subgroups. Incidence of grade ≥ 3 (G3) treatment-emergent adverse events (TEAEs) was higher with PVd vs Vd in NF (88.1 vs 61.3%) and F (96.8 vs 87.9%) subgroups; peripheral neuropathy, acute renal failure, and hypertension were the most common. Treatment discontinuation due to G3 TEAEs was greater with PVd vs Vd in NF (19.2 vs 18.5%) and F (30.1 vs 20.9%) subgroups. PVd had a longer median treatment duration vs Vd in NF (8.8 vs 5.7 mo) and F (8.9 vs 4.3 mo) subgroups. **Conclusions:** Frail pts with RRMM who received PVd had longer PFS and higher ORR than pts who received Vd, consistent with the overall OPTIMISMM results. Frail pts experienced more G3 TEAEs and treatment discontinuations with PVd vs Vd, but treatment duration was longer with PVd vs Vd. Clinical trial information: NCT01734928. Research Sponsor: Celgene, a Bristol-Myers Squibb Company.

Efficacy outcomes for pts in OPTIMISMM who received PVd vs Vd, by frailty level.

	NF PVd (n = 180)	NF Vd (n = 179)	F PVd (n = 93)	F Vd (n = 93)
Median PFS, mo	14.7	8.3	9.7	5.1
ORR,[a] n (%)	149 (82.8)	96 (53.6)	74 (79.6)	39 (41.9)
sCR	7 (3.9)	1 (0.6)	2 (2.2)	1 (1.1)
CR	22 (12.2)	8 (4.5)	9 (9.7)	1 (1.1)
VGPR	69 (38.3)	28 (15.6)	31 (33.3)	11 (11.8)
PR	51 (28.3)	59 (33.0)	32 (34.4)	26 (28.0)
SD	23 (12.8)	63 (35.2)	9 (9.7)	41 (44.1)
PD	3 (1.7)	11 (6.1)	8 (8.6)	5 (5.4)
OR for ORR (95% CI)[b]	4.45 (2.68–7.39)[c]		6.63 (3.18–13.83)[c]	

[a]ORR includes PR or better; [b]OR calculated as PVd vs Vd; [c]$P < 0.001$.

8025 **Poster Session**

Subcutaneous (SC) isatuximab administration by an on-body delivery system (OBDS) in combination with pomalidomide-dexamethasone (Pd) in patients with relapsed/refractory multiple myeloma (RRMM): Interim phase 1b study results. *First Author: HANG QUACH, St. Vincent's Hospital, University of Melbourne, Melbourne, VIC, Australia*

Background: Intravenous (IV) isatuximab (Isa) + Pd is approved for the treatment of RRMM patients (pts). SC delivery would optimize convenience of administration. Prior results showed that SC Isa administered by syringe pump has efficacy and safety profiles comparable to IV Isa; the recommended Phase 2 dose (RP2D) was 1400 mg (IMW21 P-207). **Methods:** This multicenter Phase 1b study evaluated safety, PK and efficacy of SC vs IV Isa + Pd in RRMM pts after ≥2 prior treatment lines. Pts were randomized 2:1 to SC1000 mg or IV 10 mg/kg and to SC1400 mg or IV. An expansion cohort was later implemented with SC Isa administered at the RP2D via OBDS, a wearable bolus injector applied to the abdomen by a healthcare professional. Primary endpoints (EPs) were safety, including injection site reactions (ISRs), and PK. Main secondary EPs were overall response rate (ORR) and progression-free survival (PFS). **Results:** 56 pts were randomized and treated: 12 Isa IV, 12 Isa SC1000, 10 Isa SC1400 and 22 OBDS pts. At study entry, ISS stage II–III was 67% in IV, 33% in SC1000, 60% in SC1400 and 50% in OBDS pts. On Jan 20, 2022, 33% IV, 25% SC1000, 50% SC1400 and 86% OBDS pts remained on treatment. Due to sequential accrual, median follow-up (FU) was longer in IV (20.6 mo) and SC1000 (23.8 mo) than SC1400 (18.1 mo) and OBDS (6.5 mo) pts. Infusion reactions (IRs) were infrequent (≤10% in each cohort, all Grade [G] 2), only at first IV or SC infusion/injection, with no IRs in OBDS. Local tolerability of OBDS was very good, with 5 (22.7%) pts experiencing 7 ISR episodes, all G1, out of 305 administrations (2.3%): 5 injection site erythemas, 1 injection site hemorrhage, and 1 injection site induration. Median duration of OBDS injection was 10 min. Incidence of G4 neutropenia was lower in SC1000 (42%) vs the other cohorts (55–60%). The lower % of ≥G3 treatment-related AEs in OBDS (77%) vs the other cohorts (≥80%) may be due to shorter FU. Best overall responses are shown in table; longer FU is needed for OBDS pts. Median PFS was 22 mo in IV, 12.5 mo in SC1000 and not reached in SC1400 and OBDS pts. PK and CD38 receptor occupancy results in OBDS pts are consistent with those observed in SC1400 with pump. **Conclusions:** SC Isa administered by OBDS shows a safety profile consistent with IV administration with no IRs and excellent local tolerability. Efficacy in the SC cohorts was comparable to the Phase 3 ICARIA results. Isa SC administration by OBDS is well tolerated, requires a short duration of injection and provides a convenient hands-free option. Clinical trial information: NCT04045795. Research Sponsor: Sanofi.

Efficacy.

%	IV n=12	SC 1000 n=12	SC 1400 n=10	OBDS n=22	SC 1400 + OBDS (RP2D) n=32
ORR	66.7	66.7	80.0	77.3	78.1
CR	16.7	25.0	20.0	13.6	15.6
≥VGPR	50.0	41.7	40.0	40.9	40.6
PR	16.7	25.0	40.0	36.4	37.5

CR complete response, *VGPR* very good partial response, *PR* partial response.

8026 **Poster Session**

Safety and efficacy of daratumumab use in patients with renal impairment and hemodialysis. *First Author: Mateusz Niewinski, NYU Langone Health - Long Island, Mineola, NY*

Background: Targeting CD38 in multiple myeloma (MM) using daratumumab-based regimens can prolong remission in both the newly diagnosed and relapsed settings. However clinical trials have excluded patients with creatinine clearances (CrCl) <30 mL/min, warranting real-world analysis of daratumumab use in MM patients with renal insufficiency. **Methods**: Following IRB approval, we performed a retrospective chart review of relapsed MM patients at our institution who had reduced CrCl and received at least one dose of either daratumumab between October 2018 and January 2022. All subjects received IV daratumumab, 52% went on to receive SQ. Outcomes included change in CrCl during treatment, adverse events, and survival. Survival was estimated using product-limit estimates. CrCl groups at daratumumab initiation of more or less than 30 were compared using the chi-square test or Fisher's exact test, as deemed appropriate, for categorical variables and the two-sample t-test or Mann-Whitney test for continuous data (SAS Institute Inc., Cary, NC). **Results**: 101 MM patients were included, with median age of 74 (54-92); 46 (45.5%) were female. 14% were on hemodialysis. Patients had a median of 2 prior lines of therapy. Distribution of R-ISS stages were I (20%), II (35%), and III (45%). High-risk cytogenetics were present in 20%. A median of 23 daratumumab infusions (1-60) were delivered over a median of 18 months (median IV=16, SQ=10). Daratumumab regimens included DRD (32%), DPD (35%), DKD (13%), and DVD (35%). Median CrCl at MM diagnosis and at daratumumab initiation was 45 (7.3-101) and 40 (5.3-107), respectively, with 33% having CrCl <30. Following 3, 6, and 12 months (n = 95, 89, 69) on daratumumab-based regimens, median CrCl were 45, 43, and 41, respectively. There were no differences in renal function in patients who went on to receive SQ daratumumab. 16 patients had died at the time of data collection, and the median survival was 63 months. Of the 101 patients, 16 subjects were deceased at the time of data collection, and 23% of subjects had gone on to subsequent treatments. Analysis showed that there was a progression-free survival of 54% at 5 years. The most common adverse events reported were anemia (37%) and neutropenia (15%). Infusion-related reactions were reported in 19% of patients. **Conclusions**: This is the largest real-world assessment of outcome for MM patients treated with daratumumab-containing regimens in the setting of renal insufficiency. There was no significant impact of the treatment on renal function at 12 months. Compared to published data on patients treated with CrCl>30, there does not appear to be a detriment to survival or an increase in adverse events when using daratumumab regimens in patients with more advanced renal insufficiency. Research Sponsor: None.

8027 **Poster Session**

Characteristics of long-surviving patients with multiple myeloma: Over 12 years of follow-up in the Connect MM Registry. *First Author: Howard R. Terebelo, Providence Cancer Institute, Southfield, MI*

Background: The Connect MM Registry is a large, US, multicenter, prospective observational cohort study of pts with newly diagnosed multiple myeloma (NDMM) and one of the largest, longest running MM registries. Long-term survivors (LTS), defined as patients (pts) who have ≥ 8 years of follow-up, comprise a large portion of the Connect MM Registry. The purpose of this analysis was to assess LTS demographic and clinical characteristics. **Methods**: Adult pts with NDMM (N = 3011) were enrolled from 250 community, academic, and government sites: Cohort 1 from 2009 – 2011 and Cohort 2 from 2012 – 2016. As 99% of LTS were enrolled in Cohort 1, only pts from Cohort 1 were included in this analysis. Pt data were unevaluable if there were missing treatments, disease assessments, or large gaps in activity during follow-up (n = 28). Baseline characteristics, treatment patterns, and quality of life (QoL) form completion rates were examined. **Results**: At data cutoff (5/17/21), of the 1493 pts in Cohort 1 with evaluable data, 279 were LTS and 1186 were non-LTS. LTS were generally younger and had better performance status at enrollment (Table). Most (66%) LTS received stem cell transplants and few experienced progression within the first 6 months (3%). Top first-line (1L) regimen for LTS was lenalidomide/bortezomib/dexamethasone (31%) vs bortezomib/dexamethasone (22%) in non-LTS. At data cutoff, 73% of LTS were still on treatment at their most recent visit. LTS underwent disease assessments more frequently (2.0 vs 1.3 per year) and had a higher QoL completion rate by year 5 (58% vs 46%). This analysis showed an estimated 8-year survival of 36% vs an observed 8-year survival of 39% from the SEER database. Additional analyses are ongoing. **Conclusions**: LTS were younger and healthier than non-LTS. Most LTS received triplets at induction, stem cell transplants in 1L, and were less likely to relapse within the first 6 months of treatment than non-LTS. These findings are consistent with what has been observed in MM clinical trials. Further, this analysis demonstrates the value of longitudinal data in the CONNECT MM Registry and provides insights on long surviving pts with MM. Clinical trial information: NCT01081028. Research Sponsor: Bristol Myers Squibb.

Characteristic*	Long-Term Survivors (n=279)	Non-Long Term Survivors (n=1186)
Age at informed consent, yr	62	68
Received SCT, n (%)	185 (66.3)	361 (30.4)
ECOG PS < 2, %	66.3	56.9
Fast progression, n (%)†	8 (2.9)	84 (7.1)
Visits/yr, n	3.5	3.0
Disease assessments/yr, n	2.0	1.3
New lines of therapy/yr, n	0.2	0.6
QoL questionnaire completion rate at baseline, %	96.7	94.2
QoL questionnaire completion rate at 5 yrs, %	58.4	45.6
No evidence of treatment in most recent yr of follow-up, n (%)	5 (1.8)	—

ECOG PS, Eastern Cooperative Oncology Group performance status; QoL, quality of life; SCT, stem cell transplant.
*All continuous variables reported as medians. †Defined as having progressed ≤ 6 months of start of 1L. Among patients with at least one line of therapy.

8028 **Poster Session**

Phase 1b/2 study of ciltacabtagene autoleucel, a BCMA-directed CAR-T cell therapy, in patients with relapsed/refractory multiple myeloma (CARTITUDE-1): Two years post-LPI. *First Author: Saad Zafar Usmani, Myeloma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Ciltacabtagene autoleucel (cilta-cel), a chimeric antigen receptor T (CAR-T) cell therapy with 2 B-cell maturation antigen (BCMA)–targeting single-domain antibodies, led to early, deep, and durable responses in the phase 1b/2 CARTITUDE-1 study (NCT03548207) in heavily pretreated patients (pts) with relapsed/refractory multiple myeloma (RRMM). At ~1-year (y) median follow-up (MFU), overall response rate (ORR) was 97%; 67% of pts achieved stringent complete response (sCR). 1-y progression-free survival (PFS) and overall survival (OS) rates were 77% and 89%, respectively (Berdeja 2021). Updated results 2-y post last patient in (LPI) will be presented (~30-month total MFU). Here, we report CARTITUDE-1 results at 21.7-month MFU. **Methods:** Eligible pts with RRMM received ≥3 prior lines of therapy (LOT) or were refractory to a proteasome inhibitor (PI) and immunomodulatory drug (IMiD) and had received a PI, IMiD, and anti-CD38 antibody. Bridging therapy was permitted after apheresis. Pts received a single cilta-cel infusion (target dose 0.75×10^6 CAR+ viable T cells/kg) 5–7 days after lymphodepletion. Primary objectives were to evaluate cilta-cel safety and efficacy. Response was assessed per International Myeloma Working Group criteria by independent review committee and minimal residual disease (MRD) negativity at 10^{-5} by next-generation sequencing. **Results:** As of July 22, 2021, 97 pts (59% male; median age 61 y) received cilta-cel. Pts had a median of 6 (range 3–18) prior LOT; 84% were penta-drug exposed, 88% were triple-class refractory, 42% were penta-drug refractory, and 99% were refractory to last LOT. ORR was 97.9% (95% CI 92.7–99.7), 94.9% achieved very good partial response, and 82.5% achieved sCR. Median times to first response, best response, and ≥CR were 1.0, 2.6, and 2.9 months (m), respectively; median duration of response was not reached (NR). Of 61 pts evaluable for MRD, 92% were MRD negative (10^{-5}), sustained for ≥6 m in 44% (27/61) and ≥12 m in 18% (11/61). 2-y PFS was 60.5% (95% CI 48.5–70.4). Median PFS and OS were NR. 2-y PFS rates in pts with sustained MRD negativity for ≥6 m and ≥12 m were 91% and 100%, respectively. There were no new safety signals or new events of CAR-T cell neurotoxicity, movement and neurocognitive treatment-emergent adverse events, or treatment-related deaths since 1-y MFU. 15 second primary malignancies were reported in 11 pts over ~2-y MFU. **Conclusions:** At ~2-y MFU, a single cilta-cel infusion led to deepening and durable responses in heavily pretreated pts with RRMM with a manageable safety profile. Follow-up is ongoing, and landmark 2-y post LPI data (~8 m additional follow-up; ~30 m total MFU) will be presented. Further investigations of cilta-cel are ongoing in earlier LOT and outpatient settings across the CARTITUDE program (NCT04133636, NCT04181827, NCT04923893). Clinical trial information: NCT03548207. Research Sponsor: Janssen Research & Development, LLC, Pharmaceutical/Biotech Company.

8029 **Poster Session**

Biological correlative analyses and updated clinical data of ciltacabtagene autoleucel (cilta-cel), a BCMA-directed CAR-T cell therapy, in patients with multiple myeloma (MM) and early relapse after initial therapy: CARTITUDE-2, cohort B. *First Author: Niels W.C.J. van de Donk, Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, Netherlands*

Background: In cohort B of the multicohort phase 2 CARTITUDE-2 (NCT04133636) study, the efficacy and safety of cilta-cel are being evaluated in patients (pts) with MM who had early relapse after initial therapy. These pts have functionally high-risk disease, with early relapse post autologous stem cell transplantation (ASCT) being a poor prognostic factor and representing an unmet medical need. We present updated results. **Methods:** Eligible pts had MM, received 1 prior LOT (PI and IMiD required), had disease progression per IMWG (either ≤12 mo after ASCT or ≤12 mo after start of anti-myeloma therapy for pts who did not undergo ASCT), and were tx-naive to CAR-T/anti-BCMA therapies. A single cilta-cel infusion (target dose 0.75×10^6 CAR+ viable T cells/kg) was given post lymphodepletion. Safety and efficacy were assessed, and the primary endpoint was MRD negativity at 10^{-5}. Management strategies were implemented to minimize risk of movement/neurocognitive AEs (MNTs). Pharmacokinetic (PK) analyses (C_{max} and T_{max} of CAR+ T-cell transgene levels in blood) are being conducted, as well as analyses of levels of CRS-related cytokines (eg, IL-6) over time, peak levels of cytokines by response and CRS, association of cytokine levels with ICANS, and CAR+ T cell CD4/CD8 ratio by response, CRS, and ICANS. **Results:** As of January 2022, 19 pts (median age 58.0 y [range 44–67]; 74% male; median follow-up 13.4 mo [range 5.2–21.7]) received cilta-cel. 79% of pts received prior ASCT. ORR was 100.0%, 90% achieved CR or better, and 95% achieved ≥VGPR. Median time to first response and best response were 0.95 mo (range 0.9–9.7) and 5.1 mo (range 0.9–11.8), respectively. Of pts who were MRD-evaluable (n = 15), 14 (93%) achieved MRD 10^{-5} negativity during this study. Median DOR was not reached and 12-mo event-free rate was 88.9%. The 12-mo PFS rate was 90%. Median time to onset of CRS was 8 d (range 5–11) and occurred in 16 (84.2%) pts (1 gr 4). CRS resolved in all pts. ICANS (gr 1) occurred in 1 pt; MNT (gr 3) occurred in 1 pt, previously reported. 1 pt died post cilta-cel due to PD at d 158. Preliminary PK analyses indicate that peak expansion of CAR-T cells occurred on d 13.1 (range 8.96–209.9) and median persistence was 76.9 d (range 40.99–221.8). **Conclusions:** A single cilta-cel infusion led to deep and durable responses in a functionally high-risk pt population who experienced early clinical relapse/tx failure to initial therapy, with a manageable safety profile. In this pt population with ineffective or insufficient response to ASCT, cilta-cel led to responses. Responses continue to deepen, and follow-up is ongoing. Updated and in-depth PK, cytokine, and CAR-T subset analyses and clinical correlation will be presented and provide novel insights into biological correlates of efficacy and safety in this pt population. Clinical trial information: NCT04133636. Research Sponsor: Janssen Research & Development, LLC, Pharmaceutical/Biotech Company.

8030 **Poster Session**

Health-related quality of life (HRQoL) in patients with relapsed/refractory multiple myeloma (RRMM) receiving real-life current standard of care (SOC) in the LocoMMotion study. *First Author: Michel Delforge, University of Leuven, Leuven, Belgium*

Background: Evaluation of patient (pt)-reported outcomes provides insight into how real-life SOC treatments (tx) affect HRQoL for pts with RRMM. LocoMMotion (NCT04035226) is the first prospective, multinational study of real-life SOC in triple-class exposed pts with RRMM. Here, we present measures of symptoms, functioning, and overall HRQoL. **Methods:** LocoMMotion is a prospective, noninterventional study across 76 sites (63 European; 13 US). Pts had received ≥3 prior lines of therapy (LOT) or were refractory to PI and IMiD; received PI, IMiD, and anti-CD38 mAb; and had disease progression during/after last LOT. Real-life SOC tx were defined as those used in local clinical practice. The questionnaires were EORTC QLQ-C30, 4 single items from EORTC QLQ-MY20, and EQ 5D-5L. HRQoL was assessed at baseline (BL), day 1 of each tx cycle, end of tx visit, and during the follow-up period (every 4 weeks). Improvement compared to BL health status was evaluated using established thresholds. Within-group change was assessed using mixed models for repeated measures. **Results:** Questionnaire completion for pts in the LocoMMotion study (N=248; 54.4% male; median age 68 yrs; median 4.0 [range, 1–20] cycles of SOC) was 75.6% during SOC tx. Most pts did not achieve meaningful improvement in PRO scores, defined by a literature-based minimally important difference of 10 points in mean score. This was most pronounced in pain symptoms (62% of pts had no meaningful improvement during the first 3 months of tx; 55% had no improvement during full tx duration). For the overall population, the least square (LS) mean changes from BL during SOC tx and subsequent LOT are described (Table). Pts who achieved very good partial response and better during SOC tx had greater improvement in PRO scores, including in LS mean change for pain score (-14.9 [95% confidence interval (CI): -22.9, -7.0]). **Conclusions:** In this first prospective study of real-life current SOC in triple-class exposed pts, limited gains in HRQoL were reported, most notably in pain symptoms. There is an urgent need for effective therapies that can help pts achieve deep responses and delay disease progression, as these are associated with improved HRQoL. Clinical trial information: NCT04035226. Research Sponsor: Janssen Research & Development, LLC, Pharmaceutical/Biotech Company.

LS mean changes from BL.

LS mean change from BL (95% CI)	During SOC tx N=172	During subsequent tx N=87
Physical functioning[a]	2.5 (–0.5, 5.5)	–11.8 (–17.7, –5.9)
Global health status[a]	1.9 (–1.4, 5.1)	–2.0 (–7.1, 3.2)
Pain score[b]	–1.4 (–5.8, 2.9)	1.8 (–4.7, 8.3)
Fatigue symptoms[b]	–5.3 (–8.7, –1.8)	6.1 (0.3, 12.0)
Restless or agitated[b]	–2.6 (–6.8, 1.6)	9.3 (2.1, 16.4)
Thinking about illness[a]	9.4 (4.9, 13.9)	–7.5 (–14.5, –0.5)
Worried about dying[a]	6.1 (1.9, 10.3)	–14.4 (–22.5, –6.4)
Worried about health[a]	7.9 (3.5, 12.4)	–9.7 (–16.6, –2.8)
Visual analog scale[a]	2.4 (–0.2, 5.1)	–0.6 (–5.5, 4.3)

[a]Higher score indicates better outcome. [b]Higher score indicates worse outcome.

8031 **Poster Session**

Subgroup analyses in patients with relapsed/refractory multiple myeloma (RRMM) receiving real-life current standard of care (SOC) in the LocoMMotion study. *First Author: Hermann Einsele, Universitätsklinikum Würzburg, Medizinische Klinik und Poliklinik II, Würzburg, Germany*

Background: Patients (pts) with RRMM who are triple-class exposed (proteasome inhibitor [PI], immunomodulatory drug [IMiD], and anti-CD38 monoclonal antibody [mAb]) have an urgent and currently unmet clinical need. LocoMMotion (NCT04035226) is the first prospective multinational study of real-life SOC in triple-class exposed pts with RRMM. Here we present efficacy in subgroups of pts treated with SOC therapies in the LocoMMotion study. **Methods:** LocoMMotion is a noninterventional study across 76 sites (63 European; 13 US). Eligible pts had received ≥3 prior lines of therapy (LOT) or were double refractory to a PI and an IMiD; received a PI, an IMiD, and anti-CD38 mAb; and had disease progression during/after their last LOT. Real-life SOC treatments were defined as those used in local clinical practice. Responses and disease progression were assessed by response review committee, per IMWG criteria. Subgroups were defined by baseline (BL) characteristics: age, Eastern Cooperative Oncology Group performance status (ECOG PS), renal function, ISS stage, presence of extramedullary plasmacytoma, LDH level, % of bone marrow plasma cells, number of prior LOT, triple-class or penta-drug exposure, and refractoriness. **Results:** As of May 21, 2021 (median follow-up 11.0 mo), 248 pts were enrolled and treated with median 4.0 (range, 1–20) cycles of SOC therapy. Evaluation of efficacy outcomes in subgroups demonstrated that refractoriness to 3 classes of anti-myeloma therapy, presence of extramedullary plasmacytomas, high LDH, and ECOG PS ≥1 were associated with generally worse outcomes, compared with pts who did not have these characteristics (Table). Overall response rate (ORR) ranged from 20.0–43.1% across all subgroups. Age and number of prior LOT did not have an impact on efficacy outcomes. **Conclusions:** Subgroup analyses of this first prospective study of real-life SOC tx in triple-class exposed pts with RRMM indicate that specific pt and disease characteristics were associated with poor outcomes. Triple-class refractory and non-triple-class refractory pts had poor outcomes, although the latter had longer median progression-free survival (PFS). These findings should be considered when planning bridging strategy for CAR-T therapy. Clinical trial information: NCT04035226. Research Sponsor: Janssen Research & Development, LLC, Pharmaceutical/Biotech Company.

Efficacy in select subgroups of pts in LocoMMotion.

Pts	N	Median OS, months	Median PFS, months	ORR, n, %	Median DOR,[a] months
Overall	248	12.4	4.6	74 (29.8)	7.4
Triple-class refractory	183	11.1	3.9	46 (25.1)	4.5
Non-triple-class refractory	65	NE	8.2	28 (43.1)	9.1
BL ECOG PS of 0	63	NE	5.4	19 (30.2)	5.7
BL ECOG PS of ≥1	184	10.8	4.4	55 (29.9)	7.7
Extramedullary plasmacytomas, yes	33	8.2	3.4	9 (27.3)	4.1
Extramedullary plasmacytomas, no	215	13.0	5.1	65 (30.2)	7.7
LDH (U/L) of ≤245	114	13.8	5.7	39 (34.2)	5.1
LDH (U/L) of >245	72	7.4	3.3	19 (26.4)	8.5

[a]In responders (partial response or better). DOR, duration of response; OS, overall survival.

8032 **Poster Session**

A novel, immunotherapy-based approach for the treatment of relapsed/refractory multiple myeloma (RRMM): Updated phase 1b results for daratumumab in combination with teclistamab (a BCMA x CD3 bispecific antibody). *First Author: Paula Rodríguez-Otero, Clínica Universidad de Navarra, Madrid, Spain*

Background: Teclistamab (tec; JNJ-64007957) is a BCMA × CD3 T-cell redirecting bispecific antibody under investigation in patients (pts) with RRMM. Daratumumab (dara) is a CD38 mAb with direct on-tumor and immunomodulatory actions. Initial clinical data from the phase 1b multicohort TRIMM-2 study support the combination of tec + dara for the treatment of RRMM, with tolerable safety, no overlapping toxicities, and promising efficacy. We present updated results with additional pts and longer follow-up. **Methods:** Eligible MM pts aged ≥18 y had received ≥3 prior lines of therapy (LOT; including a proteosome inhibitor [PI] and immunomodulatory drug [IMiD]) or were double-refractory to a PI and IMiD. Pts treated with anti-CD38 therapy ≤90 d prior were excluded. Pts received dara SC 1800 mg per approved schedule and tec SC 1.5–3 mg/kg QW or Q2W. Primary objectives were to identify the recommended phase 2 dose of tec for combination therapy and evaluate safety of the combination. Responses were assessed by IMWG criteria. AEs were graded per CTCAE v5.0; cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS) were graded per ASTCT guidelines. **Results:** At data cutoff (Jan 13, 2022; safety population: N=46), median follow-up was 7.2 mo (range 0.1–16.6; median age 67 y [range 50–79]; 52% female). Pts received a median of 6 prior LOT (range 2–17; 74% triple-class exposed; 63% penta-drug exposed; 15% anti-BCMA exposed). 91% of pts had ≥1 AE (grade 3/4 78%), most commonly CRS (61%; all grade 1/2; median time to onset 2 d; median duration 2 d), neutropenia (54%; grade 3/4 50%), anemia (46%; grade 3/4 28%), thrombocytopenia (33%; grade 3/4 28%), and diarrhea (33%; grade 3/4 2%). Infections occurred in 29 pts (63%; grade 3/4 28%). One pt had grade 1 ICANS that fully resolved. Among 37 response-evaluable pts, ORR was 78% (29/37); 27 pts (73%) had very good partial response (VGPR) or better (Table). Median time to first response across dosing cohorts was 1.0 mo (range 0.9–2.8); median duration of response was not reached. Upregulation of $CD38^+/CD8^+$ T cells and proinflammatory cytokines was observed with tec + dara, supporting potential synergy of the combination in pts with prior anti-CD38 exposure. Updated results will be presented. **Conclusions:** Tec + dara provides a novel immunotherapy approach for the treatment of RRMM that may yield improved clinical efficacy in heavily pretreated pts. Clinical trial information: NCT04108195. Research Sponsor: Janssen Research & Development, LLC.

Responses in evaluable pts[a] in tec + dara cohorts.

	Dara 1800 mg + Tec 1.5 mg/kg QW (n=20)[b]	Dara 1800 mg + Tec 3 mg/kg QW (n=4)	Dara 1800 mg + Tec 3 mg/kg Q2W (n=13)
Overall response, n	15	4	10
VGPR or better, n	14	4	9
Complete response or better, n	6	2	1

[a]Pts who received ≥1 study treatment and had ≥1 postbaseline response evaluation. [b]8 pts switched to tec 3 mg/kg Q2W (3 at cycle [C] 4, 3 at C5, 1 at C7, and 1 at C9).

8033 **Poster Session**

Health-related quality of life in patients with relapsed/refractory multiple myeloma (RRMM) treated with teclistamab, a B-cell maturation antigen (BCMA) x CD3 bispecific antibody: Patient-reported outcomes in MajesTEC-1. *First Author: Thomas G. Martin, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA*

Background: As multiple myeloma (MM) negatively affects patients' (pts) health-related quality of life (HRQoL), assessment of patient-reported outcomes (PROs) in addition to clinical outcomes is important. Teclistamab (tec; JNJ-64007957) is an off-the-shelf bispecific antibody that redirects CD3+ T cells to mediate T-cell activation and subsequent lysis of BCMA-expressing MM cells. Initial results from the pivotal cohort of the phase 1/2 MajesTEC-1 study demonstrated that tec was well tolerated with encouraging efficacy in pts who received ≥3 prior lines of treatment (LOT; including a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 antibody). Here we report PROs from this cohort. **Methods:** Pts (aged ≥18 years) had documented RRMM (International Myeloma Working Group criteria), progressive/measurable disease, and had previously received ≥3 prior LOT; prior anti-BCMA treatment (tx) was not allowed. Pts received weekly subcutaneous tec at the recommended phase 2 dose (1.5 mg/kg with step-up doses of 0.06 and 0.3 mg/kg). PROs were assessed at screening and every even cycle (cycles 2–8 reported here) using the EORTC QLQ-C30 (range: 0–100; higher scores indicate better global health status [GHS] but greater symptom severity [symptom scales]) and the EuroQol 5-dimensional descriptive system (visual analog scale [VAS] range: 0 [worst imaginable health state] to 100 [best imaginable]). Tx effect was assessed by a mixed-effects model with repeated measures; the proportion of pts with meaningful improvement was defined as a change ≥10 points. Time to worsening was determined using the Kaplan-Meier estimate. **Results:** A total of 110 pts were included (median follow-up: 7.8 mos). Overall PRO compliance rates were high (baseline [BL]: 85–90%; cycles 2–8: 80–94%). Tec improved overall HRQoL as evidenced by improvements in GHS scores (cycles 2–8) and reduction in pain (-4.2 [cycle 2] to -15.1 [cycle 8]; Table), with no overall change in physical functioning and fatigue. The proportions of pts with meaningful improvements from BL at cycle 8 were GHS: 50%; physical functioning: 35%; pain: 65%; fatigue: 73%; 50% of pts reported meaningful improvement in their overall health (VAS). Median time to improvement from baseline was ~1.5 months (with nausea/vomiting and fatigue taking longer to improve), while median time to worsening (all symptoms) ranged from 2 months to not estimable. **Conclusions:** Consistent with clinical outcomes, pts treated with tec reported rapid, clinically meaningful improvements in HRQoL. Clinical trial information: NCT04557098. Research Sponsor: Janssen Research & Development, LLC.

BL and least squares (LS) mean change from baseline in PRO measures.

	GHS	Physical functioning	Pain	Fatigue	VAS
BL (mean)	58.0	71.3	43.6	39.6	61.2
LS mean change					
Cycle 2	0.6	–6.7	–4.2	6.9	0
Cycle 4	6.6	0.4	–9.6	–0.6	7.9
Cycle 6	6.8	0.6	–10.7	0.8	8.9
Cycle 8	11.3	5.3	–15.1	–0.4	10.7

8034 **Poster Session**

Indirect treatment (tx) comparison of teclistamab (tec) in MajesTEC-1 versus physician's choice of therapy in the long-term follow-up of the CASTOR, POLLUX, EQUULEUS, and APOLLO trials in patients (pts) with triple-class exposed (TCE), relapsed/refractory multiple myeloma (RRMM). *First Author: Maria-Victoria Mateos, University Hospital of Salamanca/IBSAL/CIC/CIBERONC, Salamanca, Spain*

Background: Tec is a B-cell maturation antigen × CD3 bispecific antibody currently being evaluated in the single-arm, phase 1/2 MajesTEC-1 trial (NCT04557098) in pts with RRMM who had received ≥3 prior lines of therapy (LOT) and were TCE to an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. The aim of this study is to evaluate the comparative efficacy of tec versus physician's choice of therapy, as no head-to-head trials have been conducted. **Methods**: An external control arm for MajesTEC-1 was created from pts in the long-term follow-up of 4 clinical trials of daratumumab (CASTOR, POLLUX, EQUULEUS, and APOLLO) who met the eligibility criteria for MajesTEC-1. These pts (N = 427) were subsequently treated with physician's choice of therapy after discontinuing trial txs, and disease progression and best tx response were based on the investigator's assessment. Individual pt-level data from MajesTEC-1 pts who received tec (1.5 mg/kg weekly) at a clinical cutoff of Sep 7, 2021 were included. Inverse probability of tx weighting (IPTW) with average tx effect on the treated population was used to adjust for imbalances in baseline covariates of prognostic significance: refractory status, progression on last LOT, cytogenetic risk, International Staging System stage, number of prior LOT, extramedullary plasmacytoma, time since diagnosis, age, and hemoglobin. Overall response rate (ORR), rate of complete response or better (≥CR), rate of very good partial response or better (≥VGPR), progression-free survival (PFS), time to next tx (TTNT), and overall survival (OS) were assessed. For binary endpoints (ORR, ≥CR rate, ≥VGPR rate), the relative effect of tec vs physician's choice of therapy was estimated with an odds ratio (OR) and 95% confidence interval (CI) derived from a weighted logistic regression analysis. A weighted Cox proportional hazards model was used to compute hazard ratios (HRs) and 95% CIs for time-to-event endpoints (PFS, OS, and TTNT). Several sensitivity analyses were conducted. **Results**: After IPTW, baseline characteristics were comparable between the 2 cohorts. Pts treated with tec had improved outcomes vs physician's choice of therapy: ORR (OR 4.58; 95% CI 2.83–7.53; $P < 0.0001$); ≥CR rate (OR 12.62; 95% CI 5.20–38.55; $P< 0.0001$); ≥VGPR rate (OR 11.64; 95% CI 6.49–21.98; $P< 0.0001$); PFS (HR 0.62; 95%CI 0.45–0.84; $P= 0.0024$); TTNT (HR 0.38; 95% CI 0.27–0.52; $P< 0.0001$); and OS (HR 0.47; 95% CI 0.32–0.69; $P= 0.0001$). Results were similar for all sensitivity analyses. **Conclusions**: Tec showed improved efficacy versus physician's choice of therapy in all clinical outcomes, highlighting its therapeutic potential to address unmet needs in pts with TCE RRMM who received ≥3 prior LOT. Research Sponsor: Janssen Global Services, LLC.

8035 **Poster Session**

Matching-adjusted indirect treatment comparison (MAIC) of teclistamab (tec) versus belantamab mafodotin (belamaf) for the treatment of patients (pts) with triple-class exposed (TCE), relapsed/refractory multiple myeloma (RRMM). *First Author: Philippe Moreau, Hematology Clinic, University Hospital Hôtel-Dieu, Nantes, France*

Background: Pts with RRMM who are TCE to immunomodulatory drugs, proteasome inhibitors, and anti-CD38 antibodies have limited treatment options. While there is no standard of care for treatment of pts with TCE RRMM, belamaf is a recently approved, novel therapeutic option. MajesTEC-1 (NCT04557098) is a single-arm phase 1/2 study evaluating tec, a B-cell maturation antigen × CD3 bispecific antibody in pts with TCE RRMM who received ≥3 prior lines of therapy (LOT). Given the absence of a control arm in MajesTEC-1, we compared efficacy outcomes of pts who received tec at the recommended phase 2 dose in MajesTEC-1 with those of pts treated with belamaf in the phase 2 DREAMM-2 trial (NCT03525678). **Methods:** An unanchored MAIC was performed using individual pt-level data (IPD) from MajesTEC-1 (tec 1.5 mg/kg weekly; N = 150) at a clinical cutoff of Sep 7, 2021, and published summary-level data from pts who received the approved dose of belamaf in DREAMM-2 (2.5 mg/kg every 3 weeks; N = 97). The DREAMM-2 eligibility criteria were applied to pts from the intent-to-treat population of MajesTEC-1. IPD from MajesTEC-1 were weighted to match the aggregated DREAMM-2 baseline pt characteristics. Baseline characteristics of prognostic significance (refractory status, cytogenetic profile, International Staging System stage, presence of extramedullary disease, and number of prior LOT) were adjusted for in the analysis. Comparative efficacy of tec vs belamaf was estimated for overall response rate (ORR), complete response or better (≥CR) rate, progression-free survival (PFS), overall survival (OS), and duration of response (DOR). For binary endpoints (ORR and ≥CR rate), the relative effects of tec vs belamaf were quantified using an odds ratio (OR) and 95% CI derived from a weighted logistic regression analysis, while time-to-event endpoints (DOR, PFS, OS) were estimated using a weighted Cox proportional hazards model. **Results:** After adjustment, the effective sample size (ESS) of the MajesTEC-1 cohort was 33 and baseline characteristics for the reweighted MajesTEC-1 population were balanced with the DREAMM-2 population. Pts treated with tec had an improved ORR (OR 2.05; 95% CI 0.92–4.57; $P= 0.0786$), ≥CR rate (OR 2.13; 95% CI 0.80–5.65; $P= 0.1283$), PFS (HR 0.63; 95% CI 0.34–1.15; $P= 0.1338$), OS (HR 0.95; 95% CI 0.47–1.92; $P= 0.8897$), and DOR (hazard ratio [HR] 0.19; 95% CI 0.05–0.73; $P= 0.0149$) compared with belamaf. The reduced ESS following adjustment may account for the lack of statistical significance for most outcomes. **Conclusions:** These analyses demonstrated statistically improved DOR for tec vs belamaf and numerically favorable results for other outcomes, highlighting its potential as a treatment for pts with TCE RRMM who received ≥3 prior LOT. Research Sponsor: Janssen Global Services, LLC.

8036 **Poster Session**

Comparative effectiveness of teclistamab versus real-world treatments for patients with triple-class exposed (TCE), relapsed/refractory multiple myeloma (RRMM). *First Author: Amrita Y. Krishnan, City of Hope Comprehensive Cancer Center, Duarte, CA*

Background: Teclistamab is a B-cell maturation antigen × CD3 bispecific antibody currently being evaluated in MajesTEC-1 (NCT04557098), an open-label, single-arm, phase 1/2 trial in patients with RRMM who had received ≥3 prior lines of therapy (LOT) and were TCE to an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. Given the absence of a control arm in MajesTEC-1, we assessed the comparative effectiveness of teclistamab versus treatment regimens using an external control arm from a real-world database. **Methods**: An external control arm for MajesTEC-1 was created from eligible patients in the nationwide de-identified electronic health record-derived Flatiron Health multiple myeloma cohort database who started a new line of therapy (physician's choice) following triple-class exposure between January 2011 and August 2021, received ≥3 prior LOT, and satisfied key MajesTEC-1 eligibility criteria. Individual patient data from MajesTEC-1 included patients who received teclistamab (1.5 mg/kg weekly) at a clinical cutoff of Sep 7, 2021. Inverse probability of treatment weighting (IPTW) was used to adjust for imbalances in baseline covariates of prognostic significance: refractory status, progression on last LOT, cytogenetic risk, International Staging System stage, number of prior LOT, time since diagnosis, age, and hemoglobin. Outcomes of interest included progression-free survival (PFS), time to next treatment (TTNT), and overall survival (OS); these outcomes were analyzed as time-to-event data using IPTW adjusted Kaplan-Meier estimates and a weighted Cox proportional hazards model. Several sensitivity analyses were conducted. **Results**: After IPTW, baseline characteristics were comparable between the 2 cohorts. Patients treated with teclistamab had improved PFS (hazard ratio [HR] 0.43; 95% confidence interval [CI] 0.32–0.59; $P< 0.0001$), TTNT (HR 0.42; 95% CI 0.31–0.58; $P< 0.0001$), and OS (HR 0.73; 95% CI 0.48–1.09; $P= 0.13$) versus assessed real-world treatments. Results were similar for all sensitivity analyses. **Conclusions**: Teclistamab showed improved effectiveness for PFS, TTNT, and OS, compared with real-world treatments used in patients with TCE RRMM who received ≥3 prior LOT. These findings highlight the therapeutic potential of teclistamab in patients with RRMM who have limited treatment options. Research Sponsor: Janssen Global Services, LLC.

8037 **Poster Session**

Circulating tumor DNA analysis and association with relapse in patients with primary refractory multiple myeloma receiving secondary salvage therapy.

First Author: Sridurga Mithraprabhu, Alfred Hospital / Monash University, Melbourne, Australia

Background: Multiple myeloma (MM) is an incurable plasma cell malignancy with a 5 year-median overall survival (OS) in newly diagnosed (ND) patients. Real-world data reveals that 23% of transplant eligible (TE) ND MM patients relapse within 12 months of starting first-line bortezomib (1LB) based therapy and of these ~50% will fail secondary therapy and die within 18 months. It is currently impossible to identify these high-risk patients and genomic studies could potentially inform alternative secondary therapeutic options. We propose that circulating tumour DNA (ctDNA) analysis could provide a more holistic approach to determine genomics of high-risk patients than bone marrow (BM) tumour DNA analysis in this genetically heterogenous multi-site malignancy. **Methods:** Peripheral blood plasma and BM samples (n = 186) were obtained at baseline, cycle 3 day 1 (C3D1), end of the study (EOS) and/or relapse, whichever appeared earlier, from a Phase II multicentre single arm study of carfilzomib-thalidomide-dexamethasone (KTd) in 50 TE ND MM patients who were refractory or registered suboptimal response to 1LB (Australasian Leukaemia and Lymphoma Group - MM17 trial). Somatic variants were identified in BM or ctDNA with ultra-sensitive targeted amplicon sequencing of 22-genes known to be mutated in MM. Mutational spectrum was correlated to standard MM risk factors including International Staging System (ISS), response to 1LB and KTd, cytogenetics/FISH, lactate dehydrogenase (LDH) levels, progression-free survival (PFS) and OS. **Results:** Our initial analysis of ctDNA mutational proportions between patients who did not or did experience relapse on KTd revealed a significantly higher proportion of *RAS/RAF* (3% vs 25%), or *ATM/ATR/TP53* (17% vs 41%; $p < 0.0001$), respectively, in relapse patients. Subsequently, we correlated ctDNA *RAS/RAF* and/or *ATM/ATR/TP53* mutational presence to standard MM risk factors. We identified a shorter PFS and OS for ISS Stage 2 and 3 compared to Stage 1 patients ($p = 0.002$ and $p = 0.02$, respectively) and a significantly higher proportion of *RAS/RAF* or *ATM/ATR/TP53* mutations in patients with refractory as compared to sub-optimal response to 1LB therapy ($p = 0.0002$). Patients with *RAS/RAF* or *ATM/ATR/TP53* mutations in ctDNA at the time of starting salvage therapy also had a shorter PFS and OS on KTd ($p = 0.003$ and $p = 0.02$, respectively). Sequential ctDNA analysis discovered that in 87.5% of patients, one or more of the dominant mutations present at the time of relapse were already present at the start of salvage therapy. **Conclusions:** Our analysis reveals that *RAS/RAF* and *ATM/ATR/TP53* mutations in ctDNA could be prognostic biomarkers of response to secondary salvage therapy in primary refractory patients thus providing the opportunity to design targeted salvage treatment paradigms in high-risk MM patients. Research Sponsor: Black Swan Research Initiative, International Myeloma Foundation.

8038 **Poster Session**

Prevalence of ocular comorbidities in patients with multiple myeloma: An analysis of U.S. claims data.

First Author: Sikander Ailawadhi, Mayo Clinic, Jacksonville, FL

Background: Multiple myeloma (MM) predominantly affects older patients (pts) (median age at diagnosis 69 yrs) in whom comorbidities must be considered to manage the disease appropriately. Some anti-MM therapies can be associated with ocular toxicities and require careful attention when used among pts with pre-existing ocular comorbidities (OC). In 2018, 41% of Medicare enrollees had OC. Despite the potential implication on treatment decisions, information on pre-existing OC (e.g., disorders of lens, glaucoma) in MM pts is limited. This study aims to describe the prevalence of OCs among real-world pts with MM in 2011-2020 in the US. **Methods:** Adults with newly diagnosed MM (NDMM) with or without treatment, with 1L systemic therapy, and with relapsed/refractory MM (RRMM) who received up to 4 lines of systemic therapies (LOT) for MM were identified in the IQVIA PharMetrics Plus data. The index date was the date of initial MM diagnosis or a LOT initiation date. The prevalence of OC in each group was defined as the presence of any OC ICD 9/10 diagnosis codes in the 12 months prior to the index date. OCs (e.g., disorders of conjunctiva, lens, choroid, retina, glaucoma) were considered a potentially MM-related disease manifestation or MM treatment-related toxicity based on published literature and clinical expert opinion. **Results:** The median age at initial MM diagnosis was 64 yrs overall (N=49,814), and 63 yrs among treated pts (N=22,963). The median age was 63 yrs at 1L initiation and 64 yrs at 2L, 3L, and 4L initiation. The prevalence of OC at initial MM diagnosis was 39.0% overall and 35.2% among treated pts (Table). The OC prevalence was 35.8% prior to 1L initiation and higher in RRMM pts (42.1%, 44.9%, and 45.7% prior to 2L, 3L, and 4L initiation, respectively). This trend was observed across all OC categories, among MM-related OCs, and across all age groups. The prevalence of OC by MM stage was stable over the years. **Conclusions:** Approximately 40% of NDMM pts have a pre-existing OC, and the prevalence increases with the number of LOT in RRMM. While some OC may be due to aging, the impact of OC on treatment decisions for MM should be explored. Research Sponsor: Regeneron Pharmaceuticals, Inc.

Prevalence of pre-existing ocular comorbidities during 12-month baseline by cohort.

Index date	All pts *First MM dx* N = 49,814	Treated pts *First MM dx* N = 22,963	1L initiator *1L initiation* N = 22,963	2L initiator *2L initiation* N = 8,860	3L initiator *3L initiation* N = 3,667	4L initiator *4L initiation* N = 1,709
Any OCs (%) (range, 2011-2020)	39.0 (35.2–41.4)	35.2 (29.4–38.3)	35.8 (31.2–38.8)	42.1 (37.5–47.5)	44.9 (40.2–48.6)	45.7 (41.5–52.5)
By OC type						
Related to MM or MM tx*	31.7	28.1	28.6	33.3	35.6	36.9
Unrelated to MM or MM tx	13.1	12.1	12.2	15.8	18.3	17.8
By age group						
18–54	23.2	19.6	19.8	25.7	27.1	30.0
55–64	29.7	26.7	27.1	34.9	34.6	36.8
65–74	45.8	43.8	44.3	49.0	52.7	53.2
75–84	57.5	57.4	56.7	59.7	65.9	59.6
≥ 85	57.9	58.9	59.0	60.6	63.1	64.1

* Pts may have both MM related and non-MM related OCs and counted in both categories.

8039 **Poster Session**

Factors associated with dose adjustment for the bortezomib, lenalidomide, dexamethasone regimen among patients with newly diagnosed multiple myeloma.

First Author: Tao Ran, Janssen Scientific Affairs, LLC, Horsham, PA

Background: VRd (bortezomib/lenalidomide/dexamethasone) has become one of the established treatment regimens in the US for multiple myeloma (MM). Due to toxicities, dose adjustments are often required for VRd. This real-world study described the patient characteristics and factors associated with dose adjustment among MM patients treated with VRd as first line (1L) therapy. **Methods:** Adult MM patients treated with 1L VRd were selected from the Optum Clinformatics database (Nov 1, 2015-Sep 30, 2020). Patient characteristics were evaluated during a 6-month baseline period. Dose adjustments were defined based on lenalidomide (len) dose received during 1L. Receipt of > 15mg len was categorized as VRd regular, ≤15mg len as VRd lite, and initial len dose > 15mg reduced to ≤15 mg over treatment period as VRd reduced. Baseline factors associated with different VRd dose categories were studied using multinomial logistic regression. **Results:** Among the 1497 patients identified, the mean (SD) age was 69 (9.5) years (52% ≥70), 51% were male, 59% were White, 37% were frail, and 67% with Medicare. Baseline Charlson Comorbidity Index was 4.2, with hypertension (70%), hyperlipidemia (56%), renal impairment (26%), and CVD (25%) being the most prevalent comorbidities. Over half of the patients received an adjusted dose, VRd lite (33%) and VRd reduced (22%). Overall, for patients treated with 1L VRd, median follow-up was 16.2 months; median duration of 1L was 4.9 months (among those with confirmed end of therapy); and median TTNT was 14.5 months. Compared to VRd regular, use of VRd lite was over 6 times more likely to be associated with patients ≥75 years of age, about 2 times more likely to be associated with females, and about 40% less likely to be associated with commercial insurance vs. Medicare; VRd reduced was 1.3 times more likely to be associated with females, and 1.5 times more likely to be associated with frail patients (table). No differences were observed among different races. **Conclusions:** Over half of the MM patients treated with 1L VRd in the real-world were > 70 years of age and over one-third were frail. A large proportion of patients received a modified dose of VRd. Receipt of VRd lite dose was highly associated with older age (≥75 years), and receipt of VRd reduced dose was associated with frailty. These dose adjustments may potentially result in reduced efficacy of the VRd regimen in the real-world relative to controlled clinical trials, which needs to be assessed in future studies. Research Sponsor: Janssen Scientific Affairs, LLC.

Patient factors	VRd lite vs. VRd regular (ref.) Odds ratio (95% CI)	VRd reduced vs. VRd regular (ref.) Odds ratio (95% CI)
65 to < 70 vs. < 65	1.0 (0.6–1.7)	0.9 (0.6–1.5)
70 to < 75 vs. < 65	2.2 (1.3–3.8)	1.2 (0.7–2.0)
≥75 vs. < 65	6.2 (3.6–10.5)	1.6 (0.9–2.8)
Female vs. male	1.8 (1.4–2.4)	1.3 (1.0–1.8)
Commercial vs. Medicare	0.6 (0.4–0.9)	0.8 (0.5–1.3)
Frailty index > 0.2 vs. ≤0.2	1.3 (0.9–1.8)	1.5 (1.1–2.2)

8040 **Poster Session**

B-PRISM (Precision Intervention Smoldering Myeloma): A phase II trial of combination of daratumumab, bortezomib, lenalidomide, and dexamethasone in high-risk smoldering multiple myeloma.

First Author: Omar Nadeem, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: Early therapeutic intervention with lenalidomide has shown to be effective in delaying progression in patients with high-risk smoldering multiple myeloma (HR-SMM) (Lonial J Clin Oncol 2020). Quadruplet regimen of daratumumab, bortezomib, lenalidomide and dexamethasone (D-RVD) has demonstrated significant activity in multiple myeloma, achieving high rates of minimal residual disease (MRD) negativity (Voorhees Blood 2020). Thus, we proposed to examine the activity and safety of D-RVD in patients with HR-SMM. **Methods:** This is a phase II single center, single-arm, open label study evaluating the combination of D-RVD in HR-SMM. Eligibility included high risk per Mayo 2018 "20-2-20" model and other previously established criteria including Mayo 2008 criteria, presence of immunoparesis, evolving type of SMM, and high risk FISH. Primary objective is rate of sustained MRD negativity at 2 years. Secondary objectives include PFS, response rates and safety. Treatment duration with modified D-RVD is for total of 2 years (24 cycles). Daratumumab is administered subcutaneously (SQ) per standard dose and schedule, bortezomib given weekly on days 1, 8, 15 for cycles 1-6 and then biweekly until completion of cycle 24. Lenalidomide is administered on days 1-21 and dexamethasone is administered weekly. All eligible patients will undergo stem cell collection after 6 cycles of therapy. **Results:** At the time of data cut off, 20 patients have been enrolled with a median follow up of 6 months. The median age is 58 years old (range 40-73). Sixteen out of 20 (80%) patients met high risk criteria per Mayo 2018 model with median plasmacytosis of 20%, median M protein value of 2.6 g/dl and median FLC ratio of 28.2. Seven patients had high-risk FISH: 5 with 1q duplication, 2 with t(4;14). Most common toxicities of any grade included neutropenia (65%), WBC decreased (55%) insomnia (50%), constipation (45%) and hypophosphatemia (45%). Most common grade 3 toxicities included neutropenia (15%), ALT increased (5%), thrombocytopenia (5%), hyperglycemia (5%), hypertension (5%), diarrhea (5%), syncope (5%). No patients discontinued therapy due to toxicity. The overall response rate is 90% with 40% PR, 25% VGPR and 25% CR. All patients have achieved at least a MR and 50% achieved VGPR or greater with responses deepening over time. No patients have progressed on treatment. MRD was evaluable in 16 patients and 8 patients have undergone MRD testing, with MRD negativity rate of 50% (4/8) and 25% (2/8) at thresholds of 10^{-5} and 10^{-6}, respectively. Stem cells were successfully collected in all patients with mean stem cell yield of 5.78×10^6 CD34+/kg cells. **Conclusions:** D-RVD is well tolerated in patients with HR-SMM demonstrating significant early activity. Responses continue to deepen over time with patients achieving MRD negative disease. Clinical trial information: NCT04775550. Research Sponsor: Janssen.

8041 **Poster Session**

Phase II study of the combination of daratumumab, ixazomib, pomalidomide, and dexamethasone as salvage therapy in relapsed/refractory multiple myeloma: Stage 2 interim results. *First Author: Anupama Deepa Kumar, University of California-San Diego, La Jolla, CA*

Background: The combination of daratumumab (Dara), pomalidomide (POM), and dexamethasone (dex) (DPd) has previously demonstrated deep and durable responses including high rates of minimal residual disease (MRD) negativity, in patients with relapsed/refractory (R/R) MM. Quadruplet regimens may further improve results. We report updated findings from a phase 2 multicenter trial of the addition of ixazomib to DPd (DIPd) in patients with early R/R MM. **Methods:** This is a prospective, multi-center, open-label, single arm phase II trial with a primary objective to evaluate the overall response rate (ORR), safety, and efficacy of DIPd. Secondary endpoints include progression-free survival (PFS), overall survival (OS), and MRD-negativity rate. A Simon's optimal 2-stage design was used, with 14 subjects in stage 1 to assess response and 32 patients for stage 2. Eligible patients may not have had exposure Dara or ixazomib, may not have progressed on POM, and may have received ≥1 and ≤3 prior lines of therapy. The first six patients in the safety run-in received Dara 16mg/kg IV weekly x 8 doses, biweekly x 8 doses, then monthly, POM 4mg orally on days 1-21 of a 28-day cycle, ixazomib 4mg orally on days 1,8,15 every 28 days, and dex 20-40mg weekly. Grade 3-4 neutropenia was observed in 100% of patients, prompting dose reduction to ixazomib 3 mg and POM 3 mg by the DSMB. An amendment allowed subcutaneous Dara administration. MRD assessments are being performed by EuroFlow for patients in VGPR or suspected CR. Pharmacodynamic changes in patients' tumor microenvironments were established by custom panel mass cytometry to include T-cell memory and activated subpopulations, B-cell content, NK-cell subpopulations as well as MDSCs, Tregs and T-exhaustive markers, monocytes and dendritic cells. **Results:** To date, 14 subjects have been treated in stage 1, and 18 patients in stage 2. Median age was 61.5 (range 41-87) years, 50% were female and 72% white. Median number of prior regimens was 1 (range 1-3), all patients were lenalidomide-exposed, and 47% (11/23) had high-risk cytogenetic features. The most common grade 3-4 treatment emergent adverse events included neutropenia (78%), infection (30%), leukopenia (11%), respiratory conditions (7%), psychiatric disturbance (4%), and thrombosis (4%). Median time on treatment was 4 months (1-29), with 11 patients remaining on DIPd and 5 deaths (4 due to progressive disease and 1 due to sepsis). ORR to date was 84% (16/19), and the best responses included: 5 (26%) sCR; 4 (21%) VGPR; 7 (37%) PR. After a median follow up of 12 months, the median OS was 39 months and PFS was 9.5 months. **Conclusions:** The quadruplet regimen DIPd is a well-tolerated combination that has shown early safety, efficacy, and ORR in early R/R myeloma, including patients with high-risk genetic abnormalities. Clinical trial information: NCT03590652. Research Sponsor: Takeda Pharmaceutical Company, Janssen Pharmaceuticals, Bristol Myers Squibb.

8042 **Poster Session**

Idecabtagene vicleucel (Ide-cel) chimeric antigen receptor (CAR) T-cell therapy for relapsed/refractory multiple myeloma (RRMM): Real-world experience. *First Author: Doris K. Hansen, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

Background: Ide-cel, a BCMA directed CAR T-cell therapy, was FDA approved 3/26/2021 for the treatment of RRMM after 4 prior lines of therapy. We evaluated the real-world outcomes of patients treated with standard of care ide-cel under the commercial FDA label. **Methods:** Ten US academic centers contributed data to this effort independent of the manufacturer. As of 1/10/2022, 138 patients were leukapheresed with overall manufacturing failure in 6 (4%). 108 patients were infused ≥ 30 days prior to data-cut off and constitute the study population for this retrospective analysis. **Results:** Table describes the study population compared to the pivotal KarMMa-1 trial (Munshi et al, NEJM 2021). Patients in our study were less likely to have ECOG PS of 0/1 (77%) and more likely to be penta-refractory (41%). 67% of patients would not have met eligibility criteria for KarMMa. Common reasons for ineligibility (> 1 reason in 22% patients) were co-morbidities (28%), cytopenias (22%), prior therapy with alloSCT/CAR-T/other BCMA therapy (19%), CNS myeloma/non-measurable disease/plasma cell leukemia (13%), and fitness (12%). 81% of patients received bridging therapy. Toxicity was comparable to that seen in KarMMa-1. Cytokine release syndrome (CRS) was seen in 82% (> grade 3: 4%) and immune effector cell-associated neurotoxicity syndrome (ICANS) in 15% (> grade 3: 5%) of patients, respectively. Tocilizumab and steroids were used in 72% and 25% of patients, respectively. Infections were seen in 34% of patients. Day 30 response was evaluable in 104 patients. Response rates were: ≥ partial response, 83%; ≥ very good partial response, 64%; and ≥ complete response (CR), 34%. 11% of patients have died by data cut-off, 7 due to disease progression and 5 due to other causes (1 grade 5 CRS, 1 hemophagocytic lymphohistiocytosis, 1 progressive neurological weakness, 2 COVID-19). **Conclusions:** This multicenter retrospective study delineates the real-world outcomes of ide-cel CAR T-cell therapy for RRMM. Despite more patients being penta-refractory and less fit compared to the pivotal KarMMa trial, safety and 30-day responses in the real-world setting (overall response rate: 83%, CR: 34%) are comparable to the clinical trial population. Follow-up is ongoing and updated data will be presented. Research Sponsor: None.

Patient characteristics and outcomes: Comparison between KarMMa-1 (Munshi et al. NEJM 2021) and commercial standard of care ide-cel treatment at 10 U.S. centers.

	KarMMa-1, N=128	Real world, N=108
Median age, yrs	61 (33-78)	64 (36-78)
ECOG PS 0 or 1	98%	77%
Extramedullary disease	39%	53%
High-risk cytogenetics	35%	33%
Median prior regimens	6	6
Prior autologous transplant	94%	85%
Penta-refractory disease	26%	41%
ORR/CR	73%/33% (Best response)	83%/34% (Day 30)
Grade ≥ 3 CRS and ICANS	5%, 3%	5%, 5%

8043 **Poster Session**

Demographic disparities in genomic data and clinical trials for multiple myeloma. *First Author: Nidhi Aggarwal, Medical College of Georgia at Augusta University, Augusta, GA*

Background: There are considerable outcome disparities among patients with multiple myeloma (MM). African-Americans have higher risk of developing MM, earlier age at diagnosis, and higher mortality compared to Whites. While outcomes have multifactorial socioeconomic etiologies, race and ethnicity (R&E) correlate with genomic ancestry, and any role of genetics should be explored. This requires equitable representation in biological databases like The Cancer Genome Atlas (TCGA). Here, we characterize disparities in MM cases of TCGA and clinical trials (CT). **Methods:** MM incidence was obtained from North American Association of Central Cancer Registries (NAACCR) for R&E, sex and age (< 50, 50-64, 65+ years). Race includes White, Black, and Asian, along with Hispanic ethnicity, as TCGA MM is limited to these groups. Genes with oncogenic potential and > 5% mutation were stratified by R&E and age. TCGA MM cases are from USA, Canada, Italy, and Spain. On ClinicalTrials.gov, completed MM CT limited to these countries were identified. Student's t-test and chi-square test were used to analyze disparities and gene mutations. Kaplan-Meier curve was generated to evaluate survival. **Results:** TCGA MM representation is in Table, calculated as (demographic TCGA cases divided by total TCGA cases) divided by (demographic incidence divided by total incidence). Race was not reported in 20% of TCGA, 4% of CT, and 3% of NAACCR. Of cases reporting R&E, Hispanics are underrepresented by 26% in TCGA and 47% in CT relative to incidence, Blacks by 22% in TCGA and 41% in CT, and Asians by 40% in TCGA and 10% in CT. Whites are overrepresented, by 8% in TCGA and 7% in CT. More men are in TCGA than women, in all R&E. Less than 25% of patients age < 50 relative to incidence are in TCGA, in all R&E. *BCL7A* is mutated more in Blacks age < 50 (n = 20, 50%) than Whites (n = 39, 10%) (p < 0.01). *FAT4* is mutated in Whites age 65+ (n = 31, 10%) but not Blacks. In all ages, *KRAS* is mutated more in Blacks than Whites (31-35% vs. 20-25%, p < 0.05). Black patients have lower survival than Whites (p < 0.02). In patients age 65+, *KRAS* mutation is associated with 10% lower 4.5-year survival. **Conclusions:** Substantial disparities in Black, Hispanic, women, and age representation exist for MM cases in TCGA and CT. This stratification by R&E and age offers new insight on BCL7A, FAT4, and KRAS mutation in MM. Mutation status is associated with survival in older patients. Equitable demographic representation should be pursued to improve quality of available data and access to medical resources for all populations. Research Sponsor: None.

Percent of All Demographic Incidence Represented in TCGA	All Ages (TCGA n=1065, NAACCR n=26843)	Age <50 (TCGA n=94, NAACCR n=1723)	Age 50-64 (TCGA n=441, NAACCR n=7749)	Age 65+ (TCGA n=418, NAACCR n=17371)
Asian Women	32%	2%	19%	43%
Asian Men	63%	6%	106%	18%
Black Women	54%	20%	53%	52%
Black Men	74%	9%	51%	114%
White Women	82%	21%	77%	93%
White Men	93%	25%	92%	107%
Hispanic Women	49%	2%	30%	92%
Hispanic Men	74%	2%	69%	112%

8044 **Poster Session**

Time to response, duration of response, and patient-reported outcomes (PROs) with daratumumab (DARA) plus lenalidomide and dexamethasone (D-Rd) versus lenalidomide and dexamethasone (Rd) alone in transplant-ineligible patients with newly diagnosed multiple myeloma (NDMM): Subgroup analysis of the phase 3 MAIA study. *First Author: Thierry Facon, University of Lille, CHU Lille, Service des Maladies du Sang, Lille, France*

Background: In the phase 3 MAIA study, adding DARA to Rd improved progression-free survival (primary endpoint), overall survival, duration of response, and PROs in transplant-ineligible pts with NDMM. We report a MAIA subgroup analysis of time to response, duration of response, and PROs. **Methods:** Transplant-ineligible pts with NDMM received 28-day cycles of Rd (R 25 mg PO on Days 1-21; d 40 mg PO QW) ± DARA (16 mg/kg IV QW in Cycles 1-2, Q2W in Cycles 3-6, and Q4W thereafter) until disease progression or unacceptable toxicity. Secondary endpoints included time to response and duration of response. PROs were measured using the EORTC QLQ-C30, with treatment effects assessed via mixed-effects model with repeated measures. **Results:** In total, 368 pts were assigned to the D-Rd group and 369 pts to the Rd group; 162 (44%) D-Rd pts and 142 (38%) Rd pts had renal impairment (defined as baseline CrCl ≤60 mL/min). At a 56.2-mo median follow-up, median times to very good partial response or better (≥VGPR) and complete response or better (≥CR) were shorter with D-Rd vs Rd in the overall study population and in the subgroups of pts with and without renal impairment (Table). Among pts who achieved ≥CR or partial response or better (≥PR), higher proportions of D-Rd vs Rd pts had not experienced disease progression at 48 mo (Table). Among pts with renal impairment, greater improvements from baseline in pt-reported pain, fatigue, and nausea and vomiting symptom scores were observed with D-Rd vs Rd across most timepoints; a notably greater meaningful reduction in pain symptom score was seen with D-Rd vs Rd as early as Cycle 6 Day 1 (least squares mean change from baseline, –14.9 vs –7.0; *P*=0.0241). Analyses for additional pt subgroups will be presented. **Conclusions:** In transplant-ineligible pts with NDMM, D-Rd showed more rapid deep responses as well as more durable responses vs Rd, regardless of renal function. Improvements in pt-reported symptoms were generally greater with D-Rd vs Rd in pts with renal impairment. Our results support the use of D-Rd in transplant-ineligible pts with NDMM. Clinical trial information: NCT02252172. Research Sponsor: Janssen Research & Development, LLC.

	All Responders (≥PR)		Responders with Baseline CrCl >60 mL/min		Responders with Baseline CrCl ≤60 mL/min	
	D-Rd	Rd	D-Rd	Rd	D-Rd	Rd
Time to response						
Median (range), mo						
≥CR	10.7 (1.0-46.7)	13.2 (2.8-54.6)	11.0 (1.0-41.9)	13.0 (2.8-47.9)	10.4 (3.0-46.7)	13.6 (5.6-54.6)
≥VGPR	3.0 (0.9-55.1)	4.7 (0.9-43.3)	3.0 (0.9-28.9)	4.7 (0.9-43.3)	2.9 (0.9-55.1)	4.9 (1.0-41.7)
Duration of response						
Estimated 48-mo event-free rate, % (95% CI)						
≥CR	81.8 (74.3-87.2)	57.8 (43.4-69.7)	82.2 (72.9-88.5)	55.3 (37.4-70.0)	81.0 (66.5-89.7)	61.5 (34.8-79.9)
≥PR	68.7 (63.1-73.5)	47.2 (40.8-53.3)	69.8 (62.4-76.0)	48.9 (40.8-56.5)	67.2 (58.5-74.5)	44.4 (34.1-54.3)

8045 **Poster Session**

African American patients with smoldering multiple myeloma may have a lower risk of progression compared to White patients. *First Author: Theresia Akhlaghi, Department of Internal Medicine, Icahn School of Medicine, Mount Sinai Morningside and West, New York, NY*

Background: The incidence of multiple myeloma (MM) is two to threefold higher in African Americans (AAs) compared to whites when adjusted for socioeconomics, age, and sex. However, there is limited information on whether racial background affects the risk of progression from smoldering MM (SMM) to MM. **Methods:** Patients with SMM presenting to Memorial Sloan Kettering Cancer Center between the years 2000 and 2019 and who identified as either AA or white were included in the study. Baseline characteristics were collected at the time of diagnosis including laboratory, imaging, and pathology reports. Differences in distributions of continuous and discrete characteristics were assessed by Kruskal-Wallis and chi-square tests. Time to progression (TTP) was assessed using the Kaplan-Meier method with log-rank test for comparisons. Univariate and multivariate Cox proportional hazard models were used to estimate effects of risk factors on TTP with hazard ratios (HR) and 95% confidence intervals (CI). **Results:** A total of 576 patients were included (70 were AA, 12%). Median follow-up time was 3 years in AAs and 4 years in whites. Differences in baseline characteristics between AAs and whites included median age (60 years in AAs vs 64 years in whites, p = 0.01), median hemoglobin level (12.3g/dL in AA vs 12.8g/dL in whites, p = 0.02), and immunoparesis including 1 or 2 uninvolved immunoglobulins (31% and 10% in AAs vs 56% and 27% in whites, p = 0.002). There was no difference in bone marrow plasma cells, M-spike, free light chain ratio, or Mayo-2018 SMM risk score. AA race was associated with a significantly decreased risk of progression in the univariate model (HR 0.57, CI 0.34-0.94). In the multivariate model adjusting for age, sex, and variables associated with an increased risk of progression in the univariate model (bone marrow plasma cells, M-spike, free light chain ratio, immunoparesis and low albumin), AA race remained associated with a decreased risk of progression (HR 0.39, CI 0.16-0.95). Overall, AA patients with SMM had a significantly (p = 0.027) longer median TTP (9.7 vs 6.2 years), and a lower 2-year (12.6% vs 20.1%) and 5-year (34% vs 44.6%) progression rate than whites. Because AA patients were younger at diagnosis, we stratified patients by age group, < 65 vs ≥65 years. In patients < 65 years, there was no difference in progression rate. In patients aged ≥65 years, AA patients continued to have a longer TTP than whites (9.8 vs 5.2 years, p = 0.02). **Conclusions:** In our retrospective single institution experience, AA patients with SMM had a lower risk of progression to MM compared to whites. Both groups had similar Mayo-2018 risk scores, however, AA patients had a lower degree of immunoparesis at baseline. Future studies are needed to better understand if these differences are explained by differences in disease biology including genomic mechanisms, immune microenvironment, and systemic immune response. Research Sponsor: None.

8046 **Poster Session**

A patient perspective on cure in multiple myeloma: A survey of over 1,500 patients. *First Author: Ghulam Rehman Mohyuddin, University of Utah, Salt Lake City, UT*

Background: As treatments advance in multiple myeloma (MM) and increasingly deeper and longer responses are achieved, the definition of what a cure is becomes increasingly relevant. While many physicians quote that patients may achieve a "functional cure", understanding the patient perspective on the concept of cure has yet to be explored. **Methods:** HealthTree Cure Hub by the HealthTree Foundation represents an online portal for patients with plasma cell dyscrasias to help navigate their disease. It is the largest single database of patients with multiple myeloma with over 10,200 patients as of January 2022. Using this platform, we surveyed patients online from November 11th 2021 to Feb 7th 2022. Varying scenarios incorporating toxicity, disease status, and being on/off treatment were presented, and participants were asked to rate them from 1-5, with 5 being an ideal cure. Patient awareness of the term functional or operational cure was also. **Results:** A total of 1525 participants completed the survey. Table lists characteristics of the patients who completed this survey. The majority of the patients were female (55.5%), college educated (88.5%) and non-Hispanic White (70.7%). Most patients rated being off treatment permanently and having no evidence of disease as a cure (1116/1469, 75.5%), with a median score of 5 amongst respondents, indicating an ideal version of cure. Continuing to take the same pill or injection with significant toxicity and no evidence of disease had a median score of 1, a score lower than either "continuing to take same pill or injection without significant toxicity even in the evidence of disease" (median score 2) or "stopping treatment permanently even with some detectable disease" (median score 2). The majority of patients (76.3%) reported being unfamiliar with the term functional or operational cure. **Conclusions:** In the first study of patients with plasma cell dyscrasias in which patients were asked about their perceptions of what a cure is, our results highlight that drug toxicity and being on treatment profoundly impacts patient's perception of cure. Furthermore, most patients are not familiar with the term functional or operational cure. Future efforts should recruit more diverse patient populations and incorporate patient preferences in approaches to defining cure in myeloma, as well as explaining cure in easily comprehensible terms to patients. Research Sponsor: None.

Participant characteristics.

		Number/Percentage of patients for which information available
Gender		1480, 97.0%
Female	821,55.5%	
Age, years, median (range)	66 (33–90)	1477, 96.9%
Race/ethnicity, no of patients (%)		1045, 68.5%
Non-Hispanic White	739,70.7%	
Hispanic	159, 15.2%	
Black	53, 5.1%	
Other	94,9.0%	
Education Status		1023, 67.1%
College degree or higher	905, 88.5%	
Disease Status		1351, 88.6%
Monoclonal gammopathy of undetermined significance	68, 5.0%	
Smoldering Myeloma	169, 11%	
Multiple Myeloma	1074, 79.5%	
Other	40, 3.0%	

8047 **Poster Session**

Evaluating serum-free light chain ratio as a biomarker for multiple myeloma. *First Author: Theresia Akhlaghi, Department of Internal Medicine, Icahn School of Medicine, Mount Sinai Morningside and West, New York, NY*

Background: In 2014, the definition of multiple myeloma was updated to include serum free light chain (FLC) ratio ≥100 as a myeloma defining biomarker, based on retrospective data indicating a 2-year progression rate of 80% and a median time to progression (TTP) of 12 months associated with this marker. However, two recent studies have reported lower 2-year progression rates, 30-44%, and longer median TTP of 40 months in patients with FLC ratio ≥100. Because of the disparity in risk prediction by FLC ratio across studies, we were motivated to assess the risk of progression in patients with SMM and a FLC ratio ≥100. **Methods:** We performed a retrospective analysis of patients diagnosed with SMM at Memorial Sloan Kettering Cancer Center between January 2000 and December 2017. Diagnosis of SMM and progression to MM was defined according to the International Myeloma Working Group (IMWG) criteria at the time of diagnosis. Kaplan-Meier method was used to assess TTP and generate survival curves, with log-rank test for comparison between groups. **Results:** A total of 438 patients were included in the study, with a median follow-up time of 52 months. While all patients with a FLC ratio ≥100 (n = 66) had elevated involved FLC levels, 35 (53%) had an involved FLC concentration > 100 mg/L. Per current diagnostic criteria, we only included patients with an involved FLC concentration > 100 mg/L in the FLC ratio ≥100 group, and found a median TTP of 31 months (95% confidence interval [CI] 16-59 months) and a 2-year progression rate of 49% (CI 28-63%). In a sensitivity analysis including all 66 cases with FLC ratio ≥100 (independent of involved FLC concentration), we found the median TTP to be 41 months (CI 30-72 months), compared to 101 months for those with a FLC ratio < 100 (CI 78-127 months; p < 0.0001). The risk of progression within 2 years was 35% (CI 22-46%) compared to 18% (CI 14-23%; p < 0.0001). Of note, 22 patients with a FLC ratio ≥100 were monitored expectantly for > 4 years, among whom 12 patients had an involved FLC level > 100 mg/L. Ten patients (7 with involved FLC level > 100 mg/L) were followed over a period ranging from 4 to 8.5 years before eventually progressing, and 12 patients (5 with involved FLC level > 100 mg/L) were followed between 4 and 8 years and did not progress during the study period. **Conclusions:** While FLC ratio ≥100 is associated with a high risk of progression in patients with SMM, it does not infer an imminent risk of progression, defined by the IMWG as median TTP of 12 months and 2-year progression rate of at least 80%. On the contrary, select patients with FLC ratio ≥100 can be followed for many years without progressing and some may never progress despite long-term follow-up. These findings suggest that in patients where FLC ratio ≥100 is the only myeloma-defining event, other high-risk features as well as the evolution of FLCs over time should be considered in the decision to start a patient on treatment. Research Sponsor: None.

8048 **Poster Session**

Retrospective review of outcomes of patients with multiple myeloma with COVID-19 infection (two-center study). *First Author: Hamid Ehsan, Levine Cancer Institute, Atrium Health, Charlotte, NC*

Background: Coronavirus-2 has profound effects on patients (pts) with Multiple myeloma (MM). At the beginning of the pandemic, COVID-19 infection resulted an overall mortality around 54% (cook et al. BMJ 2020). Here, we report an updated morbidity and fatality for MM. **Methods:** After obtaining IRB approvals from each participating institute, retrospectively, between January 1, 2021 and August 30, 2021, we identified pts with MM and COVID-19 in two myeloma centers (Levine Cancer Institute (LCI) & the University of Kansas medical center (KUMC). **Results:** We identified 162 MM pts who had COVID-19 (LCI n=132, UKMC n=30), including 57% males, with median age of 64 years. Current or former smoking reported in 40% of pts. Most pts have associated comorbid conditions: hypertension (45%), hypogammaglobulinemia (32%), CKD (30%), DM (22%), obesity (16.6%), CHF (14%), and CAD (13.5%). Within 3 months prior to infection, treatment included immunomodulatory combinations in 35%, proteasome inhibitors in 28 %, and Daratumumab in 26.5%. Symptoms are summarized in table. 69% had Mild symptoms (no need for hospitalization), 20 % had moderate symptoms (requiring hospitalization), and 9.8% had severe symptoms (ICU level of care). The 18% of pts required oxygen: 6 pts required invasive oxygenation and 3 pts needed vasopressors. The 32% of pts had RRMM, 29.5% on maintenance, and 12% was getting induction. Regarding MM response: >VGPR in 45% and PD in 18%. The 78 pts had ASCT prior to COVID-19 infection: only 3 pts < 1 year and 3 pts < 6 months. MM response or ASCT did not affect hospitalization or mortality.The case fatality rate (CFR) was 6%. In the univariate analysis, CKD, DM, HTN and hepatic dysfunction were associated with an increased risk of hospitalization. However, in multivariate analysis, only CKD, hepatic dysfunction, and Hypogammaglobulinemia significantly increased the risk of admission with only age and lymphopenia were associated with increased COVID-19 related fatatlity. **Conclusions:** With implementation of center-specific disease control measures and universal screening, pts might have lower case severity and fatality rate than was initially reported. Research Sponsor: None.

Symptoms	Number	Frequency
Fatigue	90	56%
Cough	86	53%
Fever	65	40%
Shortness of breath	61	38%
Myalgias	48	30%
Headache	40	25%
Rhinorrhea	29	18%
Diarrhea	25	15%
Nausea	20	12%
Anosmia	14	9%
Abdominal pain	12	7%
Confusion	11	7%
Diaphoresis	11	7%
Weight loss	5	3%
Asymptomatic	46	28%

8049 **Poster Session**

Kinetics of humoral immunodeficiency with bispecific antibody therapy in multiple myeloma. *First Author: Lindsay Hammons, Mount Sinai Beth Israel, New York, NY*

Background: Bispecific antibodies (bsAb) are a promising class of therapeutics in RRMM. While hypogammaglobinemia (HGG) is anticipated due to plasma cell depletion, there is a lack of information about the degree of secondary immunodeficiency and resultant infectious complications. We investigated the kinetics of HGG in patients with RRMM on bsAb therapy. **Methods:** We identified and followed 42 patients treated on early clinical trials of bsAb at our institution between 2019 and 2021. Serial immunoglobulin levels and infections were obtained from the start of therapy until last follow up or 3 months after study exit. **Results:** 49 treatment courses were included from 42 individual patients. All patients were triple class exposed with a median of 5 prior lines of therapy. The median age was 67 (44-85) years, with 49% females. African Americans accounted for 18% of patients. 96% of patients had at least one prior ASCT. 90% of patients received bsAb targeting BCMA including 7 patients who received more than one line of BCMA targeting therapies. At a median follow up 9.5 (0.9-28.6) months, 40.8% of patients remained on bsAb therapy. At the start of therapy, the median IgG, IgA, and IgM levels were 560 (44-9436), 15 (5-3886) and 6 (5-64) mg/dL, respectively and 50% of patients had severe HGG (≤400mg/dl). Serum IgG levels reached a nadir at 3 months while, IgA and IgM at 1 month, from the start of therapy. The median nadir levels of IgG were 159 (40-2996) mg/dL, while it was < 5 mg/dL for both IgA and IgM. IgG levels were below the detectable range (< 40 mg/dl) in 28% of patients at some point during therapy. IgA and IgM were also below the detectable range (< 5 mg/dl) in 50% and 60% of patients, respectively. At last follow-up, the median IgG levels were 444 (40-1860) mg/dL and IgA 5 (5-254) mg/dL and IgM 5 (5-44) mg/dL. Additionally, 38% of patients remained severely hypogammaglobinemic. 57% (24/42) of patients received IVIG supplements in the current series. About 71% of patients had at least one infectious event and the cumulative incidence of infections progressively increased with increasing duration of therapy with risk at 3, 6, 9 12, 15 months being 41%, 57%, 64%, 67% and 70%, respectively. Among these, 54% of infection were bacterial. Viral infection accounted for 41% of infections. A third of patients had new infectious events during the first 90 days following stopping bsAb treatment. 57% (8/14) of patients did not mount a response to the primary COVID19 immunization series. Among the five patients with repeat antibody titers after the booster dose, 50% were still not able to mount an antibody response. **Conclusions:** bsAb therapy in RRMM can be associated with profound and prolonged HGG. The cumulative risk of infection correlated with the degree of HGG and progressively increases with treatment and persisted months after being off therapy. Additionally, an impaired antibody response to the COVID-19 immunization series was also noted. Research Sponsor: None.

8050 **Poster Session**

The association of agent orange (AO) exposure with monoclonal gammopathy of undetermined significance (MGUS) to multiple myeloma (MM) progression: A population-based study. *First Author: Lawrence Liu, Department of Medicine, Washington University School of Medicine, Saint Louis, MO*

Background: With limited evidence from a single center study [n=211 (11 with AO exposure)] reporting AO exposure as a risk factor for transformation, whether or not AO exposure increases the rate of transformation from MGUS to MM is unclear. Thus, we aimed to conduct a nationwide study to determine the association between AO exposure and the risk of MGUS to MM progression. **Methods:** A retrospective, matched cohort study using data from the U.S. Veterans Health Administration system was conducted. Based on a power calculation, a random sample of MGUS patients with AO exposure was selected and 1:1 matched to those with MGUS without AO exposure (matching factors: age at MGUS diagnosis, race, body mass index categories). Data abstraction confirmed MGUS and MM diagnoses. In addition, information on date of diagnosis, MGUS subtype, and monoclonal protein (M-protein) values was performed. Patients were considered to have MGUS if they had M-protein detected on serum protein electrophoresis (SPEP) with immunofixation confirmation. The association of AO exposure with progression from MGUS to MM was examined using a multivariable Fine-Gray subdistribution hazard model with death as the competing event. The covariates included M-protein at MGUS diagnosis (>1.5, ≤1.5 g/dL [reference]), MGUS subtype (Immunoglobulin A, light chain, and Immunoglobulin G [reference]), and Charlson comorbidity score at MGUS diagnosis. A sensitivity analysis was conducted using inverse probability treatment weighted survival analysis to evaluate the robustness of the conclusion. **Results:** After excluding individuals with no confirmed MGUS or M MGUS subtype, a total of 563 MGUS patients with AO exposure and 563 matched controls were included. No statistically significant difference was observed in the progression of MGUS to MM between the AO exposed group and control group (adjusted hazard ratio (aHR) 0.78, 95% confidence interval (CI) 0.53 to 1.17). The sensitivity analysis demonstrated consistent results. **Conclusions:** Our carefully designed study does not show an association between AO exposure and progression of MGUS to MM in a national cohort of Veterans. Research Sponsor: U.S. National Institutes of Health.

Multivariable analysis of progression of MGUS to MM.

Parameter	Hazard Ratio	95% Confidence Interval	P-value
AO Exposure	0.78	0.53-1.17	0.23
M-protein >1.5 g/dL	16.29	5.86-45.27	<0.0001
Immunoglobulin A MGUS	1.09	0.58-2.06	0.79
Light Chain MGUS	5.57	1.45-21.41	0.01
Comorbidity	0.99	0.91-1.08	0.78

8052 **Poster Session**

Daratumumab (DARA) in combination with bortezomib plus dexamethasone (D-Vd) or lenalidomide plus dexamethasone (D-Rd) in relapsed or refractory multiple myeloma (RRMM): Subgroup analysis of the phase 3 CASTOR and POLLUX studies in patients (pts) with early or late relapse after initial therapy. *First Author: Andrew Spencer, Malignant Haematology and Stem Cell Transplantation Service, Alfred Health-Monash University, Melbourne, Australia*

Background: High-risk multiple myeloma (MM) is often defined based on cytogenetic abnormalities (ie, t[4;14], t[14;16], and/or del17p); however, pts who relapse early (12-18 months) after initial therapy are considered a functional high-risk group that is also associated with poor prognosis. DARA, a human IgGκ monoclonal antibody targeting CD38, is approved in combination with standard-of-care regimens for MM. In the phase 3 CASTOR and POLLUX studies, D-Vd and D-Rd significantly improved progression-free survival (PFS), regardless of cytogenetic risk, and achieved higher rates of complete response or better (≥CR) and minimal residual disease (MRD)–negativity vs Vd or Rd alone in pts with RRMM. Post hoc analyses of CASTOR and POLLUX evaluated D-Vd vs Vd and D-Rd vs Rd in pt subgroups with 1 prior line of therapy based on timing of relapse (early or late) after initiation of the first line of therapy. **Methods:** In CASTOR and POLLUX, pts with RRMM and ≥1 prior line of therapy were randomized to D-Vd/Vd or D-Rd/Rd, respectively. The primary endpoint was PFS. In this analysis, the early relapse subgroup included pts with 1 prior line of therapy who relapsed <18 months after initiating their first line of therapy; pts with 1 prior line of therapy who relapsed ≥18 months after initiating their first line of therapy were included in the late relapse subgroup. **Results:** 49 and 186 pts from CASTOR and 99 and 196 pts from POLLUX were included in the early relapse and late relapse subgroups, respectively. Median follow-up was 72.6 months (CASTOR) and 79.7 months (POLLUX). PFS consistently favored the DARA-containing regimens across subgroups (Table). In CASTOR, ≥CR rates were higher with D-Vd vs Vd in the early relapse (21% vs 17%; $P = 0.7360$) and late relapse (51% vs 14%; $P < 0.0001$) subgroups. In POLLUX, ≥CR rates were higher with D-Rd vs Rd in the early relapse (53% vs 12%; $P < 0.0001$) and late relapse (62% vs 38%; $P = 0.0012$) subgroups. MRD-negativity rates (10^{-5}) were higher with D-Vd/D-Rd vs Vd/Rd regardless of relapse timing (CASTOR: early, 13% vs 0%; $P = 0.1476$; late, 23% vs 3%; $P < 0.0001$; POLLUX: early, 30% vs 4%; $P = 0.0006$; late, 34% vs 14%; $P = 0.0009$). **Conclusions:** These post hoc analyses of CASTOR and POLLUX showed PFS and depth of response benefits of DARA-containing regimens in patients with 1 prior line of therapy, regardless of relapse timing (early or late). Our results support the use of D-Vd and D-Rd in RRMM, including in pts who are considered functional high risk. Clinical trial information: NCT02136134 and NCT02076009. Research Sponsor: Janssen Research & Development, LLC.

Median PFS, months	D-Vd	Vd	HR (95% CI); *P* value	D-Rd	Rd	HR (95% CI); *P* value
Early relapse	15.4	9.0	0.51 (0.26-1.00); $P = 0.0488$	36.9	11.7	0.41 (0.26-0.65); $P = 0.0002$
Late relapse	27.7	7.9	0.20 (0.14-0.29); $P < 0.0001$	69.3	29.7	0.53 (0.37-0.77); $P = 0.0007$

8053 **Poster Session**

Outcomes for transplant-eligible, newly diagnosed Black patients (Pts) with multiple myeloma (MM): The Levine Cancer Institute (LCI) experience. *First Author: Barry Paul, Levine Cancer Institute, Charlotte, NC*

Background: Studies have revealed disparities for Black (B) pts with MM, including more advanced disease at presentation, delayed therapy with novel agents such as immunomodulatory drugs (IMIDs) and proteasome inhibitors (PIs), reduced access to autologous stem cell transplant (ASCT), and under-representation in clinical trials. However, B pts tend to be younger at diagnosis and less likely to harbor high risk disease biology, suggesting outcomes could be better relative to their White (W) counterparts. To better understand outcomes by race in the setting of more optimal treatment access, we pursued a retrospective analysis of pts treated at LCI undergoing ASCT as part of first line therapy. **Methods:** 255 pts (181 W pts, 74 B pts) transplanted between 3/2014 – 12/2018 were included. Analysis was restricted to pts with MM who underwent a single ASCT as part of first line therapy. Pts with < 1 year of follow-up and no overall survival (OS) events were excluded. Proportions were compared between groups with Fisher's exact tests; OS and progression free survival (PFS) were evaluated with Kaplan Meier methods and compared between groups with log-rank tests. **Results:** Median follow-up for B and W pts was 5.0 yrs (0.9 – 7.8 yrs) and 4.1 yrs (0.5 – 8.0 yrs). At initial presentation, median age was 59 yrs (24 – 76 yrs) and 61 yrs (35 – 78 yrs, $P = 0.038$), anemia was present in 81.3% and 64.6% ($P = 0.020$), renal impairment in 41.3% and 33.1% ($P = 0.335$), and high-risk cytogenetics [gain 1q21, t(4;14), t(14;16) or del(17p)] in 25.4% and 35.9% ($P = 0.162$) of B and W pts, respectively. Median time from diagnosis to ASCT was 0.6 yrs (0.3 – 2.4 yrs) and 0.5 yrs (0.3 – 2.0 yrs) for B and W pts. 35.2% of all B pts and 43.9% of all W pts treated at LCI during the study period underwent ASCT (48.3% and 64.4% of pts ≤70 yrs of age, $P = 0.002$), while 63.5% and 80.1% received PI/IMID-based induction therapy ($P = 0.009$) and 90.5% and 93.4% received maintenance therapy post-ASCT ($P = 0.438$), respectively. Although ≥very good partial responses were achieved in fewer B pts than W pts after induction (65.8% and 80.7%,($P = 0.014$), there was no difference after ASCT (95.8% and 93.9%, $P = 0.759$). Median PFS was 5.9 yrs (95% CI 3.4 – 6.6) and 3.6 yrs (95% CI 3.0 – 4.5) for B and W pts ($P = 0.039$). Median OS trended in favor of B pts ($P = 0.163$) with 5-year OS of 83.0% (95% CI 71.2% - 90.3%) and 74.2% (95% CI 65.8% - 80.9%), respectively. **Conclusions:** Despite disparities in optimal induction therapy, Black pts with MM who underwent frontline ASCT enjoyed better PFS relative to W pts. Optimizing access to PI/IMID-based induction therapy and ASCT will be necessary to further improve OS. Research Sponsor: None.

8054 **Poster Session**

Randomized phase II trial of bortezomib, lenalidomide, dexamthasone with/without elotuzumab for newly diagnosed, high risk multiple myeloma (SWOG-1211). *First Author: Saad Zafar Usmani, Myeloma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The introduction of immunomodulatory agents, proteasome inhibitors, and autologous stem cell transplantation (ASCT) has improved outcomes for patients with multiple myeloma (MM), but those with high risk MM (HRMM) have a poor long-term prognosis. Herein we provide survival outcomes on the first randomized trial in newly diagnosed HRMM, S1211, to follow-up on the previously reported progression-free survival (PFS) (NCT01668719, Usmani SZ et al, Lancet Haem 2021). **Methods:** S1211 is a randomized phase II trial comparing 8 cycles of lenalidomide, bortezomib and dexamethasone (RVd) induction followed by dose-attenuated RVd maintenance until disease progression with or without elotuzumab (RVd-Elo). Stem cell collection was allowed, but ASCT was deferred until progression. HRMM was defined by one of the following: gene expression profiling high-risk (GEP^{hi}), t(14;16), t(14;20), del(17p), amplification 1q21, primary plasma cell leukemia (pPCL), or elevated serum LDH (> 2X ULN). Median PFS was the primary endpoint, using a one-sided stratified log-rank test at a one-sided significance level of 0.1. Secondary endpoints included overall response rate (ORR), adverse events (AE), serious adverse events (SAE) and OS. Response was assessed using the IMWG 2009 criteria. **Results:** S1211 enrolled 103 evaluable patients, RVd n=54, RVd-Elo n=49. 74% had ISS II/III, 48% amp1q21, 38% del(17p), 11% t(14;16), 9% GEP^{hi} , 7% pPCL, 5% t(14;20) and 4% elevated LDH (17% >1 feature). With median follow-up of 72 months (mos.), no difference in median PFS was observed [RVd-Elo=29 mos., RVd= 34 mos., HR = 1.11 (80% CI=0.82, 1.49, p=0.66]. No difference in OS was observed [RVd-Elo = median not reached (NR), RVd= 68 mos., HR = 0.85 (80% CI: 0.59, 1.23), p-value = 0.58]. 76% pts had >Grade 3 AEs, no differences in the safety profile were observed. Amongst patients with gain/amp 1q21, median PFS was [RVd-Elo=31 mos., RVd= 37 mos., HR = 1.48 (80% CI= 0.95, 2.31), p=0.25], median OS was [RVd-Elo = 61 mos., RVd= 68 mos., HR = 1.23 (80% CI: 0.72, 2.10), p-value = 0.63]. In patients with del(17p), median PFS was RVd-Elo=41 mos., RVd= 30 mos.[HR = 0.98 (80% CI= 0.60, 1.58), p=0.95], median OS RVd-Elo = NR, RVd= 72 mos., [HR = 0.77 (80% CI: 0.40, 1.48), p-value = 0.61]. **Conclusions:** In the first randomized HRMM study reported to date, the addition of Elo to RVd induction and maintenance did not improve PFS and OS with a median follow-up of 6 years. Although the median PFS for Del17p subgroup on RVd-Elo arm is higher than RVd, it did not achieve statistical significance. The PFS and OS observed for gain/amp 1q21 and del17p in the RVd control arm may serve as important benchmarks for future enrichment design HRMM clinical trials. The PFS and OS in both arms of the study exceeded the original statistical assumptions and support the role for PI/IMiD combination induction/maintenance therapy for this population. Clinical trial information: NCT01668719. Research Sponsor: U.S. National Institutes of Health.

8055 **Poster Session**

Myeloma developing regimens using genomics (MyDRUG) trial: Results from the RAS mutation targeting arm. *First Author: Shaji Kumar, Mayo Clinic, Rochester, MN*

Background: Multiple myeloma (MM) is characterized by somatic mutations involving cancer-associated genes. The most commonly mutated genes are N- and K-Ras, which increase in prevalence as the disease progresses. Case reports and retrospective data suggest efficacy of targeting the MAPK pathway in N/K-Ras mutated MM. The MyDRUG trial was initiated to explore the efficacy of specific molecularly-targeted therapies in combination with standard therapies in MM. **Methods:** MyDRUG (NCT03732703) is a genomically-guided umbrella trial for patients with functional high-risk MM, defined as early relapse following primary therapy (3 years for transplant with maintenance, 18 months without), with specific genetic abnormalities. Subjects undergo molecular profiling of their MM cells and are assigned to a targeted arm if a variant allele frequency (VAF) over 25% is identified. The targeted mutated genes and respective agents (approved for non-MM indications and with a known phase 2 dose) are: KRAS/NRAS/BRAF (cobimetinib), FGFR3 (enasidenib), IDH (erdafitinib), CDKN2C (abemaciclib), *t*(11;14) (venetoclax). Patients receive the investigational drug for 2 cycles as a single agent followed by addition of an active MM combination (ixazomib, pomalidomide and dexamethasone, IPd). Limited dose escalation was performed with the single agent followed by dose assessment in combination with IPd. Here we present the results of the dose escalation portion of C1 arm exploring cobimetinib in patients with N/K-RAS or BRAF mutations. Cobimetinib was administered at 40 mg daily in combination with standard doses of IPd. **Results:** Eleven subjects with BRAF/RAS mutations were screened between August 2019 and October 2020, with 4 screen failures. Seven were enrolled, 5 males, median age 65 years, and median time from diagnosis of 30 months. N-RAS, K-RAS or BRAF mutations were seen in 4, 2, and 1 subject(s), respectively, with VAF ranging from 33-93%. Median number of prior lines of therapy was 1 (1-3), 3 patients had extramedullary disease, and 1 patient had high risk cytogenetics. Median duration of therapy was 12 months. One patient was not evaluable for dose limiting toxicity. All but 1 patient had at least one cycle delayed due to adverse events (AEs), but no dose reductions were required. No dose limiting toxicities were observed across the cycles, either during single agent therapy (Cycles 1-2) or in combination with IPd (Cycles 3 and 4). Six patients responded to therapy (4 PR, 2 VGPR). One patient was not response evaluable. Fatigue was the most common non-hematological AE followed by diarrhea. **Conclusions:** Here we report on the feasibility of genomically-guided, precision medicine therapy in K/N-RAS/BRAF-mutated MM. The MEK inhibitor cobimetinib in combination with IPd appears safe in functionally high-risk patients. Ongoing study will provide more information regarding the efficacy of this approach. Clinical trial information: NCT03732703. Research Sponsor: The Multiple Myeloma Research Foundation.

8056 **Poster Session**

Clinicopathological characteristics of high-risk multiple myeloma in Hispanic versus non-Hispanic patients in central California. *First Author: Andrew Hwang, University of California-San Francisco, Fresno, CA*

Background: Roughly 37% of Multiple Myeloma (MM) patients in the U.S. are non-white minorities. Advanced stage at diagnosis and specific cytogenetic abnormalities are associated with high-risk disease and poor prognosis. Few studies evaluated these risk factors in ethnic minorities. To further investigate, we analyzed ethnic variations in characteristics and outcomes of high-risk MM patients who were treated at our institution in Fresno, CA (49.6% Hispanic population). **Methods:** Patients diagnosed with high-risk MM at Community Medical Centers from 1-1-2011 to 12-31-2020 were included. High risk was defined by Mayo Clinic mSMART 3.0 classification. Demographic and disease-relevant information were collected. Cytogenetics, R ISS stage, 1st line treatment (doublet vs triplet), and treatment response (IMWG response criteria) were evaluated. Hispanic and non Hispanic comparisons were made by Fisher's exact test where appropriate. Progression Free Survival (PFS) and Overall Survival (OS) were evaluated by Kaplan-Meier estimates and compared via log-rank test. Univariate cox proportional hazard model for survival was used to examine the association of variables with mortality risk after 1st line therapy. **Results:** 147 MM patients were screened. 42 high risk patients were identified: 11 (26%) Hispanic, 31 (74%) non Hispanic (22 white, 8 African American, 1 East Indian). Median age at diagnosis was 65. 26 (61%) were females. 25 (59%) were R ISS stage 3. Hispanic vs non Hispanic median income was $46119 vs $65080 (p=0.035). 6 Hispanics had Medi-Cal insurance vs 2 non-Hispanics (54.6% vs 6.5%, p=0.003). More Hispanics had Lambda light chain disease (73% vs 26%; p=0.01). 13 non Hispanics had del 17p vs 0 Hispanics (p=0.009). 40/42 patients (95%) received triplet therapy. 4 Hispanics received ASCT vs 9 non Hispanics (40% vs 33.3%, p=0.716). Hispanics and non Hispanics did not have significantly different treatment responses per IMWG criteria (p=0.799). No significant difference in PFS was seen between Hispanics and non Hispanics (805 vs 793 days; p=0.089); OS was better in Hispanics (1062 days vs 453 days; p=0.008). Per univariate cox proportional Hazard model, female sex (HR 4.34) and age (HR 1.05) were associated with higher mortality while Hispanic ethnicity was associated with lower mortality (HR 0.19). **Conclusions:** Hispanic and non Hispanic high risk MM patients differed significantly in median income, insurance, and del 17p incidence. These did not translate to a difference in 1st line therapy or treatment response. OS in our study is higher in Hispanic high-risk MM patients compared to other ethnicities and warrants further investigation. Research Sponsor: None.

	Total*	Hispanic	Non Hispanic	Fisher's Exact
t(4;14)	8	3	5	0.412
t(14;16)	3	1	2	0.999
t(14;20)	0	0	0	-
1q gain	19	6	13	0.504
p53 Mutation	6	1	5	0.999
Del 17p	13	0	13	**0.009**
R ISS				0.280
Stage 1	4	2	2	
Stage 2	13	2	11	
Stage 3	25	7	18	

*Includes patients with >1 abnormality.

8057 **Poster Session**

Impact of second primary malignancy post-autologous hematopoietic stem cell transplantation on outcomes of multiple myeloma: A CIBMTR analysis. *First Author: Brittany K. Ragon, Levine Cancer Institute, Atrium Health, Charlotte, NC*

Background: Following autologous hematopoietic stem cell transplant (auto HCT), maintenance therapies improve survival, reduce relapse risk in multiple myeloma (MM), and are the *de facto* standard-of-care. However, clinical trials have shown an increased risk of second primary malignancies (SPM) with maintenance therapy, including second hematological malignancies (SHM). We examined data from the Center for International Blood and Marrow Transplant Research (CIBMTR) registry to evaluate the impact of SPM on progression-free (PFS) and overall survival (OS) and the utilization of allogeneic HCT in patients with therapy-related myeloid neoplasms (t-MN). **Methods:** Adult patients (pts) with MM who underwent first auto HCT in the United States with a melphalan conditioning regimen from 2011-2018 and subsequently received maintenance therapy were included (N=3948). The primary endpoint of interest was the impact of SPM and SHM on OS. Multivariate analytic (MVA) modelling was applied, accounting for competing risks while integrating significant covariates to determine the impact of SPM on PFS and OS. Finally, we studied the utilization and survival following allogeneic HCT for SHM. **Results:** Baseline characteristics were similar between the two groups. Maintenance regimens used were lenalidomide (2836, 72%), bortezomib (370,9 %) or lenalidomide + bortezomib (372, 9%) based combinations. At a median follow up of 37 months, 175 (5%) pts developed SPM, including 112 (64%) solid 36 (21%) myeloid, and 27 (15%) lymphoid cancers. In MVA, the development of SPM and SHM was associated with an inferior PFS (HR 2.62, $P<0.001$ and HR 5.01, $P<0.001$, respectively) and OS (HR 3.85, $P<0.001$ and 8.13, $P<0.001$, respectively). The two commonest causes of death were MM (42%) and SPM (30%) for those developing SPM. Similarly, MM (53%) and SHM (18%) were the two commonest causes of death for those developing SHM. Nine (14%,5 t-MDS and 4 t-AML) of 63 patients with SHM underwent an allogeneic HCT. Patients undergoing allogeneic HCT were more likely to have Karnofsky score ≥90 (100% *vs.* 50%, $P=0.02$) compared to those who did not. One year survival from allo SCT was 66.7% (CI 34.6-92%). **Conclusions:** The three-year cumulative incidence of SPM was 3.3 (2.6-4)% in this large contemporaneous CIBMTR cohort. Disease relapse remains the primary cause of death in MM patients who develop SPM or SHM. Given the median OS for MM is now > 10 years, longer follow-up is needed to assess the SPM and SHM risks with maintenance therapy post-auto HCT. Research Sponsor: U.S. National Institutes of Health.

8058 **Poster Session**

Early intervention for high-risk and low-risk of progression for patients with smoldering multiple myeloma. *First Author: Nathan W. Sweeney, HealthTree Foundation, Lehi, UT*

Background: Previous studies have observed smoldering multiple myeloma (SMM) patients with a biomarker criteria of > 20% bone marrow plasma cells, > 2 g/dL M protein spike, and > 20 free light chain ratio, also known as 20/2/20, are at a higher risk of progressing to multiple myeloma (MM) than others. These findings have ignited interest in pursuing early intervention for these high-risk patients. However, we asked if early intervention would be beneficial for all SMM patients regardless of the progression risk level. **Methods:** We utilized real-world data from HealthTree Cure Hub for Multiple Myeloma to first, determine whether 20/2/20 resulted in a higher risk of progression and second, analyze whether early intervention delayed progression from SMM to MM. A 2-sample t-test was used to compare 20/2/20 to non-20/2/20 patients, as well as in the comparison between SMM patients who received early intervention with treatment to without early intervention. **Results:** We found that patients who met at least two of the criteria of 20/2/20 had a tendency to progress to MM 35% faster than patients who did not meet the criteria (n = 36, p-value < 0.10). While not significant, it's still worth noting that there is a difference in the mean time to progression for these patients. Next, we found SMM patients who do not receive early intervention with treatment develop MM two times faster than those who do receive early intervention with treatment, regardless of progression risk level (n = 129, p-value < 0.001). **Conclusions:** Our results revealed that at least two of the biomarker criteria could aid in the identification of patients with a higher risk of progression. However, a casual approach of "sit and wait" for patients to develop 20/2/20 is not warranted since our findings revealed that all SMM patients benefited from treatment intervention regardless of the progression risk level. Research Sponsor: None.

8059 **Poster Session**

Analysis of long-term outcomes in R-ISS stage 2 multiple myeloma with and without the presence of high-risk cytogenetics. *First Author: Nisha Joseph, Emory University, Winship Cancer Institute, Atlanta, GA*

Background: The Revised International Staging System (R-ISS) is the current standard for risk-stratification of newly diagnosed myeloma (NDMM), incorporating albumin and β2M with high-risk cytogenetics and/or elevated LDH. (Palumbo et al, JCO 2015) R-ISS stage 2 represents a heterogeneous cohort including myeloma with and without high-risk cytogenetics, a known poor prognosticator. Here, we present a retrospective analysis on outcomes of R-ISS stage 2 NDMM utilizing our institutional database of patients treated at the Winship Cancer Institute of Emory University. **Methods:** From January 2007 to August 2016, 1,000 consecutive newly diagnosed myeloma patients treated with RVD induction therapy were identified . Demographics, clinical characteristics, and outcomes data for the patients were obtained from our institutional review board-approved myeloma database. Responses were evaluated per IMWG Uniform Response Criteria. **Results:** The median age of this cohort was 61 years (range 16-83). Other notable patient characteristics include: M/F 54.6%/45.4%, W/AA 61.8%/35.9%; ISS I/II/III 45.8%/30.8%/23.4%. R-ISS I/II/III 39.9%/48.7%/11.5%; Isotype IgG/IgA/FLC 59.2%/19.0%/15.7%; standard risk (SR)/high risk (HR) 71.2%/15.8%. ISS data was available for 75% of patients; R-ISS was available for 41% of patients. HR disease was defined as the presence of t(4;14), t(14;16), del(17p), and/or complex karyotype by conventional metaphase cytogenetics. Frequency of specific CTG abnormalities were 2.8% with t(14;16), 10% with del(17p), and 4.8% with t(4;14). With a median follow up of 88.4 months, the median PFS (mPFS) for the entire cohort was 68.7 months (95% CI 61.8-75.5) and the median OS was 128.9 months. The median PFS for HR vs SR patients was 42.4 months (95% CI 35.7-48.9) vs 80.3 months (95% CI 72.8-87.8). The median OS for SR patients was not reached, and for HR patients was 86.6 months (95% CI 70.1-103.1). The mPFS for R-ISS 1,2 and 3 was 95.4 months (95% CI 73.4-117.5), 56.6 months (95% CI 44.4-68.7), and 31.1 months (95% CI 16.3-45.9). When the R-ISS 2 cohort was divided into those without HR CTG and with HR CTG, the mPFS was 67.1 months (95% CI 53.3-80.8) versus 40.2 months (95% CI 30.1-50.3), respectively. The mOS for R-ISS I/II/III was NR, 122.7 months (95% CI 101.6-143.9), and 60.6 months (95% CI 11.6-109.5). For R-ISS 2 without and with HR CTG, the mOS was 129.1 months and 94.8 months (95% CI 61.3-128.3), respectively. **Conclusions:** The R-ISS is a validated risk model clearly defining three distinct groups in terms of long-term outcomes. However, these data suggest R-ISS stage 2 can further be characterized into two distinct groups based on the presence or absence of high risk cytogenetics. R-ISS 2 with HR-CTG portends both inferior mPFS and increased risk of death when compared to R-ISS 2 without HR-CTG (HR 2.63 versus HR 1.65), and behaves more similarly to R-ISS 3 disease. Research Sponsor: None.

8060 **Poster Session**

Retrospective, single-center, real-world experience of belantamab mafodotin in relapsed/refractory multiple myeloma. *First Author: Melody Becnel, The University of Texas MD Anderson Cancer Center, Department of Lymphoma/Myeloma, Houston, TX*

Background: Belantamab mafodotin (belamaf) is a BCMA antibody drug conjugate approved for the treatment of relapsed refractory multiple myeloma (RRMM) patients (pts) based on the pivotal phase 2 DREAMM-2 study (Lonial et al, *Lancet Oncology*, 2019), which demonstrated an overall response rate (ORR) of 32%, median progression free survival (PFS) of 2.8 months, and overall survival (OS) of 13.7 months in triple class (proteasome inhibitor, IMiD, and anti-CD38) refractory (TCR) MM. In this single-center retrospective study, we report the efficacy and safety of belamaf in RRMM pts administered in a real-world, standard of care (SOC) setting. **Methods**: All MM pts who initiated therapy with SOC belamaf, either as monotherapy or in combination, between 11/1/2020 and 11/30/2021 at MD Anderson were included in this study. Response and progression were evaluated using International Myeloma Working Group standard criteria. Keratopathy and best corrected visual acuity (BCVA) adverse events (AEs) were graded per the Keratopathy and Visual Acuity (KVA) scale. The Kaplan-Meier method was used to estimate time to event endpoints. **Results**: A total of 39 consecutive pts with a median of 7 prior lines of therapy were included in the analysis, of whom 37 pts (95%) received single agent belamaf. Median age was 66 years (range 39-89), 14 of 37 (38%) pts with available FISH had high risk disease (del 17p, t(4;14, and/or t(14;16)), 14 pts (36%) had extramedullary disease, 37 (95%) pts were TCR, 32 (82%) pts were TCR and alkylator-refractory, and 8 pts (21%) were BCMA-refractory. Notably, the majority (69%) of pts in this analysis would have been ineligible for the DREAMM-2 trial based on key eligibility criteria. Median number of belamaf doses administered was 2 (range 1-9). Among 37 pts with measurable, response evaluable baseline disease, the best ORR (≥ PR) was 27% with ≥ VGPR of 3%. The clinical benefit rate (≥ MR) was 35%. Among 8 BCMA-refractory pts, there was 1 PR and 1 MR. Median PFS was 1.8 months and median OS was 9.2 months with a median follow-up of 10.1 months. Median duration of response has not been reached among 10 responding pts. Among 33 pts with a post-treatment ocular exam, 25 pts (76%) developed any grade keratopathy (Grade 1/2/3/4, 9%/55%/12%/0%, respectively) and BCVA changes (Grade 1/2/3/4, 42%/27%/6%/0%, respectively). Median time to first keratopathy or BCVA AE was 1.3 months. The most common reasons for treatment discontinuation were disease progression (75%) and AEs (9%). **Conclusions**: Our current study in heavily pretreated RRMM pts, of whom the majority would have been ineligible for the DREAMM-2 study, demonstrates an ORR, PFS, and ocular AE profile with SOC belamaf therapy comparable to outcomes reported in the pivotal registration study. Future studies are needed to further define the optimal use and sequencing of belamaf in MM pts, particularly in context of other BCMA-targeting modalities. Research Sponsor: None.

8061 **Poster Session**

Updated survival with extended follow-up on patients with newly diagnosed multiple myeloma treated with lenalidomide, bortezomib, and dexamethasone (RVD) induction therapy and a risk-stratified maintenance approach. *First Author: Rujul H Parikh, Emory University, Winship Cancer Institute, Atlanta, GA*

Background: Lenalidomide, bortezomib, and dexamethasone (RVD) has been established as an effective and well-tolerated induction regimen in patients with newly diagnosed myeloma (NDMM). We have previously published a retrospective analysis of 1000 patients treated with RVD and risk-stratified maintenance therapy showing a median PFS of 65 months and median OS of 126 months for the entire cohort (Joseph et al, *JCO* 2020). This data has served as an important benchmark for evaluating upfront treatment strategies in NDMM. Here, we present updated survival data with extended follow up on this patient population treated at the Winship Cancer Institute of Emory University. **Methods:** From January 2007 to August 2016, 1000 consecutive newly diagnosed myeloma patients treated with RVD induction therapy (R-25 mg/day on days 1-14, V-1.3 mg/m2 on days 1,4,8,11 and D-40 mg once/twice weekly as tolerated) were identified. Demographics, clinical characteristics, and outcomes data for the patients were obtained from our institutional review board-approved myeloma database. Responses were evaluated per IMWG Uniform Response Criteria. **Results:** The median age of this cohort was 61 (range 16-83). Other notable patient characteristics include: M/F 54.6%/45.4%, W/AA 61.8%/35.9%; ISS I/II/III 45.8%/30.8%/23.4%. R-ISS I/II/III 39.9%/48.7%/11.5%; Isotype IgG/IgA/FLC 59.2%/19.0%/15.7%; standard risk(SR)/high risk (HR) 71.2%/15.8%.. High risk disease was defined as the presence of t(4;14), t(14;16), del(17p), and/or complex karyotype by conventional metaphase cytogenetics. 81.8% of patients underwent ASCT, with 16.8% having deferred ASCT. 75.3% of patients were initiated on maintenance therapy. With a median follow up of 88.4 months, the median PFS for the entire cohort was 68.7 months (95% CI 61.8-75.5) and the median OS was 128.9 months. The median PFS for HR patients was 42.4 months (95% CI 35.7-48.9), and the median PFS for SR patients was 80.3 months (95% CI 72.8-87.8). The median OS for SR patients was not reached, and for HR patients was 86.6 months (95% CI 70.1-103.1). **Conclusions:** Updated analysis with long-term follow up of this database of 1000 NDMM patients treated with RVD continues to demonstrate that, in combination with a risk-stratified maintenance strategy, RVD delivers durable remissions and impressive long-term outcomes. This study remains the largest cohort of patients treated with RVD reported to date, and continues to show the efficacy of this upfront treatment approach in newly diagnosed myeloma. Research Sponsor: None.

8062 **Poster Session**

Clinical features of patients with multiple myeloma harboring t(4;14) and impact on long-term survival. *First Author: Nisha Joseph, Emory University, Winship Cancer Institute, Atlanta, GA*

Background: Translocation (4;14) is a known adverse prognostic factor in myeloma. However, utilization of proteasome inhibitors (PIs) in myeloma has abrogated the negative impact of t(4;14) in myeloma, and some investigators question whether t(4;14) still needs to be considered a high-risk marker. Here, we present a retrospective analysis of 142 patients with t(4;14) and describe disease characteristics, treatment patterns, and long-term outcomes. **Methods:** From January 2007 to August 2016, 42 patients with newly diagnosed myeloma and t(4;14) were identified. Demographics, clinical characteristics, and outcomes data for the patients were obtained from our institutional review board-approved myeloma database. Responses were evaluated per IMWG Uniform Response Criteria. **Results:** The median age of this cohort was 59.6 years (range 33-78). Notable patient characteristics include: W/AA/Asian 25.9%/23.6%/50%; ISS I/II/III 36.4%/22.9%/24.1%; R-ISS I/II/III 0%/27.8%/25.8%. Median lab values at diagnosis include: Hgb 10.4 g/dL, Hct 30.8%, Cr 1.01, and Ca 9.4, Frequency of concurrent cytogenetic abnormalities include del(17p): 19.7%; del(13): 44.4%, and +1q21: 46.5%. A majority of patients (86.7%) were induced with either triplet or quadruplet regimens, with 88% of these regimens including a proteasome inhibitor. 78.9% of patients underwent ASCT. Of those responses captured, 75.3% achieved ≥VGPR (sCR 4.8%, CR 30.5%, VGPR 40%, PR 20%). Post-transplant, 88% achieved ≥VGPR (sCR 35.1%, CR 30.9%, VGPR 22.3%), and 82% received maintenance therapy. The most common maintenance regimens included revlimid (34.8%), bortezomib (16.5%), and RVD (11.3%); one-third of patients received triplet maintenance regimens. With a median follow up of 99.5 months, the overall mPFS and mOS for this cohort of t(4;14) patients was 47.6 m (95% CI 32.3-62.8) and 108.5 months (95% CI 87.9-129.2). In patients with both t(4;14) and del(17p), the mPFS was 20.8 months and mOS was 89.6 months; for concurrent t(4;14) and +1q21, the mPFS was 32.0 months and 89.6 months. In patients that received maintenance therapy versus no maintenance, the mPFS and mOS was 54.9 months (95% CI 47.4-62.4) and 115.3 months (95% CI 96.3-134.3) versus 14.7 months (95% CI 13.1-16.3) and 34.3 months (95% CI 10.1-58.5), respectively. **Conclusions:** Overall, the prognosis of t(4;14) myeloma patients significantly improved compared to the pre-proteasome inhibitor era. In particular, maintenance therapies (predominantly PI- based) have made a clear survival impact (doubling of mPFS to 4.5 years and mOS to 9.5 years) compared to patients that did not receive maintenance therapy. However, presence of other concomitant cytogenetic abnormalities such as +1q21 and del(17p) continues to confer poorer outcomes, and innovative approaches are needed to obtain better outcomes for this subgroup of patients. Research Sponsor: None.

8063 **Poster Session**

The impact of complex karyotype identified by conventional cytogenetics on survival outcomes of 1,000 patients with newly diagnosed myeloma (NDMM). *First Author: Dabedochukwu Obiekwe, Winship Cancer Institute of Emory Univerisity, Atlanta, GA*

Background: Complex karyotype (CK), defined as two or more cytogenetic abnormalities on conventional metaphase cytogenetics, is not routinely used for the risk-stratification or treatment determination in patients with newly diagnosed myeloma (NDMM). Here, we present a retrospective analysis utilizing our institutional data of NDMM patients treated with RVD and a risk-adapted maintenance strategy at the Winship Cancer Institute of Emory University to assess the impact of CK on long-term outcomes. **Methods**:1000 consecutive NDMM patients treated with RVD induction therapy (R25mg/day, days 1-14; V1.3 mg/m^2, days 1,4,8,11 and D40mg once/twice weekly as tolerated) were identified from January 2007 to August 2016. Demographics, clinical characteristics and outcome data for patients were obtained from our institutional review board-approved myeloma database. Responses were evaluated per IMWG Uniform Response Criteria. **Results**: The median age of this cohort was 61 (range 16-83). Notable patient characteristics include: M/F 54.6%/45.4%, W/AA 61.8%/35.9%; ISS I/II/III 45.8%/30.8%/23.4%. R-ISS I/II/III 39.9%/48.7%/11.5%; Isotype IgG/IgA/FLC 59.2%/19.0%/15.7%; standard risk(SR)/high risk(HR) 71.2%/15.8%. ISS data was available for 75% of patients; R-ISS was available for 41% of patients. HR disease defined as the presence of t(4;14), t(14;16), del(17p) and/or CK. Frequency of specific CTG abnormalities were:14.9% with +1q21, 8.3% with del(1p),12.1% with t(11;14), 25.7% with del(13), 13.9% with CK, 2.8% with t(14;16), 10% with del(17p), and 4.8% with t(4;14). 11.9% of patients were classified high risk by FISH alone, 10.0% of patients were classified as high risk by complex karyotype(CK), and 3.9% of patients were classified as high risk by the presence of both high-risk FISH and CK. With a median follow up of 88.4 months, the median PFS (mPFS) for patients HR by FISH alone was 47.6 months (95% CI 35.2-59.9), for HR by CK alone was 46.9 months (95% CI 28.1-65.7) and for HR by both was 24.0 months (95% CI 8.3-39.7). The mOS for HR by FISH alone was 94.7 months (95% CI 74.4-115.1),HR by CK alone was 105.9 months (95% CI 60.8-151.0) and HR by both was 41.0 months (95% CI 24.2-57.8). **Conclusions:** CK by conventional metaphase cytogenetics is not currently included in the risk-stratification or risk stratification models of NDMM patients. In patients with a complex karyotype at time of diagnosis, mPFS and mOS is essentially the same as patients classified HR by FISH abnormalities. When compared to SR patients, prognosis is significantly worse, therefore the standard treatment approach is likely insufficient. As many centers do not routinely perform chromosome analysis, this highlights a gap in providing appropriate risk-stratified care. Moreover, NDMM with HR features by FISH and CK portends a poor prognosis for which alternative treatment strategies may need to be explored. Research Sponsor: None.

8064 **Poster Session**

Prognostic impact of t(11;14) on PFS1 among patients with myeloma receiving triplet induction therapy. *First Author: Shama Pirmohammed, Winship Cancer Institute - Emory, Atlanta, GA*

Background: Presence of t(11;14) on plasma cells by FISH or metaphase cytogenetics is considered a standard-risk prognostic factor per IMWG risk-stratification. However, recent studies suggest inferior PFS and OS observed among t(11;14) patients relative to the standard-risk myeloma patients. In the context of the ongoing trials of BCL-2 inhibitors (venetoclax) among t(11;14) relapse/refractory myeloma patients yielding response rates closer to 90%, we review the prognostic impact of t(11;14) on PFS. These results may have implications for earlier incorporation of BCL-2 inhibitors among t(11;14) myeloma patients. **Methods:** Among the 1000 consecutive newly diagnosed myeloma patients uniformly treated with RVD induction therapy from January 2008 until August 2016, we have information on FISH probes for t(11;14) tested for 869 patients [121 - t(11;14) and 748 – no t(11;14)]. First, we explore the frequency of IMWG defined concomitant high-risk cytogenetic characteristics [del 17p, t(4;14), t (14;16)]. Next, we create a synthetic control cohort that received maintenance, and excluded patients exhibiting high-risk features to evaluate the relative prognostication conferred by presence of t(11;14). Median follow up was 91 months. Demographic and outcomes data were collected from IRB approved myeloma database and responses were evaluated per IMWG Uniform Response Criteria. **Results:** Median age is 61.2 years (range 16.3-79.83). 34% of the patients are above the age of 65. Men (14.1% vs 11.7%, p = NS) and blacks had higher rates of t(11;14) (16.1% vs 11.1%, p = 0.028). 17 (14%) had concomitant high-risk features – 4 (3.3%) had t(4;14), 3 (2.5%) had t(14;16) and 11 (9.1%) had del17p. Interestingly, the rates of amplification of 1q (26.1% vs 14.9%, p = 0.002), and del13 (34.7% vs 24.4%, p = 0.015) were higher among t(11;14) patients. Compared to the synthetic cohort, the post-induction and post-transplant responses were lower for t(11;14) patients as summarized in table 1. ≥VGPR for t(11;14) vs no t(11;14) post-induction were 48.2% vs 71.5% p < 0.001 and post-transplant were 83.1% vs 92.8% p = 0.001, respectively. The median progression-free survival for the t(11;14) and non-t(11;14) groups were 61.4 months (95% confidence interval (CI), 49.13-73.67) and 82.56 months (95% CI, 70.47-94.65) months, respectively (p = 0.002). **Conclusions:** Even with the use of modern day induction regimens and transplant, patients with t(11;14) seem to have inferior response rates compared to the other standard-risk myelomas. The lower rates of ≥VGPR post-induction and the shorter median PFS suggests BCL-2 inhibitors such as venetoclax may be incorporated earlier in myeloma treatments to improve the outcomes of t(11;14) patients on par with the other standard-risk myeloma patients. Research Sponsor: None.

8065 **Poster Session**

Immune cell differences between patients in different stages of monoclonal plasma cell disorders. *First Author: Christine Ho, Roswell Park Comprehensive Cancer Center, Buffalo, NY*

Background: Multiple myeloma (MM) is an incurable plasma cell malignancy. Precursor conditions include monoclonal gammopathy of unknown significance (MGUS) and smoldering multiple myeloma (SMM). Immune surveillance is paramount for keeping the malignancy in check, whereas a dysfunctional immune system is suspected to promote disease progression. **Methods:** We performed flow cytometric immune panel analyses including T-cell, B-cell, natural killer (NK) cell and dendritic cell (DC) subsets in MGUS, SMM, and MM patients between 2018-2021. Immune panels were analyzed on fresh peripheral blood samples drawn at diagnosis. The patient population were MGUS (n=28), SMM (n=19) and MM (n=94). Samples from MGUS and SMM patients were combined into a single group (asymptomatic) and were compared to MM patients (symptomatic). Lymphocytes were identified by CD45+ expression resolving against side-scattered light on a bivariate plot. B cell and NK cell antigen expression profiles were assessed from this lymphocyte population. T cell subsets were further determined by CD3+. The percent gated for each marker was summarized by cohort using the appropriate descriptive statistics and compared using the Mann-Whitney U exact test. Analyses were performed in SAS v9.4 (Cary, NC) using a two-sided α=0.05. **Results:** Compared to MGUS/SMM patients, MM patients had a significant lower proportion of naive B cells, NK cells, and cytolytic NK cells, and a significant higher proportion of cytolytic T cells at diagnosis (Table). Consistent with prior studies, we demonstrated an increase in exhaustion markers. There was a trend toward a higher population of CD8+ exhausted T cells in MM patients compared to MGUS/SMM patients. Since the follow up for this study was short, survival data is not mature. **Conclusions:** This study demonstrates the immune imbalance that occurs between myeloma precursor conditions and MM. There is a shift in certain cell subsets in the immune microenvironment that alters tumor immunosurveillance and tumor cell killing favoring disease progression. In data not shown, we are currently analyzing the bone marrow microenvironment and its relation to disease progression. Follow up studies could assess if therapeutic intervention could reverse the imbalance, restore homeostatic equilibrium with the goal of controlling disease long-term. Research Sponsor: None.

Summary of the baseline immune markers by disease group for blood sample.

Population	MGUS/SMM (Median %)	MM (Median %)	p_value
Naïve B cells CD19+ CD27- IgD+	4.85	3.13	0.010
Natural Killer cells CD3- CD16- CD56+	11.46	9.20	0.027
Cytolytic Natural Killer cells CD3- CD16- CD56+ CD57+	6.14	3.71	0.001
Cytolytic T cells CD3+CD16- CD56- CD57+	3.62	7.25	0.025
CD8 Exhausted T cells CD3+ CD8+ TIM3- LAG3- TIGIT+ PD1+	0.01	0.03	0.050

8066 **Poster Session**

Determinants of overall survival (OS) of primary plasma cell leukemia (pPCL): A National Cancer Database (NCDB) analysis of years 2004 to 2009.

First Author: Kevin Scott Landau, Cleveland Clinic Florida, Weston, FL

Background: Outcome data for pPCL is limited due to the rare & aggressive nature of the disease. In this retrospective analysis, we utilized NCDB to identify factors contributing to 1 & 5-year OS of pPCL patients treated at CoC-accredited facilities across USA. **Methods:** Using the NCDB, we identified N= 325 pPCL patients diagnosed between 2004-2009 after excluding entries missing relevant values. Univariate analysis was used to summarize & assess the potential survival factors individually & multivariate Cox regression analysis with backward elimination (using significance level of p<0.05) was utilized to identify the independent survival factors. Kaplan-Meier (KM) survival curves of patient cohort were also produced. SAS version 9.4 was used to analyze the data. **Results:** Multivariate Cox regression analysis with backward elimination method revealed that there were 4 significant independent survival factors including sex, Charlson-Deyo Comorbidity Index (CCI), facility type, and insurance, while age & year-of-diagnosis were not independent survival factors (Table). Male patients were more likely to die compared to female patients (HR=1.40, p=0.005); patients with CCI ≥1 had higher chance to suffer death compared to patients with CCI= 0 (HR=1.52, p=0.002); patients not treated at an academic center (AC) had lower survival compared to those treated at ACs (HR=1.35, p=0.001); and patients without private insurance (PI) were more likely to suffer death compared to those with PI (HR=1.54, p=0.001). The 1 & 5-year survival rates for whole cohort were 51.3% (95%CI: 45.8%-56.8%), and 18.9% (95%CI: 14.6%-23.2%) using KM estimate, respectively. Only 6/325 =1.8% patients underwent autologous hematopoietic stem cell transplant (HSCT). Detailed analysis will be presented. **Conclusions:** In this large analysis of pPCL patients, we identified that being female, having less comorbidities, getting treatment at ACs, and having PI had significantly greater OS. Overall, pPCL is associated with low survival rates both at 1 & 5-years and HSCT may be enormously under-utilized for pPCL patients in the real world setting. Research Sponsor: Internal hematologic malignancy research fund, Cleveland Clinic Florida.

Multivariate Cox regression model analysis for overall survivorship.

Variable	HR (95%CI)	p-value
Sex (male vs. female)	1.40 (1.11-1.78)	0.005
Charlson-score (≥1 vs. 0)	1.52 (1.16-1.99)	0.002
Facility type (other vs. Academic center)	1.35 (1.13-1.62)	0.001
Insurance (other vs. Private program)	1.54 (1.21-1.96)	0.001

Six significant variables (age, sex, CCI, facility type, insurance, and year-of-diagnosis) being identified by univariate analysis were included in the Cox model as explanatory variables, and finally age (p=0.9146) and year-of-diagnosis (p=0.0910) were eliminated by backward elimination method.

8067 **Poster Session**

COVID vaccine immune response in patients with plasma cell dyscrasia: A systematic review.

First Author: Unaiza Faizan, Rochester General Health System, Rochester, NY

Background: The defective immune system in plasma cell dyscrasia places patients at a higher risk of developing a severe infection, which is one of the leading causes of death in such patients. In an era of a global pandemic, it is essential to protect them against COVID-19, but fewer effective plasma cells lead to a suboptimal response to vaccines. There is still a lack of evidence whether the seroconversion is truly clinically relevant and if patients with plasma cell disorders would benefit from frequent boosters to maintain antibody levels. **Methods:** Online databases including PubMed, CINAHL, Ovid, and Cochrane were searched (January 11th, 2022), following the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines. Only articles published in the English language were included. Abstracts, case reports, and case series were excluded. Out of 40 studies, 5 articles were selected for a systematic review. **Results:** In all 5 studies (N=654), seroconversion post-vaccination was used as a positive response to COVID-19 vaccination. Although patients with plasma cell disorders had a lower seroconversion rate compared to controls, the overall percentage was substantial and ranged between 23-95.5%. Amongst patients on active therapy, lower seroconversion rates were seen in patients on a CD-38 inhibitor, ranging from 20.2-92.1% (N=174). Also, a significantly lower percentage was recorded in patients above 65 years and those who have been treated with multiple therapies previously. Better seroconversion rates were seen in mRNA vaccines compared to J&J. **Conclusions:** Variable seropositive rates are seen in patients with plasma cell dyscrasias, lower rates are reported in patients on active therapy, CD-38 targeting therapy, and elderly patients. Hence, these patients should receive a 4 shot series. Research Sponsor: None.

Efficacy of COVID-19 vaccines in patients with plasma cell dyscrasia.

Author	Study, Year	Study Population	n/N	Vaccine	Overall Seropositive %	On Therapy Seropositive %	Not on Therapy Seropositive %	CD-38 Therapy Seropositive %	SMM Seropositive %	Age Seropositive %
Avivi et. al	Case Control, 2021	MM vs Control	171 /171 vs 64	mRNA	78 vs 98	76	79	69	100 (N=12)	<65y 87, >65y 71
Gandhili et. al	Prospective, 2021	B cell neoplasm	82/82 (78 MM)	mRNA- and vector-based (N=63 vs 19)	23	40.5	35	6.5	NA	<70y 34, >70y 6.7
Greenberg et. al	Prospective, 2021	MM	44/44	mRNA	93	93	94	100	NA	<65y 65, >65y 35
Shah et. al	RS, 2021	PCD	89/89 (41 MM)	mRNA or Ad26.COV.S (N=78 vs 11)	95.5	100	94.4	92.1	NA	NA
Terpos et. al	Case control, 2021	PCD vs Control	276/276	mRNA or the AZD1222 (N=215 vs 61)	42.4 vs 64.2 (D22), 71 vs 90.3 (D50)* 57.3 vs 81 (D50)**	79.8 **	20.2	25.2**	60.5** (N 38)	NA

n/N=number of participants evaluated/number of participants enrolled, SMM=Smoldering multiple myeloma, y=years, RS=retrospective study, MM=multiple myeloma, PCD=plasma cell dyscrasia, *=antibody titer >30%, **=antibody titer >50%, NA=Not available, D=Day.

TPS8068 **Poster Session**

MagnetisMM-9: An open-label, multicenter, non-randomized phase 1/2 study of elranatamab in patients with relapsed/refractory multiple myeloma.

First Author: Rafael Fonseca, Division of Hematology/Oncology, Mayo Clinic Hospital, Phoenix, AZ

Background: Elranatamab (PF-06863135) is a humanized bispecific antibody that targets both B cell maturation antigen (BCMA) on multiple myeloma (MM) cells and CD3 on T cells resulting in T cell- mediated cytotoxicity. In preclinical studies, elranatamab has demonstrated anti-myeloma activity and delayed disease progression. In the ongoing phase 1 MagnetisMM-1 study, elranatamab has demonstrated clinical efficacy and a manageable safety profile in patients with relapsed/refractory MM (Bahlis et al, J Clin Oncol 2021). Elranatamab maximum tolerated dose has not yet been reached. Subcutaneous (SC) elranatamab at the recommended dose of 76 mg QW on a 28-d cycle with a 2 step-up priming dose regimen administered during the first week is currently being evaluated in a phase 2 study, MagnetisMM-3 (Lesokhin et al, Blood, 2021). **Methods:** MagnetisMM-9 (start date: Oct 2021; estimated completion date: Apr 2025) is an open-label, multicenter, non-randomized phase 1/2 study evaluating an alternative priming regimen to further mitigate cytokine release syndrome (CRS) incidence and severity and to evaluate SC elranatamab Q2W and Q4W dosing regimens in patients with relapsed/refractory MM. In part 1 of the study, patients will receive premedications and 2 step-up priming doses on cycle 1 D1 (4 mg) and D4 (20 mg), followed by elranatamab 76 mg QW for 6 cycles, and a dose Q2W thereafter if partial response or better is achieved and maintained. In part 2, higher doses of elranatamab (> 76 mg) at increased intervals between doses will be evaluated. The primary endpoint is grade ≥2 CRS rate during cycle 1. Secondary endpoints include dose-limiting toxicities (part 2 only), objective response rate, duration of response, progression-free survival, overall survival, minimal residual disease negativity rate, safety, and pharmacokinetics. Eligible patients should be ≥18 years of age with a MM diagnosis and measurable disease according to IMWG criteria, refractory to at least one proteasome inhibitor, one immunomodulatory drug, and one anti-CD38 antibody, relapsed/refractory to their last treatment regimen, and have an ECOG performance status ≤1. Key exclusion criteria are smoldering MM, active plasma cell leukemia, amyloidosis, POEMS syndrome, stem cell transplant within 12 weeks of enrollment, active, uncontrolled bacterial, fungal, or viral infections, or any other active malignancy within 3 years prior to enrollment (except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ), or previous treatment with an anti-BCMA bispecific antibody. The study is open at centers in the USA, UK, Japan, and Taiwan. Clinical trial information: NCT05014412. Research Sponsor: Pfizer.

TPS8069 **Poster Session**

CAMMA 1: A multicenter phase Ib trial evaluating the safety, pharmacokinetics, and activity of cevostamab-containing regimens in patients with relapsed or refractory multiple myeloma.

First Author: Ravi Vij, Washington University, St. Louis, MO

Background: Treatment of relapsed/refractory (R/R) multiple myeloma (MM) is challenging, especially in later lines where drug resistance reduces therapeutic options and remission duration. Prognosis is poor (estimated survival: < 1 year) for patients with MM who have received > 3 prior lines of therapy and are triple refractory to immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs) and anti-CD38 agents (Gandhi et al. 2019). Thus R/R MM constitutes a significant unmet medical need. Fragment crystallizable receptor-like 5 (FcRH5) is expressed on myeloma cells with near 100% prevalence (Li et al. 2017), constituting a novel therapeutic target. Cevostamab is an IgG1-based T-cell-engaging bispecific antibody engineered to target the most membrane-proximal domain of FcRH5 on myeloma cells and cluster of differentiation 3 (CD3) on T-cells, resulting in T-cell killing of myeloma cells. Clinical data from the first-in-human Phase I study (GO39775) suggest that cevostamab monotherapy is highly active in heavily pretreated patients with R/R MM, with an overall response rate of 56.7% at the 132–198mg dose level (Trudel et al. ASH 2021 Oral presentation). Thus, cevostamab's activity and safety profile support further development. Due to their stimulatory effects on T-cell activity, combination of cevostamab with anti-myeloma agents (pomalidomide [P] or daratumumab [D]) may be synergistic, offering the potential to further improve efficacy. CAMMA 1 (NCT04910568) is an open-label, multicenter Phase Ib trial evaluating the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics of cevostamab-containing combination regimens (Arm B: cevostamab plus P and dexamethasone [d] [Pd]; Arm C: cevostamab plus Dd) in patients with R/R MM. A modified weekly schedule for cevostamab is also under investigation (Arm A: cevostamab monotherapy). **Methods:** Patients must be aged ≥18 years, have an ECOG performance status of 0 or 1 and a life expectancy of > 12 weeks. Patients in all arms have R/R MM; Arms B and C include patients with prior IMiD and PI exposure. Patients with prior CAR-T therapy may enroll with a washout period of 12 weeks post-CAR-T infusion. Cevostamab is administered by intravenous infusion q1w (C1–2)/q2w (C3–6)/q4w (C7–13) in Arm A, q2w (C1–6)/q4w (C7+) in Arm B, and q3w (C1–8)/q4w (C9+) in Arm C. Each arm consists of a safety run-in and an expansion cohort. Enrolment for Arm A is ongoing, with patients receiving up to 13 treatment cycles. Arms B and C are planned; patients will receive treatment until disease progression or unacceptable toxicity. The primary objective is to evaluate the safety and tolerability of cevostamab plus Pd, cevostamab plus Dd and cevostamab monotherapy. Secondary objectives include assessment of activity, PK, immunogenicity, and pharmacodynamic biomarkers. Clinical trial information: NCT04910568. Research Sponsor: CAMMA 1 is a Genentech, Inc. sponsored study. Third-party medical writing assistance, under the direction of the authors, was provided by Rachel Dobb of Ashfield MedComms, an Ashfield Health company, and was funded by F. Hoffmann-La Roche Ltd., Collaborator: F. Hoffman-La Roche Ltd.

TPS8070 **Poster Session**

CAMMA 3: A multicenter phase Ib trial evaluating the safety, pharmacokinetics, and activity of subcutaneous cevostamab monotherapy in patients with relapsed or refractory multiple myeloma. *First Author: Sosana Delimpasi, Department of Hematology and Lymphoma, Evangelismos Hospital, Athens, Greece*

Background: Multiple myeloma (MM) remains an incurable disease. Although new treatment paradigms have increased survival, most patients relapse and treatment in later lines remains a challenge. Prognosis for patients refractory to immunomodulatory drugs, proteasome inhibitors and anti-CD38 antibodies is extremely poor, with an estimated survival of < 1 year (Gandhi et al. 2019). Therefore, patients with relapsed/refractory (R/R) disease represent a high unmet need, and new targets and treatment modalities are needed. Cevostamab is an IgG1-based T-cell-dependent bispecific antibody engineered to target the most membrane-proximal domain of fragment crystallizable receptor-like 5 (FcRH5) on myeloma cells, and cluster of differentiation 3 (CD3) on T cells. This dual binding results in efficient immunological synapse formation and T-cell-mediated killing of myeloma cells. In the ongoing first-in-human Phase I GO39775 study, intravenous (IV) administration of cevostamab monotherapy continues to show clinically meaningful activity and durable responses in patients with heavily pre-treated R/R MM (Trudel et al. ASH 2021), and uses Cycle (C) 1 step-up dosing for the mitigation of cytokine release syndrome (CRS). Subcutaneous (SC) delivery of antibody therapies has been shown to be effective and well tolerated and offers several advantages over IV administration in regards to improved healthcare utilization, including ease of administration, reduced treatment burden and reduced hospitalization. The slower absorption rate observed with SC versus IV antibody therapies may also support the potential for SC cevostamab to provide a further improved CRS profile (Bartlett et al. ASH 2021). CAMMA 3 (GO43227; ISRCTN26168155) is an open-label, multicenter, Phase Ib dose-escalation and dose-expansion trial evaluating the safety, tolerability, pharmacokinetics (PK) and preliminary activity of SC cevostamab monotherapy in patients with R/R MM. **Methods:** For inclusion, patients must be aged ≥18 years and must have R/R MM for which no established therapies are available or appropriate. Cevostamab is administered by SC injection in 28-day cycles, with step-up dosing in C1, q2w dosing in C2–6, and q4w dosing in C7–13. Patients may receive up to 13 cycles unless there is disease progression or unacceptable toxicity. Patients who respond to cevostamab but develop recurrent or progressive disease after 13 cycles may be eligible for cevostamab re-treatment. Primary objectives are to evaluate the safety and tolerability (including the maximum tolerated dose and dose-limiting toxicities) of SC cevostamab and to identify a recommended Phase II dose. Secondary objectives include assessment of PK, activity, and immunogenicity, and identification of biomarkers associated with response and resistance. Clinical trial information: 26168155. Research Sponsor: CAMMA 3 is a Genentech, Inc. sponsored study. Third-party medical writing assistance, under the direction of the authors, was provided by Rachel Dobb of Ashfield MedComms, an Ashfield Health company, and was funded by F. Hoffmann-La Roche Ltd., Collaborator: F. Hoffman-La Roche Ltd.

TPS8071 **Poster Session**

TTI-622-01: A phase 1a/1b dose-escalation and expansion trial of TTI-622 in patients with advanced hematologic malignancies, including multiple myeloma. *First Author: Krish Patel, Swedish Cancer Institute, Seattle, WA*

Background: CD47 is an innate immune checkpoint that binds signal regulatory protein alpha (SIRPα) and delivers a "don't eat me" signal to suppress macrophage phagocytosis. TTI-622 is a fusion protein consisting of the CD47-binding domain of human SIRPα linked to the Fc region of human IgG4. It is designed to enhance phagocytosis and antitumor activity by preventing CD47 from delivering its inhibitory signal as well as generating a moderate pro-phagocytic signal via IgG4 Fc. CD47 is significantly increased in multiple myeloma (MM) bone marrow mononuclear cells and expression inversely correlates with survival in patients. Relapsed/Refractory (R/R) MM shows particularly high expression of CD47. Preclinical studies demonstrate that the addition of proteasome inhibitors to CD47 blockade significantly increases phagocytosis of MM cells in vitro and anti-myeloma activity in vivo. The ongoing phase 1a part of this study has been previously described. The phase 1b part of the study will determine the safety and efficacy of TTI-622 when given as monotherapy or in combination with selected approved anticancer treatments in patients with hematological malignancies where new treatments with novel mechanism of action are needed. Here we describe 5 RRMM cohorts within phase 1b of the study. **Methods:** TTI-622-01 is a multi-center Phase 1a/1b study. Phase 1a was designed to determine the MTD, pharmacokinetics (PK), pharmacodynamics, and preliminary antitumor activity of QW, Q2W, and Q3W single-agent TTI-622 in R/R lymphoma using a 3+3 dose escalation schema. Phase 1b, ongoing, will determine the safety and recommended dose of TTI-622 to be given as single agent and in combination with carfilzomib + dexamethasone (Kd) in RRMM and will evaluate the preliminary efficacy. Secondary objectives are to further characterize the safety, PK and immunogenicity of TTI-622 when combined with Kd. Patients will be enrolled in 5 separate cohorts: 3 cohorts will explore different doses and administration schedules of TTI-622 combined with the approved dose of Kd; 2 cohorts will explore different doses of TTI-622 monotherapy. Cohorts will be opened in a staggered manner. In each cohort 3 patients will be dosed and followed for 28 days (21 days in the monotherapy) before expanding enrolment to approximately an additional 27 patients. Key eligibility criteria include: relapse or progression following ≥3 prior lines of therapy (including a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 antibody), carfilzomib-refractory progressive and measurable disease per IMWG at study entry; age ≥18 years; ECOG performance status ≤2; adequate organ functions; no known CNS involvement; no prior anti-CD47 or anti-SIRPα therapy. Patient recruitment is planned or ongoing at 40 sites worldwide. Clinical trial information: NCT03530683. Research Sponsor: Trillium Therapeutics Inc., which was acquired by Pfizer, Inc. in November 2021.

TPS8072 **Poster Session**

MajesTEC-3: Randomized, phase 3 study of teclistamab plus daratumumab versus investigator's choice of daratumumab, pomalidomide, and dexamethasone or daratumumab, bortezomib, and dexamethasone in patients with relapsed/refractory multiple myeloma. *First Author: Maria-Victoria Mateos, Hospital Clinico Universitario de Salamanca, Salamanca, Spain*

Background: Patients (pts) with relapsed/refractory multiple myeloma (RRMM) after prior therapy with a proteasome inhibitor (PI) and lenalidomide are challenging to treat. Daratumumab in combination with pomalidomide and dexamethasone (DPd) or bortezomib and dexamethasone (DVd) are approved for pts with RRMM; however, disease control could be further improved. There is an unmet need for new therapeutic options with different modes of action. Teclistamab (tec; JNJ-64007957) is a B-cell maturation antigen (BCMA) × CD3 bispecific antibody that redirects CD3+ T cells to mediate T-cell activation and subsequent lysis of BCMA-expressing myeloma cells. In the phase 1, MajesTEC-1 study (NCT03145181), tec monotherapy was well-tolerated and showed encouraging efficacy in heavily pretreated pts with RRMM. The combination of tec and daratumumab (tec-dara) in the phase 1b TRIMM-2 study (NCT04108195) was also well-tolerated with promising efficacy. MajesTEC-3 (NCT05083169) is a multicenter, open-label, randomized phase 3 study that will compare the efficacy of tec-dara versus investigator's choice of DPd or DVd in pts with RRMM. **Methods:** Pts (≥18 years old) must have documented MM per International Myeloma Working Group (IMWG) criteria; measurable disease; Eastern Cooperative Oncology Group performance status 0–2; received 1–3 prior treatment (tx) lines, including a PI and lenalidomide (pts with 1 prior tx line must be lenalidomide-refractory); with progressive disease on or after their last tx (or within 60 days of completing lenalidomide). Pts who received prior BCMA-directed tx or who are refractory to an anti-CD38 monoclonal antibody will be excluded. ~560 pts will be randomized 1:1 to receive 28-day cycles of tec-dara or investigator's choice of DPd or DVd (stratified by investigator's choice of DPd or DVd, ISS stage, and number of lines of prior tx). Step-up doses of tec will be given prior to the first tx dose. Dara, DPd and DVd will be administered per approved schedules. Pts will be treated until disease progression, death, intolerable toxicity, withdrawal of consent or end of study, whichever occurs first. Response will be assessed per 2016 IMWG criteria. The primary endpoint will be progression-free survival (PFS). Secondary endpoints include overall response rate, complete response or better, MRD negativity, PFS on next-line tx (PFS2), overall survival, and incidence and severity of AEs. Adverse events (AEs) will be graded by Common Terminology Criteria for AEs v5.0, except for cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome, which will be graded by American Society for Transplantation and Cellular Therapy guidelines. The study opened in October 2021 and enrollment is ongoing. Clinical trial information: NCT05083169. Research Sponsor: Janssen Research & Development, LLC.

TPS8073 **Poster Session**

Exploring alternative dosing regimens of single-agent belantamab mafodotin on safety and efficacy in patients with relapsed or refractory multiple myeloma: DREAMM-14. *First Author: Malin Hultcrantz, Myeloma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Belantamab mafodotin (belamaf: BLENREP) is a first-in-class, monomethyl auristatin F (MMAF)-containing, B-cell maturation antigen (BCMA)-directed antibody–drug conjugate (ADC). In the DREAMM-2 study, belamaf showed deep responses with a manageable safety profile in patients with relapsed/refractory multiple myeloma (RRMM). At 13 months of follow-up, the median duration of response was 11 months and overall survival was 13.7 months at the 2.5 mg/kg Q3W dose. Corneal events are common and expected with belamaf and other MMAF-containing ADCs. In DREAMM-2, corneal events were managed with dose modifications. Clinical responses were observed even with prolonged dose holds, suggesting alternative dosing regimens may lower corneal event rates without compromising efficacy. The DREAMM-14 study (NCT05064358) will investigate if an improved benefit/risk profile of single-agent belamaf can be achieved by modifying the dose, schedule, or both, relative to the approved dosing regimen (2.5 mg/kg Q3W). **Methods:** This Phase II, randomized, open-label study will include adults with RRMM who had ≥3 prior lines of therapy (LOT), including an anti-CD38 monoclonal antibody, an immunomodulatory agent, and a proteasome inhibitor. Patients with corneal epithelial disease (except nonconfluent superficial punctate keratitis) or with prior exposure to BCMA-targeted therapies, or ADCs will be excluded. Patients will be randomized into Arms A–D (n=40 each) and Arm E (n=20) in parallel and stratified by the International Staging System (I vs II vs III) and prior LOT (3 vs ≥4). Belamaf will be administered as follows—Arm A: 2.5 mg/kg Q3W; Arm B: 1.9 mg/kg Q3W; Arm C: 2.5 mg/kg Q6W; Arm D: 1.9 mg/kg Q6W; Arm E: 1.9 mg/kg Q6W with ocular event-related dose modifications based on oncology staff assessment of ocular symptoms (patient-reported symptoms using the Ocular Surface Disease Index), and visual acuity (Snellen chart or equivalent) in addition to corneal findings assessed by an eye care specialist. Patients in all Arms will have response assessments, safety assessments, and ophthalmic exams performed by an eye care specialist Q3W regardless of dosing schedule. Ocular event-related dose modifications (except in Arm E) will be guided by a modified Keratopathy and Visual Acuity scale. The primary endpoint will be incidence of ocular events. Key secondary endpoints include ocular safety and tolerability, overall safety and tolerability, pharmacokinetics, and efficacy outcomes. Follow-up for progression-free survival will be Q3W until progressive disease, start of new anticancer therapy, withdrawal of consent, end of study, or death. Status: Recruitment is ongoing. Funding: GSK (Study 209628); drug linker technology licensed from Seagen Inc.; mAb produced using POTELLIGENT Technology licensed from BioWa. Clinical trial information: NCT05064358. Research Sponsor: GlaxoSmithKline.

TPS8074 **Poster Session**

MagnetisMM-5: An open-label, multicenter, randomized phase 3 study of elranatamab as monotherapy and in combination with daratumumab in patients with relapsed/refractory multiple myeloma. *First Author: Sebastian Grosicki, Department of Hematology and Cancer Prevention, School of Public Health, Silesian Medical University, Katowice, Poland*

Background: Elranatamab (PF-06863135) is a humanized bispecific antibody that targets both B cell maturation antigen (BCMA)-expressing multiple myeloma (MM) cells and CD3-expressing T cells, with binding resulting in T cell-mediated cytotoxicity. Elranatamab has demonstrated antitumor activity and delayed tumor progression in preclinical studies, as well as promising efficacy and manageable safety in the ongoing phase 1 MagnetisMM-1 study in patients (pts) with relapsed/refractory MM (Bahlis et al, J Clin Oncol 2021). **Methods:** MagnetisMM-5 is an open-label, multicenter, randomized phase 3 study designed to evaluate the efficacy and safety of subcutaneous (SC) elranatamab monotherapy and SC elranatamab + SC daratumumab in pts with relapsed/refractory MM who have received prior therapy, including lenalidomide and a proteasome inhibitor (PI). The study consists of 2 parts. In part 1, a minimum of 20 pts will be enrolled to assess the safety of an elranatamab priming regimen and identify the recommended combination dose for SC elranatamab + SC daratumumab for part 2. The primary endpoint of part 1 is dose-limiting toxicities encompassing the elranatamab monotherapy priming duration (14 d) and the first cycle of SC elranatamab + SC daratumumab dosing (28 d). In part 2, ~450 pts will be stratified by prior lines of therapy (1 vs 2–3 vs ≥4) and prior treatment with anti-CD38 therapy (yes vs no) and enrolled in a 1:1:1 ratio to receive SC elranatamab or SC elranatamab + SC daratumumab or SC daratumumab + oral pomalidomide + oral dexamethasone. The primary endpoint of part 2 is progression-free survival (PFS), according to International Myeloma Working Group (IMWG) response criteria and blinded independent review. Secondary endpoints include PFS and PFS on next-line treatment by investigator per IMWG, overall survival, objective response rate, duration of response, complete response (CR) rate, duration of CR, time to response, overall and sustained minimal residual disease negativity rates, safety, quality of life, immunogenicity, and PK. Key inclusion criteria are age ≥18 y, MM diagnosis with measurable disease according to IMWG criteria, ECOG performance status 0–2, and clinical laboratory values within specified ranges. For part 2, pts should have received ≥1 prior line of anti-myeloma therapy, including treatment with lenalidomide and a PI. Key exclusion criteria include smoldering MM, plasma cell leukemia, amyloidosis, POEMS syndrome, stem cell transplant within 12 wk of enrollment, primary refractory MM, active, uncontrolled bacterial, fungal, or viral infections, previous treatment with BCMA-targeted therapy, anti-CD38 therapy within 6 mo of the first dose of study treatment, and previous pomalidomide therapy. MagnestisMM-5 will include sites in 28 countries. Clinical trial information: NCT05020236. Research Sponsor: Pfizer.

TPS8075 **Poster Session**

Subcutaneous daratumumab (DARA SC) versus active monitoring in patients (pts) with high-risk smoldering multiple myeloma (SMM): Randomized, open-label, phase 3 AQUILA study. *First Author: Meletios A. Dimopoulos, National and Kapodistrian University of Athens, Athens, Greece*

Background: Standard of care for SMM includes active monitoring until progression to multiple myeloma (MM); however, recent evidence suggests pts with high-risk features may benefit from early treatment. DARA is a human IgGκ monoclonal antibody targeting CD38 that is approved as monotherapy for relapsed/refractory MM (RRMM) or in combination with standard of care for RRMM or newly diagnosed MM. Results from the phase 3 COLUMBA study showed that DARA SC demonstrated similar efficacy to intravenous (IV) DARA but with a lower rate of infusion-related reactions and shorter administration time. Based on the promising single-agent activity observed with IV DARA in intermediate- or high-risk SMM pts during the phase 2 CENTAURUS study, we hypothesized that DARA SC may delay progression to MM versus active monitoring in pts with high-risk SMM. **Methods:** AQUILA is an ongoing, randomized, open-label, multicenter phase 3 study of DARA SC versus active monitoring in pts with high-risk SMM. DARA SC (DARA 1,800 mg + recombinant human hyaluronidase PH20 [rHuPH20; 2,000 U/mL; Halozyme]) is administered by manual injection over approximately 5 minutes at alternating locations on the abdomen weekly in Cycles 1 and 2, every 2 weeks in Cycles 3-6, and every 4 weeks thereafter until 39 cycles (28 days/cycle), up to 36 months, or until disease progression. Eligibility criteria include confirmed diagnosis of SMM for ≤5 years, factors indicating high risk of progression to MM (clonal bone marrow plasma cells [BMPCs] ≥10% and ≥1 of the following: serum M protein ≥30 g/L, IgA SMM, immunoparesis with reduction of 2 uninvolved Ig isotypes, serum involved:uninvolved free light chain ratio ≥8 to < 100, or clonal BMPCs > 50% to < 60% with measurable disease), and ECOG performance status ≤1. The primary endpoint is progression-free survival (PFS), assessed by an independent review committee, with disease progression defined according to International Myeloma Working Group diagnostic criteria for MM. Secondary endpoints include time to biochemical or diagnostic (SLiM-CRAB) progression, overall response rate, complete response rate, duration of response, time to response, time to first-line treatment for MM, PFS on first-line treatment for MM (PFS2), overall survival, and incidence of MM with adverse prognostic features. The study completed enrollment on May 6, 2019; 390 pts have been randomly assigned to DARA SC or active monitoring. The primary efficacy analysis will be performed after approximately 165 PFS events have been observed. Clinical trial information: NCT03301220. Research Sponsor: Janssen Research & Development, LLC.

TPS8076 **Poster Session**

Birtamimab in patients with Mayo stage IV AL amyloidosis: Rationale for confirmatory affirm-AL phase 3 study. *First Author: Morie A. Gertz, Division of Hematology, Mayo Clinic, Rochester, MN*

Background: Light chain (AL) amyloidosis is a progressive and typically fatal disorder caused by misfolded AL protein produced by plasma cells. Birtamimab is a monoclonal antibody designed to neutralize circulating soluble and deposited insoluble amyloid, thus promoting phagocytic clearance. In 2018, the phase 3 VITAL study in newly diagnosed, treatment-naive patients was terminated based on futility analysis of the primary endpoint (time to all-cause mortality [ACM] or time to cardiac hospitalization > 90 days after first study drug infusion); the final hazard ratio (HR) numerically favored birtamimab + standard of care (SOC) over placebo + SOC (0.835 [95% CI: 0.5799, 1.2011]; p = 0.330). Post-hoc analysis of ACM over 9 months revealed a substantial survival benefit (HR = 0.413 [95% CI: 0.191, 0.895]; p = 0.025) in patients at high risk for early death (Mayo Stage IV). Post-hoc analyses of secondary endpoints in this subgroup indicated meaningful improvements in health-related quality of life (assessed with 36-Item Short Form Health Survey version 2; SF-36v2) and 6-minute walk test (6MWT) distance with birtamimab + SOC (p < 0.05) at 9 months. **Methods:** The phase 3, double-blind, placebo-controlled AFFIRM-AL study (NCT04973137) will enroll up to 150 Mayo Stage IV patients with newly diagnosed, untreated AL amyloidosis. Patients will be randomized (2:1) to 24 mg/kg intravenous birtamimab or placebo every 28 days. Both arms will receive concomitant chemotherapy with a first-line bortezomib-containing regimen, with or without daratumumab (D), at the discretion of the investigator. Patients will be stratified at randomization based on their 6MWT distance (< 300 vs ≥300 meters) and initiation of D. The primary efficacy endpoint is time to ACM. Secondary endpoints are change from baseline to month 9 in the physical component summary of the SF-36v2 and 6MWT distance. This trial is powered at a significance level of 0.1 under a Special Protocol Assessment (SPA) with the U.S. Food and Drug Administration (FDA). Given the > 50% relative risk reduction for ACM observed in the post-hoc analysis of VITAL for patients with Mayo Stage IV disease, the AFFIRM-AL study is designed to confirm this effect of birtamimab. Approximately 130 global sites are planned; site initiation and patient randomization are underway. Conclusion: Treatments that improve survival in AL amyloidosis are needed, particularly for patients with advanced cardiac involvement, as median overall survival for those with Mayo Stage IV disease is ~6–9 months. The AFFIRM-AL study is designed to confirm the survival benefit observed in the VITAL study in patients with Mayo Stage IV AL amyloidosis. Clinical trial information: NCT04973137. Research Sponsor: Prothena Biosciences Ltd.

8500 **Oral Abstract Session**

Two cycles versus three cycles of neoadjuvant sintilimab plus platinum-doublet chemotherapy in patients with resectable non-small-cell lung cancer (neoSCORE): A randomized, single center, two-arm phase II trial. *First Author: Fuming Qiu, Department of Medical Oncology, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China*

Background: Neoadjuvant immune checkpoint inhibitors (ICIs) plus chemotherapy have a promising efficacy in resectable non-small-cell lung cancer (NSCLC), yet the period of neoadjuvant immunochemotherapy is undetermined. This phase II study compared the efficacy and safety of two cycles with three cycles of neoadjuvant sintilimab plus chemotherapy in resectable stage IB-IIIA NSCLC. **Methods:** This randomized, open-label phase II trial recruited patients aged 18 or older with histologically confirmed, treatment-naïve, American Joint Committee on Cancer-defined stage IB-IIIA, resectable NSCLC. Eligible patients were randomly assigned to two or three cycles of neoadjuvant treatment with intravenous sintilimab (200 mg) plus carboplatin (area under curve 5) and nab-paclitaxel (260mg/m^2, for squamous) or pemetrexed (500mg/m^2, for non-squamous) on day 1 of three-week cycle. After surgical resection, patients received totally four doses of perioperative immunochemotherapy, followed by one-year sintilimab maintenance under patient decision. Randomisation was stratified by tumor PD-L1 expression (≥1% vs < 1%). The primary endpoint was MPR rate. Secondary endpoints included complete pathology response (pCR) rate, objective response rate (ORR), 2-year disease-free survival (DFS) rate, 2-year overall survival (OS) rate and safety. This trial is registered with ClinicalTrials.gov, number: NCT04459611. **Results:** From 6/2020 to 9/2021, 60 patients were enrolled and received neoadjuvant treatment. The patient characteristics of both arms were well balanced. Among 55 patients with successful R0 resection, we observed a higher MPR rate (41.4%, 12/29) in three-cycle group compared with two-cycle group (26.9%, 7/26) (p = 0.260), meanwhile, pCR rate achieved 24.1% (7/29) and 19.2% (5/26) respectively (p = 0.660). Patients of squamous subtype generally achieved a statistically higher MPR rate (51.6%, 16/31) compared with the non-squamous subtype (12.5%, 3/24) (p = 0.002). In squamous subgroup, three cycles neoadjuvant treatment induced a MPR rate of 60% compared with 43.8% after two cycles treatment (p = 0.366).In the meantime, the MPR rate was 21.4% versus 0% in non-squamous subgroup, respectively (p = 0.239). The ORR showed no statistical difference between three-cycle group (55.2%, 16/29) and two-cycle (50%, 13/26) (p = 0.701). Patients were well-tolerated in both groups and 5% (3/60) experienced grade 3 immune related adverse events. **Conclusions:** It is the first randomized study comparing different treatment periods of immuno-chemotherapy in the neoadjuvant setting. Three cycles neoadjuvant treatment achieved a numerically higher MPR rate compared with two cycles. Patients with squamous lung cancer obtained a better MPR rate compared with non-squamous subtype. Clinical trial information: NCT04459611. Research Sponsor: None.

8501 **Oral Abstract Session**

Nivolumab + chemotherapy versus chemotherapy as neoadjuvant treatment for resectable stage IIIA NSCLC: Primary endpoint results of pathological complete response (pCR) from phase II NADIM II trial. *First Author: Mariano Provencio-Pulla, Instituto Investigacion Sanitaria Puerta de Hierro-Segovia de Arana, Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain*

Background: Non-small cell lung cancer (NSCLC) is incurable in most patients with locally advanced stage IIIA disease. Previous results indicate that the use of neoadjuvant chemoimmunotherapy could increase the percentage of cured patients being a promising therapeutic option that has to be tested in randomized clinical trials. **Methods:** NADIM II (NCT03838159) is an open-label, randomized, two-arm, phase II, multi-center clinical trial. Patients with resectable clinical stage IIIA (per AJCC 7th ed) NSCLC, ECOG PS 0-1, and no known EGFR/ALK alterations were randomized to receive Nivolumab (NIVO) 360mg + Paclitaxel 200mg/m^2 + Carboplatin AUC5 for 3 cycles every 21 days (+/- 3 days) as neoadjuvant treatment followed by surgery, or Paclitaxel 200mg/m^2 + Carboplatin AUC5 for 3 cycles every 21 days (+/- 3 days) followed by surgery. Patients with R0 resection confirmed by pathological evaluation initiated adjuvant administration of NIVO within the 3rd to 8th week (+7 days) from surgery and for 6 months. The primary endpoint was pathological complete response (pCR) by blinded independent pathological review (BIPR) in the intent-to-treat population (ITT). pCR was defined as 0% viable tumor cells in resected lung and lymph nodes; patients who did not undergo surgery were classified as non-responders. Major pathological response (MPR; ≤ 10% viable tumor) per BIPR, overall response rate (ORR), toxicity profile, and potential predictive biomarkers are secondary endpoints. **Results:** Between February 8, 2019, and November 11, 2021, 90 patients were enrolled, of whom 87 patients were valid. Neoadjuvant NIVO + chemo significantly increased the pCR rate compared to chemo in the ITT (36.2% vs 6.8%; Relative Risk (RR) 5.25 [99% CI 1.32-20.87]; P = 0.0071). NIVO + chemo also improved MPR rates vs chemo in the ITT (52 % vs 14 %), as well as ORR (74 % vs 48%). Definitive surgery occurred for 91% of pts treated with NIVO + chemo and 69% with chemo; surgery was cancelled rarely due to AEs (1 pts/experimental arm) and due to disease progression in 1 and 4 pts in the experimental and control arm respectively. Grade 3-4-related AEs were reported in 24 % vs 10% in the NIVO + chemo vs chemo arms, respectively. In the ITT experimental arm, patients with pCR had higher PD-L1 TPS (median 70%, IQR 5-90%) compared to non-responders (median 0%, IQR 0-37.5%, P = 0.0035). AUC to predict pCR was 0.734 (95% CI 0.59-0.88; P = 0.005). The pCR rate rises across increasing categories of PD-L1 TPS (< 1% 14.3%; 1-49% 41.7%; ≥50% 61.1%; P = 0.008). **Conclusions:** This study confirms the superiority of the chemo-immuno combination in patients with resectable stage IIIA NSCLC in terms of pCR, as well as the feasibility of surgery, with a moderate increase in grade 3-4 toxicity. Thus, this treatment should become the standard of care in these patients. Clinical trial information: NCT03838159. Research Sponsor: BMS.

8502 **Oral Abstract Session**

Intraoperative quality metrics and association with survival following lung cancer resection. *First Author: Brendan Heiden, Washington University School of Medicine, St. Louis, MO*

Background: Surgical resection remains the preferred treatment for functionally fit patients with clinical stage I non-small cell lung cancer (NSCLC). Process-based intra-operative quality metrics (QMs) are important for optimizing long-term outcomes following curative-intent resection. We sought to characterize overall survival using a novel surgical quality score. **Methods:** We performed a retrospective cohort study using a uniquely compiled dataset of US Veterans with clinical stage I NSCLC receiving definitive surgical treatment. Based on contemporary treatment guidelines, we defined five surgical QMs: timely surgery (within 12 weeks of diagnosis), minimally invasive approach, anatomic resection via lobectomy, adequate nodal sampling (≥10 nodes), and negative margin. Using a multivariable Cox proportional hazards model, we developed a surgical quality score reflecting the relationship between these QMs and overall survival (OS). We also examined the relationship between this score and disease-free survival (DFS). **Results:** The study included 9,628 Veterans undergoing surgical treatment between 2006 and 2016. QMs were met as follows: timely surgery (n=6,633, 68.9%), minimally invasive approach (n=3,986, 41.4%), lobectomy (n=6,843, 71.1%), adequate nodal sampling (n=3,278, 34.1%), and negative surgical margin (n=9,312, 96.7%). The median (IQR) follow-up was 6.2 (2.5-11.4) years. A normalized score from 0 (no QMs met) to 100 (all QMs met) was constructed, with higher scores reflecting progressively improved risk-adjusted OS (Table). The median (IQR) OS was 86.8 (37.8-149.6) months in the highest score quintile versus 25.3 (7.1-45.8) months in the lowest score quintile. Recurrence was detected in 2,268 (23.6%) patients. Higher surgical quality score was associated with improved DFS (multivariable-adjusted hazard ratio, aHR 0.494, 95% CI 0.245-0.997). **Conclusions:** Adherence to intra-operative QMs is associated with markedly improved overall and disease-free survival. Efforts to improve adherence to surgical QMs can dramatically improve patient outcomes following curative-intent resection of early-stage lung cancer. Research Sponsor: U.S. National Institutes of Health.

Association between surgical QMs and overall survival.

Variable[a]	aHR, 95% CI	β	p-value	Score[b]
Delayed surgery (≤12 vs >12 weeks)	0.90 (0.85-0.95)	-0.11	<0.001	2
Surgical approach (minimally invasive vs open)	0.91 (0.86-0.97)	-0.09	0.002	2
Extent of resection (vs wedge)				
Lobectomy	0.79 (0.74-0.84)	-0.24	<0.001	5
Segmentectomy	0.80 (0.70-0.92)	-0.22	0.001	4
Pneumonectomy	1.18 (0.96-1.46)	0.17	0.13	0
Nodal sampling (≥10 vs <10 nodes)	0.95 (0.89-1.01)	-0.05	0.09	1
Surgical margin (R0 vs R1+)	0.54 (0.47-0.62)	-0.61	<0.001	12

[a]Also controlling for age, sex, race, BMI, smoking status, Charlson score, number of prescriptions, hospital volume, tumor location, histology, tumor size. [b]Multiply score by 4.545 to generate the normalized score (0-100).

8503 **Oral Abstract Session**

Neoadjuvant chemoradiotherapy versus neoadjuvant chemotherapy for patients with stage III-N2M0 non-small cell lung cancer (NSCLC): A population-based study. *First Author: Marah Akhdar, Department of General Surgery and Urology, Faculty of Medicine, Jordan University of Science and Technology, Irbid, Jordan*

Background: Stage III-N2 non-small cell lung cancer (NSCLC) is a heterogeneous disease with controversial management options. Induction therapy as part of multimodal treatment is the standard of care for Stage III-N2 NSCLC. We aim to investigate the effect of adding radiotherapy to neoadjuvant chemotherapy on survival outcomes. **Methods:** All adult NSCLC patients diagnosed between 2004 and 2015 were identified in the Surveillance, Epidemiology, and End Results (SEER) database using ICD-O-3 histologic type coding. Inclusion criteria involved stage III NSCLC patients with ipsilateral lymph node involvement (N2), of any T stage, and with no known distant metastasis (M0). Our main sub-cohorts were patients who either underwent chemoradiotherapy (CRT) or chemotherapy (CT) in neoadjuvant settings. Our primary outcomes were overall survival (OS) and cancer-specific survival (CSS) in months. Cox proportional hazards model was used to analyze the effect of each treatment modality on OS and CSS in univariate and multivariate fashions. Multivariate analysis was adjusted for age, sex, marital status, T stage, resected lymph node status, tumor histology, primary site, laterality, and surgical procedure. Inverse probability treatment weighting (IPTW) was applied to create weighted samples based on study covariates. **Results:** Our analysis included 1175 patients; 799 (68.0%) underwent neoadjuvant CRT and 376 (32.0%) underwent neoadjuvant CT. Sample median age was 63 (IQR:56-69) years. T2 stage was the most prevalent (N =561, 47.7%), followed by T4 (N=243, 20.7%), T1 (N=228, 19.4%), and T3 (N=143, 12.2%). The main tumor histology was non-squamous cell carcinoma in 773 (65.8%) patients. The upper lobe was the most common primary tumor site (N =788, 67.1%). Patients underwent lobectomy (N=917, 78.0%), pneumonectomy (N=184, 15.7%), or sub-lobar resection (N=69, 5.9%). Adding radiotherapy to chemotherapy showed a slightly higher median OS than chemotherapy alone in neoadjuvant settings (51 vs. 47 months, respectively), and a higher median CSS (75 vs. 59 months, respectively). However, these differences were not statistically significant for OS or CSS (HR = 1.08, 95% CI: 0.91-1.28 and HR = 1.04, 95% CI: 0.89-1.21, respectively). After adjustment, age, T3-T4 stage, non-squamous histology, lower lobe primary site, positive resected lymph nodes, and pneumonectomy were all significant independent predictors for worse OS and CSS. IPTW analysis showed no remarkable survival advantage for CRT patients (HR = 1.15, 95% CI: 0.95-1.40 and HR= 1.12, 95% CI: 0.90-1.39) for OS and CSS, respectively. **Conclusions:** Adding radiotherapy to neoadjuvant CT did not result in significant survival benefits. Multiple prognostic factors should be taken into consideration when identifying the optimal choice and sequence of multimodal treatment for stage III-N2M0 NSCLC patients. Research Sponsor: None.

8504 **Oral Abstract Session**

Comparison of quality of life in patients randomized to high-dose once daily (QD) thoracic radiotherapy (TRT) with standard twice daily (BID) TRT in limited stage small cell lung cancer (LS-SCLC) on CALGB 30610 (Alliance, Sub-study CALGB 70702). *First Author: Apar Kishor Ganti, University of Nebraska Medical Center, Omaha, NE*

Background: The CALGB 30610 trial demonstrated that 70Gy QD TRT was not associated with a superior overall survival compared to standard BID 45Gy TRT in limited stage small cell lung cancer. Since both arms appeared to provide similar clinical benefit, other factors such as quality of life may help oncologists decide on the best treatment approach for their patients. The present analysis was conducted to compare patients' quality of life between these regimens in terms of their physical symptoms, physical functioning and psychological state. **Methods:** In the CALGB 30610 planned sub-study CALGB 70702, patients were administered the FACT-L, FACT Trial Outcome Index-Lung Cancer (FACT-L TOI), FACT-Esophageal Cancer Eating and Swallowing Indices, ECOG Acute Esophagitis Scale, Hospital Anxiety and Depression Scale (HADS), the EQ-5D at baseline and a single item assessing difficulty swallowing at baseline, 3, 5, 7, 12, 26, and 52 weeks after starting radiation therapy. Patients were also asked to assess treatment inconvenience at these time points. The primary endpoints of CALGB 70702 were FACT-L TOI and FACT eating and swallowing subscales at 12 weeks. Mean changes from baseline were compared between arms using general linear mixed models. **Results:** 417 patients consented to participate in the patient-reported outcomes substudy. The completion rate of the questionnaires was 87% at baseline and 71% at week 52. The FACT-L total score mean worsening was significantly less in the QD arm compared to the BID arm at week 3 (-1.0 vs -7.0; P=.003), and marginally less at week 5 (-5.3 vs -11.0; P=.06). The FACT-L TOI mean worsening was significantly less in the QD arm than in the BID arm at week 3 (-2.9 vs -7.6; P=.003) and greater at week 12 (-7.6 vs -2.8; P=.03). The QD arm also had a lesser EQ-5D index mean worsening at 3 weeks (-0.04 vs 0.03; P=.002). Mean increase in the acute esophagitis score (1.06 vs 2.89; P<.001) and difficulty swallowing (0.39 vs 1.14; P<.001) were significantly greater in the BID arm at week 3. Mean worsening in HADS anxiety was significantly less in the QD arm at week 5 (-1.99 vs -0.95; P=.03). There were no other significant differences at the remaining timepoints between the two arms. Across visits on the QD arm, patients felt that treatment was inconvenient at 26% (96/376) assessments, compared to 33% (116/352) in the BID arm (chi-sq P=.03). **Conclusions:** Both radiation regimens were well tolerated. However, the QD arm had better quality of life scores at week 3 and was perceived to be less inconvenient. Clinical trial information: NCT00632853. Research Sponsor: U.S. National Institutes of Health.

8505 **Oral Abstract Session**

Serplulimab, a novel anti-PD-1 antibody, plus chemotherapy versus chemotherapy alone as first-line treatment for extensive-stage small-cell lung cancer: An international randomized phase 3 study. *First Author: Ying Cheng, Department of Medical Thoracic Oncology, Jilin Cancer Hospital, Changchun, China*

Background: Monoclonal antibodies against programmed death-ligand 1 (PD-L1) have been approved for the first-line treatment of extensive-stage small-cell lung cancer (ES-SCLC) in combination with chemotherapy. However, whether a programmed death 1 (PD-1) inhibitor provides similar survival benefit in this patient population remains unclear. In this study, the efficacy and safety of serplulimab, a novel humanized monoclonal anti-PD-1 antibody, were assessed in combination with chemotherapy in previously untreated ES-SCLC patients. **Methods:** In this international, randomized, double-blind, multicenter, phase 3 trial (NCT04063163), patients with ES-SCLC who had not received prior systemic therapy were randomized (2:1) to receive serplulimab 4.5 mg/kg or placebo intravenously every 3 weeks. All patients received intravenous carboplatin and etoposide every 3 weeks for up to 4 cycles. The primary endpoint was overall survival (OS). Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), duration of response (DoR), and safety. **Results:** Between September 12, 2019 and April 27, 2021, 585 patients were randomized (serplulimab group, n = 389; placebo group, n = 196). At interim analysis, the median follow-up duration was 12.3 months. Median OS was significantly prolonged in the serplulimab group than the placebo group (15.4 *vs.*10.9 months; hazard ratio [HR] 0.63, 95% CI 0.49–0.82; P < 0.001). Median PFS assessed by the independent radiology review committee (IRRC) per RECIST v1.1 was significantly longer in the serplulimab group than the placebo group (5.8 *vs.* 4.3 months; HR 0.47, 95% CI 0.38–0.59; P < 0.001). Efficacy improvements were also observed in ORR (80.2% *vs.* 70.4%) and DoR (5.6 *vs.* 3.2 months) as assessed by IRRC per RECIST v1.1. Grade ≥3 treatment-emergent adverse events (TEAEs) related to serplulimab or placebo were reported in 129 (33.2%) and 54 (27.6%) patients in the respective groups. Incidence of immune-related TEAEs was higher in the serplulimab group compared to the placebo group (37% *vs.* 18.4%), with the largest difference in endocrine disorders (18.3% *vs.* 4.6%), which are commonly reported with anti-PD-1/PD-L1 therapies. Four deaths (1 acute coronary syndrome, 1 pyrexia, and 1 platelet count decreased in the serplulimab group; 1 thrombocytopenia in the placebo group) that might be related to study drugs were reported. **Conclusions:** Serplulimab plus chemotherapy as first-line treatment provided significant benefits and a manageable safety profile compared with chemotherapy alone in ES-SCLC patients. For the first time, OS benefits was demonstrated with a PD-1 inhibitor in a global phase 3 study among previously untreated ES-SCLC patients. Clinical trial information: NCT04063163. Research Sponsor: Shanghai Henlius Biotech, Inc.

LBA8507 **Oral Abstract Session**

SKYSCRAPER-02: Primary results of a phase III, randomized, double-blind, placebo-controlled study of atezolizumab (atezo) + carboplatin + etoposide (CE) with or without tiragolumab (tira) in patients (pts) with untreated extensive-stage small cell lung cancer (ES-SCLC). *First Author: Charles M. Rudin, Memorial Sloan Kettering Cancer Center, New York, NY*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

8508 **Poster Discussion Session**

Two-year update from KEYNOTE-799: Pembrolizumab plus concurrent chemoradiation therapy (cCRT) for unresectable, locally advanced, stage III NSCLC. *First Author: Martin Reck, LungenClinic, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany*

Background: Primary analysis (database cutoff, Oct 28, 2020) of the global KEYNOTE-799 study (NCT03631784) in patients (pts) with unresectable, locally advanced stage III NSCLC, showed that pembrolizumab (pembro; anti–PD-1) plus cCRT resulted in an ORR of 70.5% in cohort A (n = 112; squamous and nonsquamous) and 70.6% in cohort B (n = 102; nonsquamous only) and grade ≥3 pneumonitis in 9 (8.0%) and 7 (6.9%) pts, respectively. We present updated outcomes with 1 y of additional follow-up. **Methods:** In this nonrandomized, phase 2 study, eligible pts were aged ≥18 y with previously untreated, unresectable, pathologically confirmed, stage IIIA-C NSCLC with measurable disease per RECIST v1.1. Pts in cohort A (squamous and nonsquamous) received carboplatin AUC 6 plus paclitaxel 200 mg/m^2 and pembro 200 mg for one 3-wk cycle, followed by carboplatin AUC 2 plus paclitaxel 45 mg/m^2 QW for 6 wks plus 2 cycles of pembro 200 mg Q3W plus standard thoracic radiotherapy (TRT). Pts in cohort B (nonsquamous) received 3 cycles of cisplatin 75 mg/m^2, pemetrexed 500 mg/m^2, and pembro 200 mg Q3W plus standard TRT in cycles 2 and 3. All pts received 14 additional cycles of pembro 200 mg Q3W. Primary endpoints were ORR per RECIST v1.1 by blinded independent central review (BICR) and the incidence of grade ≥3 pneumonitis (per NCI CTCAE v4.0). **Results:** Of 216 pts enrolled in this study, 112 in cohort A and 102 in cohort B received treatment. Median (range) time from first dose to database cutoff (Oct 18, 2021) was 30.2 (25.3–35.5) mo in cohort A and 25.4 (14.5–35.2) mo in cohort B. ORR (95% CI) was 71.4% (62.1%–79.6%) in cohort A and 75.5% (66.0%–83.5%) in cohort B. Median duration of response (DOR) and OS were not reached (NR) in both cohorts; median PFS was 30.6 mo in cohort A, and NR in cohort B (Table). ORR was 66.7% in pts with PD-L1 TPS <1% and 77.3% in pts with PD-L1 TPS ≥1% in cohort A and 78.6% and 72.5%, respectively, in cohort B. ORR was similar by histology (squamous, 72.0%; nonsquamous, 74.1%). Grade ≥3 pneumonitis occurred in 16 pts (7.5%) overall; 9 pts (8.0%) in cohort A and 7 (6.9%) in cohort B. Treatment-related grade ≥3 AEs occurred in 64.3% and 51.0% of pts in cohort A and B, respectively. **Conclusions:** With the accrual of additional responses after >2 y of follow-up, pembro plus cCRT continues to demonstrate robust and durable responses, regardless of PD-L1 TPS and tumor histology, promising survival outcome and manageable safety in pts with previously untreated, locally advanced stage III NSCLC. Clinical trial information: NCT03631784. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

	Cohort A n = 112	Cohort B n = 102
ORR, % (95% CI)	71.4 (62.1–79.6)	75.5 (66.0–83.5)
Median DOR,[a] mo (range)	NR (1.9+ to 32.5+)	NR (1.6+ to 32.5+)
DOR ≥24 mo, %	64.0	68.7
Median PFS,[a] mo (95% CI)	30.6 (16.6–NR)	NR (20.6–NR)
24-mo rate, %	55.3	60.6
Median OS,[a] mo (95% CI)	NR (26.1–NR)	NR (33.0–NR)
24-mo rate, %	64.3	71.2

"+" indicates no PD by time of last disease assessment.
[a]Kaplan-Meier estimate.

8509 **Poster Discussion Session**

Consolidation nivolumab plus ipilimumab or nivolumab alone following concurrent chemoradiation for patients with unresectable stage III non-small cell lung cancer: BTCRC LUN 16-081. *First Author: Greg Andrew Durm, Indiana University Melvin and Bren Simon Comprehensive Cancer Center, Indianapolis, IN*

Background: The PACIFIC trial demonstrated that a year of consolidation PD-(L)1 inhibition following concurrent chemoradiation (CRT) for unresectable stage III NSCLC improves overall survival (OS). The optimal duration of consolidation IO therapy in this setting is undefined. Studies in metastatic NSCLC demonstrate that combination PD-(L)1/CTLA-4 inhibition improves OS over chemotherapy alone. This trial evaluated the use of combination Nivolumab (N) plus Ipilimumab (IPI) or N alone for up to 6 months in unresectable stage III NSCLC after concurrent CRT. **Methods:** This is a randomized phase II, multicenter trial of 105 pts with unresectable stage IIIA/IIIB NSCLC. All pts received concurrent CRT and were then enrolled and randomized 1:1 to receive N 480mg IV q4wks (Arm A) for up to 24 weeks or N 3mg/kg IV q2 wks + IPI 1mg/kg IV q6 wks (Arm B) for up to 24 weeks. The primary endpoint is 18-month PFS compared to historical controls of CRT alone for arm A (30%) and CRT followed by Durva for arm B (44%). Secondary endpoints include OS and toxicity. **Results:** From 9/2017 to 4/2021, 105 pts were enrolled and randomized, 54 to N alone (A) and 51 to N + IPI (B). The baseline characteristics for arm A/B: median age (65/63), male (44.4%/56.9%), stage IIIA (55.6%/56.9%), stage IIIB (44.4%/43.1%), non-squamous (57.4%/54.9%), and squamous (42.6%/45.1%). The percentage of pts completing the full treatment was 70.4% on A and 56.9% on B ($p = 0.15$). Median f/u was 24.5 and 24.1 months on A and B, respectively. The 18-month PFS was 62.3% on A ($p < 0.1$) and 67% on B ($p < 0.1$), and median PFS was 25.8 months and 25.4 months, respectively. Median OS was not reached on either arm, but the 18- and 24-month OS estimates were 82.1% and 76.6% for A and 85.5% and 82.8% for B, respectively. Treatment-related adverse events (trAE) on arm A/B were 72.2%/80.4%, and grade ≥3 trAEs on arm A/B were 38.9%/52.9%. There was 1 grade 5 event on each arm (COVID19-A, Cardiac Arrest-B). The number of pts with grade ≥2 pneumonitis were 12 (22.2%) on A and 15 (29.4%) on B, with 5 (9.3%) and 8 (15.7%) grade ≥3 events, respectively. The most common (> 10%) non-pneumonitis trAEs on A were fatigue (31.5%), rash (16.7%), dyspnea (14.8%), and hypothyroidism (13%), and on B were fatigue (31.4%), diarrhea (19.6%), dyspnea (19.6%), pruritus (17.7%), hypothyroidism (15.7%), rash (15.7%), arthralgia (11.8%), and nausea (11.8%). **Conclusions:** Following concurrent CRT for unresectable stage III NSCLC, both N and N + IPI demonstrated improved 18-month PFS compared with historical controls despite a shortened interval (6 months) of treatment. OS data are still maturing but 18- and 24-month OS estimates compare favorably to prior consolidation trials. Toxicity for N alone was similar to prior single-agent trials, and the combination of N + IPI resulted in a higher incidence of trAE's, although consistent with prior reports. Clinical trial information: NCT03285321. Research Sponsor: Bristol Myers Squibb.

8510 **Poster Discussion Session**

The Selective Personalized Radio-immunotherapy for Locally Advanced NSCLC Trial (SPRINT): Initial results. *First Author: Nitin Ohri, Montefiore Medical Center and Albert Einstein College of Medicine, Bronx, NY*

Background: Standard therapy for unresectable locally advanced non-small cell lung cancer (LA-NSCLC) is concurrent chemoradiotherapy followed by adjuvant durvalumab. We performed a prospective trial testing sequential pembrolizumab and risk-adapted radiotherapy without chemotherapy for biomarker-selected LA-NSCLC patients. **Methods:** Patients with stage III NSCLC or unresectable stage II NSCLC, ECOG performance status 0-1, and no contraindications to protocol-specified therapy were eligible for this trial. Subjects with PD-L1 tumor proportion score (TPS) ≥ 50% underwent baseline FDG-PET/CT, received three cycles of induction pembrolizumab (200 mg, every 21 days), underwent restaging FDG-PET/CT, received risk-adapted thoracic radiotherapy (55 Gy delivered to tumors or lymph nodes with metabolic tumor volume exceeding 20 cc and 48 Gy delivered to smaller lesions, all in 20 daily fractions), and then received up to 13 cycles of additional pembrolizumab. The primary study endpoint was one-year progression-free survival (PFS). Here we report response rates following induction pembrolizumab, PFS and overall survival (OS) rates, and adverse event rates (CTCAE v. 4.03). **Results:** Twenty-five subjects with PD-L1 TPS ≥ 50% from three institutions were enrolled between August 2018 and November 2021. Median age was 71 (interquartile range [IQR] 62 to 77). One subject had stage II disease, 13 had stage IIIA disease, nine had stage IIIB disease, and two had stage IIIC disease. Median PD-L1 TPS was 75% (IQR 60 to 80%). Two subjects (8%) developed disease progression during induction pembrolizumab, and two subjects discontinued pembrolizumab after one infusion due to immune-related adverse events. Using RECIST 1.1 criteria, 12 subjects (48%) exhibited a partial (n = 11) or complete (n = 1) response following induction pembrolizumab on CT. Using PERCIST criteria, 12 subjects (48%) exhibited a partial response following induction pembrolizumab on PET. Four subjects had responses on PET but not on CT, and four had responses on CT but not on PET. With a median follow-up duration of 13 months, the actuarial 1-year PFS rate is 74%, and the actuarial 1-year OS rate is 95%. Grade 3 adverse events have been limited to single cases of anemia, arthritis, diarrhea, esophagitis, and pneumonitis, and no grade 4-5 adverse events have occurred. Exploratory analyses suggest that response to induction pembrolizumab on PET predicts efficacy of this treatment approach, with a 1-year PFS rate of 100% for responders, compared to 61% for non-responders (logrank p = 0.007). **Conclusions:** Treatment with pembrolizumab and risk-adapted radiotherapy is a promising treatment approach for LA-NSCLC patients with PD-L1 TPS ≥ 50%. Response on PET following induction pembrolizumab may be useful for identifying patients who can be treated successfully without chemotherapy. Clinical trial information: NCT03523702. Research Sponsor: Merck.

LBA8511 **Poster Discussion Session**

Neoadjuvant nivolumab (NIVO) + platinum-doublet chemotherapy (chemo) versus chemo for resectable (IB–IIIA) non-small cell lung cancer (NSCLC): Association of pathological regression with event-free survival (EFS) in CheckMate 816. *First Author: Mariano Provencio-Pulla, Hospital Universitario Puerta de Hierro, Madrid, Spain*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

8512 **Poster Discussion Session**

EORTC-1416-LCG/ETOP 8-15 – PEARLS/KEYNOTE-091 study of pembrolizumab versus placebo for completely resected early-stage non-small cell lung cancer (NSCLC): Outcomes in subgroups related to surgery, disease burden, and adjuvant chemotherapy use. *First Author: Mary E.R. O'Brien, The Institute of Cancer Research and the Royal Marsden NHS Foundation Trust, Surrey, United Kingdom*

Background: At the second interim analysis (IA2) of the triple-blind, phase 3 PEARLS/KEYNOTE-091 study (NCT02504372), pembrolizumab significantly improved DFS compared with placebo in patients (pts) with completely resected stage IB (T ≥4 cm) to IIIA NSCLC per AJCC v7, regardless of PD-L1 expression (N = 1177, HR 0.76, 95% CI 0.63-0.91, $P = 0.0014$). We present DFS in subgroups related to surgery, disease burden, and adjuvant chemotherapy use. **Methods:** Pts had pathologically confirmed, completely resected stage IB (T ≥4 cm) to IIIA NSCLC of any PD-L1 expression and ECOG PS 0-1. Systematic complete or lobe-specific mediastinal lymph node dissection was recommended; minimally, the subcarinal and 1 lobe-specific lymph node must have been examined. Adjuvant chemotherapy of ≤4 cycles was given as indicated by local guidelines. Eligible pts were randomized 1:1 to pembrolizumab 200 mg or placebo Q3W for 18 doses (~1 y). Treatment effects on DFS were assessed in prespecified subgroups of with and without adjuvant chemotherapy and in exploratory subgroups defined by surgery type, pN stage, tumor size, no. of adjuvant chemotherapy cycles, and adjuvant regimen; only subgroups of > 50 pts were analyzed. Data cutoff for IA2 was September 20, 2021 (median time from randomization to cutoff, 35.6 mo). **Results:** By surgery type, the HR (95% CI) for DFS was 0.78 (0.64-0.96) for lobectomy (n = 925), 0.85 (0.43-1.69) for bilobectomy (n = 92), and 0.71 (0.40-1.24) for pneumonectomy (n = 127). For subgroups based on nodal status, HR (95% CI) for DFS was 0.63 (0.46-0.86) for pN0 (n = 490), 0.77 (0.57-1.03) for pN1 (n = 456), and 1.00 (0.71-1.41) for pN2 (n = 231). By tumor size, and irrespective of nodal status, the HR (95% CI) for DFS was 0.91 (0.69-1.20) for size ≤4 cm (n = 491) and 0.70 (0.55-0.89) for size > 4 cm (n = 685). The HR (95% CI) for DFS was 0.73 (0.60-0.89) in pts who received adjuvant chemotherapy (n = 1010) and 1.25 (0.76-2.05) in those who did not (n = 167). Among pts who received adjuvant chemotherapy, HR (95% CI) for DFS by number of cycles was 0.59 (0.28-1.26) for 1-2 (n = 67) and 0.74 (0.61-0.91) for 3-4 (n = 943); by regimen, it was 0.74 (0.55-0.98) for cisplatin + vinorelbine (n = 491), 0.51 (0.31-0.83) for carboplatin + vinorelbine (n = 151), 1.21 (0.73-1.98) for carboplatin + paclitaxel (n = 135), 0.65 (0.30-1.40) for cisplatin + gemcitabine (n = 57), and 0.68 (0.41-1.14) for other regimen (n = 176). **Conclusions:** Pembrolizumab generally improved DFS versus placebo regardless of type of surgery, lymph node involvement, tumor size, and type and extent of adjuvant chemotherapy in pts with completely resected stage IB (T ≥4 cm) to IIIA NSCLC. These data support the benefit of pembrolizumab as adjuvant therapy for early-stage NSCLC following complete resection and, if indicated, adjuvant chemotherapy. Clinical trial information: NCT02504372. Research Sponsor: Merck Sharp & Dohme Corp, a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

8513 **Poster Discussion Session**

Safety results of NRG-LU004: Phase I trial of accelerated or conventionally fractionated radiotherapy combined with durvalumab in PD-L1–high locally advanced non-small cell lung cancer. *First Author: Steven H. Lin, Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: In advanced non-small cell lung cancer (NSCLC), high Programmed-Death-1 Ligand (PD-L1) (>50%) expression demonstrate superior response and survival with immune checkpoint inhibitors compared to chemotherapy. We hypothesize that it is safe and feasible to substitute durvalumab instead of chemotherapy concurrently with radiotherapy (RT) in patients with Locally Advanced-NSCLC (LA-NSCLC) and high PD-L1. **Methods:** NRG-LU004 (NCT03801902) is a Phase I study for patients with stage II-III unresectable or inoperable, LA-NSCLC with PD-L1> 50% (Dako 22C3 or Ventana SP263) expression. There were safety and expansion phases with a primary endpoint of safety. Patients started with 1500 mg durvalumab Q4 weeks and thoracic RT within 2 weeks from 1st infusion. Durvalumab continued once a month up to 1 year. In the safety cohort, 6 patients in cohort 1 were treated with accelerated fractionated RT (ACRT) to 60 Gy in 15 fractions, followed by a required safety hold for 90 days. During cohort 1 safety hold, cohort 2 patients were treated with conventional RT 60 Gy in 30 fractions (CONV) followed by a 60-day safety hold. A cohort advanced to the expansion phase to enroll 6 more patients if safety criteria (0-1 patients with a dose limiting toxicity [DLT]) were met. If both cohorts were deemed safe, patients would be randomized 1:1 to ACRT or CONV with safety defined as < 4 of 12 evaluable patients per arm experiencing a DLT. Feasibility was defined as at least 80% of patients in each arm receiving at least 80% of the planned dose of durvalumab during the first 8 weeks. **Results:** 24 evaluable patients enrolled between January 2019 and June 2021. No DLTs were reported in cohort 1, and 1 (unrelated bronchopulmonary hemorrhage leading to discontinuation of durvalumab) in cohort 2. Both safety cohorts advanced to the expansion phase. All but one patient (CONV) received RT per protocol/with an acceptable variation. At the time of analysis, 24% had received all 13 cycles of durvalumab. For the ACRT cohort, there were 4 grade 3, 1 grade 4 (lymphopenia), and 1 grade 5 AE (lung infection, assessed as unrelated to therapy). For CONV, there were 8 grade 3, 0 grade 4, and 1 grade 5 AE (respiratory failure, unrelated to therapy). For feasibility, 10 of 12 (85%) patients in the ACRT cohort received the second dose of durvalumab (2 not received due to shingles and unrelated death), while 9 of 12 (75%) of the CONV cohort received the second dose (reasons for not receiving: viral hepatitis, bronchopulmonary hemorrhage, and respiratory failure, all assessed as unrelated to therapy). **Conclusions:** Chemotherapy-free thoracic RT approaches (ACRT or CONV RT) are safe, when given with concurrent durvalumab in patients with PD-L1 high LA-NSCLC. A trial to compare immunoradiotherapy and consolidation durvalumab to standard chemoradiation and consolidation durvalumab is planned. Clinical trial information: NCT03801902. Research Sponsor: U.S. National Institutes of Health.

8514 **Poster Discussion Session**

Distinct genomic and immunophenotypic features of solid-predominant versus nonsolid-predominant stage I lung adenocarcinomas and association with disease recurrence after surgical resection. *First Author: Joao Victor V. Alessi, Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, MA*

Background: Compared to lung adenocarcinomas (LUAD) with nonsolid-predominant histology (lepidic, acinar, papillary, micropapillary), those with predominantly solid features have a higher risk of disease recurrence after surgical resection. However, little is known about the genomic landscape and immunophenotype of solid vs nonsolid stage I LUAD. **Methods:** We collected clinicopathologic data from patients with resected stage I NSCLC (AJCC 8th Edition), which underwent next-generation sequencing to identify genomic alterations and tumor mutational burden (TMB). A subset of these samples also had multiplexed immunofluorescence for CD8+, FOXP3+, PD-1+, and PD-L1 to determine differences in tumor immune cells subsets according to histologic subtype. Disease free-survival (DFS) was compared in patients based on their predominant histologic subtype (solid vs nonsolid). **Results:** Among 658 LUADs, 11.4% (N = 75) had solid-predominant and 88.6% (N = 583) nonsolid-predominant histology. After a median follow-up of 50 months from the time of surgery, 145 patients (22.0%) experienced recurrence. Compared to nonsolid-predominant LUAD, those with solid predominance had a significantly lower prevalence of activating *EGFR*, *BRAF*^{V600E}, and *METex14* mutations as well as *ALK*/*RET*/*ROS*1 rearrangements (9.3% versus 31.6%, P < 0.001), no difference in *KRAS*^{G12C} frequency (24% versus 16.8%, P = 0.14), a higher TMB (median 12.2 versus 7.2 mutations/megabase; P < 0.001), and a shorter median DFS from the time of surgical resection (43.2 months versus not reached, HR: 3.3 [95% CI: 2.2-4.9], P < 0.001). The detrimental effect of solid-predominant LUAD in DFS remained significant after adjusting for other factors such as tumor stage, surgery type, smoking status, and TMB (HR: 2.66 [95% CI: 1.71-4.11], P < 0.001]. Among LUADs profiled by multiplex immunofluorescence, compared to tumors with nonsolid-predominant subtype (N = 197), those with solid predominance (N = 23) had significantly higher numbers of CD8+, FOXP3+, PD-1+ immune cells, and PD-1+ CD8+ T cells, both intratumorally (P < 0.001) and at the tumor-stroma interface (P < 0.001). Solid-predominant subtype was also associated with a higher median PD-L1 expression level on tumor (5% versus 1%; P = 0.01) and immune cells (16% versus 7%, P = 0.02). **Conclusions:** Among patients with surgically-resected stage I LUAD, solid-predominant histology was associated with distinct genotypic and immunologic characteristics. These findings may aid in identifying patients at greater risk of recurrence after surgery. Research Sponsor: None.

8515 **Poster Discussion Session**

Surfaceome profiling to reveal unique therapeutic vulnerabilities in transcriptional subtypes of small cell lung cancer (SCLC). *First Author: Taofeek K. Owonikoko, UPMC Hillman Cancer Center, Pittsburgh, PA*

Background: Effective treatment options for SCLC remain limited and new treatment approaches are needed to improve outcome. We sought to validate the initial observation in cell lines and limited tissue samples of SCLC of a differential expression of cancer/testis (CT) antigens and TACSD2 gene that encodes surface protein, Trop2 across various subtypes of SCLC. We also tested whether overall surfaceome profile as previously described in other tumor types will show hierarchical priority of expression between transcriptionally defined SCLC subtypes. **Methods:** We conducted a comprehensive surfaceome profiling of SCLC samples using data generated by RNA sequencing (whole transcriptome) at Caris Life Sciences (Phoenix, AZ). SCLC tumors were stratified into 5 subgroups (SCLC-A/N/Y/P and -mixed) based on the relative expression of the four transcription factors. Expression values were converted to z-scores (the expression value for each gene is normalized to the average expression of that specific gene such that the z-score reflects the number of standard deviations above or below the average). The highest positive z-score among the 4 transcription factors determined subgroup. If all transcription factor z-scores for a given sample were negative, the sample was assigned to 'Mixed' subgroup. Significance was tested by Chi-square, Fisher's exact test, or Mann-Whitney U test. **Results:** We employed data generated from 674 SCLC samples; median age of 66 years and male (48.7%). The SCLC subtype distribution was 241 (35.8%), 120 (17.8%), 40 (5.9%), 143 (21.2%), 130 (19.3%) for types A, N, P, Y and mixed respectively. Supervised analysis for TACSTD2 expression showed highest levels in YAP1 subtype and was overall significantly increased in SCLC-Y (~3-fold) and SCLC-P (~2-fold) subtypes compared to A, N and mixed subtypes. Similarly, SCLC-Y subtype showed the highest median expression as well as the strongest correlation with most TACSTD2-interacting and regulatory genes. A top 10 list of candidate surface protein gene out of 3699 surfaceome genes was defined for each subtype based on the strength of correlation. The top candidate surface protein gene and CT antigen gene respectively by subtype were: SCN3A (r = 0.7033, p = 1.08^{E-101}) and NOL4, (r = 0.574, p = 2.46^{E-60}) for SCLC-A; SSTR2, (r = 0.742, p = 8.18^{E-119}) and TMEFF1, (r = 0.3601, p = 4.53^{E-22}) for SCLC-N; TMPRSS13 (r = 0.5699, p = 2.64^{E-59}) and LY6K (r = 0.4778, p = 9.80^{E-40}) for SCLC-P; and CYBRD1 (r = 0.8559, p = 1.18^{E-194}) and CTAGE5 (r = 0.5521, p = 4.95^{E-55}) for SCLC-Y. **Conclusions:** SCLC-Y subtype showed the highest expression of TACSTD2 and its interacting and regulatory genes. This subtype could serve as an enrichment factor for antibody-drug-construct targeting TROP2. Several candidate CT antigens and surfaceome genes showing strong correlation with lineage-defining transcription factors offer additional therapeutic targets in SCLC. Research Sponsor: None.

8516 **Poster Discussion Session**

Sintilimab plus anlotinib as second or further-line therapy for small cell lung cancer: An objective performance trial. *First Author: Shuxiang Ma, Henan Cancer Hospital, Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China*

Background: Small cell lung cancer (SCLC) tends to progress rapidly on first-line therapies, with limited subsequent-line treatment options. **Methods:** In this single-arm objective performance trial, adult patients with extensive-disease SCLC (ED-SCLC) received intravenous sintilimab 200 mg on day 1 and oral anlotinib 12 mg on days 1-14. Treatment lasted for 3 weeks per cycle and was continued until disease progression, unacceptable toxicities, or death. The primary endpoint was the superiority of progression-free survival (PFS) *versus* a PFS of 2.8 months with historical topotecan control. **Results:** Forty-two patients were enrolled, and 39 patients were evaluable for efficacy. Twenty-six patients (66.7%) had ED-SCLC, and 13 (33.3%) relapsed after concurrent chemoradiotherapy. The median follow-up was 11.9 months. The median PFS was 6.0 months (95%CI: 4.8-7.2). The 6- and 12-month PFS rate was 50.5% and 27.8%, respectively. Fourteen patients died by the data cut-off date, and overall survival (OS) was immature (16.1 months, 95%CI: 9.4-22.7). The 12- and 18-month OS rate was 56.7% and 42.5%, respectively. Three patients attained complete response and 16 achieved partial response, and 12 patients had stable disease; the objective response rate was 48.7% and the disease control rate was 79.5%. Forty patients (95.2%) had at least one treatment-related adverse event (TRAE). The most frequent TRAEs were hypothyroidism (45.2%), hypoproteinemia (40.5%) and elevated gamma-glutamyl transpeptidase (38.1%). **Conclusions:** Immunotherapy with sintilimab plus antiangiogenic drug anlotinib demonstrated promising antitumor activities as second or further-line therapy for ED-SCLC and had manageable toxicities. The findings support further development of this combination regimen for ED-SCLC. Clinical trial information: NCT04055792. Research Sponsor: None.

8517 **Poster Discussion Session**

Primary analysis from the phase 2 study of continuous talazoparib (TALA) plus intermittent low-dose temozolomide (TMZ) in patients with relapsed or refractory extensive-stage small cell lung cancer (ES-SCLC). *First Author: Jonathan W. Goldman, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA*

Background: TALA exhibits cytotoxic effects by inhibiting poly (ADP-ribose) polymerase (PARP) proteins 1 and 2 in addition to "trapping" PARP on DNA. TMZ has been shown to increase anti-tumor response when combined with TALA in SCLC models (Wainberg AACR 2016). TALA plus TMZ as second-line therapy for ES-SCLC may improve disease-related outcomes. **Methods:** This is a phase 2, open-label, single-arm study of the safety and efficacy of TALA plus TMZ in patients with ES-SCLC, relapsed or refractory to a first-line platinum-based regimen. Participants receive TALA 0.75 mg (or 0.5 mg if creatinine clearance < 60 mL/min) po daily on 28-day cycles with TMZ 37.5 mg/m2 po on days 1-5. The primary endpoint is objective response rate (ORR) based on RECIST 1.1 criteria, versus a historical control of 15% ORR in second-line topotecan, with the null hypothesis rejected for 8 or more confirmed responses among 28 evaluable subjects (29% ORR). Secondary endpoints include progression-free survival, overall survival, duration of response, and time to response. Exploratory endpoints include biomarker studies such as status of DNA damage response genes (DDR) and patient reported outcomes. A Simon two-stage design was utilized to reach a total accrual of 28 evaluable patients. **Results:** Thirty-one subjects were enrolled, of which 3 were non-evaluable due to ineligibility (1) or early withdrawal of consent prior to first disease assessment (2). Eleven of 28 evaluable subjects (39.3%) achieved a confirmed partial response. The ORR was similar among platinum-refractory (3/6), -resistant (4/9), and -sensitive subgroups (4/13). The median time to response was 1.8 months (m), duration of response 5.8 m, progression free survival 4.5 m, and overall survival 11.9 m. Adverse events (AEs) were manageable, with grade ≥ 3 AEs being thrombocytopenia (61.3%), anemia (54.8%), neutropenia (41.9%), and atypical pneumonia (3.2%), which responded well to dose-hold or dose-reduction and transfusion or growth factor support as needed. Cell free DNA and tissue analysis demonstrated no germline DDR mutations among the trial subjects, but somatic DDR mutations at baseline and acquired during treatment were common. Three subjects remain on study treatment. **Conclusions:** The study exceeded its target response rate. This is the second trial to demonstrate a benefit of PARP inhibition with low-dose TMZ in SCLC (see Farago Cancer Discovery 2019). A phase 3 study is appropriate to confirm the benefit of this approach compared to currently approved options. Clinical trial information: NCT03672773. Research Sponsor: Pfizer.

8518 **Poster Discussion Session**

Targeting genomic instability in extrapulmonary small cell neuroendocrine cancers: A phase II study with ATR inhibitor berzosertib and topotecan. *First Author: Nobuyuki Takahashi, National Cancer Institute, Bethesda, MD*

Background: Extra-pulmonary small cell neuroendocrine cancers (EP-SCNC) are rare cancers with no standard treatments at relapse that share molecular similarities with small cell lung cancer (SCLC). Concurrent inhibition of ataxia telangiectasia and Rad3 related (ATR) and topoisomerase 1, key enzymes for maintaining genomic stability, exacerbated replication stress in SCLC cells and produced durable antitumor responses in patients with relapsed SCLC (Cancer Cell 2021; PMID: 33848478). **Methods:** Combination of berzosertib and topotecan was evaluated in patients with relapsed EP-SCNC (NCT02487095). Berzosertib was administered at 210 mg/m^2 on days 2 and 5 and topotecan 1.25 mg/m^2 on days 1-5 in 21-day cycles. Whole exome sequencing (WES) and transcriptome analyses were performed to assess the genomic features associated with response. **Results:** Fifteen patients with EP-SCNC involving various primary sites were enrolled [three each: cervix, transformed SCLC; two each: bladder, breast, prostate; one each: gallbladder, ovary, rectum]. Two patients (13.3%: breast and rectum) achieved a confirmed partial response (PR; -72.2% and -48.5% tumor reduction in size) lasting 6.9 and 5.8 months. Responses occurred irrespective of platinum-sensitivity or prior treatment with topotecan or immunotherapy. Pre-treatment tumor gene expression profiles of EP-SCNC patients who achieved clinical benefit revealed enrichment of neuroendocrine differentiation (normalized enrichment score and p-value of a gene set enrichment analysis: 2.1 and 2.1 x 10^{-4}). Principal component analysis showed convergent gene expression profiles of both SCLC and EP-SCNC patients who achieved PR. Pre-treatment tumor of a breast small cell cancer patient who achieved durable response revealed amplifications of multiple genes driving replication stress such as *KRAS* and *CCND1*. Longitudinal tumor sampling of the patient through treatment course revealed increasing intratumor heterogeneity as a potential resistant mechanism. **Conclusions:** Combination of berzosertib and topotecan is a novel therapeutic paradigm for patients with EP-SCNCs. Both SCLCs and EP-SCNCs responding to this approach show a similar transcriptional phenotype characterized by high replication stress. Clinical trial information: NCT02487095. Research Sponsor: U.S. National Institutes of Health.

8519 **Poster Session**

Adjuvant icotinib versus observation in patients with completely resected, EGFR-mutated, stage IB non–small cell lung cancer (GASTO1003, CORIN): A randomized phase II trial. *First Author: Ning Li, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: The role of adjuvant therapy in patients with completely resected stage IB non-small-cell lung cancer (NSCLC) remains to be determined. Icotinib is standard-of-care therapy for patients with advanced NSCLC harboring epidermal growth factor receptor (EGFR) mutation. This phase II study investigated whether adjuvant therapy with icotinib improves the clinical outcome compared with observation in patients with EGFR mutation-positive resected stage IB NSCLC. **Methods:** This phase II, open-label, randomized study (GASTO1003, CORIN) was conducted at Sun Yat-sen University Cancer Center. From May 2013 to December 2020, patients with completely resected, EGFR mutation-positive, stage IB (7th TNM staging for NSCLC) NSCLC without adjuvant chemotherapy according to physician and patient choices were enrolled. The patients were assigned in a 1:1 ratio to receive adjuvant therapy with icotinib (125mg, three times daily) for 12 months or to undergo observation. Therapy continued until disease progression or intolerable toxicity. The primary endpoint was disease-free survival (DFS). Secondary endpoints included overall survival (OS) and toxicity. Survival endpoints were assessed in the intention-to-treat population. **Results:** Three patients withdrew consent and were excluded. A total of 128 patients were enrolled and randomized, with 63 patients in the icotinib group and 65 patients in the observation group. Baseline characteristics were well balanced between the groups. The median duration of follow-up was 34.9 months. A total of 13 recurrence events occurred, including 2 in the icotinib arm and 11 in the observation arm. DFS was significantly longer among those in the icotinib arm than among those in the observation arm (hazard ratio: 0.20, 95% confidence interval, 0.04-0.89; P = 0.018). The 3-year DFS for the icotinib and observation arms were 95.3% and 86.7%, respectively. The OS data were immature with 3 deaths in the observation arm. The safety profile was consistent with the known safety profile of icotinib. Icotinib was well tolerated with no unexpected adverse events. No treatment-related death occurred. **Conclusions:** Adjuvant icotinib shows prolonged DFS and acceptable toxicity in patients with completely resected EGFR-mutated stage IB NSCLC. Ajuvant icotinib provides a treatment option for these patients. Clinical trial information: NCT02264210. Research Sponsor: Betta pharmaceuticals.

8520 **Poster Session**

Patients' preferences for adjuvant osimertinib in non–small cell lung cancer (NSCLC) after complete surgical resection: What makes it worth it to patients? (PATT)—The Roswell Park (RP) Comprehensive Cancer Center experience. *First Author: Angel Mier-Hicks, Roswell Park Comprehensive Cancer Center, New York, NY*

Background: There are clinical controversies surrounding the US FDA approval of Osimertinib in December 2020 as adjuvant therapy, based on disease-free survival (DFS) improvement in patients (pts) with surgically resected stage IB-IIIA EGFRm NSCLC. We initiated a survey study to investigate our hypothesis that DFS benefit alone even without significant OS maybe deemed a valuable endpoint to pts after considering trade-offs. **Methods:** Participants were recruited from pts seen at the RP Thoracic Clinic from 01/21 to 12/21. Eligible pts who were being evaluated for adjuvant systemic therapy following surgical resection were given a self-administered survey based on the validated questionnaire by Blinman et al, which was modified to provide explanation of the differences between OS and DFS and the ADAURA trial results. Survey responses were collected in an online repository. Associations between survey responses and demographics were assessed using Fisher's exact test. Changes in preference responses were assessed using McNemar's test. **Results:** A total of 524 pts with NSCLC were screened, of which 101 pts were eligible to receive the survey. 51 pts (50%) responded to the survey. Median age of respondents was 69yrs (37-83), majority were female (69%, n = 35,), married (61%, n = 31), retired (63%, n = 32), had at least some college or higher education level(54%, n = 28), with history of smoking (84%, n = 43) and with stage IIIA (43%, n = 22) adenocarcinoma (80%, n = 41). To evaluate toxicity-related tradeoffs (Q1), a ≥12 mo. improvement in OS benefit was needed for 66% of pts to consider adjuvant Osi. However, an increase of ≥ 6 mo. of DFS was enough for 66% of pts to justify taking a daily medication (Q2). One mo. increase in DFS or OS was not enough for 60% and 78% of pts respectively to justify taking the medication. A threshold 1% increase in 5-year OS was sufficient to persuade patients to take Osi for three years, even with respect to toxicity side effects (p = 0.023). (Q3). Finally, in the hypothetical cost-based scenario (Q4), there was no indication that pts were willing to pay more for each incremental increase in OS. There appears to be some association between employment status (p = .033) or educational degree (p = .049) for tolerance of side effects if there is at least 1 additional year of DFS or OS. **Conclusions:** We observed that the value patients ascribe to adjuvant Osimertinib is influenced by factors besides efficacy. Knowing pts' preferences for cancer treatments can better inform regulatory bodies in formulating cost-sharing structure for cancer therapies. Our study highlights the importance of shared decision making based on individual pts' preferences. Research Sponsor: None.

8521 **Poster Session**

Predictors of adjuvant chemotherapy refusal in lung cancer: A National Cancer Database Study. *First Author: Anjan Katel, Kathmandu University School of Medical Sciences, Kirtipur, Nepal*

Background: Adjuvant chemotherapy (AC) have been shown to improve overall survival in non-small cell lung cancer (NSCLC). Despite showing significant survival benefit across various age groups, patients are known to refuse AC. However, the factors associated with such a decision remain poorly understood in lung cancer. We therefore sought to investigate the factors associated with AC refusal in a nationally representative database in the United States (US). **Methods:** From 2004 to 2017, adults (≥20 years) with histologically confirmed non-small cell lung cancer (NSCLC) who underwent complete resection and were deemed to be chemotherapy eligible (node-positive or size ≥5 cm) were identified in the National Cancer Database (NCDB). Annual trends and factors associated with refusal of AC in chemotherapy-eligible NSCLC patients were evaluated using Joinpoint regression and multivariable logistic regression. **Results:** Among the 44,957 patients who met the inclusion criteria, 18,468 (3,678 (8.2%)) were noted to refuse chemotherapy in the NCDB. Patients refusing adjuvant chemotherapy were more likely to be elderly (OR 1.08, 95% CI, 1.07-1.08; *P*< .001), uninsured when compared with government insurance (OR 1.79, 95% CI, 1.38-2.33; *P*< .001), treated in the Western region of the when compared with patients in the Northeast (OR 1.47, 95% CI, 1.28-1.68; *P*< .001). They were also more likely to have a higher Charlson score versus patients with Charlson score of zero (OR 1.31, 95% CI, 1.18-1.46; *P*< .001), have squamous cell carcinoma versus adenocarcinoma (OR 1.20, 95% CI, 1.11-1.31; *P*< .001), undergo pneumonectomy versus lobectomy (OR 1.31, 95% CI, 1.16-1.47, *P*< .001), and have ≥2 weeks hospital length of stay versus < 2 weeks (OR 2.25, 95% CI, 1.93-2.63; *P*< .001). **Conclusions:** In our analysis, we identified several sociodemographic and clinicopathologic variables that were independently associated with chemotherapy refusal. We saw the number of patients refusing AC increased sharply during the study period. Our study shows that in addition to poor post-operative recovery, underlying sociodemographic factors might predict patients at risk for refusing adjuvant chemotherapy in lung cancer. Further understanding of these factors might help devise effective interventions to motivate patients to undergo potentially life-extending chemotherapy in lung cancer. Research Sponsor: None.

8522 **Poster Session**

The Lung ART adjuvant radiotherapy phase 3 randomized trial: Impact of quality of resection in stage IIIAN2 patients. *First Author: Pascal Alexandre Thomas, Centre Hospitalier Universitaire Marseille, Marseille, France*

Background: Lung ART is an international phase 3 trial whose main objective was to evaluate the impact of post-operative conformal radiotherapy (PORT) on disease-free survival (DFS) in patients with completely resected pathologically proven N2 non-small cell lung cancer (NSCLC), with or without neo- or adjuvant chemotherapy. Previously communicated results showed no impact of PORT on DFS. However, as quality of surgical resection and extent of lymph node dissection were expected to be critically important in the interpretation of results, surgical and pathological reports were centrally reviewed by a surgical committee. **Methods:** A surgical advisory committee composed of 4 expert thoracic surgeons reviewed anonymized surgical and pathological reports of all included patients. Pre-defined classification rules were defined using published guidelines from the International Association for the Study of Lung Cancer and the European Society of Thoracic Surgeons. Tumor resection was defined as complete (no residual tumor and adequate lymph node assessment), uncertain (highest mediastinal nodal station involved, incomplete nodal exploration, involved N2 removed in fragments) or incomplete (presence of residual tumor). Nodal exploration was classified as sampling, selective dissection or extensive dissection. **Results:** 501 patients were included in the Lung ART trial. Before surgical committee review intervention, all patients except 2 had complete resection. 496 patients' reports were analyzed by the surgical advisory committee. The basic characteristics are specified in the following table: **Conclusions:** Monitoring of the quality of nodal exploration and of resection should be implemented in randomized studies evaluating peri-operative strategies in NSCLC in order to provide reliable and generalizable results. Clinical trial information: NCT00410683. Research Sponsor: French National Cancer Institute, Programme Hospitalier de Recherche Clinique from the French Health Ministry, Gustave Roussy, Cancer Research UK, Swiss State Secretary for Education, Research, and Innovation, Swiss Cancer Research Foundation, Swiss Cance.

Pre-op chemotherapy (n(%))	All included patients (n = 501)	
	96 (19%)	
	Right tumors (n = 281)	Left tumors (n = 218)
Type of surgery (n(%))		
- (bi-)lobectomy	258 (92%)	176 (81%)
- pneumonectomy	19 (7%)	36 (17%)
- other	4 (1%)	6 (3%)
Mediastinal nodes examined (median n(interquartile range))	11 (6-17)	8 (5-13)
Mediastinal nodes involved (median n(interquartile range))	2 (1-3)	1 (1-2)

Nodal dissection was performed according to lobar location specific recommendations in 69% patients. Regarding nodal dissection: 28% patients had sampling, 17% selective dissection and 55% systematic dissection. Resection was considered complete (R0) in 28%, uncertain in 42%, microscopically incomplete (R1) in 30% and macroscopically incomplete (R2) in 2 patients. 3-year DFS according to R0, R(un) and R1 status was respectively, 70% (95%CI 28-not reached (NR)), 24% (17-34) and 26% (15-84) in the PORT arm, and 62% (21-NR), 24% (15-44) and 16% (10-23) in the control arm.

8523 **Poster Session**

Checkpoint inhibitor consolidation after definitive chemoradiation for stage III non–small cell lung cancer: Real-world experience in a large academic health system. *First Author: Nikhil Yegya-Raman, University of Pennsylvania, Philadelphia, PA*

Background: The PACIFIC trial demonstrated a 10% improvement in 5-year survival with the addition of consolidation durvalumab versus placebo after chemoradiation (CRT) in good performance status patients (pts) with stage III non-small cell lung cancer (NSCLC). However, not all patients who complete CRT go on to receive consolidation durvalumab. We sought to describe real-world use of consolidation durvalumab or other immune checkpoint inhibitors (ICI) in this setting within a single academic health system. **Methods:** We retrospectively identified pts with unresectable stage III NSCLC treated with definitive CRT between October 2017 and October 2020 within the University of Pennsylvania Health System, including two urban hospitals and two satellite centers. Pts either received consolidation ICI (ICI group) or did not (no ICI group). Baseline characteristics of the groups were compared with the Chi-squared, Fisher exact, or Wilcoxon rank-sum test as appropriate. Overall survival (OS), measured from the last day of CRT, was compared using the Kaplan-Meier method and log-rank test. **Results:** Of the 148 consecutively treated pts who completed CRT, 108 (73%) received consolidation ICI; 40 (27%) did not. Within the ICI group, 42% completed 1 year (yr) of treatment. Within the no ICI group, reasons for non-receipt included disease progression (n = 14, 35%), CRT toxicity (n = 7, 18%), comorbidity or decline unrelated to CRT (n = 7, 18%), provider choice (n = 6, 15%) due to EGFR mutation (n = 5) or atypical histology (n = 1), pt refusal (n = 3, 8%), and death without progression (n = 3, 8%). The ICI group had better performance status (ECOG 0/1/2, 46%/49%/5% ICI vs 25%/48%/28% no ICI, p < 0.001) lower Charlson Comorbidity Index (median, 5 [IQR 4-6] ICI vs 6 [IQR 5-8] no ICI, p = 0.02), and lower rates of active autoimmune disease or immunosuppression (5% ICI vs 15% no ICI, p = 0.03). There were no differences between groups in age (median, 68 yrs [IQR 63-73] ICI vs 71 yrs [IQR 65-73] no ICI, p = 0.25), sex (female, 60% ICI vs 50% no ICI, p = 0.27), race (Black, 19% ICI vs 20% no ICI, p = 0.82), stage (IIIA/B/C, 42%/48%/11% ICI vs 40%/50%/10% no ICI, p = 0.96), and PD-L1 expression (< 1%/1-50%/ > 50%/unknown, 36%/25%/29%/10% ICI vs 40%/25%/28%/8% no ICI, p = 0.97). 1- and 2-yr OS were 83% and 61% in the ICI group versus 52% and 34% in the no ICI group, respectively (p < 0.001). Within the no ICI group, OS was worse among those with versus those without disease progression (PD) post-CRT (1-yr OS 24% vs 74%, p = 0.03). **Conclusions:** In this retrospective study within a large academic health system, we found that over one-quarter of pts who completed chemoradiation for stage III NSCLC did not receive consolidation ICI, most commonly due to disease progression, CRT toxicity, or comorbidity. Survival amongst these pts is particularly poor, especially for those who experience PD shortly after CRT. Research Sponsor: None.

8524 **Poster Session**

Analysis of patients with relapsed small cell lung cancer (SCLC) receiving single-agent lurbinectedin in the phase 3 ATLANTIS trial. *First Author: Alejandro Navarro, Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain*

Background: Lurbinectedin, a selective inhibitor of oncogenic transcription, received accelerated approval from the US FDA in June 2020 as monotherapy (3.2 mg/m^2 IV every 21 days) for adults with metastatic SCLC with disease progression on or after platinum-based chemotherapy. This approval was based on the overall response rate (35.2%) and duration of response (DOR; 5.3 months) observed in 105 patients from a phase 2 trial. The ATLANTIS trial (NCT02566993) investigated the combination of lurbinectedin 2.0 mg/m^2 IV + doxorubicin (DOX) 40.0 mg/m^2 IV versus topotecan or CAV. This *post hoc* analysis explored the efficacy and safety of single-agent lurbinectedin in patients who completed 10 cycles of the combination and then switched to lurbinectedin monotherapy per protocol. **Methods:** Eligible patients were ≥18 years of age with limited-stage or extensive-stage SCLC, 1 prior line of platinum-based chemotherapy (PD-1/PD-L1 inhibitors were also permitted), ECOG PS ≤2, and chemotherapy-free interval ≥30 days. Tumor assessments were per an independent review committee (IRC). **Results:** Patients who completed 10 cycles of lurbinectedin + DOX and switched to lurbinectedin monotherapy (n = 50) had a median age of 61.5 years (range: 43, 77); 62% were male; and 100% had an ECOG PS < 2. The overall median number of cycles was 15 (range: 11, 47) and included a median of 5 (1, 37) cycles on monotherapy. The majority of patients who switched to lurbinectedin monotherapy maintained or improved their tumor response (**Table**). All 3 patients who achieved a complete response (CR) on combination therapy maintained their CR on monotherapy. Of the 26 patients with a partial response (PR) on combination therapy, 3 (12%) achieved a CR and 15 (58%) maintained their PR. Of the 19 patients with stable disease (SD) on combination therapy, 3 (16%) improved from SD to PR (n = 2) or CR (n = 1) and 8 (42%) maintained SD. The median DOR was 8.3 months (95% CI: 7.1, 11.0). The median overall survival (OS) was 20.7 months (95% CI: 15.7, 24.8). Grade 3/4 hematologic abnormalities based on laboratory assessment included lymphopenia (36%), anemia (16%), thrombocytopenia (12%), neutropenia (12%), and leukopenia (10%). Febrile neutropenia was reported in 4% of patients. **Conclusions:** Patients with relapsed SCLC in ATLANTIS who completed 10 cycles of lurbinectedin + DOX combination and switched to lurbinectedin monotherapy tended to maintain or improve their tumor response (including an increase in CRs), with favorable OS and DOR and acceptable tolerability with no new safety signals. Clinical trial information: NCT02566993. Research Sponsor: PharmaMar.

	Best response to lurbinectedin monotherapy (3.2 mg/m^2; n = 50), n[a]				
Best response to lurbinectedin + DOX, n	**CR**	**PR**	**SD**	**PD**	**Total**
CR	3	–	–	–	3
PR	3	15	–	8	26
SD	1	2	8	8	19
Total	7	17	8	16	48[b]

PD, progressive disease.
[a]41 patients at 3.2 mg/m^2, 3 patients at 2.6 mg/m^2, and 6 patients at 2.0 mg/m^2.
[b]2/50 patients did not have a tumor assessment on monotherapy per IRC.

8525 **Poster Session**

A real-world (rw) evidence study quantifying the clinical value of multi-gene testing in early-stage lung adenocarcinoma (LUAD). *First Author: Nathan A. Pennell, Cleveland Clinic, Cleveland, OH*

Background: Resected early-stage NSCLC has high risk of recurrence, and tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICI), each requiring testing for precision biomarkers, have recently been approved in the adjuvant (adj) setting. We assessed the potential value of multi-gene testing in early NSCLC via enabling timely 1L therapy selection at recurrence and through avoidance of adj ICI in pts with driver alterations unlikely to benefit per current guidelines and the label for atezolizumab in first line (1L) NSCLC. **Methods:** Using the nationwide (~280 US cancer clinics) de-identified EHR-derived rw Flatiron Health- Foundation Medicine clinico-genomic database, we selected 6,725 evaluable pts with LUAD who underwent tissue comprehensive genomic profiling (CGP) as part of routine cancer care (01/2011 – 06/2021). We focused on alterations in 4 drivers (*EGFR*, *ALK*, *ROS1*, *RET*) and studied prevalence in early-stage specimens versus advanced (adv) specimens, as well as the rate of timely delivery of 1L therapy at recurrence for pts receiving CGP in early disease. We estimated the cost implications of adj ICI in pts with PD-L1+ LUAD and an *ALK*, *ROS1*, or *RET* fusion with a probabilistic decision tree. **Results:** CGP was performed on 1,490 specimens collected prior to adv disease (stage I 36%, II 27%, IIIA 37%) and ordered prior to adv diagnosis for 981 pts (15% of total, median 10 weeks after initial diagnosis). In specimens collected in early (n = 1,490) or adv (n = 5,130) stage LUAD, CGP identified drivers in *EGFR* (early/adv: 13%/16%), *ALK* (2.0%/4.2%), *ROS1* (0.7%/1.1%), *RET* (1.0%/1.1%), and prevalence was similar when limiting to PD-L1+ cases. Studying 596 pts with recurrence and CGP on samples collected prior to recurrence, pts with CGP results obtained before (n = 196) vs after (n = 400) recurrence had less time between recurrence and start of any 1L therapy (median 3.1 vs 5.9 weeks, $p < 0.001$). In the subset with a targetable driver detected, 32/42 (76%) with CGP before recurrence initiated matched 1L TKI while 43/67 (64%) with CGP after recurrence received matched 1L TKI ($p = 0.2$). Through avoidance of ICI in PD-L1+ early LUAD with an *ALK*/*ROS1*/*RET* driver, we estimate universal CGP (compared to *EGFR* single-gene testing) could reduce per pt expected costs by $875 (an average incremental $4,050 treatment cost reduction compared to a $3,175 increase in diagnostic cost per pt). **Conclusions:** CGP of early-stage LUAD can identify *EGFR*, *ALK*, *ROS1* and *RET* drivers and enable appropriate selection of precision therapies and timely use of effective 1L therapy at recurrence. Assuming adj ICI maintains the lack of activity in *RET*/*ROS1* as seen for *ALK*, CGP could represent a cost-effective approach for avoiding futile adj ICI and reducing the risk of subsequent TKI-associated toxicity. Additional analysis of driver+ pts receiving adj ICI is needed to help balance the risk/benefit for these high risk pts. Research Sponsor: Foundation Medicine.

8526 **Poster Session**

Racial disparities in the clinical use of durvalumab for patients with stage III unresectable non–small cell lung cancer treated at Veterans Health Administration facilities. *First Author: Amanda Moore, College of Pharmacy, The University of Texas at Austin, Austin, TX*

Background: Evidence from the PACIFIC study and real-world data highlight the benefit of durvalumab in patients with stage III unresectable non-small cell lung cancer (UR-NSCLC). However, limited literature exists regarding disparities in durvalumab treatment patterns such as treatment initiation delays (TID), treatment interruptions (TI), number of doses, duration of therapy (DOT), adverse effects (AEs), and treatment discontinuation (TD) in minority populations. **Methods:** Patients with stage III UR-NSCLC and a self-reported racial identity of Black or White treated with durvalumab following chemoradiotherapy (CRT) at any Veterans Health Administration (VHA) facility from January 1, 2017 to June 30, 2020 were included. Patients were followed from their date of durvalumab initiation through the earliest of their last VHA visit, loss to follow up, death, or end of the study; therefore, all patients had the opportunity to be treated for 12 months. Patients were excluded if durvalumab therapy was ongoing at the end of the study. Patient charts were retrospectively reviewed for baseline characteristics and durvalumab treatment patterns including TID (>42 days from end of CRT to durvalumab start), TI (>28 days between doses), number of doses, DOT, AEs, and TD. Nominal variables were compared using chi-square/Fisher's exact tests. Continuous variables were compared using Student's t-tests/Wilcoxon Rank Sum tests. **Results:** Among 924 patients, Black patients were younger than White patients (median age 67 years [IQR, 63-71] vs. 70 years [IQR, 65-73]; $p<0.01$), more likely to be current smokers (54% vs. 45%; $p=0.03$), with more chronic liver disease (22% vs. 9%; $p<0.01$), but less COPD (63% vs. 72%; $p=0.01$). Black patients experienced more TI (25% vs. 18%; $p=0.03$) but TID, number of doses, DOT, and TD were similar between the groups. Black patients were less likely to have an immune-related AE (irAE) (28% vs. 36%; $p=0.03$) (and less pneumonitis (7% vs. 14%; $p<0.01$)). Toxicity was the reason for TD in 12% of Black patients vs. 20% of White patients ($p=0.01$), with no other significant ($\alpha < 0.05$) differences in reported reasons for TID, TI, or TD between the groups. **Conclusions:** In this real-world study, Black patients experienced similar TID, number of doses, and DOT as White patients. Black patients were less likely to experience an irAE (including pneumonitis) but experienced more TI; TD were similar but more likely to be from toxicity for White patients. Future research is needed to validate these findings. Research Sponsor: AstraZeneca.

Race and durvalumab treatment patterns.

Outcome	White (n=726)	Black (n=198)	P-value
Patients with TID	38%	45%	0.07
Patients with TI	18%	25%	0.03
Number of doses, median (IQR)	15 (7-24)	18 (7-25)	0.25
DOT (months), median (IQR)	8.7 (2.9-11.8)	9.8 (3.6-12.0)	0.08
Patients with irAEs	36%	28%	0.03
Pneumonitis	14%	7%	<0.01
Patients with TD	60%	54%	0.09

8527 **Poster Session**

PD-L1 score as a prognostic biomarker in Asian patients with early-stage, EGFR-mutated lung cancer. *First Author: Stephanie Saw, National Cancer Centre Singapore, Singapore, Singapore*

Background: Adjuvant Atezolizumab was recently approved in stage II-IIIA non-small cell lung cancer (NSCLC) with PD-L1 ≥1%. However, disease-free survival (DFS) benefit was mainly driven by PD-L1 ≥50% and among *EGFR*-mutated subgroup, atezolizumab did not demonstrate DFS benefit when PD-L1 0% patients were included. We sought to determine the prognostic value of PD-L1 score in early-stage *EGFR*-mutated NSCLC. **Methods:** Consecutive patients with Stage IA-IIIA NSCLC diagnosed 1/1/2010 – 31/12/2019 who underwent curative surgery at National Cancer Centre Singapore with evaluable *EGFR* and PD-L1 status were included. Co-primary endpoints were 2-year DFS and 5-year overall survival (OS) by Kaplan-Meier method. **Results:** 455 patients were included (267 *EGFR*-mutant; 188 *EGFR*-wildtype). Median age at diagnosis was 65 years, 52.3% (238/455) were males and 62.9% (286/455) were never-smokers. Adenocarcinomas comprised 92.1% (419/455) and 92.5% (421/455) had R0 resection. Stage IA comprised 42.4% (193/455), Stage IB 23.1% (105/455), Stage II 15.8% (72/455) and Stage IIIA 18.7% (85/455). Among *EGFR*-mutant, 45.3% (121/267) were Ex19del and 41.9% (112/267) were L858R. PD-L1 ≥1% among *EGFR*-mutant and *EGFR*-wildtype was 55.8% (149/267) and 60.1% (113/188) respectively ($p = 0.361$). PDL1 ≥50% was significantly associated with higher stage at diagnosis among *EGFR*-mutant ($p < 0.001$) but not *EGFR*-wildtype ($p = 0.319$). At median follow up of 47 months, 178 patients had relapsed. Among *EGFR*-mutant, 2-year DFS comparing PD-L1 0% and PD-L1 ≥1% was 79.0% and 68.9% ($p = 0.006$) while 5-year OS was 87.6% and 70.6% ($p = 0.006$) respectively. 2-year DFS and 5-year OS by PD-L1 tertile (as shown in table) revealed that higher PD-L1 score was prognostically worse for both DFS and OS among *EGFR*-mutant. A similar trend was observed among *EGFR*-wildtype but did not reach statistical significance, apart from PD-L1 ≥50% which had significantly inferior DFS. **Conclusions:** Higher PD-L1 score was significantly associated with worse DFS and OS among early-stage *EGFR*-mutated NSCLC, possibly due to higher stage at diagnosis among PDL1 ≥50%. Our study highlights the poor prognosis of PDL1 ≥50% *EGFR*-mutated NSCLC in a pre-osimertinib era and underscores the importance of personalised risk-stratified adjuvant strategies. Research Sponsor: Singapore National Medical Research Council (NMRC; grant No. NMRC/TCR/007-NCC/2013 and NMRC/OFLCG/002-2018).

		2-year DFS (95% CI)	HR (95% CI)	p value	5-year OS (95% CI)	HR (95% CI)	p value
***EGFR*-mutant**	PD-L1 0% (n = 118)	79.0% (70.3%-85.4%)	1		87.6% (77.4%-93.4%)	1	
	PD-L1 1-49% (n = 133)	71.9% (63.4%-78.8%)	1.58 (1.06-2.36)	0.025	70.6% (56.5%-80.9%)	2.38 (1.18-4.82)	0.016
	PD-L1 ≥50% (n = 16)	43.8% (19.8%-65.6%)	2.89 (1.51-5.53)	0.001	68.7% (34.3%-87.7%)	3.14 (1.17-8.43)	0.023
***EGFR*-wildtype**	PD-L1 0% (n = 75)	76.8% (65.3%-84.9%)	1		76.9% (62.5%-86.4%)	1	
	PD-L1 1-49% (n = 71)	70.6% (58.3%-80%)	1.41 (0.85-2.35)	0.179	61.7% (42.9%-75.9%)	1.17 (0.61-2.21)	0.639
	PD-L1 ≥50% (n = 42)	42.2% (26.8%-56.8%)	2.22 (1.30-3.81)	0.004	57.2% (39.6%-71.4%)	1.64 (0.85-3.17)	0.141

8528 **Poster Session**

Pre-existing interstitial lung abnormalities are independent risk factors for interstitial lung disease during durvalumab treatment after chemoradiotherapy in patients with locally advanced non–small lung cancer. *First Author: Wakako Daido, Department of Respiratory Medicine, Hiroshima University Hospital, Hiroshima, Japan*

Background: The standard treatment for locally advanced non-small cell lung cancer (NSCLC) is chemoradiotherapy (CRT) followed by treatment of durvalumab, one of immune checkpoint inhibitors (ICI). Interstitial lung disease (ILD) is a clinically life-threatening toxicity of CRT or durvalumab. The patient-characteristics or dose-volume histogram parameters of radiotherapy have been reported to be the risk factors for radiation-induced pneumonitis. However, the risk factors for ILD during durvalumab therapy has not been established. Interstitial lung abnormalities (ILA) are generated by aging or smoking, and manifest as minor interstitial shadow on lung computed tomography (CT). We previously reported that ILA were risk factors for ICI-induced ILD in patients with advanced NSCLC, as well as non-lung cancer. Therefore, we investigated whether ILA could be risk factors for ILD during the durvalumab therapy. **Methods:** We retrospectively enrolled NSCLC patients who received durvalumab after CRT at 10 institutions from July 2018 to June 2021. Patient-information, patient-characteristics, dose-volume histogram parameters, chest CT findings, and laboratory data, were obtained. CT findings were examined using CT obtained after CRT and prior to durvalumab therapy. **Results:** A total of 153 patients were enrolled, and the prevalence of ILA was 37.8% (56 patients) before durvalumab treatment. Among the enrolled patients, 94 (63.5%) developed ILD during durvalumab therapy. The proportion of patients with grade 1, grade 2, or grade 3 ILD was observed to be 29.7% (44 patients), 25.7% (38 patients), and 8% (12 patients), respectively. Univariate logistic regression analysis revealed that higher age, higher dose volume histogram parameters (V5, V20, mean lung dose), and the presence of ILA were significant risk factors for grade 2 or more ILD. Multivariate logistic regression analysis showed that ILA, especially ground grass attenuation in ILA, was an independent risk factor for grade 2 or more ILD (odds ratio: 7.02, 95% CI: 2.95-16.69, $p < 0.0001$). **Conclusions:** Pre-existing ILA are risk factors for ILD during durvalumab treatment after CRT. This observation is consistent with previously reported findings in patients with advanced lung cancer and non-lung cancer. Therefore, we should pay more attention to the development of grade 2 or more ILD during durvalumab treatment in patients with ILA. Research Sponsor: None.

8529 **Poster Session**

Observer performance study to examine the feasibility of the AI-powered PD-L1 analyzer to assist pathologists' assessment of PD-L1 expression using tumor proportion score in non–small cell lung cancer. *First Author: Seokhwi Kim, Department of Pathology, Ajou University School of Medicine, Suwon, South Korea*

Background: Programmed death ligand 1 (PD-L1) expression is the standard biomarker for PD-L1 inhibitors in advanced non-small cell lung cancer (NSCLC). However, evaluation of PD-L1 tumor proportion score (TPS) by pathologists causes inter-observer variation and demands time to interpret. This study aimed to evaluate the benefit of the artificial intelligence (AI) algorithm in assisting pathologists to determine TPS on PD-L1 immunohistochemistry (IHC) whole-slide images (WSIs) in NSCLC. **Methods:** Lunit SCOPE PD-L1, an AI-powered PD-L1 TPS analyzer, was developed from 393,565 tumor cells annotated by board-certified pathologists for PD-L1 expression in 802 WSIs stained by 22C3 pharmDx IHC. The AI model was developed based on a region-based convolutional neural network, and the model can detect and count PD-L1 positive or negative tumor cells from WSIs to calculate TPS. Seven independent board-certified pathologists scored ground truth (GT) of PD-L1 TPS from 199 WSI of NSCLC stained by 22C3 pharmDx IHC. TPS from each GT reader was grouped as negative (< 1%), low (1% to 49%), or high (≥ 50%). The GT of each slide was determined by the consensus of GT readers. Another twelve independent board-certified pathologists scored PD-L1 TPS from the same WSIs as observer performance testers (OPT). They scored TPS twice with a washout interval of 4 weeks, with or without AI assistance. TPS accuracy change and reading time of OPT reader according to the presence or absence of AI assistance were analyzed. **Results:** The standalone accuracy of the AI model was 0.809 (95% CI: 0.690–0.941). With AI assistance, the overall accuracy of TPS had been changed from 0.799 (95% confidence interval [CI]: 0.764–0.836) to 0.832 (95% CI: 0.796–0.869) (P = 0.004). AI assistance increased the accuracy rate in 11 out of 12 OPT readers. The result of the generalized linear mixed model revealed that AI assistance and specimen type affected the probability of correct answer, while the order of reading did not (Table). The mean time to read with AI was 195.4±506.5 (mean±standard deviation) seconds, which was significantly shorter than the mean time to read without AI (285.1±1578.4, P <0.001). **Conclusions:** This study demonstrates that an AI-powered PD-L1 TPS analyzer can assist board-certified pathologists in evaluating TPS of NSCLC by improving the accuracy of TPS group evaluation and reducing the time to read slides. Research Sponsor: Lunit Inc.

Generalized linear mixed model of various factors that can influence the result of evaluating the correct TPS group.

Factors	Odds ratio	95% confidence interval	z-value	P-value
With artificial intelligence assistance (vs. without artificial intelligence assistance)	1.241	1.071, 1.438	2.879	0.004
2nd session (vs. 1st session)	1.060	0.915, 1.228	0.774	0.439
Surgical resection (vs. Core needle biopsy)	0.661	0.566, 0.772	-5.263	<0.001

8530 **Poster Session**

Driver coexistence characteristics of ALK-fusion in Chinese patients with lung cancer. *First Author: Min Gao, Shandong Cancer Hospital Affiliated to Shandong University, Jinan, China*

Background: *ALK* fusions and other driver mutations are usually mutually exclusive. With the widespread application of genetic testing techniques, the coexistence of *ALK* fusions and other driver mutations could be detected, such as *ALK* fusion and EGFR driver mutations. However, there were no systematical studies about the coexistence of *ALK* fusions and other driver mutations. Here, we retrospectively investigated the coexistence of ALK fusions and other driver mutations. **Methods:** Samples with *ALK* fusions were extracted from a Chinese lung cancer cohort, which from OncoPanscan (Genetron Health) based sequencing of tissue. Driver mutations of *EGFR*, *ROS1*, *RET*, *NTRK1/2/3*, *BRAF*, *MET*, *KRAS* and *ERBB2* could be detected. **Results:** In the cohort, 692 samples with *ALK* fusions contained the intact kinase domain. These samples could be classified into three forms: canonical fusions (only *EML4* partner, n = 601), single non-canonical fusions (only non-*EML4* partner, n = 51) and complex non-canonical fusions (two or more partners, n = 40). Among the 692 samples, only 20 samples (20/692, 2.89%) coexisted with other driver mutations, which indicated that the driver coexistence were rare. 70% (14/20) of driver coexistence were happened on canonical fusions (*EML4-ALK*) samples. They were coexisting with *EGFR* L858R (3), *EGFR* L858R plus *ROS1* fusion (1), *EGFR* L858R plus *MET* amplification (1), *KRAS* G12C/D/*N* (3), *MET* amplification (3), *MET* Exon14 skipping (1), *ERBB2* amplification (1), and *MET* amplification plus *ERBB2* amplification (1), respectively. 20% (4/20) of driver coexistence samples were single non-canonical ALK fusions coexisting with *EGFR* 19del (1) or 20ins (1) or L858R (1) or *MET* amplification (1). Another 10% (2/20) samples were complex non-canonical *ALK* fusions coexisting with *EGFR* G719S (1) or *RET* fusion (1). Most co-mutations have corresponding targeted inhibitors, maybe these patients can be treated by combined or sequential therapies. Among canonical fusions, single non-canonical fusions and complex non-canonical fusions of *ALK*, the frequency of the samples without coexistence of driver mutations was respectively 97.67% (587/601), 92.16% (47/51), 95.00% (38/40), without significant difference (P = 0.056). Maybe single/complex non-canonical fusions are also strong drivers as canonical fusions. **Conclusions:** In this cohort, very few of *ALK* fusion patients coexisted with other driver mutations. Among the co-existence samples, *ALK* fusion were mainly coexisting with the site mutations of *EGFR* and *KRAS*, amplifications of *MET* and *ERBB2*, fusions of *ROS1* and *RET*. These samples maybe obtain more effective outcomes by combined or sequential therapies. Research Sponsor: None.

8531 **Poster Session**

Spatial meta-transcriptomics reveal intratumor bacterial association with lung cancer cells showing a distinct oncogenic signature. *First Author: Chen Zhao, Thoracic and Gastrointestinal Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD*

Background: The lung intratumor microbiome influences lung cancer tumorigenesis and treatment responses, but detailed data on the extent, location, and effects of microbes within lung tumors is missing, information needed to improve treatment outcomes and prognosis. **Methods:** To address this gap, we developed a novel spatial meta-transcriptomic method simultaneously detecting the expression level of 1,811 host genes and three microbe targets (16S rRNA, 28S rRNA and CMV). After rigorous validation, we analyzed the spatial meta-transcriptomic profiles of tumor cells, T cells, macrophages, other immune cells, and stroma in tumor samples from 12 patients with early-stage lung cancer. **Results:** Bacterial burden was significantly higher in tumor cells compared to T cells, macrophages, other immune cells, and stroma. This burden increased from tumor-adjacent normal lung and tertiary lymphoid structures to tumor cells to the airways, suggesting that lung intratumor bacteria derive from the latter route of entry. Expression of oncogenic β-catenin and epithelial-mesenchymal transition pathway genes was strongly correlated with bacterial burden, as were tumor subtypes, mutation profile, histology and smoking history. **Conclusions:** Intratumor bacteria were enriched with tumor cells and associated with multiple oncogenic pathways, supporting a rationale for reducing the local intratumor microbiome in lung cancer to optimize clinical outcomes. This research was supported in part by the Intramural Research Programs of the NCI and NIAID. Other funding sources included ASCO Young Investigator Award, SITC-AstraZeneca Immunotherapy in Lung Cancer (Early Stage NSCLC) Clinical Fellowship Award, NIH Bench-to-Bedside and Back Program (BtB), NCI R00 award (CA226400), Emerson Collective Cancer Research fund, Lung Cancer Research Foundation (LCRF) pilot grant and W.W. Smith Trust Foundation award. This study was approved by NCI institutional review board (NCT00242723 and NCT02146170) and Animal Use and Care Committee at the University of Pennsylvania (#806875). Research Sponsor: U.S. National Institutes of Health, Conquer Cancer Foundation of the American Society of Clinical Oncology, Other Foundation, Other Government Agency, ASCO YIA 2019.

8532 **Poster Session**

Low skeletal muscle area and association with toxicity and hospitalization with chemotherapy in advanced non–small cell lung cancer. *First Author: Anurag Saraf, Harvard Radiation Oncology Program, Boston, MA*

Background: Significant toxicity is common in the treatment of advanced non-small cell lung cancer (NSCLC) and can be associated with adverse events, such as unplanned hospitalization, and worse clinical outcomes. Baseline low skeletal muscle (SM) area is a marker of sarcopenia and has been associated with worse survival in other malignancies, but the association of SM area and toxicity in NSCLC is less studied. **Methods:** Patients with locally advanced or oligo-metastatic NSCLC treated with combined chemotherapy and radiotherapy with or without surgery from 2002-2013 at a single institution were reviewed. A deep-learning pipeline utilized existing pre-treatment computed tomography scans to calculate SM area at the 3rd lumbar vertebral level. Gold standard SM index (SMI) was calculated, adjusting for height, sex, and dichotomized per previously validated cut-off values. Grade 3 or higher hematologic (G3+ heme) toxicity, was assessed per NCI CTCAE v5.0, within 21-days of first chemotherapy cycle. Hospital use was defined as unplanned ED visit or inpatient hospitalization during chemotherapy. Multivariate analysis (MVA) of toxicity endpoints with SMI and baseline characteristics were analyzed by logistic regression analysis, and with overall survival (OS) using Cox regression analysis. **Results:** A total of 369 patients met inclusion criteria with median follow-up of 23.0mo (range 1-193mo), median age of 64y (range 29-88y), and were mostly male (51%). Most were clinical stage (AJCC 7th edition) IIIA (44%), IIIB (31%), or IV (10%), while 10% had upfront surgery and adjuvant chemotherapy. Most common regimen was cisplatin-based (48%). Median OS was 25.5mo and PFS was 14.0mo. Patients with low SMI were more likely to be younger (median age 70y vs 62y), ECOG performance status (PS) > 0 (74% vs 59%), lower BMI (median BMI 23.3 vs 27.7), and not receive cisplatin-based regimen (35% vs 53%). There was no difference in histology, stage, surgery, or every 3-week (q3w) chemotherapy dosing. On MVA, low SMI was associated with increased risk of G3+ heme toxicity (OR 1.74, p = 0.04) and increased hospital use (OR 1.79, p = 0.04). G3+ heme toxicity was also associated with surgery and q3w dosing, but not age, PS, BMI, or regimen. Hospital use was also associated with BMI, surgery, and cisplatin-based regimen, but not age, PS, or q3w dosing. G3+ heme toxicity (HR 1.48, p < 0.01), older age (HR 1.02, p = 0.02), and stage 4 (HR 3.32, p < 0.01) were associated with worse survival on MVA, but not low SMI (HR 1.25, p = 0.11), PS, BMI, surgery, or regimen. **Conclusions:** Low SMI predicted higher risk of G3+ toxicity during first cycle of chemotherapy. High-risk patients with low SMI experienced significant adverse events and should be considered for more aggressive symptom management or alternative treatment strategies. Research Sponsor: U.S. National Institutes of Health.

8533 **Poster Session**

Postoperative ctDNA in indicating the recurrence risk and monitoring the effect of adjuvant therapy in surgical non–small cell lung cancers. *First Author: Xiaoru Tian, Xuanwu Hospital Captical Medical University, Beijing, China*

Background: Circulating tumor DNA (ctDNA) has emerged as a potential novel biomarker to predict molecular residue disease in lung cancer after definitive treatment. Herein, we investigated the value of ctDNA in prognosing risk of relapse and monitoring the effect of adjuvant therapy in surgical non-small cell lung cancer (NSCLC) patients. **Methods:** Forty-one surgical NSCLC patients were enrolled. Tumor tissues were collected at surgery and subjected to targeted NGS of 1021 cancer-related genes. The serial peripheral blood samples were collected at postoperative one month and then at every third or sixth month and subjected to ultra-deep targeted NGS covering 338 genes. **Results:** From 41 eligible patients including 18 patients with stage I disease, 2 with stage II and 21 with stage III, 41 tumor tissues and 137 plasma samples were enrolled and successfully tested. In tissue samples, 323 somatic variations were identified, with a median of 8 (range, 1-21) gene variations detected in each patient. *TP53* was the most common mutation (63.41%), followed by *EGFR* (58.53%), *LRP1B* (17.07%) and *KRAS* (14.63%). The first-postoperative ctDNA positive was found in 13 of 41 patients (31.71%), 9 stage III, 2 stage II and 2 stage I. During a median 9.47 months follow-up, 38.46% (5/13) patients with detectable ctDNA in the first postoperative blood sample experienced recurrence, while 3.57% (1/28) patients with undetectable ctDNA ultimately recurred. The DFS can be stratified by the first-postoperative ctDNA status, with ctDNA-positive groups having significantly reduced DFS ($p < 0.05$). We detected ctDNA in at least one time point after surgery in 17 patients (41.46%), 5 of them (29.41%) experienced recurrence. Twenty-four patients without ctDNA detection during postoperative surveillance, one (4.17%) of them ultimately recurred. Serial ctDNA detection revealed disease recurrence ahead of radiologic imaging by a median of 5.25 months (range, 0.98-14.19). Among the 41 patients, 6 patients had surgery alone, 35 patients received adjuvant therapy. For these 35 patients, ctDNA analysis can stratify patients before and after adjuvant therapy. Recurrence ratio was 33.33% (4/12) in patients with detectable and 4.34% (1/23) in patients with undetectable ctDNA before adjuvant therapy. For ctDNA analysis after adjuvant therapy, no patients (11/11) with negative ctDNA had disease-recurrence while 33.33% (1/3) patients with positive ctDNA experienced recurrence. All four patients with clearance ctDNA by adjuvant therapy remained disease free. **Conclusions:** For NSCLC patients, postoperative ctDNA is a prognostic marker, which reveals disease recurrence ahead of radiographic examination. Importantly, ctDNA-detecting may facilitate personalized adjuvant therapy, and applying adjuvant therapy to the patients with detectable ctDNA could bring clinical benefits for them. Research Sponsor: None.

8534 **Poster Session**

Analysis of circulating tumor DNA in the phase 2 BTCRC LUN 16-081 trial of consolidation nivolumab with or without ipilimumab after chemoradiation in stage III non–small cell lung cancer. *First Author: Soyeong Jun, Stanford Cancer Institute, Stanford University, Stanford, CA*

Background: The current standard of care for patients with inoperable stage III non-small cell lung cancer (NSCLC) includes chemoradiation (CRT) followed by up to 1 year of checkpoint inhibitor (CPI) therapy. However, many patients are not able to complete 1 year of treatment and the optimal duration of consolidation therapy remains unknown. Identifying minimal residual disease (MRD) via detection of circulating tumor DNA (ctDNA) may help inform the optimal duration of treatment. Here we report the results of a preplanned correlative study evaluating the association between detectable ctDNA and survival outcomes from the BTCRC LUN 16-081 phase 2 trial of consolidation nivolumab or nivolumab plus ipilimumab following CRT in patients with unresectable Stage III NSCLC (NCT03285321). **Methods:** Following CRT, patients with unresectable stage IIIA/B NSCLC were randomized 1:1 to receive nivolumab 480 mg IV Q4weeks for up to 6 cycles or nivolumab 240 mg IV Q2weeks plus ipilimumab 1 mg/kg IV Q6weeks for up to 4 cycles. Plasma samples for ctDNA analysis were collected after completion of CRT, prior to C2D1 of CPI, and at the end of treatment or withdrawal from the study. Tumor genotyping and ctDNA analysis were performed using CAPP-Seq with a panel targeting 260 genes recurrently mutated in NSCLC. Patient-specific tumor variants were identified using tumor tissue or baseline plasma and matched leukocyte DNA samples. Tumor variants were then monitored in plasma samples using a tumor mutation-informed bioinformatic strategy. **Results:** Thirty-nine patients received either nivolumab (n = 25; cycles: median = 6, range 1-6), or nivolumab plus ipilimumab (n = 14; cycles; median = 2, range = 1-6). Patients with detectable ctDNA MRD after completion of CRT demonstrated significantly inferior progression free survival (PFS) than patients who were MRD-negative (12-month 29% vs 76%, 24-month 29% vs 68%, $P = 0.003$), prior to C2D1 of CPI (12-month 0% vs 85%, 24-month 0% vs 72%, $P < 0.0001$) and at the end of CPI (12-month 14% vs 90%, 24-month 14% vs 79%, $P < 0.0001$). Patients with undetectable ctDNA MRD at the end of CPI (median cycles = 5.5; range 1-6) demonstrated 24-month overall survival of 91%. Additionally, patients with decreasing or undetectable ctDNA levels after one cycle of CPI had improved outcomes compared to patients with increasing ctDNA levels (24-month PFS 73% vs 0%, $P < 0.0001$). Progression of disease occurred within 10.8 months of starting CPI in all patients with increasing ctDNA levels at C2D1. **Conclusions:** Detectable ctDNA before, during, and after consolidation CPI is strongly associated with inferior survival outcomes. Furthermore, less than 12 months of CPI consolidation can result in MRD negativity and high rates of long term PFS. Clinical trial information: NCT03285321. Research Sponsor: U.S. National Institutes of Health.

8535 **Poster Session**

Monitoring PD-L1 expression on circulating stromal cells in blood predicts PFS and OS in patients with metastatic NSCLC treated with PD-L1/PD-1 immunotherapy. *First Author: Jillian Moran, Creatv MicroTech, Inc., Monmouth Junction, NJ*

Background: Cancer Associated Macrophage Like cells (CAMLs), a circulating stromal cell found in cancer patients (pts) blood, are phagocytic giant macrophages that appear to parallel the inflammatory PD-L1 state of the tumor microenvironment. Previously, we demonstrated in local non-small cell lung carcinoma (NSCLC), CAML PD-L1 expression is dynamic and predicts response to PD-L1/PD-1 immunotherapies (IMTs) following sequential sampling before and after chemotherapy (chemo) induction (~30days) based on progression free (PFS) & overall survival (OS). However this has not been tested in metastatic NSCLC (mNSCLC). Here,we report the results of monitoring PD-L1 expression in CAMLs before and after chemo induction (~30 days) to evaluate its predictive value in mNSCLC pts treated with or without IMT. **Methods:** A single blind multi-year prospective study was undertaken to test the relationship of PD-L1 expression in CAMLs to PFS & OS, pre & post chemo induction, in recurrent mNSCLC with (n = 41) or without (n = 41) additional anti-PD-L1/PD-1 IMTs. This included three IMTs: atezolizumab (n = 4), nivolumab (n = 8) or pembrolizumab (n = 29). We recruited 82 pts with pathologically confirmed recurrent mNSCLC prior to treatment for newly recurrent metastatic disease. Blood samples (15 mL) were taken at Baseline (BL), prior to chemo, and ~30 days after chemotherapy (T1). Blood was filtered by CellSieve filtration & CAMLs' expression scored as a binary high/low, to evaluate PFS & OS hazard ratios (HRs) by censored univariate & multivariate analysis at 18 months. **Results:** CAMLs were found in 97% of all tested samples, 94% at BL & 100% at T1. CAML PD-L1 at BL was found not to be associated with PFS or OS in pts treated with chemo alone (PFS p = 0.620 & OS p = 0.673) or chemo+IMT (PFS p = 0.353 & OS = 0.477) at 18 months. At T1, high CAML PD-L1 in pts treated with chemo alone had no significantly different PFS (HR = 1.3, p = 0.694) or OS (HR = 1.6 p = 0.503). However, high CAML PD-L1 at T1 in pts treated with chemo+IMT had significantly better PFS (HR = 3.1, 95%CI = 1.3-7.3, p = 0.019), and OS (HR = 3.4, 95%CI = 1.4-8.3, p = 0.014). Further subtyping & analysis is ongoing to evaluate PFS and OS at 24 months. **Conclusions:** Our data suggests that in mNSCLC, PD-L1 expression in circulating CAMLs dynamically upregulates after induction with chemotherapy and appears to predict patients with increased benefit to PD-L1/PD-1 IMTs, though additional studies are needed to validate these findings. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

8536 **Poster Session**

A phase II study of durvalumab (MEDI4736) immediately after completion of chemoradiotherapy in unresectable stage III non–small cell lung cancer: TORG1937 (DATE study). *First Author: Shinji Nakamichi, Department of Pulmonary Medicine and Oncology, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan*

Background: Concurrent chemoradiotherapy followed by durvalumab maintenance for up to 12 months is the standard of care for patients with unresectable stage III non-small cell lung cancer (NSCLC). However, the best timing of starting durvalumab after completion of chemoradiation has not been identified. Progression-free survival (PFS) and overall survival (OS) were better in the subgroup of patients administered durvalumab within 14 days after last radiation to randomization according to the PACIFIC study (Antonia SJ, et al. 2017, 2018 NEJM). **Methods:** This study was a prospective, single-arm, multicenter, phase II clinical trial. Eligibility criteria included patients with unresectable stage III NSCLC, ECOG PS 0-1, age < 75 years old. Patients who did not have disease progression after definitive concurrent chemoradiotherapy (CCRT) (chemotherapy: 2 cycles of platinum-based doublet chemotherapy, radiotherapy: 60 Gy/30 Fr) received durvalumab (10 mg/kg, every 2 weeks for up to 12 months) from the next day (allowed up to 5 days) after last radiation. The primary endpoint was 1-year PFS rate from registration assessed by an independent review committee. The planned sample size was 47 with a threshold value of 50% based on results of the PACIFIC study, an expected value of 63%, one-sided alpha of 20% and power of 80% in 1-year PFS rate. **Results:** From January 2020 to August 2020, 50 patients were enrolled from 16 institutions and 47 patients were evaluable for efficacy and safety. Forty-two patients received durvalumab maintenance therapy. Patient characteristics were: male/female 41/6; median age 65 (range 42-75); ECOG PS 0/1 28/19; IIIA/IIIB/IIIC 19/21/7. The 1-year PFS rate from registration was 75.0% (60% CI: 69.0 to 80.0). The 1-year OS rate from registration was 97.7% (95%CI: 84.6 to 99.7). ORR, median PFS and median OS were 78.7%, 14.2 months (95%CI: 13.4 to not reached (NR)) and NR, respectively. Grade 3/4 adverse events were pneumonitis (4.3%), neutropenia (44.7%), febrile neutropenia (4.3%). There was no treatment-related death. **Conclusions:** Our study met the primary endpoint. Durvalumab can be safely administered immediately after completion of CCRT for patients with unresectable stage III NSCLC, no additional or unexpected toxicity occurred as a reference to the PACIFIC study. Clinical trial information: jRCTs031190117. Research Sponsor: AstraZeneca.

8537 **Poster Session**

Neoadjuvant nivolumab in early-stage non–small cell lung cancer (NSCLC): Five-year outcomes. *First Author: Samuel Rosner, Johns Hopkins University, Baltimore, MD*

Background: Neoadjuvant (neoadj) immune checkpoint blockade (ICB) with anti-PD-1 therapy has shown increasing promise for early stage NSCLC, with long-term clinical outcomes still maturing. Our group reported the first phase I/II trial of neoadj nivolumab (nivo) in resectable NSCLC, finding therapy to be safe and feasible. We now present final clinical results from this cohort, representing the longest follow up data for neoadj anti-PD-1 to date. **Methods:** Two doses of neoadj nivo (3 mg/kg) were given prior to resection in 21 patients (pts) with resectable NSCLC. 5-year (yr) follow-up data, including recurrence-free survival (RFS), overall survival (OS) and association with pathologic response were tabulated. Event time distributions were estimated with the Kaplan-Meier method. All p-values are two-sided with 0.05 significance level. **Results:** At a median follow up of 63 months, 3-, 4- and 5-yr survival rates were 85, 80, and 80% respectively. RFS rates at 3-, 4- and 5-yrs were 65, 60, and 60% respectively. As previously reported, major pathologic response (MPR: ≤10% viable tumor) was 45%, and pathologic complete response (pCR) rate was 10%. The hazard ratio (HR) for pathologic down-staging was in the direction of improved RFS, without meeting statistical significance (HR 0.36, 95% CI 0.07-1.75, p = 0.2). RFS HR estimates for MPR and an alternative pathologic cut-off of less than 50% residual tumor (RT), were 0.61, (95% CI 0.15-2.44, p = 0.48) and 0.36, (95% CI 0.09-1.51, p = 0.16) respectively. The direction of the effect of pre-treatment PD-L1 positivity (≥1%) was to improve RFS (HR 0.36, 95% CI 0.07-1.85, p = 0.22). At 5-yr follow up, 8 of 9 (89%) pts with MPR were alive and no cancer deaths have occurred. Amongst pts with MPR, 1/9 pts had a cancer recurrence in the mediastinum treated successfully with definitive chemoradiotherapy. Both pts with pCR are alive and without recurrence. Patterns of all recurrences in this cohort are summarized in table 1. No long-term immune-related adverse events have occurred other than one G3 dermatologic event. **Conclusions:** The 5-yr clinical outcomes for neoadj nivo in resectable NSCLC compare favorably to historical trends. MPR trended toward improved RFS, while definitive conclusions are limited by our cohort size and overall low recurrence rate. Thresholds of %RT beyond pCR and MPR in this setting should be explored in larger prospective studies. PD-L1 expression may play a role in predicting long-term response, but larger prospective studies are needed. Clinical trial information: NCT02259621. Research Sponsor: Cancer Research Institute and Stand Up 2 Cancer.

Pre-treatment stage	Histology	PD-L1 (%)	Notable Mutations	%RT	Adjuvant chemotherapy (Y/N)	RFS duration (months)	Local vs. Distant Recurrence (L/D)	Alive (Y/N)
IIIA	Squam	0	TP53	80	N	10.4	D	N
IIA	Adeno	0	Kras G12c, STK11	75	Y	1.8	D	Y
IIIA	Adeno	N/A	-	5	N	8.5	L	Y
IIIA	Squam	25	-	30	N	20.3	D	N
IIIA	Adeno	60	Ros1	95	N	23.1	D	Y
IIB	Adeno	0	F11R-NRG1 fusion	100	N	29.3	L	N
IA	Adeno	0	-	100	N	46.5	L	Y

8538 **Poster Session**

Prognostic role of preoperative chemosensitivity in patients with non–small cell lung cancer (NSCLC) treated with preoperative chemotherapy: A study of National Cancer Database (NCDB). *First Author: Lei Deng, Roswell Park Comprehensive Cancer Center, Buffalo, NY*

Background: Response to preoperative systemic therapy may provide valuable information regarding tumor biology and prognosis. This is increasingly relevant nowadays considering the promising results from preoperative chemoimmunotherapy. This study aims to examine the prognostic role of preoperative chemosensitivity defined by TNM stage change in NSCLC. **Methods:** Patients with histologically confirmed clinical stage II-III NSCLC who have received preoperative chemotherapy followed by R0 curative surgery were identified in the NCDB between 2006 and 2017. Patients who have developed metastasis at the time of surgery, received any perioperative radiotherapy or single agent chemotherapy, or died within 90 days of surgery, were excluded. Preoperative chemosensitivity is categorized as ypT0N0, downstaged (pTNM < cTNM, excluding ypT0N0), and not downstaged (pTNM ≥ cTNM). Logistic regression was used to evaluate associations between chemosensitivity and demographic, clinical, and pathological factors. Log-rank was used for survival analysis and adjusted by cox regression for age, gender, race, year of diagnosis, academic center, insurance, comorbidity, histology, and clinical stage. **Results:** A total of 1266 patients were included, of whom 104 (8.2%) had ypT0N0, 575 (45.4%) were downstaged, while 587 (46.4%) were not. Female, diagnosis in recent years, treatment at academic centers, and squamous histology were significantly associated with better chemosensitivity, while clinical TNM stage, age, race, and comorbidity were not. Five-year overall survival rate is 81.2%, 57.7%, and 46.2%, respectively (log-rank p < 0.001). After Cox regression adjustment, compared with not downstaged, ypT0N0 (HR 0.28, 95% CI 0.17 – 0.45) and downstaged (HR 0.61, 95% CI 0.51 – 0.74) were independently associated with improved postoperative survival. **Conclusions:** Preoperative chemosensitivity defined by TNM stage change before and after chemotherapy may prognosticate NSCLC after curative surgery. It may be a useful clinical tool to identify patients with high risk of treatment failure after neoadjuvant chemoimmunotherapy in the future. Research Sponsor: U.S. National Institutes of Health.

Cox regression model of variables significantly associated with postoperative survival.

Characteristic	HR	95% CI	p-value
Age at Diagnosis	1.01	1.00, 1.02	0.003
Year of diagnosis			0.021
2010-2013 vs. 2006-2009	0.84	0.68, 1.03	
2014-2017 vs. 2006-2009	0.72	0.57, 0.91	
Comorbidity (Yes vs. No)	1.26	1.06, 1.50	0.008
Clinical stage (III vs. II)	1.45	1.19, 1.75	<0.001
Preoperative Chemosensitivity			<0.001
Downstaged vs. Not downstaged	0.61	0.51, 0.74	
ypT0N0 vs. Not downstaged	0.28	0.17, 0.45	

8539 **Poster Session**

Racial disparities in receipt of curative surgery for early-stage non–small cell lung cancer in Florida. *First Author: Qinran Liu, Department of Public Health Sciences, Miller School of Medicine, University of Miami, Miami, FL*

Background: Lung cancer is the leading cause of cancer death in the United States. Receipt of curative-intent surgery for early-stage non–small cell lung cancer (NSCLC) is associated with disparities in race and socioeconomic status, which is subsequently related to the outcome of NSCLC. This study aimed to examine the racial disparity in receipt of curative-intent surgery among early-stage NSCLC in Florida. **Methods:** A total of 80,458 patients with early-stage NSCLC diagnosed from 2005 to 2017 were identified from the statewide cancer registry, Florida Cancer Data System (FCDS). Percentage of patients receiving curative-intent surgery was calculated for each race/ethnicity. FCDS data was linked to discharge data containing comorbidity information for each lung cancer patient. There was a 94% match between FCDS and discharge data. Multivariable logistic regression was used to determine the impact of race on receipt of curative-intent surgery for early-stage NSCLC. **Results:** Among 80,458 patients with early-stage NSCLC, 66,761 (83.0%) were White, 5,503 (6.8%) were Black and 6,981 (8.7%) were Hispanic. Of note, 69.5% Hispanic patients lived in South Florida. Asian patients (59.9%) had the highest proportion of curative surgery, followed by Hispanics (57.8%), Whites (52.9%) and Blacks (42.6%). In the multivariable model, patients with Charlson Comorbidity Index (CCI)≥3 had 34% lower odds of having curative surgery (OR, 0.66; 95% CI, 0.62 to 0.7) compared to patients who did not have any comorbidity (CCI=0). Highest poverty levels had 27% lower odds of receiving curative-intent surgery compared to lowest (OR: 0.73; 95% CI: 0.68 to 0.78). After adjusting for sociodemographic factors (i.e., age, sex, race, insurance, region) and clinical factors (i.e., histology, AJCC stage, CCI, smoking status), Blacks had 27% lower odds of receiving curative-intent surgery (OR, 0.73; 95% CI, 0.68 to 0.79), whereas Hispanics had 22% (OR, 1.22; 95% CI, 1.14 to 1.30) and Asians had 19% (OR, 1.19; 95% CI, 0.98 to 1.46) higher odds than Whites. In the stratified analysis by regions, Blacks had lower odds of receiving curative-intent surgery than Whites in all regions across Florida while Hispanics had higher odds of receiving surgery than Whites only in South Florida (OR, 1.29; 95% CI, 1.18 to 1.41). **Conclusions:** There are persistent racial disparities in receipt of curative-intent surgery for early-stage NSCLC in Florida. Specifically, Blacks are receiving less curative-intent surgery, despite adjustments for comorbidities, socio-economic status, and insurance. Ethno-regional differences within different regions of Florida are evident with Hispanics surpassing all other races in receipt of curative treatment in heavily Hispanic South Florida. Research Sponsor: This study is supported by grant 20B16 from the Bankhead Coley Research Program of the State of Florida.

8540 **Poster Session**

Minimal residual disease (MRD) detection by ctDNA in relation to radiographic disease progression in patients with stage I-III non–small cell lung cancer (NSCLC) treated with definitive radiation therapy. *First Author: Emily S. Lebow, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The standard of care for patients with inoperable early stage or locally advanced NSCLC is definitive stereotactic body radiotherapy (SBRT) or conventional radiation therapy (RT) with systemic therapy. Circulating tumor DNA (ctDNA) testing can be used for the assessment of MRD and predict risk of recurrence. Few studies have prospectively evaluated MRD detection and ctDNA dynamics specifically among patients with early or locally advanced NSCLC receiving definitive RT. **Methods:** In a prospective clinical cohort of patients with stage I-III NSCLC (n = 17), serial plasma samples (n = 70) were collected before and after SBRT as well as before, during, and after conventional RT with or without concurrent systemic therapy and adjuvant durvalumab. Patients were followed-up for a median of 29 months (range: 4 to 54 months) with the last serial plasma collected at a median of 5 months from completion of RT (range: 1 – 26 months). A personalized, tumor-informed multiplex PCR assay (Signatera™ bespoke mPCR NGS assay) was used for the detection and quantification of ctDNA and tracked 16 tumor variants among 16 patients and 15 tumor variants in one patient. This study evaluated the prognostic value of ctDNA, correlating MRD status with clinical outcomes, in addition to ctDNA clearance kinetics during RT. **Results:** Among 17 patients with early-stage and locally advanced NSCLC, baseline ctDNA was detected in 82% of patients (14/17). Clinical progression was confirmed radiographically for 53% (9/17). All events of clinical progression were detectable by ctDNA (sensitivity 100%, 0.63 – 1.0), with a median lead-time of 5.5 months for MRD detection compared to radiographic disease progression. Durable ctDNA clearance was observed in 29% (5/17) of patients, all of whom then remained recurrence-free until the end of follow-up (median 12 months; specificity 100%, 95% CI 0.6 – 1.0). Transient ctDNA clearance was observed in 3 patients, and recurrent ctDNA was detected before or at the time of disease progression in all 3. ctDNA status after treatment at a single time point and longitudinally were highly predictive of disease recurrence (p < 0.0001). **Conclusions:** ctDNA detection is feasible for patients with stage I-III NSCLC undergoing definitive chemoradiation. and can serve as a powerful predictive biomarker for disease recurrence. High baseline detection rate is essential for feasibility of a ctDNA-based MRD assay. Residual detectable ctDNA represents a powerful predictive tool to identify patients who might benefit from intensification of adjuvant therapy following definitive RT. Research Sponsor: Natera Inc.

8541 **Poster Session**

Durvalumab (durva) after chemoradiotherapy (CRT) in unresectable, stage III, EGFR mutation-positive (EGFRm) NSCLC: A post hoc subgroup analysis from PACIFIC. *First Author: Jarushka Naidoo, Department of Oncology, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD*

Background: Standard of care for patients (pts) with unresectable (UR) stage III NSCLC is the 'PACIFIC regimen', based on data from the phase 3 placebo (pbo)-controlled trial where consolidation durva following CRT improved overall survival (OS; hazard ratio [HR], 0.68 [95% CI, 0.53, 0.87]) and progression-free survival (PFS; HR, 0.52 [95% CI 0.42, 0.65]), in an all-comer population. However, the benefit of immunotherapy (IO) in pts with EGFRm stage III NSCLC is unclear. We report a *post hoc* exploratory efficacy and safety analysis from 35 pts with EGFRm NSCLC from the PACIFIC trial (NCT02125461). **Methods:** Pts with stage III UR-NSCLC, WHO performance status (PS) 0/1 and no progression after ≥2 cycles platinum-based concurrent CRT were randomized 2:1 (1–42 days post CRT) to receive durva (10mg/kg IV q2w for up to 1 year) or pbo, stratified by age, sex, and smoking history; enrollment was not restricted by oncogenic driver gene mutation status or PD-L1 expression. Primary endpoints: PFS (BICR; RECIST v1.1) and OS; key secondary endpoints: objective response rate (ORR) and safety. Treatment effects for the EGFRm subgroup were estimated using an unstratified Cox proportional hazard model; medians were estimated using the Kaplan–Meier method. Statistical analyses were exploratory. Data cut-off (DCO) for the EGFRm subgroup efficacy analysis was 11 January 2021. **Results:** Of 713 pts randomized, 35 had EGFRm NSCLC based on local testing (durva n = 24, pbo n = 11). In the EGFRm subgroup, more pts in the pbo vs durva arm were male (73% vs 54%), had stage IIIA disease (64% vs 46%), PS 0 (64% vs 54%) and received pre-CRT induction chemotherapy (36% vs 8%). More pts in the durva arm were Asian (63% vs 55%) and had PD-L1 on < 25% tumor cells (67% vs 36%); median age was consistent across arms. At DCO, median duration of follow-up for survival was 42.7 months (range, 3.7–74.3 months) for all randomized pts in the subgroup. Median PFS was 11.2 months (95% CI 7.3, 20.7) with durva vs 10.9 months (95% CI 1.9, not evaluable [NE]) with pbo; HR 0.91 (95% CI 0.39, 2.13). Median OS was 46.8 months (95% CI 29.9, NE) with durva vs 43.0 months (95% CI 14.9, NE) with pbo; HR 1.02 (95% CI 0.39, 2.63). ORR was 26.1% (95% CI, 10.2, 48.4) and 18.2% (95% CI 2.3, 51.8) with durva and pbo, respectively. The safety profile for durva was consistent with the overall population. In the durva and pbo subgroup arms, radiation pneumonitis was reported in 42% vs 36% of pts, and pneumonitis was reported in 17% vs 18% of pts (1 grade 3, pbo arm), respectively. **Conclusions:** In this *post hoc* exploratory analysis of 35 pts, PFS and OS outcomes with durva were similar to pbo in the EGFRm population, with wide CIs. The benefit of IO in this population remains unclear. The ongoing LAURA study (NCT03521154) is investigating the efficacy and safety of maintenance osimertinib in pts with locally advanced EGFRm stage III UR-NSCLC with no progression after CRT. Clinical trial information: NCT02125461. Research Sponsor: AstraZeneca.

8542 **Poster Session**

Multimodal prediction of response to neoadjuvant nivolumab and chemotherapy for surgically resectable stage IIIA non–small cell lung cancer. *First Author: Loïc Ferrer, SOPHiA GENETICS, Pessac, France*

Background: The NADIM trial (NCT03081689), led by the Spanish Lung Cancer Group, assessed the antitumor activity and safety of neoadjuvant chemoimmunotherapy for resectable stage IIIA NSCLC. Patients received neoadjuvant nivolumab and paclitaxel-carboplatin for three cycles before surgical resection, followed by one year of adjuvant nivolumab. At 24 months, progression-free survival (PFS) was 77%, suggesting that neoadjuvant chemoimmunotherapy represents a promising option in this setting. Pathological complete response (pCR) could potentially be used as an important surrogate endpoint for survival. We present here a re-analysis of the NADIM cohort aiming to develop a machine learning algorithm to predict the pCR status based on multimodal baseline data. **Methods:** We combined baseline clinical data (e.g., age, smoking status), biological data (e.g., tumor histology, mutations), radiology reports and radiomics analysis of the baseline CT scan in a multimodal analysis. While 46 patients were enrolled in the NADIM trial, only 28 had a complete set of data available for this retrospective study. For each patient, tumors were segmented on the baseline CT-scan in 3D by a Deep Learning algorithm. Radiomics features were extracted following the IBSI standards and combined with the other data modalities. A filter-based variable selection method was applied before training several machine learning algorithms. The optimization criterion was the Area Under the ROC Curve (AUC). Due to the small size of the cohort, a leave-one-out cross-validation approach was used to properly estimate the model performance. For a sub-cohort of 20 patients for which data have been collected longitudinally during the neoadjuvant treatment, an additional Delta-radiomics model was used to predict the pCR status. **Results:** An XGBoost algorithm with a linear base learner displayed an AUC of 0.69, a precision of 75%, a sensitivity of 83% and a specificity of 50%. Features with highest weight in the algorithm were a mix of radiological, radiomics, biological and clinical features (including the neutrophils to lymphocytes ratio, mutations and histology) highlighting the importance of a truly multimodal analysis. Indeed, withdrawing a specific data modality (e.g., radiomics or biological features), led to a decrease of ~15% of the AUC. Inclusion of the Delta-radiomics analysis on the data collected longitudinally prior to surgery led to an improved AUC of 0.76 in that patient sub-cohort. **Conclusions:** This study is, to our knowledge, the first to offer a multimodal analysis of the response to neoadjuvant treatment for surgically resectable stage IIIA NSCLC and is a proof of concept that a machine learning algorithm can be used to predict the pCR in this context. These preliminary results are being confirmed in the ongoing NADIM II trial. Clinical trial information: NCT03838159. Research Sponsor: None.

8543 **Poster Session**

Identifying biomarkers associated with disease-free survival in stage I non–small cell lung cancer. *First Author: Christopher W. Seder, Rush University Medical Center, Chicago, IL*

Background: Patients with early stage, non-small cell lung cancer (NSCLC) with solitary pulmonary lesions ≤4 cm typically have favorable outcomes. However, disease recurrence impacts up to 30% of patients, leading to either additional surgical or systemic interventions. New methods to risk stratify patients based on clinical and molecular parameters may improve our ability to select cases that would benefit from more frequent surveillance or enrollment in clinical trials evaluating systemic therapy. **Methods:** We retrospectively analyzed data from 179 patients with early stage ($T_{1a\text{-}2a}N_0M_0$) NSCLC from a single institution. All patients had anatomic resection, negative margins, and systematic nodal sampling. Clinical and demographic data were abstracted from patient charts and tumor samples were molecularly profiled using the Tempus xT solid tumor assay (DNA-seq of 595-648 genes at 500x coverage, whole exome-capture RNA-seq). Pathogenic alterations (single nucleotide variants and insertion/deletions) and RNA expression were examined. Bivariate Cox-proportional Hazards models were used to assess the association of individual clinical, demographic, and molecular variables with recurrence-free survival, defined as the time from surgery until recurrence or death. **Results:** Our dataset included 166 stage IA1-3 patients and 13 stage IB patients, of which 36 patients experienced a recurrence or death event after surgery. Clinical and DNA-seq data was available for all patients, and RNA expression data was available for 172 patients. Across all patients, the most common somatically mutated genes were *TP53* (33% of tumors) and *KRAS* (16% of tumors), consistent with previous studies. Increasing $\log_{10}$.RNA expression for *NTRK1* (HR: 5.95; 95% CI, 1.16-30.4; p = 0.027) and CD274 (PD-L1) (HR: 7.88; 95% CI, 1.61-38.6; p = 0.013) and decreasing $\log_{10}$.RNA expression for *EGFR* (HR: 0.24; 95% CI, 0.05-1.21; p = 0.071) and *ERBB2* (Her2) (HR: 0.20; 95% CI, 0.04-0.97; p = 0.042) were associated with increased risk of recurrence or death. **Conclusions:** Increased expression of *NTRK1* and *CD274* (PD-L1) and decreased expression of *EGFR* and *ERBB2* (Her2) were associated with a increased risk for recurrence following surgery. This may have mechanistic implications for heightened tumor aggressiveness and/or metastatic potential. Future work will expand our cohort and validate our findings in a broader set of early-stage NSCLC patients. Research Sponsor: Swim Across America.

8544 **Poster Session**

Multi-omic and spatial dissection of immunotherapy response groups in non–small cell lung cancer (NSCLC). *First Author: Kenneth John O'Byrne, Princess Alexandra Hospital Brisbane, Queensland, Australia*

Background: Immune checkpoint inhibitors (ICI) have shown durable benefit in a subset of non-small cell lung cancer (NSCLC) patients. The composition of the tumour microenvironment (TME) is becomingly increasingly recognised as an important factor to predict response to therapy. **Methods:** Here, we applied digital spatial profiling of the tumour and stromal compartments from a 2nd line NSCLC ICI-treated cohort (n = 41 patient) and standard of care (SOC), platinum treated NSCLC cohort (n = 47), to identify tissue-based signatures of response to therapy. **Results:** We demonstrate by mIHC that the interaction of $CD68^+$ macrophages with $PD1^+$, $FoxP3^+$ cells is significantly enriched in ICI refractory tumours (p = 0.012). Patients sensitive to ICI therapy expressed higher levels of IL2 receptor alpha (CD25, p = 0.028) within the tumour compartments, which corresponded with the increased expression of *IL2* mRNA (p = 0.001) within their stroma. Immuno-inhibitory markers CTLA-4 (p = 0.021) and IDO-1 (p = 0.023) were supressed in ICI-responsive patients. Tumour CD44 (p = 0.02) was depleted in the response group and corresponded inversely with significantly higher stromal expression of one of its ligands, *SPP1* (osteopontin, p = 0.008). Analysis of dysregulated transcripts indicated the potential inhibition of stromal interferon-gamma (IFNγ) activity, estrogen-receptor and Wnt-1 signalling activity within the tumour cells of ICI responsive patients. Cox survival analysis indicated tumour CD44 expression was associated with poorer prognosis (HR = 1.61, p = 0.01), consistent with its depletion in ICI sensitive patients. Similarly, stromal CTLA-4 (HR = 1.78, p = 0.003) and MDSC/M2 macrophage marker ARG1 (HR = 2.37, p = 0.01) were associated with poorer outcome while BAD (HR = 0.5, p = 0.01) appeared protective. The SOC cohort paralleled similar roles for immune checkpoints and pro-apoptotic markers, with LAG3 (HR = 3.81, p = 0.04) indicating poorer outcome, and BIM (HR = 0.16, p = 0.014) with improved outcome. Interestingly, stromal mRNA for E-selectin (HR = 652, p = 0.001), CCL17 (HR = 70, p = 0.006) and MTOR (HR = 1065, p = 0.008) were highly associated with poorer outcome in ICI treated patients, indicating pro-tumourigenic features in the tumour microenvironment that may facilitate ICI resistance. **Conclusions:** Through multi-modal approaches, we have dissected the characteristics of NSCLC treatment groups and provide evidence for the role of several markers including *IL2,* CD25, CD44 and *SPP1* in the efficacy of current generations of ICI therapy. Research Sponsor: Princess Alexandra Research Foundation.

8545 **Poster Session**

Association of the KRAS genotype and clinicopathologic findings of resected non–small cell lung cancer. *First Author: Yuko Oya, Department of Thoracic Oncology, Aichi Cancer Center Hospital, Nagoya, Japan*

Background: This study assessed the clinicopathological background of early-stage KRAS-mutated non-small-cell lung cancer and analyzed the biological process of KRAS-mutated tumor using an RNA sequencing procedure. **Methods:** We used a cohort of consecutive series of 179 surgically resected early-stage non-small-cell lung cancers harboring *KRAS*mutations and analyzed the clinicopathological features, including the KRAS genotypes, affecting the recurrence-free survival and prognosis. Consequently, we performed RNA sequencing to determine the gene expression profiles of nineteen *KRAS*-mutated non-small-cell cancers. **Results:** The most common *KRAS* genotype was p.G12C (57; 31.8%). A high p-stage (hazard ratio [HR], 4.181; P < 0.0001) and solid predominant adenocarcinoma histology (HR, 2.343; P = 0.0076) were significant independent prognostic factors for the recurrence-free survival. A high p-stage (HR, 3.793; P < 0.0001), solid predominant adenocarcinoma histology (HR, 2.373; P = 0.0147), and *KRAS* p.G12V genotype (HR, 1.975; P = 0.0407) were significant independent prognostic factors for the overall survival. A gene expression analysis of the two factors revealed the p.G12V genotype to be closer to those of stem cells, and the traits of e an enhanced fatty acid and amino acid metabolism as well as a solid predominant phenotype were shown to an acquired a trait that can withstand hypoxia and the effect of prostaglandin-endoperoxide synthase **Conclusions:** The *KRAS* p.G12V genotype and solid predominant adenocarcinoma phenotype may be independent predictive factors of a poor clinical course in resected early-stage non-small-cell lung cancers, possibly due to the differentiation tendency observed in stem cells, the trait of an enhanced fatty acid and amino acid metabolism, and the effect of prostaglandin-endoperoxide synthase. Research Sponsor: None.

8546 **Poster Session**

Molecular characteristics of ERBB2-activating mutations in Chinese patients with NSCLC. *First Author: Fan Xu, Affiliated Hospital of Chengde Medical University, Chengde City, China*

Background: Activating mutations in the ERBB2 gene were shown to play an oncogenic role similar to that of ERBB2 amplification. Thus, ERBB2 mutations have emerged as therapeutic targets in non-small cell lung cancers (NSCLC). However, Activating ERBB2 mutations have not been described in detail like other driver gene mutations, such as epidermal growth factor receptor (EGFR)-activating mutations. **Methods:** In this study, we retrospectively analyzed activating ERBB2 mutations using next-generation sequencing(NGS). From May 2019 to January 2022, 21745 patients who were diagnosed with NSCLC were detected. **Results:** A total of 686 activating ERBB2 mutations were found, and 12 patients carried double ERBB2-activating mutations. In this cohort, the average age of patients was 58 years (range, 13-90 years). 59.6% of the patients were female and 88.2% were diagnosed with lung adenocarcinoma .A total of 47 ERBB2-activating mutation subtypes were defined in 674 patients. The most common activating mutations were Y772_A775dup (55.0%, 371/674), followed by G776delinsVC (8.3%, 56/674), S310F (7.7%, 52/674), G778_P780dup (5.6%, 38/674) and V659E (4.1%, 28/674). All other mutations occurred in 14 or fewer patients. ERBB2-activating mutations occurred most frequently in the tyrosine kinase domain (TKD) (80.1%), which included mutations in exon 20 (76.2%), exon 19 (3.0%), and exon 21 (1.2%),In addition, 13.2% of activating ERBB2 mutations occur in the extracellular domain, and 5.5% in the Transmembrane domain. 23.1%(156/674) patients with ERBB2 activating mutations could be evaluated for concurrent mutations, tumor mutational burden (TMB) and microsatellite instability (MSI) status. Among these patients, ERBB2-activating mutations were most frequently co-mutated with TP53(54/156) and EGFR(21/156). The frequency of EGFR mutations was much higher in non-TKD mutation patients than in TKD mutation patients (56.7% vs. 3.2%, P < 0.001), but no difference was observed for TP53. All these patients were microsatellite stable (MSS) and low TMB (< 10 mutations/megabase). **Conclusions:** We report mutational landscape and characteristics of ERBB2 in Chinese NSCLC patients .The prevalence of activating ERBB2 mutations was 3.1% in Chinese NSCLC patients. 80.1% of ERBB2 activating mutations were in TKD and 19.9% were in the non-TKD. The non-TKD mutations might also be used as a therapeutic target in ERBB2-directed target therapy. Research Sponsor: None.

8547 **Poster Session**

Dynamic monitoring circulating tumor DNA in plasma samples by PEAC technology for patients with early-stage non–small cell lung cancer after surgery. *First Author: Ning Li, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Local recurrence or distant metastasis after surgery is not rare for early-stage Non-Small Cell Lung Cancer (NSCLC) patients. Present clinicopathological parameters, such as TNM stages and pathological subtype, are limited effective, as Positive Predictive Value (PPV) is low while Negative Predictive Value (NPV) is high. In recent years, circulating tumor DNA (ctDNA) has emerged as a noninvasive method for early diagnosis, prognostic stratification, disease surveillance, and treatment response evaluation. We assessed whether circulating tumor DNA (ctDNA) detected by PEAC technology could be a biomarker for minimal residual disease (MRD) and prediction of postoperative relapse in early-stage NSCLC. **Methods:** We enrolled 132 NSCLC patients with EGFR, KRAS, NRAS, BRAF and PIK3CA mutations, and obtained plasma samples at five perioperative time points (before surgery, 3-7 days, 6-months, 12-months and 18-months after surgery). Using PEAC technology, somatic mutations in plasma samples were identified and utilized for ctDNA-based MRD analysis. Clinical follow-ups were collected. **Results:** Our data showed that 32.0% (8 of 25) of patients with positive preoperative ctDNA experienced postoperative relapse, compared with 7.2% (6 of 83) in ctDNA negative patients, demonstrating that preoperative ctDNA status is an effective prognosis factor for NSCLC. In time point of 3-7 days after surgery, plasma samples were obtained from 47 patients, of which 33.3% (2 of 6) with positive ctDNA experienced postoperative relapse, while only 4.9% (2 of 41) in ctDNA negative patients. The result suggests that ctDNA positive in plasma samples of 3-7 days after surgery might be a strong biomarker for MRD detection and relapse prediction. For ctDNA surveillance, plasma samples from 6-months, 12-months and 18-months after surgery were collected and detected. At any one of the three tests ctDNA is positive, 20.0% (8 of 40) patients experienced clinical relapse, while 5.1% (3 of 59) patients with ctDNA negative status at all times relapse. A total of 14 recurrence events had occurred, ctDNA positivity precedes radiological recurrence by a median of 150.5 days (90.5 – 182, P = 0.006). **Conclusions:** Perioperative ctDNA analysis using PEAC technology is effective in early detection of MRD and relapse prediction, and hence could benefit NSCLC patient management in clinical settings. Clinical trial information: NCT03465241. Research Sponsor: Sun Yat-sen University.

8548 **Poster Session**

Optimization of treatment options for EGFR-mutant, stage III, unresectable NSCLC: A systematic review and meta-analysis. *First Author: Lian Liu, Qilu Hospital of Shandong University, Jinan, China*

Background: The PACIFIC study established a new treatment standard for Stage III unresectable NSCLC, but CRT followed by durvalumab failed to bring survival benefit to patients with EGFR mutations. EGFR-TKIs have been successful in the setting of first-line treatment of advanced NSCLC and postoperative adjuvant treatment of NSCLC. We explored whether locally advanced inoperable patients with EGFR mutations can benefit from EGFR-TKIs and the possibly best treatment regimen through meta-analysis. **Methods:** Studies involving unresectable stage III NSCLC with EGFR mutations published in PubMed, Embase, Cochrane, ClinicalTrials.gov, and abstracts of important international conferences (ASCO, ESMO, WCLC) from January 1, 2000 to September 30, 2021 were screened. An integrative analysis was performed using STATA (version 16.0), and a network meta-analysis based on a Bayesian framework was performed using R (version 3.6.1) for the studies with a control group. The primary endpoints were progression-free survival (PFS) and overall survival (OS). **Results:** A total of 3291 patients were identified in 17 studies, including 5 treatment measures including concurrent chemoradiotherapy (CRT), CRT followed by durvalumab (CRT+Durva), TKI monotherapy, radiotherapy combined with TKI (RT+TKI), and CRT combined with TKI (CRT+TKI). PFS with TKI-free treatments (CRT, CRT+Durva) was significantly shorter than TKI-containing ones (TKI, RT+TKI, CRT+TKI) (HR 2.17, 95%CI 1.47-3.19), but its advantage only translated into borderline OS benefit (1.27, 0.99-1.63). In detail, the PFS with TKI-containing measures, including TKI monotherapy (0.66, 0.50-0.87), RT+TKI (0.37, 0.28-0.50), or CRT+TKI (0.14, 0.03-0.75) were all significantly longer than CRT. Furthermore, the PFS with both RT+TKI (0.40, 0.21-0.76) and CRT+TKI (0.15, 0.03-0.74) were significantly longer than CRT+Durva, while no statistical difference existed in PFS between RT+TKI and CRT+TKI. However, TKI alone had significantly shorter PFS than RT+TKI (1.78, 1.17-2.67). There was no statistical difference in OS among all the treatments, with RT+TKI ranking first in the Bayesian ranking. The integrated analysis found that RT+TKI had the longest OS (65.7 months, 55.5-76.0 months) and PFS (21.8 months, 18.0-25.7 months) and the highest response rate (77.7%, 68.8%-86.6%). Severe neutropenia was the most common with CRT+TKI, while RT+TKI brought the highest incidences of radiation pneumonitis and esophagitis. **Conclusions:** For EGFR mutant Stage III unresectable NSCLC, RT and TKI are both essential. RT+TKI and CRT+TKI have significantly longer PFS than CRT±immunotherapy, and RT+TKI has OS benefit trends. Due to the lack of sufficient studies on CRT+TKI, it is urgent to conduct large randomized clinical trials to explore the optimal treatment for these patients. Research Sponsor: None.

8549 **Poster Session**

The use of artificial intelligence with uncertainty estimation to predict lung cancer relapse from histopathology. *First Author: James M Dolezal, University of Chicago, Chicago, IL*

Background: First-line treatment of early stage non-small cell lung cancer (NSCLC) is surgical resection, but with a 5-year survival of only 54%, rates of future relapse are high. Identifying patients at high risk of relapse can help guide adjuvant treatment decisions. Deep convolutional neural network (DCNN) AI models trained on tumor histology have shown incredible flexibility as potential biomarkers, both in lung cancer and more generally across many malignancies. While DCNN models can obtain extremely accurate results when used for routine purposes such as diagnosis, subtyping, and grading of malignancies, most models trained for prognostication or treatment response prediction do not reach performance sufficient for clinical application. Uncertainty quantification (UQ) – a family of techniques that give DCNN models the ability to report confidence alongside predictions – is an underexplored avenue in cancer AI that may help further improve performance and clinical application of models designed to provide clinicians with estimations of risk. **Methods:** To explore the potential use of UQ in clinically-oriented DCNN models, we trained models on a single-institution, retrospective digital tumor histology slide cohort from patients with Stage I-III NSCLC who underwent surgical resection to predict risk of future relapse. Estimation of uncertainty was performed using dropout as a Bayesian approximation, and uncertainty thresholds were calculated from training sets using a novel method to identify and remove low-confidence predictions. For comparison, a separate multivariate logistic regression was trained in cross-validation using known clinical risk factors. **Results:** We trained DCNN models on slides from 198 patients (40 relapsed, 158 without relapse). In this cohort, 130 patients had stage I disease (65.6%), 42 had stage II (21.2%), and 26 had stage III (13.2%). The average age was 69 years, 85% were current or previous smokers, and 38 received guideline-concordant adjuvant chemotherapy. Without UQ, a DCNN model predicted risk of future relapse with an average area under receiver operator curve (AUROC) of 0.74 across three-fold cross-validation. Using UQ estimation, 63% of slides were reported with high confidence. Relapse prediction was significantly improved in the high-confidence cohort, with an average AUROC of 0.83 in cross-validation. With a specificity of 70%, this corresponds to an average sensitivity of 86.8% across the three cross-folds (79.1%, 85.5%, and 95.7%). In comparison, a clinical-only multivariate regression model predicted relapse with a cross-validated AUROC of 0.67. **Conclusions:** This method of uncertainty quantification appears to be a powerful tool to predict lung cancer recurrence risk from digital histopathology while simultaneously providing clinicians with a measurement of algorithm trustworthiness. Research Sponsor: U.S. National Institutes of Health.

8550 **Poster Session**

Effect of durvalumab in patients with unresectable stage 3 non–small cell lung cancer post-chemoradiotherapy. *First Author: Aswani Thurlapati, Department of Internal Medicine, LSU Health Science Center, Shreveport, LA*

Background: The PACIFIC study (PS) concluded that the use of durvalumab from 1 to 42 days after concurrent chemoradiotherapy (CXRT) in stage 3 unresectable non-small cell lung cancer (NSCLC) increased the median overall survival (mOS) from 29 to 48 months. It also showed a benefit in tumors with PD-L1 <25%. However, a post-hoc analysis of the PS showed no survival benefit with durvalumab in patients with PD-L1 <1% but was not statistically powered. Currently in the US, durvalumab is approved irrespective of PDL-1 percentage, whereas in Europe it is not approved for tumors with PDL-1 <1%. Also, there was no survival benefit in starting durvalumab within and after 2 weeks of CXRT. Our objectives in this study are to analyze the impact of PDL-1 expression and the date of initiation of durvalumab post CXRT on mOS. **Methods:** We conducted a retrospective observational study of stage 3 unresectable NSCLC patients who received durvalumab post CXRT at LSU Health Shreveport from 2018 to 2021. A survival analysis was done including the following variables: age, race, sex, tumor histology, tumor PD-L1 percentage, and date of initiation of durvalumab post CXRT. P-value <0.05 was considered statistically significant. **Results:** We identified 83 patients who received durvalumab after CXRT for treatment of stage 3 unresectable NSCLC. Baseline characteristics are provided in table 1. Among all the tumors, 25% had a PDL-1 <1%. 33% of the study population received durvalumab less than 30 days after CXRT and 67% received it after 30 days. The mOS was not impacted by race, sex, or tumor hisotology. Compared to higher PDL-1 percentage, patients with PD-L1 <1% had a statistically significant lower survival probability. At 14 months, 87% of patients with a PD-L1 <1% were alive compared to 100% in those with a PD-L1 1-50% or a PD-L1 >50%. Less than 35% of patients with PD-L1 <1% survived beyond 30 months compared to 45% for PD-L1 1-50% and 100% for PD-L1 >50% (p-value 0.02). Patients who received durvalumab 30-60 days after concurrent CXRT had a lower OS at 30 months compared to those who started before 30 days (44% versus 90%). However, statistical significance was not reached (p-value 0.45). **Conclusions:** This study demonstrates that patients with a PD-L1 tumor expression of <1% had a statistically significant lower survival probability compared to those with a PD-L1 expression of 1-50% and > 50% in this patient population. Time from CXRT to the start of durvalumab was not shown to affect survival outcomes. Research Sponsor: None.

Baseline characteristics of the study group.

Characteristics	
Age	63 (42 to 88)
Sex	
Male	56 (67.5%)
Female	27 (32.5%)
Race	
White	37 (45.1%)
African American	45 (54.9%)
Tumor Histology	
SCC	44 (53%)
Adenocarcinoma	32 (38.6%)
Other	7 (8.4%)
PDL-1 expression	
PDL-1 <1%	21 (25.3%)
PDL-1 1-50%	20 (24.1%)
PDL-1 >50%	20 (24.1%)
Unknown	22 (26.5%)
Start of Durvalumab post CXRT (in days)	
<30	28 (33.7%)
30-60	36 (43.4%)
>60	19 (22.9%)

8551 **Poster Session**

Equity for under-served populations in lung cancer screening and treatment: Does mobile low-dose CT scanning lead to stage shift and diagnosis with potential cures at 4 years of follow-up? *First Author: Derek Raghavan, Levine Cancer Institute, Atrium Health, Charlotte, NC*

Background: Randomized trials proved that screening high-risk patients with LDCT of chest reduces lung cancer mortality. Under-served patients have missed this benefit in most studies through access issues. We showed that mobile LDCT improves access and now assess if this translates to equity of survival. **Methods:** We used two coaches with BodyTom © portable 32 slice low-dose CT scanners (Samsung) to screen uninsured and under-served heavy smokers for lung cancer (Oncologist, 2019). All films were reviewed by central panel using LUNG RADS technique. Protocol was approved by Advarra IRB. Medicare pts were excluded as insurance covered them for LDCT (causing negative bias for diagnosis as the elderly are at high risk). **Results:** We initially screened 1200 uninsured/under-insured subjects, mean age 61 years (range 55-64), with average pack year history of 47.8 (30-150); 61% male; 18% Black, 3% Hispanic/Latino; 78% rural. We found 97 pts with LUNG RADS 4 (high risk) lesions, 30 lung cancers (2.5%), including 18 at stage I-III treated with curative intent (60%); 5 incidental non-lung cancers (renal CA 2, head & neck CA 1, pancreas CA 2); > 50% with intercurrent cardiovascular disease and COPD seen on LDCT. Of eligible first-screen subjects, 51% attended 12 month repeat LDCT and 27% attended third LDCT. One pt (6%) treated with curative intent has relapsed to date (median follow up 2.5 years, with 25% beyond 3 years). An additional 288 screened pts revealed 9 lung cancers (5 stage I-III), confirming shift to early stage disease at diagnosis. **Conclusions:** Mobile LDCT yields higher screening rate for under-served pts than prior hallmark trials, with shift to early-stage detection of lung cancer, with sustained treatment-induced remissions beyond 4 years. This approach could be applied to improve national lung cancer survival in the under-served. Research Sponsor: BMS Foundation; Leon Levine Foundation.

8552 **Poster Session**

Epidemiology and clinical impact of EGFR mutation in patients with lung cancer after radical surgical treatment. *First Author: Maciej Bryl, E.J. Zeyland Wielkopolska Center of Pulmonology and Thoracic Surgery, Poznan, Poland*

Background: The epidemiology of epidermal growth factor receptor (EGFR) mutation in lung adenocarcinoma and its clinical impact are well-known. However, most studies have focused on advanced-stage inoperable cancer. Data on the frequency of EGFR mutation in surgically resected lung cancer are limited. Recent studies have shown a promising effect of Osimertinib in adjuvant settings. Hence, the need to estimate the target population in the real-world data. This study aimed to assess the occurrence of EGFR mutation in patients after radical surgical treatment of lung adenocarcinoma and explore its prognostic impact compared to EGFR negative group. **Methods:** This single-center retrospective analysis included the group of 732 consecutive Caucasian patients with histopathologically confirmed lung adenocarcinoma, evaluated for EGFR mutations expression, who underwent anatomical resection between January 2016, and December 2020. EGFR status was assessed by cobas EGFR mutation test v2. The frequency of EGFR mutations, disease-free survival (DFS) and overall survival (OS) in EGFR positive and EGFR negative groups were analyzed. **Results:** EGFR mutations were found in 65 surgical patients (8.9%) and did not differ from patients with advanced stages of lung adenocarcinoma (7.9%). EGFR mutations occurred more frequently in females than males, 48 out of 344 (14%) and 17 out of 388 (4.4%), respectively. Deletions within exon 19 and the L858R mutation in exon 21 constituted 49.2% and 24.6% of all mutations, respectively, while others comprised 26.2%. One case of L858R mutation coincided with T790M in exon 20 mutation. Detailed results divided by stages are presented in the Table. The occurrence of EGFR mutation had no significant influence on DFS and OS in patients after radical resection. **Conclusions:** The frequency of EGFR mutation in postoperative lung cancer was comparable to the occurrence in the general lung cancer population. EGFR mutation did not affect DFS and OS in patients after radical resection. Research Sponsor: None.

Summary of the EGFR mutation results by stage.

Stage[1]	EGFR mutation-positive patients [n (%)]	Total numer of patients
IA	12 (7.3)	165
IB	20 (10.2)	196
IIA	5 (10.9)	46
IIB	8 (5.9)	136
IIIA	16 (10.8)	148
IIIB	4 (9.8)	41

[1]According to the 8th edition of IASLC guidelines.

8553 **Poster Session**

Lung cancer risk in persons enrolled in low-dose CT screening (LDCT) versus incidental lung nodule programs (ILNP).

First Author: Wei Liao, Baptist Cancer Center, Multidisciplinary Thoracic Oncology Department, Memphis, TN

Background: LDCT screening saves lives, but <10% of eligible persons participate; eligibility criteria are imperfect; geographic, racial and socio-economic disparities have emerged. ILNP may expand access to early detection. We compared rates of lung cancer diagnosis in LDCT and ILNP population subsets. **Methods:** Prospective observational cohort study of enrollees in LDCT and ILNP in a community healthcare system in AR, MS and TN. We compared LDCT vs 4 ILNP cohorts (C) based on USPSTF 2021 LDCT eligibility criteria: <50 years (C1, too young); >80 years (C2, too old); 50 – 80 years (C3, ineligible smoking history); 50 – 80 years (C4, eligible). For certain analyses, we stratified the LDCT cohort by baseline (T0) Lung-RADS score (0-2 v 3-4). We used a Cox model to calculate crude and adjusted hazard ratios (aHR) for lung cancer diagnosis within 24 months of enrollment. **Results:** From 2015-2021, 7050 persons were in LDCT- 6073 (86%) Lung-RADS 0-2 (no/benign lesions), 977 (14%) Lung-RADS 3 or 4 (possibly malignant lesion) on T0 scan; 17,579 were in ILNP, 16%, 10%, 57% and 16% respectively in C1-4. Demographics and tobacco use history of the ILNP cohorts differed strikingly; C4 was very similar to LDCT (Table). Black persons were significantly more in C1 (too young) and C3 (insufficient tobacco use). Diagnosis of lung cancer at 36 months ranged from 1% in C1 to 15% in C4, compared to 3% in LDCT; aHR for lung cancer diagnosis within 2 years ranged from 0.23 to 5.12 (all LDCT ref), but ranged from 0.04 to 1.02 with reference to LDCT Lung-RADS 3-4. Most patients in LDCT and ILNP C2-4 had early stage. There were proportionately more Black lung cancer patients in C1-4, and 3 times more Black patients in C3 and 4 than in LDCT. **Conclusions:** ILNP provides early-detection access to a larger, more diverse population than LDCT, potentially alleviating race and socio-economics-based outcomes disparities. Research Sponsor: None.

	LDCT*	LNP*			
		C1	C2	C3	C4
	N = 7050	N = 2888	N = 1824	N = 10093	N = 2774
Demographics					
Age: Median yrs (Q1-Q3)	65(60 - 70)	44(40 - 47)	85(82 - 88)	66(58 - 72)	66(60 - 71)
Female	50	59	58	55	50
Black race	**19**	**38**	**19**	**29**	**19**
Uninsured	1	18	3	9	4
Smoking history					
Former	32	13	41	29	29
Never	0	46	45	45	0
≥20 Pack years	87	19	34	14	100
Missing	10	57	48	62	0
Quit Duration <15 years	88	42	12	16	100
Missing	2	45	32	38	0
Largest lesion, median mm (Q1 - Q3)	4(2 - 6)	7(5 - 10)	8(5 - 15)	7(5 - 11)	9(5 - 15)
Cumulative # of Lung Cancer Patients (n, %)					
12 months	149(2)	19(1)	96(5)	314(3)	371(13)
24	183(3)	19(1)	102(6)	345(3)	408(15)
36	205(3)	20(1)	102(6)	364(4)	426(15)
Black race	**15**	**40**	**18**	**30**	**22**
Histology					
Adeno	45	55	48	52	47
Squamous	31	10	29	18	29
Small	16	10	5	12	12
Clinical Stage					
Stage I/II	60	30	52	57	56
Stage III	18	20	18	21	22
Stage IV	19	50	26	22	20
aHR (95% CI)					
Ref all LDCT	-	0.23 (0.14, 0.38)	1.93 (1.50, 2.48)	1.21 (1.01, 1.46)	5.12 (4.34, 6.05)
Ref Lung-RADS 3-4	-	0.04 (0.03, 0.07)	0.39 (0.30, 0.51)	0.24 (0.19, 0.29)	1.02 (0.85, 1.24)

*Numbers are column % unless otherwise stated.

8554 **Poster Session**

Treatment interruptions and discontinuations among patients with stage III unresectable non–small cell lung cancer treated with durvalumab at the Veterans Health Administration.

First Author: Munaf Alkadimi, University of Texas Health science center at San Antonio, San Anonio, TX

Background: The PD-1/PD-L1 pathway is a mechanism of immune evasion and disruption of this pathway with immune checkpoint inhibitors (ICIs) has shown clinical benefit in multiple malignancies. Based on results from the PACIFIC trial, durvalumab is approved as consolidation therapy in patients (pts) with stage III unresectable non-small cell lung cancer (UR-NSCLC) without progression following concurrent chemoradiotherapy (cCRT). Durvalumab has been used extensively in Veterans Health Administration (VHA) facilities, providing an opportunity to evaluate durvalumab treatment interruptions (TI), treatment discontinuations (TD), and the reasons for these on a national scale. **Methods:** Patients with stage III UR-NSCLC receiving durvalumab consolidation immunotherapy at the VHA between January 1, 2017 and June 30, 2020 with a minimum follow up for 12 months were included using ICD-10, HCPCS, and J codes and followed from their durvalumab start date through the earliest of last VHA visit, loss to follow up, death, or end of study (excluded if durvalumab therapy was ongoing at the end of the study, because the full treatment course could not be determined). TI were defined as durvalumab infusions separated by >28 days. Reasons for TI and TD are presented descriptively. Durations are reported using medians and interquartile ranges (IQR). **Results:** 935 pts were included (median age = 69 years; 95% males; 96% current or former smokers; 70% with COPD; histologies [squamous (50%), non-squamous (43%), other/missing (7%)]; and 77% with carboplatin-paclitaxel as their platinum-based CRT). Durvalumab TI were experienced by 19% of pts (median [IQR] number of TI = 1 [1-1], median [IQR] TI duration = 53 days [39-90]). The main reasons for TI were toxicity (8%) and social reasons (3%) (Table). The median duration of treatment (DoT) with durvalumab (TI included) was 9.0 months (IQR 2.9-11.8). Durvalumab TD occurred in 59% of pts. Top reasons for discontinuation across all 935 pts included disease progression (24%) and toxicity (18%) (Table). **Conclusions:** In this real world analysis of national VHA data, durvalumab DoT was similar to PACIFIC despite having a patient population with worse prognostic factors (e.g. more males, squamous, COPD) with 8% of VHA pts experiencing TI and 18% TD due to toxicity. Patients could benefit from additional efforts to prevent, identify, and manage toxicities in the UR-NSCLC population Research Sponsor: Astrazeneca.

Reported reasons* for durvalumab TI and TD.

	TI % of all (N=935) patients	TD % of all (N=935) patients
Progression	<1 %	24%
Toxicity	8 %	18 %
Patient preference	1 %	6 %
Physician preference	1 %	1 %
Death		4 %
Decline in performance status	1 %	2 %
Social reasons	3 %	<1 %
Insurance & System related	<1 %	<1 %
Other	6 %	3 %

*>1 reason possible for each TI.

8555 **Poster Session**

Texture-based CT radiomics distinguishes radiation and immunotherapy induced pneumonitis in stage III NSCLC.

First Author: Lukas Delasos, Cleveland Clinic Foundation, Cleveland, OH

Background: Recent changes to the standard of care for unresectable stage III NSCLC include chemoradiation followed by consolidative immunotherapy (IO). Pneumonitis is a well-known complication of radiotherapy (RT) and has been increasingly reported in association with IO. Although rare, pneumonitis can cause severe morbidity and possibly death in extreme cases. Differentiating RT and IO-induced pneumonitis (RTP vs IOP) is crucial for acute management and future considerations of individualized treatment. However, the clinical and radiological features of RTP and IOP may be similar and often indistinguishable on computed tomography (CT). Texture-based CT radiomics has previously been used to distinguish benign and malignant nodules on lung CT. In this study, we explore if radiomic features extracted from lung CT can distinguish between RTP and IOP. **Methods:** From 236 patients with stage III NSCLC who underwent chemoradiation followed by consolidative durvalumab, we identified 110 cases of treatment-related pneumonitis. IOP cases were identified through a retrospective review of electronic medical records and independently verified by a thoracic oncologist using features such as bilateral lung involvement, inflammatory changes outside the field of RT, temporal relationship to IO, and response to treatment. Inflammatory lesions were manually annotated using Slicer 3D. After excluding cases without discernible cause and non-identifiable lung lesions (n = 61), we included 49 cases in the study (RTP n = 20; IOP n = 29). A total of 555 features from Gabor, Laws, Laplace, and Haralick feature families were extracted on a pixel level from post-treatment CT images. A support vector machine (SVM) classifier was trained with the most discriminating features identified by Wilcoxon rank-sum test feature selection method. The classifier performance for distinguishing RTP vs. IOP was assessed by averaging the area under the receiver operating characteristic curve (AUC) values computed over 100 iterations of threefold cross-validation. **Results:** We identified the top 5 radiomic texture features distinguishing RTP from IOP including Haralick entropy, Haralick info, Laws median, and high- and low-frequency Gabor. Using 3-fold cross-validation, the SVM classifier model built on the radiomic features achieved an AUC of 0.83 (95% confidence interval, 0.78 - 0.86). **Conclusions:** Pneumonitis is a severe complication of both RT and IO that must be taken into consideration when evaluating future risks of IO-based therapies. The distinction between RTP and IOP remains challenging based on CT findings alone. Radiomic texture features analysis of post-treatment CT images can potentially differentiate RTP from IOP in stage III NSCLC patients who received RT followed by consolidative durvalumab. Additional multi-site independent validation of these quantitative image-based biomarkers is warranted. Research Sponsor: None.

8556 **Poster Session**

Durvalumab treatment initiation delays in patients with unresectable stage III non–small cell lung cancer treated at Veterans Health Administration facilities.

First Author: Paromita Datta, South Texas Veterans Health Care System, San Antonio, TX

Background: Durvalumab is an FDA-approved immunotherapy for the treatment of adults with UnResectable stage III non-small cell lung cancer (UR-NSCLC) without disease progression following concurrent chemoradiotherapy (CRT). There are limited real-world data regarding Durvalumab treatment initiation delays (TIDs) and reasons for them in the UR-NSCLC population. **Methods:** Patients with stage III UR-NSCLC receiving consolidation Durvalumab at the Veterans Health Administration (VHA) between January 1, 2017 and June 30, 2020 were selected from the VHA database using ICD-10, HCPCS, and J codes. All had the opportunity to be treated for 12 months and were followed from Durvalumab initiation through the earliest of their last VHA visit, loss to follow up, death, or the study's end (and excluded if Durvalumab therapy was ongoing at the study's end). Trained data abstractors determined the occurrence and reasons for TIDs (> 6 weeks from end of CRT to initiation of Durvalumab as in the PACIFIC trial) by chart review. **Results:** 935 patients were eligible for analysis (median age = 69 years; 95% males; 16% with ECOG performance status >1). TIDs occurred in 39% of the patients (Table). Durvalumab was initiated 61 days (median) from the end of CRT in TID patients vs. 31 days for those without TIDs. There were no significant (α<0.05) differences in age, race, smoking status, histology, or ECOG performance status and no comorbidity differences (except in patients with a history of cerebrovascular accident, for whom TIDs were more likely) between the TID/No-TID patients. Patients without timely post-CRT scans were more likely to have a TID. Of the 367 patients who experienced TIDs, 200 had documented reasons for the delay, consisting of other (not categorized) (28.5%), physician preference (20%), toxicity (11%), patient preference (10.5%), decline in performance status (10%), system issues (9.5%), social reasons (9%), and progression (0.5%). **Conclusions:** This is one of the largest retrospective cohort studies reporting real-world data in patients with UR-NSCLC receiving Durvalumab. TIDs were associated with increased time to post-CRT scans. This potential issue can be improved with care coordination and involvement of cancer navigators. Additional studies are needed to assess the impact of TIDs on survival outcomes. Research Sponsor: AstraZeneca.

Times to post-CRT scans and treatment patterns among TID vs. No-TID patients.

	TID (n=367)	No-TID (n=568)	P-value
Time from end of CRT to first scan, median days (IQR)	39 (25-56) n=329	28 (18-35) n=478	<0.01
Missing/unknown	n=38	n=90	
% <6 weeks	53% (174/329)	87% (416/478)	<0.01
% ≥6 weeks	47% (155/329)	13% (62/478)	<0.01
Durvalumab duration of therapy, median months (IQR)	8.7 (2.9-11.8) n=364	9.4 (3.1-11.9) n=563	0.61
Durvalumab discontinuations, %	61%	58%	0.36
Completed planned treatment, %	39%	42%	0.36

8557 **Poster Session**

Clinical activity of pembrolizumab monotherapy in diffuse malignant peritoneal mesothelioma. *First Author: Xiao Wang, University of Pennsylvania, Philadelphia, PA*

Background: Among patients with malignant mesothelioma, pembrolizumab has demonstrated activity in diffuse pleural mesothelioma (DPM), with limited data available for those with diffuse malignant peritoneal mesothelioma (DMPM). DMPM represents a clinically distinct entity from DPM and disease specific outcomes data is needed. We present real world data on the efficacy of pembrolizumab in DMPM. **Methods:** In this retrospective study, we identified patients with DMPM treated with pembrolizumab at two tertiary care cancer centers between 1/1/2009 and 1/1/2021. Clinicopathologic features were annotated. Median progression free survival (mPFS) and median overall survival (mOS) were calculated using Kaplan-Meier curves. Best overall response rate (BOR) was determined using RECIST 1.1 criteria. Association of partial response with disease characteristics was evaluated using Fisher's exact test. **Results:** We identified 24 patients with DMPM who received pembrolizumab (median age 62 years, 63% never smokers, 58% female, 75% had epithelioid histology). All patients received systemic chemotherapy prior to pembrolizumab (median prior lines of therapy: 3). BOR was 17% (3 partial responses, 10 stable disease, 5 progressive disease, 6 lost to follow-up). With a median follow up time of 29.2 months, mPFS was 4.9 months and mOS 20.9 months from pembrolizumab initiation. Three patients experienced PFS of > 2 years. Among the 14 patients who underwent next generation sequencing of tumor tissue, there were 8 somatic BAP1 alterations. Among the 17 patients tested for PDL1, 6 had positive PDL1 expression (1-80%). There was no association between partial response and presence of a BAP1 somatic alteration (p = 0.453), PDL1 positivity (p = 0.7) or non-epithelioid histology (p = 0.55). **Conclusions:** Pembrolizumab is active in a PDL1 unselected cohort of patients with DMPM. The overall response rate of 17% and mPFS of 4.9 months in this 75% epithelioid histology cohort warrants further investigation to identify those most likely to respond to immunotherapy, especially among epithelioid histology. Research Sponsor: This research was supported, in part, by the National Institutes of Health/National Cancer Institute (P30 CA008748).

8558 **Poster Session**

Positive impact of academic center care on overall survival in malignant pleural mesothelioma (MPM): A National Cancer Database (NCDB) socioeconomic factor analysis. *First Author: Logan Roof, Cleveland Clinic, Cleveland, OH*

Background: MPM is a rare cancer with a poor prognosis. Median survival for untreated patients is 4-13 months, and for treated patients is 6-18 months. Despite asbestos regulations in the United States, annual deaths from MPM rose from 2,479 in 1999 to 2,597 in 2015. Given recent treatment advances, including improvements in multimodality therapy and the introduction of immunotherapy as a treatment option in the frontline setting, the impact that patient demographics and treatment factors have on survival outcomes for MPM requires further evaluation. **Methods:** We identified all patients with MPM in the NCDB from 2004 to 2017. Differences in demographic, disease, and treatment characteristics were assessed by year of diagnosis using Chi-square test. The effect of age, race, insurance status, income, distance to treatment center, and education level on overall survival (OS) was assessed by log-rank test. **Results:** There were 15,287 MPM diagnoses in the NCDB between 2004-2010 and 17,059 diagnoses between 2011-2017. OS improved between the two time periods, with median OS of 9.46 months (95% CI: 9.23-9.63) and 5-year OS rate of 8.3% (95% CI: 7.9-8.7%) in patients from 2004-2011 and median OS of 11.33 months (95% CI: 11.01-11.7) and 5-year OS rate of 12.4% (95% CI: 11.8-13.1%) in patients after 2011, despite an increase in stage IV disease in the latter group. Older patients (≥65 years-old), males, patients with stage IV disease, patients with government primary payer insurance, and patients from urban areas all had significantly worse OS. Patients without comorbidities and those treated at an academic center had significantly better OS. OS was found to significantly increase as both income and education level increase. Patients diagnosed after 2011 were significantly older, were more frequently female, had more stage IV disease, were more frequently treated at academic centers, more commonly had government primary payer insurance, and lived significantly further away from their treatment center. Patients' time to treatment was significantly increased after 2011 (from 28 to 31 days). **Conclusions:** Socioeconomic factors play an important role in survival outcomes for patients with MPM. Many of these are linked with access to healthcare resources, which may increase the likelihood of evaluation at academic centers. For a rare malignancy such as mesothelioma, subspecialty care consisting of a comprehensive thoracic surgical evaluation and appropriate multimodality treatment are of great importance. Time to treatment increased during the study period yet OS improved, which our findings suggest are a result of an increase in evaluation and treatment at academic centers by providers skilled in delivering care to MPM patients. Research Sponsor: None.

8559 **Poster Session**

Phase I clinical safety and preliminary efficacy of PD-1-mesoCAR-T cells in the treatment of malignant pleural/peritoneal mesothelioma. *First Author: Qing Xu, Department of Oncology, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai, China*

Background: Malignant pleural/peritoneal mesothelioma (MPM) is an aggressive cancer characterized by poor therapeutic response and poor survival. Programmed cell death protein-1 (PD-1)-mediated immunosuppression is believed to be associated with T cell exhaustion and dysfunction in solid tumors. We generated chimeric antigen receptor (CAR-T) cells that can secret PD-1 nanobodies and target mesothelin (PD-1-mesoCAR-T). After identifying the anti-tumor activity and cytotoxicity of PD-1-mesoCAR-T cells by pharmacokinetics and pharmacodynamics, we conducted a proof-of-concept clinical trial in the Shanghai Tenth People's Hospital affiliated to Tongji University and the Mengchao Tumor Hospital affiliated to Shanghai University to evaluate the safety and efficacy of PD-1-mesoCAR-T cells in a dose-escalation study for malignant pleural/peritoneal mesothelioma. 6 patients received one or more infusions of the CAR-T cells with prior lymphodepletion and the longest survival is up to 18 months. **Methods:** This open-label, single-arm, multicenter, phase 1 study was enrolled patients with pathological diagnosis with malignant mesothelioma whose mesothelin expression in immunohistochemical samples was equal or greater than 50%. Immunohistochemical samples derived from surgical tissue, puncture tissue or pleural effusion. PD-1-mesoCAR-T cells were administered intravenously ranging 1×10^6–1.5×10^7/kg. Safety and efficacy were assessed in response-evaluable patients (ie, patients who received at least one dose of PD-1-mesoCAR-T and had at least one post-baseline response evaluation). **Results:** From July 20, 2020 to January 31, 2022, 9 patients were screened and enrolled and only 6 patients were evaluable. Mesothelin positive rate in the samples of these patients were from 50% to 100%. Three patients of them had PD-L1 positive staining in specimen. All patients underwent lymphodepletion before infusion. Two of patients (33.3%) had cytokine release syndrome, which were grade 1 and grade 3, respectively. Four patients (66.7%) developed fever. Two patients (25%) had grade 3 pulmonary infection. Stable disease was sustained for ≥3 months in 5 patients; 1 exhibited complete response and one partial response on PET or CT scan. The objective response rate (ORR) was 33.3%, but increased to 66.7% in the patients with PD-L1 positive. Only one patient of these patients appeared progression of disease after infusion. All enrolled patients are alive and observed continually. **Conclusions:** The clinical study of 6 patients with malignant mesothelioma shows that PD-1-mesoCAR-T cells are safe and feasible, indicating a promising curative effect. Effect of the CAR-T cells on the long term survival will be observed continually. Clinical trial information: 01722149. Research Sponsor: Shanghai Cell Therapy Group.

8560 **Poster Session**

Atezolizumab and bevacizumab in patients with relapsed mesothelioma: MIST4—a phase IIa trial with cellular and molecular correlates of efficacy. *First Author: Dean Anthony Fennell, University of Leicester, Leicester, United Kingdom*

Background: Targeting the PD1-PDL1 axis has demonstrated significant efficacy in patients with relapsed malignant mesothelioma (MM) however the factors that determine sensitivity are unknown. Combined inhibition of vascular endothelial growth factor (VEGF) may potentiate efficacy through remodelling of the tumour microenvironment and inhibition of angiogenesis. We therefore developed a multi-centre molecularly stratified phase IIa trial to test this hypothesis and to uncover cellular and molecular determinants of efficacy as arm 4 of the Mesothelioma Stratified Therapy umbrella trial (NCT03654833, MiST4). **Methods:** Patients with any histological subtype or site of MM (pleural or peritoneal) were enrolled. Key inclusion factors: histological confirmation of MM with an available archival tissue block, ECOG performance status 0-1, prior platinum-based 1st line chemotherapy (any line allowed), evidence of disease progression with measurable disease by CT (RECIST 1.1), and adequate haematological/organ function. Patients received Atezolizumab 1200mg iv q3w with bevacizumab 15mg/kg iv q3w (AtzBev). Primary endpoint was disease control rate at 12 weeks (DCR12w). The null hypothesis was rejected if ≥ 11 patients had disease control (A'Hern design). Secondary endpoints: DCR at 24 weeks (DCR24w), best objective response rate and toxicity (NCI CTCAE 4.03). Patients could undergo an optional re-biopsy upon disease progression. Baseline BAP1, p16ink4a, PD-L1 (DAKO22C3), gut microbiome 16s RNA metagenomics, multiplex immunofluorescence, and whole exome and RNA transcriptome sequencing was conducted to explore cellular and molecular correlates of sensitivity. **Results:** Between January 2020 and February 2021, 26 patients with MM started treatment and received at least one dose of AtzBev. The median age of pts was 68 (range, 44-80) years, 69% were male, 77% epithelioid, 85% ECOG PS1, > 1 prior systemic therapy 54%. The median cycles of Atz dosing was 4.5 (IQR, 2-8) and Bev dosing was 4.5 (IQR, 2-7). DCR12w: 53.8% (95% confidence limit (CI), 33.4% – 73.4%), DCR24w: 23.1% (95%CI, 9.0% – 43.6%). Best responses (evaluable within 24w): partial – 3.8% (95%CI, 0.1- 19.6%); stable disease – 69.2% (48.2 – 85.7%); progression – 15.4% (4.4 – 34.9%). Adverse events (any cause): ≥ grade 3 toxicities affected 35% of pts. **Conclusions:** MiST4 met its primary endpoint however responses were heterogeneous. Analysis of cellular and molecular correlates are ongoing and will be presented. Clinical trial information: NCT03654833. Research Sponsor: british Lung Foundation Asthma Research UK, Victor Dahdaleh Foundation.

8561 **Poster Session**

Final survival outcomes and immune biomarker analysis of a randomized, open-label, phase I/II study combining oncolytic adenovirus ONCOS-102 with pemetrexed/cisplatin (P/C) in patients with unresectable malignant pleural mesothelioma (MPM). *First Author: Santiago Ponce, Medical Oncology, Hospital Universitario 12 Octubre,, Madrid, Spain*

Background: MPM is an aggressive malignancy without curative treatment. ONCOS-102 is an oncolytic adenovirus expressing GM-CSF (Ad5/3-D24-GMCSF) with a clinically documented ability to stimulate local and systemic immune responses and remodulate the tumor microenvironment, both as a monotherapy and in combination with anti-PD1 blockade. The study objectives included determining safety and tolerability, efficacy and immunological activation in repeat tumor biopsies, and correlations with clinical outcomes. **Methods:** Following a safety run-in of n = 6 pts, 25 patients were randomized to receive ONCOS-102 intratumorally under CT or US guidance at a dose of 3×10^{11} Virus Particles on Day 1, 4, 8, 36, 78 and 120, plus six cycles of P/C starting on Day 22, or control comprising six cycles of P/C only. Both treatment-naïve (1L) and previously treated patients (2L) were enrolled. Imaging was done at baseline, Day 43-64 and 127-148 and tumor biopsy were collected at baseline and at Day 36. Final survival analysis (n = 25) was performed after 30 mo follow up. Multiplex immunofluorescence for immune cell subsets, RNASeq and qPCR was performed on repeat tumor samples. **Results:** The most frequent adverse events were anaemia, neutropenia and asthenia reported by > 50% in both groups with more frequent reports of pyrexia and nausea in the experimental (exp) group. No difference in the rate of severe events (Gr 3/4 acc to NCI CTCAE vs 4.0) were observed. 30-month survival rate (n = 25) was 34.3 % vs 18.2 % (NS) with mOS of 19.3 mo (95% CI: 4.6, NA) vs 18.3 mo (95% CI: 3.1, 28.9) in the exp group vs control. For patients treated in the 1L setting, 30 mo survival was 33.3 % in the exp group (n = 8) and 0% in the control group (n = 6) with mOS of 25.0 months and 13.5 months, respectively (NS). mPFS was unchanged from prior cut-offs; 9.8 months in the exp group and 7.6 in the control (NS). ONCOS-102 + P/C induced a pronounced increase in tumor infiltration by CD4+, CD8+ and granzyme B expressing CD8+ T-cells as well as M1:M2 macrophage polarization in patients with disease control (n = 13) vs progressing patients (n = 3). The data from RNAseq and qPCR analysis will be presented. **Conclusions:** The addition of ONCOS-102 to P/C was well tolerated by MPM patients and resulted in numerically improved 30-month survival rate in the overall population, and improved mOS in chemotherapy-naïve patients, albeit not statistically significant. Substantial immunological activation in tumor associated with ONCOS-102 was demonstrated, correlating with clinical benefit. Further exploration of ONCOS-102 as a treatment option in MPM is warranted Clinical trial information: NCT02879669. Research Sponsor: Targovax ASA.

8562 **Poster Session**

PD-L1, VISTA, and CD47 expression and prognosis impact in malignant pleural mesothelioma. *First Author: Mercedes Herrera, Department of Medical Oncology, Hospital Universitario 12 de Octubre, Madrid, Spain*

Background: Malignant Pleural Mesothelioma (MPM) has been characterized by an immune suppressive microenvironment. The immune checkpoint (IC) VISTA is notably expressed in MPM, in contrast to other IC proteins such us PD-L1. Recently, CD47 has been described as a possible diagnostic biomarker for MPM, although its impact in prognosis has not been established yet. **Methods:** This is a retrospective observational study of immunotherapy naïve MPM patients. Immunochemistry (IHC) assessment of PD-L1, VISTA and CD47 protein expression was performed on tissue microarray of 46 surgical samples. Means were compared using Mann-Whitney U test. Correlation was estimated using Pearson's coefficients. Overall survival (OS) was assessed using Kaplan–Meier curves and Cox proportional hazard models. A two-sided alpha error of 0.05 was used to assess statistical significance. Statistical analysis was conducted with Stata/SE version 16.1. **Results:** A total of 46 patients, 71.7% (33/46) male, were included in our study. Among them, 77.8% (35/45) had stage IIIB-IV, 84.8% (39/46) had received systemic therapy and 16.7% (7/42) had undergone radical-intent surgery. Asbestos exposure was confirmed in 65,7% (23/35) patients. Regarding the histological subtype, 71.7% (33/46) were epithelioid (Ep) and 13.0% (6/46) non-epithelioid (NEp), including 5 sarcomatoid and 1 biphasic. In IHC analysis, VISTA and CD47 were expressed in 63.0% (29/46) and 58.7% (27/46), respectively, whereas only 28.3% (13/46) patients had positive PD-L1 expression (≥1%). Median expression of VISTA, CD47 and PD-L1 in tumor samples was 41.8 (95% IC 0.5 - 50.7), 26.3 (95% IC 0 - 45.8) and 0 (95% IC 0-0.5), respectively. VISTA and CD47 expression were significantly higher in the Ep subgroup vs. the NEp subgroup (VISTA 39.4% vs 7.2% p = 0.028; CD47 37.3 vs. 0.8 p = 0.01). Additionally, we found a significant positive correlation between VISTA and CD47 protein expression (Pearson's r = 0.55, p < 0.001), which was consistent with the results we found in an independent MPM patient series from TCGA PanCancer Atlas (N = 87) based on RNA expression (r = 0.46; p < 0.001). Median OS, available in 40/46 cases, was 16.6 months (95% CI 12.03-20.43). On multivariate analysis, CD47 ≥1% expression was significantly associated with longer OS (29.7 vs 10.53 months, HR 0.35, [IC 95% 0.14-0.86]; p = 0.02) after adjusting for histological subtype, PDL1 and VISTA expression. In contrast, PD-L1 ≥1% showed a trend towards worse prognosis (10.3 vs 19.3 months), without reaching statistical significance (HR 2.23 [95% IC 0.95-5.23]; p = 0.065). No OS differences were found regarding VISTA expression. **Conclusions:** To our knowledge, this is the first study to describe VISTA and CD47 correlation in MPM. Moreover, we demonstrate CD47 expression to be an independent prognostic marker in MPM, suggesting C47 may play a key role in tumor biology of MPM, for which further validation and functional studies are necessary. Research Sponsor: None.

8563 **Poster Session**

Safety and efficacy of SHR-1316 combined with chemotherapy and sequential chest radiotherapy as first-line therapy for extensive-stage small cell lung cancer (ES-SCLC): The results from a phase II single-arm trial. *First Author: Dawei Chen, Shandong Cancer Hospital Affiliated to Shandong University, Jinan, China*

Background: Impower133 and CASPIAN studies showed that PD-L1 antibody combined with first-line chemotherapy could prolong the overall survival. Previous studies have shown that radiotherapy could potentially promote tumor antigen presentation and reverse immunosuppressive microenvironment in tumor. The purpose of this study was to explore the efficacy and safety of SHR-1316 (PD-L1 antibody) combined with chemotherapy and sequential chest radiotherapy as first-line therapy for ES-SCLC. **Methods:** Key inclusion factors were 18-75 years old, histologically or cytologically confirmed ES-SCLC, ECOG performance status 0-1, no previous systematic treatment. Patients (pts) included in this study received 4~6 cycles of SHR-1316 (20mg/kg, D1, q3w) combined with EP/EC (cisplatin 75mg/m^2 D1-3 q3w or carboplatin AUC = 5, D1 q3w; etoposide 100mg/m^2, D1-5, q3w), sequentially SHR-1316 combined with chest radiotherapy (≥3Gy*10f or ≥2Gy*25f, involved- field irradiation), and then entered the maintenance treatment stage until disease progression or intolerable side effects. The main endpoints included PFS, ORR and safety. **Results:** From October 2020 to December 2021, 31 pts with ES-SCLC received at least one dose of SHR-1316. The median age was 64 (range: 37-75) with 25(80.6%) male, 22(71%) former smokers and 31 (100%) ECOG performance status 1. 17 (54.8%) pts were with brain metastasis, 8 (25.8%) pts with liver metastasis, 8 (25.8%) pts with kidney/adrenal metastasis, 7(22.6%) pts with bone metastasis. At the data cutoff date, 15 pts remained on treatment, the average number of treatment cycles was 5.19. 24 pts had at least one 1 post-treatment tumor assessment. The median PFS was 7.56 months, the confirmed ORR and DCR in all pts were 50% (12/24) and 87.5% (21/24), respectively. The confirmed ORR and DCR in pts with brain metastasis were 38.5% (5/13) and 76.9% (10/13), and were 63.6% (7/11) and 100% (11/11) in pts without brain metastasis. In pts received chest radiotherapy, the confirmed ORR and DCR were 80% (8/10) and 100% (10/10). During the study period, 23 (74.2%) pts had adverse drug reactions, and 16 (51.6%) pts had grade 3 or 4 adverse drug reactions, including 12 (38.7%) neutropenia 8 (25.8%) leukopenia, 2 (6.5%) thrombocytopenia, 2 (6.5%) anemia, 1(3.2%) lymphocytopenia, 1(3.2%) amylase increased. No grade 5 adverse drug reaction was observed. **Conclusions:** SHR-1316 combined with chemotherapy and sequential chest radiotherapy as first-line therapy for ES-SCLC showed promising efficacy and acceptable safety. It is worthy of further clinical exploration. Clinical trial information: NCT04562337. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co. Ltd.

8564 **Poster Session**

Preliminary safety and efficacy of camrelizumab plus nab-paclitaxel and carboplatin as frontline setting in extensive-stage small cell lung cancer (ES-SCLC) from a phase II trial. *First Author: Shengxiang Ren, Oncology Department, Shanghai Pulmonary Hospital, Shanghai, China*

Background: Impower133 and CASPIAN studies showed that PD-L1 antibody combined with first-line chemotherapy could prolong the overall survival. Our previous study showed that nab-paclitaxel had a promising efficacy as later line setting in ES-SCLC. This phase II trial aimed to evaluate the efficacy and safety of camrelizumab plus nab-paclitaxel and carboplatin as front-line setting in ES-SCLC. **Methods:** Key inclusion factors were18-75 years old, histologically or cytologically confirmed ES-SCLC, ECOG performance status 0-1, no previous systematic treatment. Patients (pts) received 4 ~ 6 cycles of camrelizumab (200mg, D1, q3w) combined with nab-paclitaxel (230mg/kg, D1, q3w) plus carboplatin (AUC = 5, D1, q3w), then camrelizumab maintenance until disease progression or intolerable side effects. The primary endpoint was 6 months progression free survival rate. Secondary endpoints included PFS, ORR and safety. **Results:** From April 2021 to December 2021, 36 pts who received at least one dose of camrelizumab were included into this report. The median age was 60.5 (range: 32-73) with 30 (83.3%) males, 19 (52.8%) former smokers, and 36 (100%) ECOG performance status 1. The median drug exposure was 5 cycles, and 18 (50%) pts entered the maintenance stage. 33 pts had at least one 1 post-treatment tumor assessment. Among them, 32 partial responses (5 unconfirmed), 1 progressive disease (new lesion). The confirmed ORR was 81.8% (27/33), the unconfirmed ORR was 97% (32/33), DCR was 97% (32/33). The median PFS was 7.27 months (95% CI: 4.7 – 9.8 months). 24 (66.7%) pts had at least one adverse event, and 10 (27.8%) pts experienced grade 3 or 4 adverse events, including 10 (27.8%) neutropenia, 4 (11.1%) leukopenia, 2 (5.6%) thrombocytopenia, 2 (5.6%) anemia, 2 (5.6%) hepatic function abnormal,1(2.8%) alanine aminotransferase increased, 1(2.8%) hyperglycaemia, 1(2.8%) diabetes mellitus, and no grade 5 adverse event happened. **Conclusions:** Camrelizumab plus nab-paclitaxel and carboplatin had promising efficacy and safety profile as first-line setting in ES-SCLC, further validation is warranted. Clinical trial information: NCT04790539. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co. Ltd.

8565 **Poster Session**

Phase I/II investigator-initiated study of olaparib and temozolomide in SCLC: Updated analysis and CNS outcomes. *First Author: Catherine Belle Meador, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: Temozolomide has activity in small-cell lung cancer (SCLC), including patients (pts) with brain metastases (mets; Pietanza M, Clin Cancer Res 2012). Inhibition of Poly (ADP-ribose) polymerase (PARP) is another therapeutic strategy in SCLC. We hypothesized that olaparib plus temozolomide may be safe and effective for pts with relapsed SCLC and clinically active against CNS disease (Farago A, Cancer Discovery 2019). Here, we present an updated analysis of this combination in pts with relapsed SCLC, including a second cohort testing an alternative dosing strategy and an exploratory analysis of CNS-specific outcomes. **Methods:** In this phase I/II trial of olaparib plus temozolomide in pts with recurrent SCLC, pts were sequentially enrolled into two cohorts defined by dosing schedule. In cohort 1, olaparib was dosed on D1-7 of each 21d cycle. In cohort 2, olaparib was dosed on D1-21. Temozolomide was dosed on D1-7 in both cohorts. Each cohort had a phase I portion (conventional 3+3 dose-escalation) for determination of MTD and RP2D and a phase II portion with primary endpoint of ORR. Per protocol, eligible pts could have untreated asymptomatic brain mets < 1cm and, after mandatory baseline imaging, CNS imaging was performed at investigator's discretion. A post-hoc exploratory analysis of CNS-specific outcomes was performed using modified RECIST criteria (Long GV, Lancet Oncol 2012) in which brain mets ≥5mm were considered measurable, and intracranial response was independently assessed by an attending radiologist. **Results:** 66 pts with median of 2 prior lines of therapy (range, 1-7) were enrolled, 50 pts in cohort 1 and 16 pts in cohort 2. 33/66 (50%) pts had history of brain mets, 15/66 (23%) pts had untreated brain mets at enrollment. The confirmed ORR of cohort 2 was 7% (1/14 evaluable pts, 95% CI: 0.2-33.9%), and the updated confirmed ORR of the entire study population was 34% (21/62 evaluable pts, 95% CI: 22.3-47.0%). The most common adverse events were hematologic toxicities (thrombocytopenia, anemia, and neutropenia). 22/50 (44%) of cohort 1 pts and 4/16 (25%) of cohort 2 pts required dose reduction. Of 15 pts with untreated brain mets, best overall intracranial response (including both confirmed and unconfirmed responses) was CR in 6 pts, PR in 4 pts, SD in 3 pts and PD in 1 for a CNS disease control rate of 87% (95% CI: 59.5-98.3%). Of 10 pts with CR/PR as their best intracranial response, 4 responses were confirmed. With non-CNS progression as a competing risk, the probability of CNS progression among the entire study population was 17% (95% CI: 8.8-26.7%) at 6 months and 21% (95% CI: 12.1-32.0%) at 12 months. **Conclusions:** Olaparib and temozolomide may be an effective therapy for relapsed SCLC, especially for pts with CNS disease where we observed a high rate of intracranial disease control. Ongoing analyses regarding optimal dosing schedule will inform potential for future use of this combination. Clinical trial information: NCT02446704. Research Sponsor: AstraZeneca.

8566 **Poster Session**

Interim results of an ongoing phase 1/2a study of HPN328, a tri-specific, half-life extended, DLL3-targeting, T-cell engager, in patients with small cell lung cancer and other neuroendocrine cancers. *First Author: Melissa Lynne Johnson, Tennessee Oncology, Sarah Cannon Research Institute, Nashville, TN*

Background: HPN328 is a delta like canonical Notch ligand 3 (DLL3)-targeting T-cell engager (TCE) derived from the TriTAC platform, designed to minimize off-target toxicities. HPN328 contains 3 binding domains, engineered to redirect T cells to kill DLL3-expressing cancer cells: anti-DLL3 for target engagement, anti-CD3 for T-cell engagement, and anti-albumin for half-life extension. **Methods:** This ongoing Ph1/2a study is evaluating HPN328 in patients (pts) with metastatic small cell lung cancer (SCLC) and other neuroendocrine (NE) cancers associated with DLL3 expression. Eligible pts must have disease that is relapsed/refractory to standard systemic therapy. Primary endpoints are safety, tolerability, and determination of MTD/RP2D. Secondary objectives are pharmacokinetics (PK), pharmacodynamics, immunogenicity, and preliminary anti-tumor activity (RECIST 1.1). HPN328 is administered IV, once weekly. AEs are graded by CTCAE 5.0, and ASTCT for cytokine release syndrome (CRS). **Results:** As of Feb 3rd, 2022, 16 pts were enrolled in 8 dose-escalation cohorts at doses from 0.015mg to 12.0mg (SCLC n = 10 (62.5%); NE prostate cancer (NEPC) n = 2 (12.5%); other NE neoplasms (NEN) n = 4 (25%)). Median pt age was 61 (43-73) yrs. Pts received a median of 3 (1-5) prior treatments; 75% received a PD-1 blocker. At baseline, 6 pts (37.5%) had treated brain metastases and 8 (50%) had liver metastases. Median treatment duration was 10.6 (3.3-31.3 plus) weeks. Treatment is ongoing in 7 pts (44%; median 16.5 weeks). CRS was reported in 5 pts (31%); events were grade 1 or 2, occurred within 24 hrs of the 1st or 2nd dose and did not recur with rechallenge. No ≥ Grade-3 CRS occurred. No dose-limiting toxicities were observed, and no AEs led to discontinuation. HPN328 exhibited linear PK, with dose-proportional increases in exposure and a median half-life of 71 hrs. Small, transient increases in select cytokines and chemokines were observed up to 24 hrs post dose. T-cell activation and margination were observed, consistent with target engagement. DLL3 expression was confirmed on IHC analysis of most baseline biopsies. 15 pts were efficacy evaluable. 6 of 15 (40%) had decrease in sum of target lesion diameters (4 SCLC, 1 NEPC, 1 NEN). 3 of 9 (33%) SCLC pts across all doses had > 30% decrease (weeks on treatment: 17.2, 16.9 [ongoing], and 25.1 [ongoing, confirmed PR]). At doses ≥1.215mg, 2 of 4 (50%) SCLC pts had > 30% decrease and 1 had > 20% decrease. 4 pts (25%) had stable disease: 2 SCLC, 1 NEPC, 1 NEN (Thymic atypical carcinoid). **Conclusions:** HPN328 is a novel half-life extended DLL3-targeting TCE that is well tolerated and clinically active. AEs have been transient, manageable, and consistent with class. No ≥ Grade-3 CRS occurred. Tumor shrinkage has been observed, including 1 confirmed PR. Dose escalation is ongoing; updated data will be presented. Clinical trial information: NCT04471727. Research Sponsor: Harpoon Therapeutics, Inc.

8567 **Poster Session**

Impact of underrepresented populations on clinical outcomes of chemo-immunotherapy for extensive-stage small cell lung cancer: Real-world prospective cohort study. *First Author: Motohiro Tamiya, Department of Thoracic Oncology, Osaka International Cancer Institute, Osaka, Japan*

Background: Chemo-immunotherapy is the standard 1st-line therapy for patients with extensive-stage small cell lung cancer (ES-SCLC). Prospective data about underrepresented populations outside the clinical trial such as elderly or poor risk has not been revealed. **Methods:** We conducted a 32-hospitals prospective cohort study of consecutive patients with ES-SCLC who received carboplatin and etoposide with atezolizumab as 1st-line therapy between September 2019 and September 2020. The primary outcome was 6-months progression-free survival (PFS) probability of all patients. The secondary outcomes were overall survival (OS), PFS, time to treatment failure, objective response rate, safety, and differences in efficacy and safety depending on whether or not the key eligible study criteria of previous trials are met. **Results:** In total, 207 patients with ES-SCLC were analyzed. The median age was 72 years, and 64 patients (31%) were elderly (≥75 years). Most patients (89%) had a performance status (PS) of 0 or 1. As a result, 132 (64%) was categorized as eligible patients. The 6-months PFS probability of all patients was 38.8 % (95%CI:32.4-45.7%). Between eligible and ineligible patients, there was significant difference of patients who attained disease control (93% versus 77%, p = 0.002). Median PFS was significantly longer in eligible patients than ineligible patients (5.1 vs. 4.7 months; P = .03, HR 0.72 (95% CI 0.53–0.97)), and median OS was longer in eligible patients than ineligible patients, without any significant difference (15.8 vs. 13.1 months; P = .10, HR 0.73 (95% CI 0.51–1.07)). Survival analysis identified a PS score of 0-1 (HR: 0.60, 95% CI: 0.39-0.97, p = 0.03) as a significant predictor of better PFS, while PS score of 0-1 (HR: 0.51, 95% CI: 0.31-0.89, p = 0.01) and younger patients (< 75 years) (HR: 0.66, 95% CI: 0.45-0.97, p = 0.03) as significant-good predictor of OS. The rate of severe AEs was higher in ineligible patients than in eligible (39% vs. 27%, respectively; p = 0.07), although the difference was not significant. Older age was significantly associated with severe AEs (p = 0.049). **Conclusions:** The real-world efficacy of chemo-immunotherapy for ES-SCLC was similar to that of pivotal clinical trials. However, trial-ineligible patients with ES-SCLC had poor treatment outcome and the higher rates of severe adverse events in this prospective cohort study. Our study suggests that positive results among the trial eligible patients may not translate to ineligible patients. Clinical trial information: UMIN000038064. Research Sponsor: Chugai pharmaceutical.

8568 **Poster Session**

Impact of trilaciclib on multilineage chemotherapy-induced myelosuppression events in patients with extensive-stage small cell lung cancer: Post-hoc analyses of data from randomized clinical trials. *First Author: Jerome H. Goldschmidt, Blue Ridge Cancer Care, Blacksburg, VA*

Background: Trilaciclib is a short-acting CDK4/6 inhibitor administered prior to chemotherapy for multilineage myeloprotection. Reduced occurrence of chemotherapy-induced myelosuppression (CIM) events across neutrophil, red blood cell, and platelet lineages was reported in 3 Phase 2 clinical trials of trilaciclib versus placebo in patients with extensive-stage small cell lung cancer (ES-SCLC). In this post-hoc trial analysis, we further assessed the impact of trilaciclib on the occurrence of single and concurrent multilineage CIM events. **Methods:** Analyses were conducted separately by line of chemotherapy. In the first-line (1L) setting, pooled data from the G1T28-05 and G1T28-02 trials, in which trilaciclib or placebo was administered prior to etoposide, carboplatin, and atezolizumab [E/P/A] and E/P, respectively, were used. In the 2/3L setting, analyses were based on data from the G1T28-03 trial where patients received trilaciclib or placebo prior to topotecan. The proportion of patients with single and concurrent multilineage CIM events and incidence rate were estimated per cycle and during the first 4 cycles of chemotherapy. Severe (grade ≥ 3 per CTCAE definition) CIM events of neutropenia (SN), anemia (SA), and thrombocytopenia (ST) were assessed. Concurrent CIM events were defined as having 2 or 3 lineage-specific CIM events overlap for ≥ 1 day. As sensitivity analyses, the occurrence of CIM events in patients with ES-SCLC receiving 1L treatment in the G1T28-05 and G1T28-02 studies was analyzed separately. **Results:** Compared with placebo, fewer patients receiving trilaciclib had single-lineage CIM events and concurrent events in 2 or 3 lineages during cycles 1–4 of 1L chemotherapy using pooled data from G1T28-05 and G1T28-02 (Table). A similar trend was observed in the 2/3L setting. Generally, SN occurred more frequently in earlier cycles, whereas SA and ST tended to occur later. The sensitivity analysis in each individual 1L trial yielded consistent results with the pooled analysis. **Conclusions:** Patients with ES-SCLC receiving trilaciclib prior to chemotherapy had fewer single and concurrent multilineage CIM events than patients receiving placebo. Clinical trial information: NCT03041311, NCT02499770, NCT02514447. Research Sponsor: G1 Therapeutics, Inc.

CIM events per 21-day cycle among 1L and 2/3L patients with ES-SCLC during cycles 1–4.

	1L Pooled (G1T28-05 and G1T28-02)		2/3L (G1T28-03)	
Proportion of patients with events (%) Incidence rate per cycle	Trilaciclib (n = 90)	Placebo (n = 90)	Trilaciclib (n = 32)	Placebo (n = 28)
SN	14.4 0.047	56.7 0.211	40.6 0.157	46.4 0.206
SA	8.9 0.027	17.8 0.053	6.3 0.018	25.0 0.078
ST	0.0 0.000	12.2 0.038	25.0 0.069	14.3 0.058
Concurrent SN and SA	2.2 0.006	4.4 0.009	6.3 0.018	10.7 0.030
Concurrent SN and ST	0.0 0.000	13.3 0.035	37.5 0.118	35.7 0.105
Concurrent SA and ST	2.2 0.009	3.3 0.009	3.1 0.018	3.6 0.009
Concurrent SN, SA, and ST	0.0 0.000	2.2 0.009	15.6 0.044	32.1 0.113

8569 **Poster Session**

Exploratory analysis using cfDNA-based fragmentomics to predict disease recurrence in limited disease small cell lung cancer. *First Author: Sehhoon Park, Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea*

Background: The current standard of care (SOC) for limited disease (LD) small cell lung cancer (SCLC) is definitive concurrent chemoradiotherapy (CCRT). Despite the high response rate to SOC, up to 70% of the patients potentially experience disease recurrence and fail to show the prolonged clinical benefit. We investigated the feasibility of cell-free DNA (cfDNA) based genomic alteration and fragmentomic analysis using pre-and post-treatment samples to investigate the predictive value of disease recurrence in LD-SCLC. **Methods:** The blood sample from fifty LD-SCLC who were treated with definitive CCRT were collected before and after the treatment. Target sequencing, AlphaLiquid scan (IMBdx, Korea), composed of 106 target genes, was conducted using cfDNA and peripheral blood mononuclear cells. Based on the recurrence-free survival (RFS) interval of 12 months, patients were categorized into group with persistent response (PeR, n = 29) and non-PeR (n = 21). Fragmentomics analyses were collected using the proportion of cfDNA fragments sized in P1 (100 – 155 bp) and P2 (160 – 180 bp) ranges. **Results:** Initial analysis was conducted based on the gene of interest. Patients with *RB1* mutation (n = 11) detected in follow-up sample demonstrated significant shorter RFS compared to the *RB1* wild type (WT) patients (n = 39) (7.9 mon. vs. NR, $P = 0.002$). Among the patients who were available for our fragmentomics analysis in follow up samples (n = 19), non-PeR (n = 9) group were significantly high in P1 range ($P = 0.003$) and low in P2 range ($P = 0.002$) compared to PeR group (n = 10). AUCs using the fragment proportion in P1, proportion in P2, and the fragmentation ratio (proportion in P1 / proportion in P2), were 0.889, 0.911, and 0.889, respectively. The survival analysis using fragmentation ratio showed significantly longer RFS in fragmentation ratio low group compared to the high group (7.6 mon. vs. NR, $P = 0.002$). Integrating *RB1* mutation status with fragmentation ratio, patients with both *RB1* WT and fragmentation ratio low (n = 9) showed the most favorable outcomes ($P = 0.006$). On the contrary, patients with either *RB1* mutated or high in fragmentation ratio (n = 10) showed median RFS of rest than 12 months. **Conclusions:** In this study, we investigated the clinical feasibility of cfDNA detected mutation and size of the fragment in disease recurrence of LD-SCLC using the sample collected before and after definitive CCRT. It is observed that patients with either *RB1* mutation or high fragmentation ratio detected from cfDNA after the completion of CCRT are likely to experience early disease recurrence. Our findings suggest that cfDNA could provide supplementary information in predicting early treatment failure and support the clinical decision in selecting high-risk patients who might need intense monitoring and additional consolidative treatment. Research Sponsor: None.

8570 **Poster Session**

Stereotactic radiosurgery (SRS) versus whole brain radiation therapy (WBRT) in patients with small cell lung cancer (SCLC) and intracranial metastatic disease (IMD): A systematic review and meta-analysis. *First Author: Karolina Gaebe, University of Toronto, Toronto, ON, Canada*

Background: Patients with SCLC are at high risk for the development of IMD and, subsequently, rapid intracranial progression. SRS has supplanted WBRT as first-line treatment for IMD in most solid cancers, but WBRT remains first-line treatment for IMD in SCLC patients. Data on SRS in SCLC are limited to small retrospective studies. **Methods:** Studies reporting on SRS in SCLC patients with IMD were collected from EMBASE, MEDLINE, CENTRAL, and grey literature sources (n = 3,732 studies). Random-effects meta-analysis pooled hazard ratios (HR) for overall survival (OS) between SRS and WBRT ± SRS boost, as well as medians for OS in months (mo) and risk rates for intracranial local (LC) and intracranial distant control (DC) in single-arm SRS studies. **Results:** OS following SRS was non-inferior compared with WBRT ± SRS boost (HR 0.90; 95% confidence interval (95CI), 0.73-1.10; n = 7 studies; n = 18,130 patients), and superior compared with WBRT alone (HR 0.80; 95CI, 0.66-0.96; n = 7 studies; n = 16,961 patients). Pooled median OS from single-arm studies following SRS was 8.99 mo (95CI, 7.86-10.15; n = 14 studies; n = 1,682 patients). Pooled LC and DC estimates following SRS were 81% (95CI, 67%-99%) and 66% (95CI, 50%- 86%), respectively, at 6 mo, and 78% (95CI, 61%-98%) and 58% (95CI, 46%-75%), respectively, at 12 mo. **Conclusions:** This systematic review and meta-analysis provides evidence that SRS may achieve analogous survival outcomes compared with WBRT in patients with SCLC and IMD, indicating that a subset of SCLC patients may benefit from first-line SRS treatment. Prospective trials should investigate the impact of metastatic burden as well as LC and DC differences between WBRT- and SRS-treated SCLC patients. Research Sponsor: None.

8571 **Poster Session**

Adverse events self-reported by patients (pts) with extensive-stage small cell lung cancer (ES-SCLC) treated with durvalumab (D) plus platinum-etoposide (EP) or EP in the CASPIAN study. *First Author: Mustafa Özgüroğlu, Istanbul University-Cerrahpaşa, Cerrahpaşa School of Medicine, Istanbul, Turkey*

Background: The CASPIAN phase 3 study established D+EP as a global standard of care in ES-SCLC. Patient-Reported Outcomes - Common Terminology Criteria for Adverse Events (PRO-CTCAE) was developed to complement standard adverse event (AE) reporting in oncology trials. Here we describe patient-reported symptomatic AEs using PRO-CTCAE in CASPIAN, the first time the PRO-CTCAE tool has been piloted in SCLC research. **Methods:** In CASPIAN, treatment-naïve pts (WHO PS 0/1) with ES-SCLC received 4 cycles of D+EP q3w followed by maintenance D q4w until progressive disease (PD), or up to 6 cycles of EP q3w. As part of exploratory analyses, where validated local language versions were available (in English, German, Japanese or Spanish), pts were asked to complete the PRO-CTCAE by e-device at baseline, q3w during EP (in both arms), then q4w until PD, followed by day 28 post-PD, 2 months post-PD, and q8w until second progression/death. Presence/absence, frequency or severity were examined during the first 24 weeks after starting treatment across 11 AEs selected as being relevant to pts with ES-SCLC (Table). **Results:** In total, 164 of the 537 pts randomized to D+EP and EP in CASPIAN (31%; D+EP: 83; EP: 81) were asked to complete the PRO-CTCAE. At baseline, the PRO-CTCAE was completed by 84% of these pts in the D+EP arm and 81% in the EP arm; compliance rates > 60% were achieved up to cycle 32 for D+EP and cycle 6 for EP. Examined AEs were reported by a minority of pts before starting treatment in both arms (range D+EP vs EP: 4% vs 3% for hand-foot syndrome to 34% vs 41% for dry mouth). Baseline AE rates were generally maintained in both arms up to 24 weeks after starting treatment, except for itchy skin, which showed a numerical increase from 13% at baseline to a peak of 34% at cycle 6 in the D+EP arm and 12% at baseline to a peak of 42% at cycle 8 in the EP arm; and dizziness, which showed a numerical increase from 16% at baseline to a peak of 40% at cycle 5 in the D+EP arm, while rates were maintained vs baseline in the EP arm. Most pts reporting these AEs indicated that they occurred rarely or occasionally, or were mild or moderate in severity. **Conclusions:** Self-reported data from pts in CASPIAN showed that the 11 AEs examined during the 24 weeks after starting treatment were reported by a minority of pts, mostly with rare or occasional occurrence, and mild to moderate severity. Rates and patterns of AEs over time were broadly similar in the D+EP and EP arms. These results complement the CASPIAN safety profile and give insight into pts' experience of treatment. Clinical trial information: NCT03043872. Research Sponsor: AstraZeneca.

Primary attribute examined	AEs
Presence/absence	Rash; pain, swelling, or redness at a site of drug injection or IV
Frequency	Arm or leg swelling; pain in the abdomen; shivering or shaking chills
Severity	Itchy skin; numbness or tingling in hands or feet; dizziness; mouth and throat sores; hand-foot syndrome; dry mouth

8572 **Poster Session**

The efficacy and safety of taletrectinib in patients with TKI-naïve or crizotinib-pretreated ROS1-positive non–small cell lung cancer (NSCLC). *First Author: Wei Li, Oncology Department, Shanghai Pulmonary Hospital, Shanghai, China*

Background: Taletrectinib (AB-106 / DS-6051b) is a next-generation, potent, CNS- penetrant, selective ROS1 tyrosine kinase inhibitor. The ongoing TRUST study (NCT04395677) is a multicenter, open-label, single-arm, Phase 2 study of taletrectinib in Chinese ROS1-positive NSCLC patients who are TKI -naïve or crizotinib-pretreated. Here we present the updated efficacy and safety results of the study. **Methods:** The eligible ROS1-positive NSCLC patients were enrolled into either TKI-naïve or crizotinib-pretreated cohorts, and treated with taletrectinib 600mg once daily. The study endpoints included overall response rate (ORR), duration of response (DOR), disease control rate (DCR), overall intracranial response rate (IC-ORR), progression-free survival (PFS), and safety profile. **Results:** As of the data cutoff date of September 7, 2021, 61 of the 86 stage IV patients enrolled in the study have at least three postbaseline tumor assessment of which 40 patients in the TKI-naïve cohort, and 21 patients in the crizotinib-pretreated cohort (50% patients having at least one prior chemotherapy). In the TKI -naïve cohort, the confirmed ORR by investigators per RECIST 1.1 was 90.0%: [95%CI: 76.3%; 97.2%] (36/40); and the DCR was 95% [95%CI: 83.1%; 99.4%] (38/40). In the crizotinib-pretreated cohort, the confirmed ORR by investigators was 47.6% [95%CI: 25.7%; 70.2%] (10/21); and DCR was 76.2%: [52.8%; 91.8%] (16/21). The mDOR and mPFS are not reached yet for both cohorts. Of 6 patients having brain metastasis and measurable target brain lesions at baseline, the intracranial ORR and IC-DCR were 83.3% and 100%, respectively. Of 4 patients with ROS1 G2032R mutation, 3 patients achieved partial response (PR), and 1 patient achieved stable disease (SD). The most common treatment-related adverse events (TRAEs) include diarrhea, nausea, vomiting, transaminase elevation, anemia, neutrophil count decrease, etc. were Grade 1 or 2, and the most common AEs (below 10%) were ALT/AST increased but reversible. **Conclusions:** Taletrectinib demonstrated meaningful clinical efficacy in both TKI-naïve and crizotinib-pretreated ROS1 positive NSCLC patients. In particular, taletrectinib showed clinical effectiveness in patients with ROS1 secondary G2032 mutations and patients with brain metastasis. Taletrectinib was well tolerated in this patient population. Clinical trial information: NCT04395677. Research Sponsor: AnHeart Therapeutics Inc.

8573 **Poster Session**

Efficacy and safety of camrelizumab combined with chemotherapy (irinotecan combined with platinum) followed by camrelizumab combined with apatinib in the first-line treatment of advanced small cell lung cancer: A phase II study. *First Author: Jun Ni, Department of Pulmonary and Critical Care Medicine, Peking Union Medical Hospital, Chinese Academy of Medical Science & Peking Union Medical College, Beijing, China*

Background: The treatment mode of small cell lung cancer (SCLC) is mainly based on the comprehensive treatment of chemotherapy and radiotherapy. IMpower133 study, suggesting that immune checkpoint inhibitors combined with chemotherapy first-line treatment for advanced SCLC may bring new research directions of clinical benefit. Previous study suggested that the combination of anti-PD-1 antibody camrelizumab and VEGFR-2 inhibitor apatinib significantly improved antitumor effects. The aim of this study was to evaluate the efficacy and safety of camrelizumab combined with chemotherapy (irinotecan combined with platinum) followed by camrelizumab combined with apatinib in the first-line treatment of SCLC. **Methods:** Extensive-stage small cell lung cancer patients were enrolled in this single-center, single-arm study. During the induction treatment phase, Patients received camrelizumab (200mg q3w), irinotecan (65 mg/m2, q3w) and platinum (cisplatin: 30 mg/m2, carboplatin: AUC=4~5), after 4-6 cycles, the patient entered the maintenance phase, and then patients received camrelizumab combined with apatinib until disease progression or unacceptable toxicity. Treatment efficacy was assessed every 3 cycles (6 weeks). The primary endpoint is progression-free survival (PFS). Secondary endpoints are objective response rate (ORR), disease control rate (DCR) , duration of response (DoR) and overall survival (OS), which are based on RECIST 1.1. **Results:** At data cut-off (Jan 10, 2022), 20 extensive-stage SCLC patients were enrolled in the study, of which 18 patients were evaluable. Median age was 64 years, male accounts for 85.0% (17/20). Median follow-up was 5.0 months (range 0.4~17.6 months). Of 18 evaluable patients, no one achieved complete response Partial response was achieved by 17 (94.4%) patients and stable disease exhibited by 1 (5.6%) patient. The ORR and DCR were 94.4% and 100%, respectively. mPFS and mDoR have not been reached. In terms of adverse events (AEs), reactive cutaneous capillary hyperplasia (RCCEP) was observed in 10 (47.6%) patients 10 patients. Grade III-IV AEs were observed in 7 (35.0%) patients with neutropenia, thrombocytopenia, hemoglobin reduction, leukopenia, rash. The rest were grade I-II AEs. **Conclusions:** The treatment in this study showed impressive ORR and DCR, and acceptable toxicity, and may be a promising method as a first line treatment. Clinical trial information: NCT04453930. Research Sponsor: Jiangsu Hengrui Medicine Co.,Ltd.

8574 **Poster Session**

Total metabolic tumor volume on 18F-fluorodeoxyglucose-positron emission tomography ([18F]-FDG-PET) scan: A potential prognostic factor in extensive-stage small cell lung cancer. *First Author: Elisa Andrini, Department of Experimental, Diagnostic, and Specialty Medicine – DIMES, Sant'Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy*

Background: Small-cell lung cancer (SCLC) is a highly aggressive neuroendocrine lung cancer, accounting for 10-15% of all lung cancers, commonly classified in limited stage (LS-SCLC) and extensive stage (ES-SCLC). Despite the introduction of chemoimmunotherapy as new standard first-line therapy for ES-SCLC, the benefit of addition of the programmed-death ligand 1 (PD-L1) inhibitors is limited to a subset of patients, suggesting the importance to identify predictive biomarkers of response. [18F]FDG-PET/CT is commonly used for the staging and therapeutic planning of SCLC patients. Metabolic parameters derived from [18F]FDG-PET could predict patient outcomes by measuring the extension of metabolically active tumor (metabolic tumor volume [MTV]) or its metabolic heterogeneity (total lesion glycolysis [TLG]). **Methods:** We retrospectively collected patients with pathologically confirmed diagnosis of SCLC, who had undergone an [18F]FDG PET/CT scan within 30 days from the start of first-line treatment for ES-SCLC. Patients with LS-SCLC at diagnosis were included if presenting relapse at pre-treatment scans performed at least 90 days from the end of treatment with radical intent. We calculated metabolic parameters, MTV and TLG, by summing each single lesion's MTV and TLD respectively. The primary endpoint of the study was overall survival (OS), defined as the time from [18F]FDG PET/CT scan acquisition to death from any cause. **Results:** A total of 86 SCLC patients ES-SCLC were included. Patients with hyponatremia, hypoalbuminemia and elevated LDH levels were associated with greater number of lesions, greater total MTV, and higher total TLG at [18F]FDG-PET/CT/CT scan. At a median follow-up of 20.9 months, the median OS was 11.1 months. Median survival was longer among patients with Na + ≥135 mEq/L, with normal albumin levels and in those with normal LDH levels and without bone metastases. Patients with low total MTV had longer OS compared with those with high total MTV (11.9 months vs 4.8 months, respectively). High total MTV was independently associated with the risk of death ($p < 0.001$) but not with the risk of progression. **Conclusions:** Our preliminary data showed that total MTV could provide prognostic information in patients with ES-SCLC, suggesting a potential role as stratification factor in immunotherapy-based clinical trials. Research Sponsor: None.

8576 **Poster Session**

Nab-PTX and nab-PTX combined with immune checkpoint inhibitors for relapsed small cell lung cancer. *First Author: Rui Wan, State Key Laboratory of Molecular Oncology, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: Despite sensitivity to first-line chemotherapy, most small cell lung cancer (SCLC) patients experience disease progression after initial treatment. Nab-PTX showed comparable anti-tumor activity for relapsed SCLC. Whether immune checkpoint inhibitors (ICIs) combined with nab-PTX could improve clinical outcome for relapsed SCLC has not been fully evaluated. The aim of this study is to evaluate efficacy and safety of nab-PTX and nab-PTX combined with ICIs for relapsed SCLC. **Methods:** We retrospectively reviewed relapsed SCLC patients who were given nab-PTX (130mg/m2, day1,8 /Q3 weeks) or nab-PTX combined with ICIs (PD-1 or PD-L1), from Feb 2017 to Sep 2021. Clinical data were collected from electronic medical records. The clinical outcome, including progression-free survival (PFS) and overall survival (OS) were assessed using the Kaplan-Meier method and standard Log-rank test. **Results:** A total of 56 patients with relapsed SCLC were included, 29 and 27 patients received nab-PTX (group A) and nab-PTX combined with ICIs (group B), respectively. Baseline characteristics were well balanced between the groups. Patient characteristics (group A: group B) were as follows; median age 57: 59, male 25(86.2%): 24(88.9%), heavy smoking 23(79.3%): 18(66.7%), ECOG-PS 1 19(65.5%) :19(70.4%), extensive disease 28(96.6%) :25(92.6%), liver metastasis 10(34.5%) :12(44.4%), brain metastasis 8(27.6%) :10(37%), refractory relapse 10(34.5%) :11(40.7%). ORR in group A and B were 17.2% vs 40.7%, and DCR in group A and B were 72.4% vs 66.7%, respectively. The median PFS and median OS were similar between group A and B (median PFS, 2.8months vs 3.2months; median OS, 9.3 months vs 11.0months). PFS and OS according baseline characteristics were showed in the table. Toxicity profile of group B was tolerable as well as group A. **Conclusions:** This retrospective study indicated nab-PTX combined with ICIs failure to improve clinical outcome for relapsed SCLC when compared with nab-PTX monotherapy. Research Sponsor: None.

Progression-free survival and overall survival according to baseline characteristics.

Subgroup	Treatment	median PFS (months)	*p* value	median OS (months)	*p* value
Liver metastasis	Group A(n=10)	1.6		7.6	
	Group B(n=12)	1.5	0.255	6.1	0.664
Brain metastasis	Group A(n=8)	1.6		12.8	
	Group B(n=10)	2.6	0.755	10.5	0.24
Sensitive relapse	Group A(n=19)	2.9		10.8	
	Group B(n=16)	3.2	0.872	10.5	0.289
Refractory relapse	Group A(n=10)	1.6		9.1	
	Group B(n=11)	3.2	0.749	11	0.862

8577 **Poster Session**

Genomic analysis and prediction of therapeutic vulnerabilities of small cell lung cancer from rovalpituzumab tesirine phase III trial (MERU). *First Author: Weilong Zhao, AbbVie Bay Area, South San Francisco, CA*

Background: Predicting variable therapeutic responses that are driven by the genetic and transcriptomic heterogeneity of Small Cell Lung Cancer (SCLC) offers an opportunity for implementing precision therapies within the cancer cells and tumor microenvironment (TME). MERU was a Phase III study of Rovalpituzumab Tesirine (Rova-T) as maintenance therapy following first-line platinum-based chemotherapy in participants with extensive stage SCLC. In this study, we comprehensively analyzed the baseline genomic data in the MERU cohort to interrogate SCLC's heterogeneous TME and tumor-intrinsic molecular and genetic drivers for therapeutic vulnerabilities. **Methods:** RNA-seq and Whole-Exome-Sequencing (WES) data were collected from archival tumor samples of 306 of 740 subjects enrolled in MERU. RNA-seq reads were aligned with STAR and quantified for gene expression by HTSeq. WES reads were analyzed for somatic mutation and copy number variation using AbbVie's tumor-only WES pipeline. TME heterogeneity was evaluated using gene-set variation analysis of pan-cancer TME gene signatures. SCLC subtyping was performed using expression of 4 transcriptional factors (TF): ASCL1, NEUROD1, POU2F3, and YAP1. A computational framework of mapping MERU transcriptome expression profile to Cancer Dependency Map (DepMap) dataset was developed to synthetically screen MERU samples' drug sensitivity. **Results:** TF subtyping reveals high prevalence of SCLC-A and -N subtypes in the MERU cohort, consistent with high expression of DLL3 in these two neuroendocrine subtypes. Correlation of TME gene signature scores identified two distinct clusters in the MERU cohort with correspondingly polarized immune-suppressive and -inflamed phenotypes. The pro-inflammatory score combining IFN-gamma and TGF-beta signatures, predicted prognosis in the MERU cohort better than the previously reported SCLC-I signature (Hazard Ratio: 0.71 [95% CI 0.38-1.3] vs. 1.29 [95% CI 0.65-2.6]). WES analysis identified high prevalence of TP53 and RB1 mutations, in line with the reported prevalence of these genetic drivers in SCLC. The clinical characteristics including gender, smoking status, and prior treatment, are not significantly associated with either TF or TME subgroup. The computational drug screen framework maps 83% of MERU samples to DepMap SCLC cell lines. The correlation of subtype TF expression with drug sensitivity was highly concordant between MERU and DepMap. Collectively, this approach demonstrated that molecular subtyping can be leveraged to broadly predict drug response in SCLC patients. **Conclusions:** Our comprehensive genomic analysis of the MERU cohort provides new insights into SCLC heterogeneity from both tumor-intrinsic and tumor-immune interaction perspectives and shall contribute to the development of predictive biomarkers and therapeutic opportunities for SCLC. Research Sponsor: AbbVie Inc.

8578 **Poster Session**

The predictive value of YAP-1 for efficacy of immunotherapy among patients with ES-SCLC. *First Author: Yuqing Chen, Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China*

Background: IMpower133 showed benefits in both progression-free survival (PFS) and overall survival (OS) of etoposide/carboplatin plus atezolizumab (ECT) regimen in extensive-stage small-cell lung cancer (ES-SCLC), but the absolute benefit was limited. Previous studies have classified SCLC patients by RNA-seq clustering analysis to explore the dominant population for treatment, but was difficult for clinical application. We aimed to explore whether expressive status of Yes-Associated Protein 1 (YAP-1) can screen dominant population of immunotherapy among ES-SCLC patients. **Methods:** We selected ES-SCLC patients treated in our hospital from Jan, 2018 to Jul, 2021, and enrolled 21 patients with ES-SCLC received ECT regimen whose formaldehyde-fixed, paraffin-embedded sample was reachable. Assessments of complete remission (CR), partial remission (PR), disease stable (SD) and progressive disease (PD) were according to the efficacy evaluation criteria of solid tumor (RECIST) version 1.1. Immunohistochemistry (IHC) of YAP-1 (ET1608-30, 1/100) was conducted. The H-score was calculated by IHC Profiler. All statistical analyses were evaluated using SPSS 22.0, X-tile 3.6.1, and Excel. P values < 0.05 were considered statistically significant. **Results:** Baseline information was provided in table. The median H-score of responders (CR/PR patients) and non-responders were 13.97 (95%CI: 8.97-16.30) and 23.72 (95%CI: 8.13-75.40) that were significantly different ($P < 0.05$). H-score and PFS showed negative correlation by spearman (r = -0.603). Patients were divided into two groups as low expression group (H-score ≤25.00, n = 16) and high expression group (H-score > 25.00, n = 5) according to the cut-off value of H-score. The median PFS of these two groups were 7.1m (95%CI: 2.6-11.6m) and 3.4m (95%CI: 0.9-5.9m), respectively. K-M curves of PFS were significantly different ($P < 0.05$). **Conclusions:** Our preliminary results have indicated a potential efficacy predictive value of YAP-1 protein. And the expression level of YAP-1 protein was negatively correlated with efficacy of ECT in ES-SCLC patients. Research Sponsor: None.

		Responders n = 13	Non-responders n = 8	Total	P-value
Age(years)	Median(range)	64(55-72)	62(54-68)	62(54-72)	
	≤65	9(69.23%)	7(87.50%)	16(76.19%)	0.30
	> 65	4(30.77%)	1(12.50%)	5(23.81%)	
Gender	Male	11(84.62%)	8(100.00%)	19(90.48%)	0.27
	Female	2(15.38%)	0(0.00%)	2(9.52%)	
Smoke	Smoker	10(76.92%)	8(100.00%)	18(85.71%)	0.16
	Non-smoker	3(23.08%)	0(0.00%)	3(14.29%)	
Type	Pure SCLC	12(92.31%)	6(75.00%)	18(85.71%)	0.29
	Combined SCLC	1(7.69%)	2(25.00%)	3(14.29%)	
Therapy(line)	1st(ECT)	10(76.92%)	7(87.50%)	17(80.95%)	0.57
	2nd(ECT)	3(23.08%)	1(12.50%)	4(19.05%)	
Ki-67 index	< 90	2(15.38%)	2(25.00%)	4(19.05%)	0.54
	≥90	11(84.62%)	6(75.00%)	17(80.95%)	
NSE	< 22.69	4(30.77%)	1(12.50%)	5(23.81%)	0.99
	22.69-36.16	4(30.77%)	2(25.00%)	6(28.57%)	
	37.00-57.59	0(0.00%)	3(37.50%)	3(14.29%)	
	> 57.59	5(38.46%)	2(25.00%)	7(33.33%)	

8579 **Poster Session**

A phase I study of anlotinib with concurrent chemoradiotherapy for limited-stage small cell lung cancer. *First Author: Dingzhi Huang, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China*

Background: Concurrent chemoradiotherapy (CCRT) is the standard treatment for limited-stage small-cell lung cancer (LS-SCLC). However, LS-SCLC remains an area of high unmet medical need. Anlotinib is an antiangiogenic multi-target tyrosine kinase inhibitor. In the phase II ALTER-1202 trial, anlotinib significantly improved clinical outcomes in advanced small-cell lung cancer. We report here a phase 1 trial of anlotinib with CCRT for LS-SCLC. **Methods:** This is a prospective, single-arm, phase I clinical trial using a 3+3 design. Patients aged between 18 and 75 with previously untreated LS-SCLC, PS 0-1 and adequate organ function are eligible. Patients received anlotinib (12mg, qd, d1-14, q3w) and chemotherapy (etoposide, 100 mg/m^2, d1-3, q3w and cisplatin, 25 mg/m^2, d1-3, q3w) for cycle 1, then anlotinib [dose escalation at 3 levels (DL1-3) 8mg, 10mg and 12mg, qd, d1-14, q3w], chemotherapy (etoposide, 50 mg/m^2, d1-5, q4w and cisplatin, 25 mg/m^2, d1-3, q4w) and thoracic radiotherapy (60-66 Gy in 30-33 daily 2-Gy fractions starting on day 1 of cycle 2) for cycles 2–3, then anlotinib (12mg, qd, d1-14, q3w) and chemotherapy (etoposide, 100 mg/m2, d1-3, q3w and cisplatin, 25 mg/m^2, d1-3, q3w) for cycles 4-6. Cycles 5-6 were given as appropriate according to the patient's physical condition. Prophylactic cranial radiation was given according to the judgment of the investigator after CCRT. The purpose of this study is to determine the maximum tolerated dose (MTD) of anlotinib when combination with CCRT. **Results:** Twelve patients were enrolled from May 2020 to September 2021. No DLTs were observed in DL1 (3 patients) or DL2 (3 patients). At DL3 (6 patients), 1 patient had a DLT of grade 3 pulmonary embolism. Grade 3 adverse events were white blood cell count decreased, neutrophil count decreased, lymphocyte count decreased, hypertension, albumin decreased and pulmonary embolism. One patient had grade 3 pulmonary embolism and grade 4 neutrophil count decreased in DL3 at cycle 1. One patient had grade 2 radiation pneumonitis after cycle 5 and grade 1 radiation esophagitis at cycle 3 in DL3. One patient had grade 2 radiation esophagitis at cycle 3 in DL2. The MTD was not reached. **Conclusions:** Combined treatment with anlotinib and CCRT for limited-stage small cell lung cancer is well tolerated and further clinical investigation is warranted. Clinical trial information: NCT04882033. Research Sponsor: None.

8580 **Poster Session**

Efficacy and safety of lurbinectedin as second-line therapy in Chinese patients with small cell lung cancer: Preliminary results of a phase 1 study. *First Author: Ying Cheng, Department of Medical Thoracic Oncology, Jilin Cancer Hospital, Changchun, China*

Background: Lurbinectedin (Zepzelca), a selective inhibitor of oncogenic transcription, was granted accelerated approval on June 15, 2020, by the FDA for adult patients (pts) with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy, based on the results from SCLC cohort in PM1183-B-005-14 trial. Here we report the preliminary results of a phase 1 study (LY01017/CT-CHN-101) which aimed to evaluate the safety, tolerability, pharmacokinetics (PK) characters and preliminary efficacy of lurbinectedin in Chinese pts with advanced solid tumors including relapsed SCLC. **Methods:** In the dose-escalation stage, 10 pts with advanced solid tumors received lurbinectedin (2.5-3.2 mg/m^2) as 1-hour i.v. infusion q3wk in a classical 3+3 design, without primary granulocyte colony-stimulating factor (G-CSF) prophylaxis during Cycle 1. In the dose-expansion stage, 22 pts with relapsed SCLC after first-line platinum-based chemotherapy were treated with single-agent lurbinectedin at the recommended dose (RD) defined in the dose-escalation stage, with or without G-CSF support. Endpoints included safety (CTCAE v5.0), tolerability, PK, and confirmed objective response rate (ORR; RECIST v1.1). The data cutoff was January 13, 2022. **Results:** No dose-limiting toxicity (DLT) was observed in the first 3 pts treated at 2.5 mg/m^2, while 1/7 pts treated at 3.2 mg/m^2 had DLT (grade 4 neutropenia lasting ≥3 days) in Cycle 1, thus 3.2mg/m^2 without G-CSF prophylaxis was defined as the RD of the dose-expansion stage. At cutoff, 22 SCLC pts treated in the dose-expansion stage were still ongoing, with 21 and 22 pts evaluable for efficacy and safety, respectively. The investigator-assessed confirmed ORR was 42.9% (9/21, partial responses). The duration of response (DOR) is pending. The most common grade 3-4 treatment-related adverse events (TRAEs) were neutropenia (16 [72.7%]), leukopenia (13 [59.1%]), thrombocytopenia (9 [40.9%]), increased ALT (4 [18.2%]), anemia (3 [13.6%]), and increased AST (2 [9.1%]). Serious treatment-related adverse events, including neutropenia (5 [22.7%]), leukopenia (4 [18.2%]), thrombocytopenia (3 [13.6%]), increased ALT (2 [9.1%]), increased AST (2 [9.1%]), vomiting (2 [9.1%]), febrile neutropenia (1 [4.5%]), and edema (1 [4.5%]), were reported in 10 pts (45.5%). No cases of infection, sepsis and Hy's law were reported. A total of 40.9% (9/22) had dose delay and 31.8% (7/22) had dose reduction, mainly attributed to hematological toxicities. No discontinuations occurred due to AEs. No treatment-related deaths were reported. **Conclusions:** Lurbinectedin at the RD (3.2mg/m^2) shows promising efficacy as second-line therapy in Chinese pts with SCLC, with acceptable tolerability and manageable safety profile. Clinical trial information: NCT04638491. Research Sponsor: Pharma Mar, S.A, Pharmaceutical/Biotech Company.

8581 **Poster Session**

A phase 1/2 trial of lurbinectedin (L) in combination with pembrolizumab (P) in relapsed small cell lung cancer (SCLC): The LUPER study. *First Author: Antonio Calles, Hospital General Universitario Gregorio Marañón, Madrid, Spain*

Background: L is a novel anticancer agent that inhibits trans-activated transcription and modulates the tumor microenvironment. L is approved by the FDA for metastatic SCLC patients (pts) with progressive disease (PD) on or after platinum-based chemotherapy (CT). The LUPER study is assessing the safety, tolerability, and preliminary efficacy of L+P as second-line regimen for SCLC pts after failure of platinum-based CT. Phase 1 data are presented here. **Methods:** In this phase 1/2 trial (NCT04358237), adult pts with histologically confirmed SCLC, PD to a previous CT-containing regimen (≥4 weeks before study initiation), no prior exposure to immunotherapy, ECOG PS of 0-1, and measurable disease as per RECIST 1.1 are eligible. Pts with treated, stable, and asymptomatic brain metastases (BMs) are allowed. A 3+3 dose-escalation was done to determine the recommended phase 2 dose (RP2D) of L+P. L was dosed at 2.4 mg/m^2 and 3.2 mg/m^2 IV Q3W in the dose level (DL)1 and 2, respectively, in combination with fixed dose of P (200 mg IV Q3W). The RP2D was the highest DL at which 0/3 pts or ≤1/6 pts experienced dose-limiting toxicities (DLTs) during the first cycle. Treatment was administered until PD, unacceptable toxicity, or consent withdrawal. Secondary endpoints include safety as per CTCAE 5.0, preliminary efficacy, and pharmacokinetics. **Results:** Thirteen pts were enrolled across 3 hospitals in Spain (DL1, n = 7; DL2, n = 6). Median age was 66 (range 43–78) years, 46.2% were female, 61.5% had ECOG PS of 1, 38.5% had platinum-free interval < 90 days, 30.8% had LDH > upper normal limit, and 15.4% had BMs. One DLT (G3 asthenia) and one G4 neutropenia lasting > 3 days (controlled with G-CSF prophylaxis upon C2, without requiring dose delay or modification) occurred in the DL1. No DLT were reported in the DL2. The RP2D was identified as 3.2 mg/m^2 L and 200 mg P IV Q3W. At data cutoff (Jan 21, 2022), 5 (38.4%) pts remained on treatment (1 pt in DL1 discontinued due to COVID-19 in cycle 1). Median duration of treatment was 2.1 (0–11.8) months, 5 (38.5%) pts had ≥8 cycles, and median relative dose intensity of L and P were 91.1% and 95.7%, respectively. Immune-related AEs (G2 pneumonitis; G3 ALT increased) led to P discontinuation in 2 (15.4%) pts. Responses were shown in both DLs, with ORR of 30.8% (1 confirmed complete response and 3 partial responses); 3 pts had stable disease (SD; including 1 patient with SD > 12 weeks) and 5 (38.5%) pts experienced PD. **Conclusions:** This is the first report to demonstrate a manageable safety profile and preliminary efficacy of second-line L+P for relapsed SCLC pts. This combination warrants further confirmation in the ongoing expansion phase 2. Clinical trial information: NCT04358237. Research Sponsor: PharmaMar, MSD.

8582 **Poster Session**

Circulating tumor DNA (ctDNA) mutations associate with response in patients (pts) with extensive-stage small cell lung cancer (ES-SCLC) treated with talazoparib (TALA) and temozolomide (TMZ). *First Author: Maria A Velez, David Geffen School of Medicine at UCLA, Los Angeles, CA*

Background: Poly (ADP-ribose) polymerase (PARP) inhibition in combination with TMZ is a promising treatment strategy for ES-SCLC. In SCLC models, TALA, a potent PARP inhibitor, exhibits cytotoxic effects by impairing PARP proteins 1/2 and trapping PARP on DNA while TMZ potentiates antitumor response by contributing to genomic instability (Wainberg 2016). A prior analysis of ctDNA in 15 pts treated on trial with TALA and TMZ suggested that mutations in DNA damage repair (DDR) genes occurred with this combination and may associate with response (Mulroy ASCO 2021). **Methods:** Pts with relapsed or refractory ES-SCLC were treated with TALA 0.75 mg po daily with TMZ 37.5 mg/m2 po on days 1-5 of 28-day cycles in a phase 2 clinical trial (UCLA/TRIO-US L-07, NCT03672773). ctDNA was collected and assessed based on allele frequency and plasma copy number at baseline and every 8 weeks during treatment with the Guardant360 assay (Redwood City, CA). DDR status was defined as a mutation known or likely to result in aberrant expression of *ATM* or *BRCA1/2* (other DDR genes not detected by assay) (Pearl 2015). Germline DDR mutations were evaluated with matched-normal (PBMC) whole exome sequencing (WES) with archival specimens by Tempus (Chicago, IL). Response to treatment was defined by RECIST 1.1 criteria. Fisher s exact tests were used to compare proportions of patients, with P-values <0.05 considered statistically significant (www.r-project.org, Vienna, AU). **Results:** For 27 pts with evaluable response, 78 ctDNA samples were collected. The most common baseline somatic alterations were mutations in *TP53* (23 pts), *RB1* (8 pts), *ATM* (5 pts), and *BRCA2* (5 pts). There were no patients with germline DDR mutations. Overall, 22/27 (81.5%) had disease control (DC), including 11 with confirmed partial responses (PR) and 11 with stable disease while 5 had progressive disease. All those with PRs and ctDNA burden >0.2% at baseline experienced a ctDNA decrease at 8 weeks of treatment. DDR mutations were found in 18/27 (66.7%) pts. Of those with ≥ 1 follow-up ctDNA time point collected, 13/17 (76.4%) pts had at least one new mutation detected while on treatment, most commonly in *ATM* (6 pts). The appearance of new mutations associated with DC (P=0.042) and with a trend towards improved progression free survival (PFS, 5.9 m vs 3.6 m, P=0.099). All 5 pts with DDR mutations present at baseline had DC with TALA and TMZ, and 9/11 (81.8%) of those with PR had DDR mutations detected at some point during the trial, although the trend toward DC enrichment with DDR mutations did not maintain statistical significance (P=0.24). **Conclusions:** Mutations in DDR genes occur on treatment with TALA and TMZ and may associate with disease control. Validation in a larger cohort will be pursued. Research Sponsor: Pfizer.

8583 **Poster Session**

A pilot study of ipilimumab and nivolumab in recurrent extensive-stage small cell lung cancer after platinum-based chemotherapy. *First Author: Anne C. Chiang, Yale Cancer Center, New Haven, CT*

Background: Immunotherapy has shown efficacy in the treatment of recurrent, extensive-stage small cell lung cancer (ES-SCLC). In the Checkmate 032 trial, ipilimumab and nivolumab combination therapy resulted in a 21% objective response rate in relapsed SCLC. At present, there are no biomarkers used in clinical practice to predict treatment responsiveness in SCLC. Ipilimumab and nivolumab act by blocking key co-inhibitory immune pathways of CTLA-4 and PD-1/PD-L1, respectively, leading to reinvigoration of anti-tumor cytotoxic T cell responses and a decrease in immune suppressive tumor infiltrating leukocytes. The ratio of intratumor Teff (CD8+) cells to Treg (CD4+/Foxp3+) cells (Teff/Treg) could be a more reliable biomarker than effector cell infiltration alone. **Methods:** In this open-label, single arm trial, we enrolled patients with ES-SCLC who previously received platinum-based chemotherapy; prior anti-PD-1 /PD-L1 therapy was allowed. Patients were treated with nivolumab 1 mg/kg and ipilimumab 3 mg/kg, for a total of 4 doses each and received nivolumab 480 mg beginning with cycle 5, every 4 weeks until progression, unacceptable toxicity or study discontinuation. On-study biopsies were performed prior to initiation of therapy and during week 4 for the biomarker primary objective—to correlate disease response with intratumor Teff/Treg changes. Secondary objectives include determining ORR, DOR, PFS, and OS. **Results:** Twenty-two patients (median age 63.5 [range 54-80] years, ECOG 0/ 1/2 [41%/50%/9%], sex M/F [45%/55%]) were enrolled and received treatment. Fourteen (64%) had paired biopsies while on treatment. Fifteen patients were evaluable per RECIST with an ORR of 13% (2/15, 2 partial responses [13%]) and DCR was 40% (6/15, 4 stable disease [27%]). Grade 3 treatment-related adverse events (TRAEs) occurred in 9/22 [40%]. Grade 4 TRAEs occurred in 2/22 [9%] (elevated lipase and elevated bilirubin) and Grade 5 TRAEs occurred in 1/22 patients (hepatic failure). Out of the 9 patients previously treated with anti- PD-1/PD-L1 therapy, 1 had a partial response and 2 had stable disease. Multiplexed quantitative immunofluorescence analysis revealed changes of both CD8+ effector T cells and Tregs in the tumor micro-environment associated with clinical benefit to immunotherapy. **Conclusions:** Combination immunotherapy with ipilimumab and nivolumab shows clinical efficacy in relapsed extensive-stage SCLC, including those previously treated with anti-PD-1/ PDL-1 therapy. Obtaining paired biopsies was shown to be successful in this prospective trial to study the tumor microenvironment in SCLC tumors treated with checkpoint inhibitors. Early biomarker evaluation during week 4 shows local immunomodulatory effect of treatment and supports exploration as predictive biomarker in this population. Clinical trial information: 03670056. Research Sponsor: Bristol Myers Squibb.

8584 **Poster Session**

Trends in treatment patterns associated with small cell lung cancer in a U.S. Medicare population. *First Author: Robert A. Ramirez, Vanderbilt University Medical Center, Nashville, TN*

Background: Characterizing changes in the incident small cell lung cancer (SCLC) patient population and SCLC treatment landscape is essential for understanding drivers of outcomes among patients diagnosed with SCLC. The objective of this study was to examine trends in patient characteristics and treatment patterns for SCLC in a Medicare population. **Methods:** A retrospective analysis was conducted using the Surveillance, Epidemiology, and End Results (SEER)–Medicare linked data. Patients were included if they had a record with a diagnosis of SCLC in the database from 1/1/2007 – 12/31/2017 and were ≥65 years of age at diagnosis. Patients also had continuous enrollment for ≥180 days pre-SCLC diagnosis. Characteristics and treatment patterns were stratified by year of SCLC diagnosis. **Results:** 13,516 patients met the study criteria. Overall, 57.7% were female, mean age was 74 years, 89.5% were white, and 45.6% had a history of tobacco use. The majority (73.1%) were diagnosed with stage IV disease. Just over half (55.4%) of patients initiated first line (1L) treatment and mean time from diagnosis to 1L treatment was 6 weeks. Only 36.7% of those initiating 1L went on to second line (2L). Platinum-based chemotherapy (carboplatin or cisplatin + etoposide) was by far the most common 1L regimen (91.3%). 44.7% of patients received monotherapy in 2L, with topotecan being the most common (28.4%) regimen. Carboplatin + etoposide was used for approximately 20% of 2L patients. Over time, the demographic characteristics of patients diagnosed with SCLC was fairly stable with the exception of patients reporting a history of tobacco use, which more than tripled, increasing from 19.3% to 67.7% between 2007 and 2017. Between 2007 and 2017 the share of SCLC patients initiating 1L treatment increased 8.2% from 53.8% to 58.2% and the share initiating 2L fluctuated between 35% and 39%. Platinum-based chemotherapy was consistently used by the vast majority (88.7%–96.6%) of patients in 1L during the study period. Other chemo monotherapy (e.g., topotecan) and platinum-based chemotherapy with or without irinotecan were the most common 2L regimens from 2007-2014. Use of checkpoint inhibitors (CPIs) in 2L began in 2015 and became the most common 2L treatment following platinum-based chemotherapy by 2017 with 41.5% of patients receiving a CPI in 2L. **Conclusions:** While an increasing share of SCLC patients are pursuing treatment, less than 60% of SCLC patients receive any anticancer therapy. Fewer still receive more than one line of treatment, highlighting the ongoing need for effective therapies for SCLC. Research Sponsor: Ipsen.

8585 **Poster Session**

Lenvatinib for the treatment of thymic epithelial tumors (TETs): A real-life multicenter experience. *First Author: Jose Carlos Benitez, Gustave Roussy, Villejuif, France*

Background: TETs are rare malignancies of the anterior mediastinum being thymoma (T) B3 and thymic carcinoma (TC) the most aggressive subtypes. There is no standard treatment after platinum-based chemotherapy in refractory or metastatic setting. A phase 2 trial has reported clinical benefit for lenvatinib 24mg (objective response rate [ORR] of 38%), a novel multi-targeted inhibitor of VEGFR, FGFR, RET, c-Kit, and other kinases; significant toxicity grade 3 hypertension was 64%. No real-life data exists. **Methods:** We selected patients (pts) under lenvatinib as a second-line or beyond for refractory TETs from 8 International centers from France (belonging to the nationwide network RYTHMIC) and United States. We analyzed epidemiologic, clinical and pathological characteristics of patients with TET's. The toxicity was evaluated according to CTCAE v4, with a local evaluation of efficacy and we assessed toxicity profile and survival outcomes. **Results:** From March 2020 to December 2021, 29 pts were enrolled. Median age at diagnosis was 49 (24-71), 51.7% were women, 6/29 (20.7%) reported auto-immune disorders (AIDs). TC was the most frequent subtype (n=18, 62.1%), followed by B3 and B2. Lenvatinib was used as a second line for 52% of pts, mainly starting from 14 mg/daily (n=20, 69%) and one pts with concomitant pembrolizumab. The ORR was 17% (95%CI 3.0-32.0) with partial responses only seen in TC, and the disease control rate was 76% (95%CI 59.0-92.0). Response was observed with the dose of 24mg in 3 pts and 14mg in 2 pts, with a median follow-up period of 5 months (m) (95%CI 3.2-6.7), PFS at 6 and 12 m was 64% and 30%, respectively. Toxicity is summarized in table 1. Dose de-escalations were needed in 27.5% of pts. **Conclusions:** We confirm the activity of lenvatinib in pts with advanced or metastatic T and TC, despite the use of lower doses than the phase 2 study. Research Sponsor: None.

Toxicity profile of the cohort later to starting lenvatinib.

	TOXICITY			
Syndrome	**Any grade**	**%**	**Grade ≥3**	**%**
High blood pressure	12	41,3	0	0
Asthenia	7	24,2	1	3,4
Diarrhea	4	13,7	0	0
Mucositis	4	13,7	2	6,9
Hypothyroidism	3	10,3	0	0
Liver toxicity	2	6,9	2	6,9
Abdominal pain	2	6,9	0	0
Neuropathy	2	6,9	0	0
Palmo-plantar SD	1	3,4	0	0
Anemia	2	6,9	0	0
Thrombopenia	1	3,4	0	0
Neutropenia	1	3,4	0	0
Headache	1	3,4	0	0
Edema	1	3,4	0	0
Fever	1	3,4	0	0
Alopecia	1	3,4	0	0

8586 **Poster Session**

CD47 expression patterns in thymic epithelial tumors. *First Author: Thomas Yang Sun, Stanford University, Palo Alto, CA*

Background: Blockade of CD47, an immunoglobulin overexpressed on solid tumor cells that inhibits macrophage phagocytosis, is a promising anti-cancer immunotherapy which has not yet been explored in thymic epithelial tumors (TETs). TETs, including thymomas and thymic carcinomas, are rare tumors with limited immunotherapy treatment options due to the high rates of immune-related adverse effects observed with PD-1/PD-L1 checkpoint inhibitors. This study aimed to examine CD47 protein expression in TETs. **Methods:** A clinically annotated tissue microarray of 67 TETs consisting of 64 thymomas and 3 thymic carcinomas, as well as 14 thymic controls were included. Each sample with an average of 3 cores was stained for CD47 epithelial expression (rabbit monoclonal antibody SP279, Abcam, USA). Samples were scored for intensity as follows: 0 = none, 1 = weak, 2 = moderate, and 3 = strong. An H-score, defined as intensity x percentage of tumor involved, was also assigned and ranged from 0 to 300. Samples with an intensity score of < 2 or an H-score of < 150 were categorized as $CD47^{low}$, while the rest as $CD47^{high}$. Multivariate linear regression analysis accounted for WHO subtype, stage, resection status and presence of paraneoplastic syndrome (Prism 9, Graphpad). **Results:** Compared to normal thymic tissue, TETs were more frequently CD47 positive and had significantly higher levels of CD47 expression. CD47 was present in 91% of TETs, compared to 64.3% of normal thymus. Importantly, the level of expression was significantly higher in TETs by 16-fold (mean H-score 75.0 vs 4.6, p = 0.003). Among tumors, univariate analyses showed that higher CD47 expression was correlated with a lower stage (p = 0.032) and more complete resection (p = 0.058). A multivariate analysis accounting for these factors showed that CD47 expression by both H-score and intensity were each highly correlated with WHO histology subtype (p = 0.0005; p = 0.0017 respectively) with lower grade subtypes more frequently found in $CD47^{high}$ tumors. The most frequent subtype in $CD47^{high}$, when compared to $CD47^{low}$ tumors, was AB (61.5% vs 13.7%) and the least frequent was B2 (0% vs 37.3%). Tumors with the highest grade (subtype C, thymic carcinomas) were exclusively $CD47^{low}$. $CD47^{high}$ tumors were associated with an increased incidence of paraneoplastic syndromes (52.4% vs 12.0%, p = 0.0014). **Conclusions:** CD47 expression was found in the vast majority of TETs, and in significantly higher levels than normal thymic tissue. Among tumors, those with higher CD47 expression tended to have lower grade and stage, as well as higher frequency of paraneoplastic syndromes. This study is the first to examine CD47 expression in TETs. Given the prevalent expression of CD47 found in TETs and current available CD47 targeted agents, this study lends support for further investigation of this novel therapeutic approach. Research Sponsor: None.

8587 **Poster Session**

Genomic characterization of thymic epithelial tumor from real-world data. *First Author: Kana Kurokawa, Department of Respiratory Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan*

Background: Thymic epithelial tumors (TETs), including thymic carcinomas and thymomas, are rare neoplasms arising in the mediastinum. Chemotherapy is still the mainstay of treatment and few therapeutic options are available for patients with advanced or metastatic TETs. Due to their rarity, the sample size in the previous reports about the genomic profiles of TETs was small and the results varied from study to study, which hinders the development of treatment. Herein, we investigated the comprehensive genomic characteristics of TETs evaluated in a large genomic database profiled in a real-world setting. **Methods:** Tissue biopsy-based comprehensive genomic profiling was performed in the course of routine clinical care. We included data from two different cohorts: Foundation Medicine Inc. (FMI) in the US (Frampton GM, et al. Nat Biotechnol 2013) and the Center for Cancer Genomics and Advanced Therapeutics (C-CAT) in Japan, which is engaged in a national project for collecting genomic analysis and clinical results from patients. Samples profiled at Foundation Medicine were examined for all classes of alterations in 253 genes targeted across all assays. Tumor mutational burden (TMB) and microsatellite instability (MSI) were calculated as previously described (Chalmers ZR, et al. Genome Med 2017. Trabucco, et al. J Mol Diagn 2019). Patients' background including histology, age, and sex were also investigated, and genetic alteration, TMB, and MSI were stratified by them. **Results:** A total of 794 patients were collected for our study, including 722 cases from FMI and 72 cases from C-CAT. In the FMI data, 414 cases of thymic carcinoma and 308 cases of thymoma were included. *CDKN2A* (39.9%), *TP53* (30.2%) and *CDKN2B* (24.6%) were frequently altered in thymic carcinoma, versus *TP53* (7.8%), *DNMT3A* (6.8%), *CDKN2A* (5.8%) and *CDKN2B* (4.6%) in thymoma. TMB-High (≥ 10muts/Mb) and MSI-High were present in 7.0% and 2.3% of thymic carcinomas, and 1.6% and 0.3% of thymomas, respectively. Comparison of the thymic carcinoma cohort based on age < 60 vs 60+ years found a significant difference in prevalence of *NFKBIA* alterations (2.7% age < 60 vs 11.7% age ≥ 60, p = 0.034), while a similar comparison of the thymoma cohort found no significant differences between age groups. An analysis based on sex did not find any significant differences between groups. 55 cases of thymic carcinoma and 17 cases of thymoma were included from C-CAT data. In thymic carcinoma, *CDKN2A* (27.3%), *TP53* (23.6%) and *CDKN2B* (20.0%) were also frequently altered, while alterations of *TSC1* (23.5%) and *CD22*, *LTK*, *NOTCH1*, *KMT2A*, *SETD2*, *ATM* (17.6% each) were found in thymoma. **Conclusions:** To the best of our knowledge, this is the largest cohort in which genomic alterations, TMB, and MSI status of TETs were investigated. We suggest that several gene mutations, TMB, and MSI status might be potential targets for treatment and lead to therapeutic development opportunities, especially in thymic carcinoma. Research Sponsor: None.

8588 **Poster Session**

Impaired seroconversion after SARS-COV-2 mRNA vaccine in patients with thymic epithelial tumors. *First Author: Erica Pietroluongo, Department of Clinical Medicine and Surgery, University Federico II, Naples, Italy*

Background: Thymic epithelial tumors (TET) are rare malignancies associated with dysregulation of the immune system and humoral and cell mediated immunity abnormalities. Anti-syndrome coronavirus type 2 (SARS-CoV-2) vaccine is effective at preventing COVID-19 morbidity and mortality. No published data are available regarding the immunization in TET patients (pts). The aim of this study was to evaluate the immunization in TET pts who received two doses of mRNA vaccine, by longitudinal serological detection of SARS-COV-2 spike-binding IgG antibody. **Methods:** Starting from April 2021 to October 2021, consecutive TET pts referred to the Rare Tumors Coordinating Center of Campania Region (CRCTR - Naples, Italy) were enrolled. All study subjects received two doses of COVID-19 mRNA vaccine (BNT162b2 by Pfizer-BioNTech). SARS-CoV-2 spike-binding IgG antibody (Ab) serological levels were analyzed by centralized chemiluminescent immunoassay (CLIA) at different time-points, including before 1^{st} vaccine dose (T0) and 1 month after 2^{nd} dose (T2). Cut-off for Ab titers positivity was > 25 AU/mL. **Results:** Forty pts were enrolled; 23 (57.5%) were female and 17 (42.5%) male. Eleven pts (27.5%) suffered from thymic carcinoma, 28 (70%) thymoma, and 1 (2.5%) thymic hyperplasia. At the time of study enrollment, 20 pts (50%) had no evidence of disease (NED) and were in follow-up; the remaining 20 pts had evidence of disease (ED) by imaging and were receiving systemic treatment (55% oral low-dose etoposide-based therapy, 40% somatostatin analogs + prednisone, 5% supportive care). Immune system disorders were diagnosed in 29 TET pts (72.5%): 19 pts (47.5%) had Good's Syndrome (GS) and 10 (25%) other immune disorders. At T0, all enrolled pts had negative Ab titers and no prior SARS-CoV-2 infection. At T2, Ab data were available for 37 pts (92.5%): 18 pts (48.7%) had positive Ab titers, whereas 19 (51.3%) did not achieve seroconversion. Among pts with ED, seroconversion was achieved only in 2 cases (11.8%). Lack of seroconversion at T2 was significantly associated with ED (Fisher's exact test p: 0.0001) and with the presence of GS (Fisher's exact test p: 0.0489). No significant association of seroconversion with other immune disorders and disease features was found. **Conclusions:** Our data showed that TET pts with ED had substantially higher probability of impaired seroconversion after SARS-COV-2 vaccine as compared with NED pts. We warrant further studies to evaluate the role of disease status, anti-tumor treatments and immune disorders in post-vaccine immunization of TET pts. Research Sponsor: None.

8589 **Poster Session**

Immunological signature of patients with thymic epithelial tumors. *First Author: Rocco Morra, Department of Clinical Medicine and Surgery, University Federico II, Naples, Italy*

Background: Thymic epithelial tumors (TETs) are complex diseases frequently associated with immune disorders, including Good Syndrome (GS). Etiopathogenesis of immune dysregulations in TETs patients is still not totally explained. The aim of this study was to evaluate differences in immune cell phenotype, as well as in the serum expression levels of a panel of cytokines, chemokines, and growth factors in patients with TETs and GS with or without autoimmune disorders (AD). **Methods:** From May 2019 to June 2020, consecutive patients with TETs and GS were recruited at Rare Tumors Coordinating Center of Campania Region (CRCTR – Naples, Italy). We analyzed the immunophenotype from peripheral blood focusing on selected immune cell subsets (monocytes, neutrophils, eosinophils, CD4+T cells, CD8+T cells, B-cells, NK cells and NKT- cells, T regulatory cells) processed for blood cell count and immunophenotyping, according to the 8-color immunophenotyping kit and Treg detection kit (CD4/CD25/CD127), and a panel of cytokines, chemokines, and growth factors from peripheral blood serum screened with pre-formed kits by Bioplex multiplex. D'Agostino-Pearson normality test was used to evaluate whether the continuous data were normally distributed, and a two-tailed t-test for independent samples was used. p-values < 0.05 were considered statistically significant. **Results:** Overall, 29 patients were enrolled [17 (58.6%) with and 12 (41.4%) without AD]. Sixteen patients (55.2%) were female and 13 patients (44.8%) were male. Tumor histology included thymoma in all the patients with AD, whereas there were 10 cases of thymoma and 2 of thymic carcinoma in the group of patients without AD. The analysis of leucocytes by blood cell count showed a statistically significant higher number of leucocytes, ascribable to T lymphocytes (p = 0.023), B lymphopenia (p = 0.003) and decrease of T regulatory cells (p = 0.009) in TET patients with AD, as compared with TET patients without AD. Moreover, TET patients with AD showed significantly higher circulating levels of IL-15 (p = 0.032), VEGF (p = 0.007), IP-10 (p = 0.013), GM-CSF (p = 0.042), IL-6 (p = 0.031), and MIP-1α (p = 0.017) with respect to TET patients without AD. **Conclusions:** To our knowledge, this is the first report describing a profound alteration in B and T lymphocytes in TET patients associated with AD. The observed differences may be potentially important in the clinical management of this complex disease. Additional studies are needed to better understand the immunophenotypic alterations in TETs patients. Research Sponsor: None.

TPS8590 **Poster Session**

Neoadjuvant and adjuvant capmatinib in resectable non–small cell lung cancer with *MET* exon 14 skipping mutation or high *MET* amplification: GEOMETRY-N trial. *First Author: Jay M. Lee, David Geffen School of Medicine at UCLA, Los Angeles, CA*

Background: Neoadjuvant therapy is the earliest opportunity to eliminate micrometastatic disease. Emerging data suggest that neoadjuvant therapy in non-small cell lung cancer (NSCLC) can elicit major pathological responses (MPRs) that translate into prolonged survival outcomes, serving as an early surrogate for efficacy. Adjuvant therapy can improve overall and disease-free survival (DFS) in patients with completely resected NSCLC. DFS observed with osimertinib in patients with early-stage *EGFR*-mutated tumors supports evaluation of other tyrosine kinase inhibitors (TKIs) in the neoadjuvant and adjuvant settings. In early-stage NSCLC, *MET* exon 14 skipping mutation (*MET*ex14) and de novo *MET* amplification (*MET*amp) are estimated to occur in up to 2.8% and 1.7% of patients, respectively. Capmatinib, a selective MET TKI, is FDA approved for patients with metastatic *MET*ex14 NSCLC. It was studied in GEOMETRY mono-1 in patients with advanced/metastatic NSCLC with *MET*ex14 or *MET*amp. In 2 treatment-naive *MET*ex14 cohorts, overall response rate (ORR) was 68% and 66%. In a treatment-naive high-level *MET*amp cohort, ORR was 40%. Capmatinib had a tolerable safety profile; most adverse events were reversible with dose adjustments. Based on the ORRs and safety profile observed in treatment-naive patients with advanced/metastatic *MET*-dysregulated NSCLC, GEOMETRY-N (NCT04926831), a Phase II, 2-cohort, 2-stage study, is evaluating the efficacy and safety of neoadjuvant and adjuvant capmatinib therapy in improving the MPR rate and outcomes in patients with *MET*ex14 or high-level *MET*amp NSCLC. **Methods:** Adults with resectable, histologically confirmed NSCLC stage IB-IIIA, N2 and select IIIB (T3N2 or T4N2) with either *MET*ex14 (cohort A) or high-level *MET*amp (gene copy number ≥10; cohort B) are eligible. *MET*ex14 must be determined by a Clinical Laboratory Improvement Amendments (CLIA)-certified lab. *MET*amp must be determined by fluorescence in situ hybridization at a CLIA-certified lab or by FoundationOne CDx next-generation sequencing. Prior systemic anticancer therapy is prohibited. Patients will receive capmatinib 400 mg twice daily for 8 weeks before surgical resection, followed by 3 years of adjuvant capmatinib. In the 2-stage design, stage 1 will enroll 9 patients per cohort, with MPR evaluated in each cohort after 9 patients have completed neoadjuvant therapy; stage 2, enrolling 10 more patients in a cohort, will proceed only if ≥1 of 9 participants has an MPR. About 42 patients will be enrolled, with 19 evaluable patients per cohort. Primary endpoint is MPR rate (local assessment). Secondary endpoints are complete pathological response rate (central and local review), ORR (local assessment), DFS, and safety. Following treatment, there will be a 2-year survival follow-up. Enrollment has started; expected first patient first visit: March 31, 2022. Clinical trial information: NCT04926831. Research Sponsor: Novartis Pharmaceuticals.

TPS8591 **Poster Session**

Phase III study with atezolizumab versus placebo in patients with malignant pleural mesothelioma after pleurectomy/decortication (AtezoMeso study). *First Author: Maria Pagano, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy*

Background: Surgery for malignant pleural mesothelioma (MPM) is indicated mainly in multimodal approaches and in clinical trial settings. Different studies have shown significantly lower complication rates, lower peri-operative morbidity and mortality with pleural/decortication (P/D), with similar overall survival rates. The biology of mesothelioma shows significant heterogeneity. Surgical tumor reduction may create a host environment more amenable to immunotherapy by reducing the ratio of tumor cells versus antitumor effector T lymphocytes, reducing the quantities of intratumor and/or systemic immunosuppressive cells, and ablating tumor-derived paracrine factors that promote local recruitment of immunosuppressive cells. Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit. The AtezoMeso Study evaluates the introduction of atezolizumab-ATEZO in MPM, patients (pts) after P/D and platinum/pemetrexed perioperative therapy. **Methods:** This is a double-blind, placebo controlled, phase III trial, in 20 Italian centers. Main inclusion criteria are P/D without macroscopic residual and ECOG-PS 0-1. Pts who underwent to P/D without macroscopic residual disease and have received at least 4 cycles of perioperative therapy with cisplatin/carboplatin and pemetrexed, will be randomized (2:1) to receive ATEZO or placebo. Therapy will be administered at dose of 1,200 mg iv, every 21 days, for 12 months or until recurrence, unacceptable toxicity or patient/physician decision. Randomization will be done through a centralized system, using histology (epithelioid vs nonepithelioid) and stage (I vs > I) as stratification factors. Pts will be radiologically evaluated after surgical before starting therapy and then every 12 weeks for 24 months or until recurrence. Quality of life (QoL) will be evaluated with the EQ-5D questionnaire administered at baseline and every 12 weeks. Tissue tumor samples will be centrally analyzed to determinate the genomic profile using FoundationOne CDx platform. The primary endpoint is the evaluation of the atezolizumab efficacy in terms of disease free survival (DFS). Secondary endpoints include the safety and efficacy in terms of overall survivall and QoL. Assuming a median DFS equal to 9 months in placebo arm, an accrual time of 24 months and a follow-up time of 24 months, a sample size of 162 pts will allow to detect true hazard ratios of 0.62 with power 0.8, at a confidence level of 95%. At February 14th, 2022, 3 pts have been enrolled. Clinical trial information: 2020-003762-39; GOIRC-02-2019. Research Sponsor: Roche.

TPS8592 **Poster Session**

Assessing the predictive value of ctDNA on relapse in patients with resected stage IB-IIIA NSCLC treated with adjuvant chemotherapy plus concomitant atezolizumab followed by atezolizumab: BTCRC LUN 19-396. *First Author: Fatemeh Ardeshir-Larijani, Indiana University, Melvin and Bren Simon Cancer Center, Indianapolis, IN*

Background: A standard of care treatment for most patients with stage II and III non-small cell lung cancer (NSCLC) and a PD-L1 > 1% is surgery followed by adjuvant (adj) histology-specific chemotherapy followed by 1 year of atezolizumab. The benefit of adding atezolizumab concomitantly to chemotherapy in the adj setting has not been reported. In addition, the optimal duration of adjuvant therapy is undefined. Emerging data have demonstrated the potential for ctDNA to predict clinical recurrence in patients with surgically resected lung, breast, and colon cancer. The current study explores the predictive value of ctDNA for early relapse in patients treated with adj chemotherapy plus atezolizumab. **Methods:** The LUN19-396 is a phase II biomarker study that enrolls pts with resected NSCLC stage IB (tumors ≥ 4cm), IIA, IIB, and select IIIA (T3N1-2, T4N0-2). The ctDNA will be assessed within 60 days post-surgery and then every 3 months up to 12 months. All pts will receive treatment with 4 cycles of Cisplatin 60-75mg/m2 + Docetaxel 60-75mg/m2 + Atezolizumab 1200mg IV on day 1 q 3w (for patients with squamous cell cancer) or Cisplatin 60-75mg/m2 + Pemetrexed 500mg/m2 + Atezolizumab 1200mg on day 1 IV q 3w (for patients with non-squamous cell), followed by up to 13 additional cycles of Atezolizumab 1200mg IV every 3w. This trial will enroll a total of 100 pts to achieve more than 80% power. The primary objective is to estimate the percentage of pts with detectable ctDNA after surgery who have clearance of ctDNA at designated time points during adjuvant therapy. The key secondary objective is to estimate the 1-year disease-free survival in pts with undetectable ctDNA after 4 cycles of adj chemotherapy plus atezolizumab who had detectable ctDNA after surgery. This trial has enrolled 17 pts as of February 8, 2022. Clinical trial information: NCT04367311. Research Sponsor: Genentech.

TPS8593 **Poster Session**

A phase 1/2 study of REGN5093-M114, a METxMET antibody-drug conjugate, in patients with mesenchymal epithelial transition factor (MET)-overexpressing NSCLC. *First Author: Alexander E. Drilon, Department of Medicine, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY*

Background: MET, also called hepatocyte growth factor receptor (HGFR), is a high-affinity transmembrane protein receptor for HGF. MET is overexpressed in various malignancies, including non-small cell lung cancer (NSCLC). MET overexpression can accompany *MET* exon 14 alteration or de novo/acquired *MET* amplification. REGN5093-M114 is an antibody drug conjugate composed of a novel linker-payload (M114, carrying the maytansine derivative M24, a potent inhibitor of microtubule assembly) covalently bound to lysine residues on a MET-targeting human IgG4p bispecific antibody, REGN5093. In preclinical models of MET overexpressing cancers, REGN5093-M114 demonstrated significant dose-dependent antitumor activity. **Methods:** This is an open label, phase 1/2, first-in-human, multicenter dose-escalation study with cohort expansion evaluating REGN5093-M114 in patients with MET-overexpressing NSCLC (NCT04982224). Patients must have advanced stage NSCLC for which there are no approved therapies available expected to confer clinical benefit, with tumor overexpressing MET (≥75% tumor cell staining at 2+) as centrally confirmed by immunohistochemistry. For the expansion phase, patients must have at least one lesion that is measurable by RECIST 1.1. REGN5093-M114 will be administered intravenously once every 3 weeks over 30 minutes until disease progression, intolerable adverse events, withdrawal of consent, or study withdrawal. The primary objectives in dose escalation are to evaluate safety, tolerability, PK, and maximum tolerated dose and/or recommended phase 2 dosing regimen of REGN5093-M114. PKs will include the assessment of REGN5093-M114, total antibody, and payload M24 concentrations. The primary objective in dose expansion is to assess preliminary anti-tumor activity of REGN5093-M114 in MET-overexpressing NSCLC as measured by the objective response rate. The secondary objectives of both phases of the study include an evaluation of treatment durability, and the immunogenicity of REGN5093-M114. This study is currently open to enrollment. Clinical trial information: NCT04982224. Research Sponsor: Regeneron Pharmaceuticals, Inc.

TPS8594 **Poster Session**

LIBRETTO-001 cohort 7: A single-arm, phase 2 study of neoadjuvant selpercatinib in patients with resectable stage IB-IIIA *RET* fusion-positive NSCLC. *First Author: Ravi Rajaram, Department of Thoracic and Cardiovascular Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Despite definitive surgery and perioperative chemotherapy, many patients with locoregional non-small cell lung cancer (NSCLC) continue to experience recurrent disease and limited survival. Although targeted therapies are standard treatment for metastatic NSCLC with genomic alterations, their use in the early-stage setting is still being characterized. Initial studies examining targeted therapy in neoadjuvant setting for early-stage epidermal growth factor receptor positive NSCLC has shown promise. Selpercatinib is a highly selective, potent, and central nervous system active rearranged during transfection (RET) inhibitor with demonstrated robust and sustained antitumor activity and manageable toxicity in patients with *RET* fusion-positive advanced NSCLC. Cohort 7 of the Phase 2, open-label, single arm LIBRETTO-001 study evaluates efficacy and safety of neoadjuvant selpercatinib in patients with resectable stage IB-IIIA *RET* fusion-positive NSCLC (NCT03157128). **Methods:** Key eligibility criteria include age ≥18 years; histologically confirmed stage IB–IIIA NSCLC (AJCC, version 8); presence of *RET* fusion in tumor (by PCR or NGS) or blood (by NGS) (pre-treatment biopsy confirmed); resectable and operable tumor; measurable disease (RECIST 1.1); and ECOG performance status 0-1. Key exclusion criteria include presence of other known oncogenic drivers; and concurrent investigational anticancer therapy. Eligible patients will undergo full staging including radiographic tumor measurements using CT, PET, and brain MRI at baseline and after two 28-day cycles of neoadjuvant selpercatinib, followed by surgery. Dosing regimen is 160 mg twice daily. Resected tumor specimens will be sent to an Independent Pathology Review Committee (IPRC) for evaluation. Patients may then be treated with stage-appropriate adjuvant therapy/surveillance, based on the treating physician's decision, followed by selpercatinib until disease recurrence, unacceptable toxicity, withdrawal, or death, for a maximum treatment duration of 3 years. The primary endpoint is to determine the rate of major pathologic response (MPR) by IPRC, defined as ≤ 10% residual viable tumor cells in the surgically resected specimen. Efficacy based on the MPR will be assessed using the Simon's 2-stage design. In Stage I, 9 patients will be enrolled; if ≤1 patient achieves an MPR, the study will be stopped. Otherwise, at least 10 additional patients will be enrolled, with a total of 19 patients undergoing surgery. The rate of pathologic complete response (pCR) by IPRC, disease-free survival, and overall survival will be assessed as secondary endpoints. pCR rate will be determined at the time of surgery, indicating no remaining viable tumor cells. Safety of peri-operative treatment will be assessed, including 30- and 90-day post-operative readmission and mortality rates. Clinical trial information: NCT03157128. Research Sponsor: Eli Lilly and Company.

TPS8595 **Poster Session**

A first-in-human phase 1 study of the next-generation RET inhibitor, LOXO-260, in RET inhibitor refractory patients with RET-altered cancers (trial in progress). *First Author: Nathan A. Pennell, Department of Hematology and Medical Oncology, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH*

Background: *RET* fusions are found in 1-2% of lung adenocarcinomas and 10-20% of papillary thyroid carcinomas. Activating *RET* mutations occur in 50-60% of medullary thyroid cancers (MTCs). Selpercatinib was the first selective RET inhibitor approved by the FDA and is indicated for patients (pts) with *RET* fusion-positive NSCLC and thyroid cancer, and *RET* mutant MTC. Despite marked and durable activity, acquired resistance can eventually develop through a variety of mechanisms. These include acquisition of RET G810X mutations at the solvent front of the ATP pocket. LOXO-260 is a highly potent and selective inhibitor of RET designed to have activity against both solvent front and gatekeeper mutations, expressed alone or together, while maintaining potency against *RET* fusions or mutations (Kolakowski GR. et al. 2021 *Cancer Research* 81 (13 Suppl) 1464). **Methods:** LOXO-NGR-21001 is a global, open-label, first-in-human phase 1 study of LOXO-260 in pts with *RET* fusion-positive advanced solid tumors and *RET* mutant MTC who received a prior selective RET inhibitor. Phase 1a dose escalation will utilize a modified i3+3 design, allowing for pt backfill to previously cleared dose levels. Phase 1b dose expansion will evaluate LOXO-260 in specific expansion cohorts: *RET* fusion-positive NSCLC or thyroid cancers and *RET* mutant MTC. The primary objectives in dose escalation are to determine the MTD/RP2D and safety of LOXO-260. Key secondary objectives include characterization of PK and preliminary antitumor activity of LOXO-260 per RECIST v1.1. The primary objective of dose expansion is to assess the antitumor activity of LOXO-260 based on investigator-assessed overall response rate (ORR). Key secondary objectives are to characterize the PK and antitumor activity of LOXO-260 based on progression-free survival (PFS), time to response (TTR), and duration of response (DOR). Eligible pts must have received a prior selective RET inhibitor, have a documented *RET* fusion or *RET* mutation and a diagnosis of locally advanced, unresectable and/or metastatic cancer per disease-specific criteria, and must have progressed or be intolerant to standard therapies or must have refused such a therapy. Pts must be ≥18 years old and have an ECOG PS of 0-2. Key exclusion criteria include presence of serious cardiac conditions, interstitial lung disease, symptomatic CNS metastases, or carcinomatous meningitis. Clinical trial information: NCT05241834. Research Sponsor: Loxo Oncology.

TPS8596 **Poster Session**

LCMC LEADER neoadjuvant screening trial: LCMC4 evaluation of actionable drivers in early-stage lung cancers. *First Author: Boris Sepesi, Thoracic and Cardiovascular Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Comprehensive genomic profiling (CGP) has transformed the care of patients with advanced non-small cell lung cancer (NSCLC), giving many patients access to precision targeted treatment and immunotherapy with remarkable improvements in outcomes. Studies show that patients with lung cancers with oncogenic drivers are the least likely group to benefit from checkpoint inhibitors and are better served by enrollment in studies of targeted therapies. Early-stage NSCLC is now poised to benefit from these precision approaches with the regulatory approval of the first tyrosine kinase inhibitors and checkpoint inhibitors for the adjuvant treatment of resected NSCLC, each requiring testing for precision biomarkers. Neoadjuvant precision therapy for NSCLC has the potential to further improve treatment outcomes. **Methods:** The LCMC4 Evaluation of Actionable Drivers in EaRly Stage Lung Cancer (LEADER) Neoadjuvant Screening Trial (NCT04712877) is a collaborative diagnostic study developed by the Lung Cancer Mutation Consortium (LCMC), supported by the Thoracic Surgery Oncology Group and the Lung Cancer Research Foundation. The primary objective is to determine the proportion of patients with stage IA2-III lung cancers who possess actionable oncogenic drivers, defined as 1 of 11 actionable genomic alterations: mutations in *EGFR, BRAF*^{V600E} , *MET* exon 14, *KRAS* G12C, and *HER2*, rearrangements in *ALK, RET, NTRK, and ROS1,* and amplification of *MET* and *HER2*. The study will also assess the feasibility of CGP to detect actionable oncogenic drivers in patients with suspected early-stage lung cancers scheduled to undergo biopsies to establish the diagnosis of lung cancer. The protocol will enroll 1000 patients with operable stage IA2-III (TNM 8th edition) lung cancer who will undergo CGP utilizing the Foundation Medicine 324 gene assay as well as paired liquid biopsy analysis. Results will enable selection of neoadjuvant therapy and enrollment onto independent therapeutic trials with genomically matched neoadjuvant treatment, standard therapies, or other trials if no driver is detected. The approach will be considered feasible if >35% of non-squamous NSCLCs have 1 of the 11 actionable alterations. Tumor mutational burden and PD-L1 IHC will be assessed. Plasma specimens collected pre- and post neoadjuvant treatment and post-surgery will be used for research to study the ability of circulating tumor DNA to assess neoadjuvant treatment response and minimal residual disease. 26 academic sites in the US plan to enroll patients. Clinical trial information: NCT04712877. Research Sponsor: Genentech, Other Foundation, Pharmaceutical/Biotech Company.

TPS8597 **Poster Session**

Phase 3, randomized, placebo-controlled study of stereotactic body radiotherapy (SBRT) with or without pembrolizumab in patients with unresected stage I or II non–small cell lung cancer (NSCLC): KEYNOTE-867. *First Author: Salma K. Jabbour, Department of Radiation Oncology, Rutgers Cancer Institute of New Jersey, Robert Wood Johnson Medical School, Rutgers University, New Brunswick, NJ*

Background: Anti–PD-(L)1-directed therapy following radiotherapy or following concurrent chemoradiation is associated with significantly longer PFS and OS in patients with advanced or metastatic NSCLC, including those with locally advanced inoperable tumors. KEYNOTE-867 (NCT03924869) evaluates the efficacy and safety of SBRT with or without pembrolizumab in patients with unresected stage I or II NSCLC. **Methods:** In this phase 3, randomized, placebo-controlled study, approximately 530 adult patients with previously untreated, unresected, histologically/cytologically confirmed stage I or II (T1 to limited T3, N0, M0) NSCLC are randomized 1:1 to receive thoracic SBRT to primary tumors for ≤2 wk (Table) and either pembrolizumab 200 mg or placebo every 3 wk for 17 cycles (approximately 1 year) or until disease recurrence, development of unacceptable AEs, SBRT not started for any reason, or study withdrawal. Randomization is stratified by disease stage (I vs II), ECOG PS (0 or 1 vs 2), geographic region (East Asia vs non-East Asia), and reason for not receiving surgery (medically inoperable vs refused surgery). Imaging assessment by blinded independent central review (BICR) occurs at 12 wk (≥10 wk after SBRT completion), followed by every 16 wk for 3 y, and then every 6 mo. Primary endpoints are event-free survival (EFS) by BICR and OS. Secondary endpoints include time to death or distant metastases and safety; exploratory endpoints are time to subsequent treatment, disease-specific survival, and time to recurrence/progression on subsequent line of therapy. AEs are monitored throughout the trial until 30 d after last dose (90 for serious AEs) and graded according to NCI CTCAE version 4.0. EFS and OS are analyzed by the nonparametric Kaplan-Meier method, treatment differences by stratified log-rank test, and hazard ratios by stratified Cox proportional hazard model with Efron's method of tie handling. Enrollment started on June 17, 2019, and is ongoing at 168 sites around the world. Clinical trial information: NCT03924869. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Stereotactic body radiotherapy regimen.[a]

Unit Dose Strength(s)	
Peripheral tumors	45–60 Gy in 3 fractions (preferred regimen); 48–50 Gy in 4 fractions or 50–55 Gy in 5 fractions (acceptable regimens)
Tumors abutting the chest wall	48–50 Gy in 4 fractions; 50–55 Gy in 5 fractions
Central tumors	50–55 Gy in 5 fractions; 60–70 Gy in 8 fractions

[a]Regimens have been amended since the original protocol.

TPS8598 **Poster Session**

Phase 2 randomized trial of neoadjuvant or palliative chemotherapy with or without immunotherapy for peritoneal mesothelioma (Alliance A092001). *First Author: Aaron Scott Mansfield, Mayo Clinic, Rochester, MN*

Background: Peritoneal mesothelioma is a rare and poorly studied disease with few treatment options. For patients who are not surgical candidates, treatment recommendations for systemic therapy have been extrapolated from clinical trials for pleural mesothelioma that commonly exclude patients with peritoneal mesothelioma. Recently, the combination of the PD-1 inhibitor nivolumab and the CTLA-4 inhibitor ipilimumab received FDA-approval for the frontline treatment of non-resectable pleural mesothelioma. Additionally, a prospective, non-randomized phase 2 trial demonstrated activity with combined PD-L1 (atezolizumab) and VEGF (bevacizumab) blockade in peritoneal mesothelioma. In parallel, encouraging activity with combined chemo-immunotherapy has been reported in pleural mesothelioma. Given the benefits observed with immunotherapy, and the potential to improve upon those with chemotherapy and VEGF inhibition, we seek to determine whether the addition of the PD-L1 inhibitor atezolizumab improves outcomes with chemotherapy and bevacizumab in patients with newly diagnosed peritoneal mesothelioma. **Methods:** A092001 is a prospective, randomized phase 2 clinical trial. All patients with newly diagnosed peritoneal mesothelioma will be randomized 1:1 using a dynamic allocation Pocock-Simon procedure to receive carboplatin, pemetrexed, and bevacizumab, with or without atezolizumab, every 21 days for four cycles. Patients who are eligible to proceed with surgery after four cycles of therapy will then do so. Patients who are not eligible to proceed with surgery may receive maintenance bevacizumab and atezolizumab, or second-line atezolizumab with bevacizumab until progression of disease or toxicity. The primary objective is to determine whether frontline treatment with carboplatin, pemetrexed, bevacizumab and atezolizumab results in a superior best response rate (RR) to carboplatin, pemetrexed and bevacizumab as determined by RECIST. With 31 eligible patients per arm (62 eligible total), this randomized design has 80% power to detect an improvement in the RR from 20% to 45%, with a 1-sided significance level of 0.10 where an interim futility analysis will be conducted after 32 patients are enrolled. As stratification factors we have included eligibility for cytoreductive surgery at diagnosis, and histologic subtype. Secondary endpoints include assessment of progression-free survival, overall survival, and adverse events. As integrated biomarkers, we will determine if soluble mesothelin-related peptides and megakaryocyte potentiating factor correlate with responses. This trial was recently approved by the National Cancer Institute Central IRB and is activating at sites across the country. Support: U10CA180821, U10CA180882. Clinical trial information: NCT05001880. Research Sponsor: U.S. National Institutes of Health.

TPS8599 **Poster Session**

DREAM3R: Durvalumab with chemotherapy as first-line treatment in advanced pleural mesothelioma—A phase 3 randomized trial. *First Author: Patrick M. Forde, The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD*

Background: Combination PD1/CTLA4 immune checkpoint blockade and platinum-pemetrexed (CP) chemotherapy are standard first-line options for the treatment of unresectable malignant pleural mesothelioma (MPM). Two recent, single-arm, phase 2 trials (DREAM and PrE0505) combining the PD-L1 inhibitor durvalumab and standard first line CP both exceeded pre-specified efficacy criteria. The Phase 3 DREAM3R trial aims to determine the effectiveness of including durvalumab with first line CP chemotherapy in advanced MPM. **Methods:** Treatment-naïve patients with advanced MPM will be randomized (2:1) to either durvalumab 1500 mg every 3 weeks plus chemotherapy (cisplatin 75 mg/m2 or carboplatin AUC 5 and pemetrexed 500 mg/m2) every 3 weeks for 4-6 cycles (Arm A), followed by durvalumab 1500 mg every 4 weeks until disease progression, unacceptable toxicity or patient withdrawal, versus doublet chemotherapy alone for 4-6 cycles with all patients monitored for progression. The target sample size is 480 patients recruited over 27 months, with follow up for an additional 24 months. This provides over 85% power if the true hazard ratio for overall survival (OS) is 0.70, with 2-sided alpha of 0.05, assuming a median OS of 15 months in the control group. Key eligibility criteria include: MPM of any histological subtype; measurable disease per RECIST 1.1 modified for mesothelioma (mRECIST 1.1); ECOG PS 0-1; and adequate hematologic, renal, and liver function. Exclusions: Prior systemic anticancer treatment for MPM, diagnosis based solely on cytology or fine needle aspiration biopsy, contraindication to immunotherapy or conditions requiring immunosuppressive agents or corticosteroids. Patients will be further stratified at randomization by: Age (18-70 years vs. > 70), sex, histology (epithelioid vs. non-epithelioid), planned platinum (cisplatin vs. carboplatin) and geographic region (USA vs. ANZ). The primary endpoint is OS. Secondary endpoints include progression-free survival; objective tumor response; adverse events; health-related quality of life; and healthcare resource use in ANZ. Tertiary correlative objectives aim to further explore and validate potential prognostic and/or predictive biomarkers (including those identified in the DREAM and PrE0505 studies, PD-L1 expression, tumor mutation burden, genomic characteristics, and HLA subtypes) via tissue and serial blood samples. An imaging databank will be assembled for validation of radiological measures of response, and studies of possible radiomic biomarkers in mesothelioma. The study is active and enrolling in both ANZ and in the US. Clinical trial information: NCT04334759 and ACTRN 12620001199909. Research Sponsor: AstraZeneca.

TPS8600 **Poster Session**

An open-label, multicenter, phase 2 study of the safety and efficacy of navtemadlin (KRT-232) in patients with *TP53* wild-type relapsed/refractory small cell lung cancer. *First Author: Afshin Dowlati, University Hospitals Seidman Cancer Center and Case Western Reserve University, Cleveland, OH*

Background: Small cell lung cancer (SCLC) is a highly aggressive neuroendocrine tumor characterized by early metastasis and a high recurrence rate with currently available treatment options. Although SCLC is generally sensitive to initial chemotherapy, responses are not durable and most patients eventually relapse. Prognosis is poorer in the relapsed/refractory (R/R) setting and currently available treatment options, including checkpoint inhibitors, are associated with a median overall survival of 2-9 months (Chauhan 2020; Trigo 2020; Chung 2020). Approximately 15% of patients have a *TP53* wild-type ($TP53^{WT}$) gene. In patients with extensive-stage SCLC, $TP53^{WT}$ is paradoxically associated with an inferior response to chemotherapy (Dowlati 2016). Thus, the presence of $TP53^{WT}$ may help identify a small subset of patients with an even greater unmet need. Murine double minute 2 (MDM2) is the key negative regulator of the tumor suppressor protein, p53, which can induce apoptosis of malignant cells by shifting the balance between prosurvival and proapoptotic BCL-2 family members. In SCLC cell lines, MDM2 inhibition restored p53 function leading to downregulation of prosurvival Bcl-2 and Mcl-1 proteins, and upregulation of the proapoptotic Bim protein, thereby inducing cancer cell death (Yu 2019). Navtemadlin (KRT-232) is a potent, selective, orally available MDM2 inhibitor that restores p53 function to drive apoptosis of $TP53^{WT}$ malignancies. Treatment with navtemadlin may be an effective strategy for patients with $TP53^{WT}$ SCLC. **Methods:** The open-label, multicenter Phase 2 KRT-232-112 study (NCT05027867) is evaluating navtemadlin in $TP53^{WT}$ patients with R/R SCLC. Eligibility criteria include age ≥18 years, ECOG performance status ≤2, presence of measurable disease and demonstrated radiographic progression after ≥1 prior platinum-containing therapy with no curative therapy available. Patients must have received a checkpoint inhibitor if available and not contraindicated. Patients with symptomatic or uncontrolled central nervous system metastases or those with prior MDM2 inhibitor treatment will be excluded. In part 1 of the study, approximately 20 patients will be randomly assigned to receive oral navtemadlin once daily in 21-day cycles at 240 mg 7 days (D) on/14D off (Arm A) or 180 mg 7D on/14D off (Arm B) until disease progression or unacceptable toxicity. In part 2, an additional 18 patients will be enrolled in each arm selected for expansion. The primary endpoint is objective response rate per RECIST v1.1. Secondary endpoints include duration of response, progression-free survival, overall survival, disease control rate, and safety. This trial is ongoing and will enroll patients at approximately 40 global sites. Clinical trial information: NCT05027867. Research Sponsor: Kartos Therapeutics, Inc.

TPS8601 **Poster Session**

TRUST-II: A global phase II study for taletrectinib in *ROS1* fusion–positive lung cancer and other solid tumors. *First Author: Misako Nagasaka, University of California Irvine School of Medicine and Chao Family Comprehensive Cancer Center, Orange, CA*

Background: Taletrectinib (AB-106/DS-6051b) is a next-generation, brain-penetrant, ROS1/ NTRK tyrosine kinase inhibitor (TKI) and has shown clinically meaningful effect and safety profile in ROS1+ Non-Small Cell Lung Cancer (NSCLC) patients in phase 1 studies (Fujiwara et al, Oncotarget 2018; 9(34): 23729-23737; Ou et al, JTO Clin Res Rep. 2020 Oct 21;2(1):100108). Taletrectinib has also demonstrated activity against ROS1 G2032R resistance mutation and CNS metastases in the ongoing phase 2 TRUST study (NCT04395677) in China. Also, taletrectinib has shown preliminary efficacy against NTRK positive solid tumors in an ongoing phase 2 study (NCT04617054). **Methods:** TRUST-II study (NCT04919811) is a phase 2, global, multicenter, open-label, single-arm multicohort study evaluating the efficacy and safety of taletrectinib for *ROS1* fusion-positive advanced metastatic NSCLC and other solid tumors. Taletrectinib will be given at 600 mg once daily in 21-day cycle. The patients with ROS1 fusions detected by local tests are eligible to enroll with retrospective confirmation by a central laboratory. The study consists of four cohorts: cohort 1: systemic chemotherapy naïve or ≤ one prior line and ROS1 TKI naïve NSCLC (N = 53); cohort 2: previously treated with one ROS1 TKI (crizotinib or entrectinib) and with progression who are either chemotherapy naïve or ≤ one line of platinum and/or pemetrexed based therapy for NSCLC (N = 46); cohort 3: ≤ 2 prior ROS1 TKIs and with progression who are either chemotherapy naïve or ≤ 2 lines of platinum and/or pemetrexed based therapy for NSCLC (N = 10); and cohort 4: systemic chemotherapy naïve or ≤ 2 prior lines of chemotherapy, but ROS1-TKI naïve ROS1 positive solid tumor other than NSCLC (N = 10). The primary endpoint is objective response rate (ORR) (RECIST v1.1) by independent review committee (IRC) assessment for cohorts 1 and 2. Key secondary endpoints include IRC-assessed duration of response, IRC-assessed intra-cranial ORR, progression free survival (PFS), overall survival (OS), and safety. This study is currently recruiting in Japan, Republic of Korea, and USA. Additional accrual is planned in Canada, China, and European Union. Clinical trial information: NCT04919811. Research Sponsor: AnHeart Therapeutics Inc.

TPS8603 **Poster Session**

Phase 2 study of tarlatamab, a DLL3-targeting, half life–extended, bispecific T-cell engager (HLE BiTE) immuno-oncology therapy, in relapsed/refractory small cell lung cancer (SCLC). *First Author: Suresh S. Ramalingam, Winship Cancer Institute of Emory University, Atlanta, GA*

Background: SCLC is characterized by rapid growth and early development of metastases. Platinum-based first-line chemotherapy is associated with a high initial response rate; however, disease recurrence is common. Delta-like ligand 3 (DLL3) is a Notch ligand that is upregulated and aberrantly expressed on the cell surface in most SCLC, making it a compelling therapeutic target. Tarlatamab is an HLE BiTE immuno-oncology therapy designed to bind DLL3 on target cancer cells and CD3 on T cells, forming a cytolytic synapse inducing T cell activation and expansion and T cell-dependent killing of tumor cells. Interim results of an ongoing first-in-human study in patients with relapsed/refractory SCLC (NCT03319940) show preliminary evidence for tarlatamab efficacy in pretreated patients with confirmed partial responses in 20% of patients and duration of response of 8.7 months (Owonikoko TK, et al. Abstract 8510. Presented at: ASCO Annual Meeting, June 4–8, 2021; Virtual). Grade ≥ 3 treatment-related AEs (TRAEs) occurred in 27% of patients and TRAEs resulted in discontinuation in 5% of patients. This promising efficacy/safety profile supports further study of tarlatamab in SCLC. **Methods:** NCT05060016 is a phase 2, open-label study evaluating tarlatamab in patients with relapsed/refractory SCLC after two or more lines of prior treatment. Part 1 is a dose characterization phase in which subjects will be randomized 1:1 to two active doses of tarlatamab. Part 2 will continue enrollment for the selected target dose only based on interim analysis of Part 1. Key eligibility criteria include adults with histologically or cytologically confirmed SCLC whose disease progressed/recurred after two or more lines of prior treatment including at least 1 platinum-based regimen (including a PD-L1 inhibitor, if standard of care, with certain exceptions per protocol), treated brain metastases, ECOG performance status ≤1, and life expectancy ≥ 12 weeks in the opinion of the investigator. The primary endpoint for the primary analysis is ORR per RECIST 1.1 as assessed by blinded independent central review. Secondary objectives are to evaluate antitumor activity by additional measures (duration of response, progression-free survival, disease control rate and duration, overall survival), safety and tolerability, immunogenicity, and pharmacokinetics. Sites in North America, Asia and Europe are participating in the trial with subjects already enrolled and enrollment ongoing. Clinical trial information: NCT05060016. Research Sponsor: Amgen Inc.

TPS8604 **Poster Session**

MC1923 phase II clinical trial of durvalumab (MEDI4736) and topotecan or lurbinectedin in patients with relapsed extensive-stage small cell lung cancer previously treated with chemotherapy and immunotherapy. *First Author: Konstantinos Leventakos, Department of Oncology, Mayo Clinic, Rochester, MN*

Background: Chemoimmunotherapy followed by durvalumab maintenance yields a median overall survival of 12.9 months in patients with extensive stage Small Cell Lung Cancer (ES SCLC), which is an improvement over chemotherapy alone. However, 90% of these patients will have progressive disease. While topotecan and lurbinectedin have established modest activity in the second line, it is unknown whether continuing immunotherapy in this setting confers additional benefit. In preclinical studies lurbinectedin, a DNA minor groove binder, used with immune checkpoint inhibitors has synergistic effects. **Methods:** This phase 2 trial is enrolling patients with ES SCLC who have progressed on platinum based chemoimmunotherapy, to three treatment groups. Group 1 includes patients with platinum sensitive SCLC who will receive durvalumab (1500 mg given as an intravenous [IV] infusion once every 3 weeks) and topotecan (1.25 mg/m^2/day IV for 5 consecutive days every 3 weeks). In Groups 2A and 2B, patients with platinum sensitive and platinum resistant disease respectively, receive durvalumab and lurbinectedin (3.2 mg/m^2 IV on Day 1 of every 21-day cycle). Patients with platinum sensitive disease are assigned to Groups 1 or 2A based on the preferences of the treating physician and the patient. Patients with treated/stable CNS metastases are eligible. The primary endpoint is the proportion of patients who are alive at 6 months (6OS) for Group 1 and the proportion of patients who are alive and progression-free at 6 months (6PFS) in Groups 2A and 2B. Secondary endpoints include safety, adverse event profile, response rate, PFS, and OS. The sample size is based on a 2-stage Simon Optimal Design. For Treatment Group 1, with 22 eligible patients there is 80% power to detect a true 6-month OS rate (6OS) of 75%, with 10% alpha under the null hypothesis that the true 6OS is at most 50%. For Treatment Group 2A, with 20 eligible patients this design has 80% power to detect a true 6-month PFS rate (6PFS) of 65%, with 10% alpha under the null hypothesis that the true 6PFS is at most 40%. For Treatment Group 2B, with 22 eligible patients this design has 80% power to detect a true 6-month PFS rate (6PFS) of 40%, with 10% alpha under the null hypothesis that the true 6PFS is at most 19%. To account for possible drop-outs, accrual targets will be 24, 22, and 24 patients to Groups 1, 2A, and 2B respectively. For the safety analyses, 6 patients will be enrolled at the starting dose level for each treatment group (1, 2) and then briefly closed to accrual to assess adverse events. If we observe 2+ DLTs in these 6 treated patients during Cycle 1 within a treatment group (1 vs. 2), we will declare the combination treatment too toxic and lower the starting dose of chemotherapy for the next 6 patients. The study was open for all 3 groups as of January 2022 and has accrued 2 patients. Clinical trial information: NCT04607954. Research Sponsor: AstraZeneca.

TPS8606 **Poster Session**

KeyVibe-008: Randomized, phase 3 study of first-line vibostolimab plus pembrolizumab plus etoposide/platinum versus atezolizumab plus EP in extensive-stage small cell lung cancer. *First Author: Jacob Sands, Dana-Farber Cancer Institute, Boston, MA*

Background: Current standard of care immunotherapy plus chemotherapy options for first-line extensive-stage small-cell lung cancer (ES-SCLC) are associated with modest improvements in median OS and PFS. In the KEYNOTE-604 study, first-line pembrolizumab plus etoposide/platinum (EP) significantly improved PFS (HR 0.75; 95% CI, 0.61–0.91; $P = 0.0023$) compared with placebo plus EP in ES-SCLC; OS was also longer with pembrolizumab plus EP vs placebo plus EP but did not reach statistical significance (HR 0.80; 95% CI, 0.64–0.98; $P = 0.0164$). Preclinical and clinical data suggest that blocking the interaction between the T-cell immunoreceptor with immunoglobulin and ITIM domains (TIGIT) and its ligands CD112 and CD155 with the anti-TIGIT humanized monoclonal antibody vibostolimab (MK-7684) yields promising antitumor activity when combined with pembrolizumab, with or without chemotherapy, including in patients with lung cancer. The current phase 3 study, KeyVibe-008 (NCT05224141), is comparing the efficacy and safety of first-line treatment with MK-7684A, a co-formulation of vibostolimab plus pembrolizumab, in combination with EP vs atezolizumab plus EP in patients with ES-SCLC. **Methods:** This multicenter, randomized, double-blind, phase 3 study is enrolling patients aged ≥18 years with histologically or cytologically confirmed, previously untreated ES-SCLC. Patients must have measurable disease per RECIST v1.1; ECOG PS of 0 or 1; no active CNS metastases/carcinomatous meningitis, autoimmune disease, neurologic paraneoplastic syndromes, pneumonitis, or interstitial lung disease; and must provide a pretreatment tumor sample. Patients are randomized 1:1 to receive up to 4 cycles of EP (cisplatin or carboplatin) in combination with MK-7684A (vibostolimab 200 mg + pembrolizumab 200 mg) Q3W or atezolizumab (1200 mg) Q3W, followed by MK-7684A or atezolizumab, respectively, until disease progression, unacceptable AEs, intercurrent illness, protocol violation, or investigator/patient decision. Randomization is stratified by ECOG PS (0 vs 1), LDH (≤ULN vs > ULN), liver metastases (yes vs no), and brain metastases (yes vs no). The primary endpoint is OS. Secondary endpoints include PFS, ORR, and duration of response per RECIST v1.1 by blinded independent central review; safety; and patient-reported outcomes (PROs). Tumor imaging occurs at baseline, every 6 weeks until 48 weeks, and every 9 weeks thereafter until disease progression, start of new anticancer treatment, withdrawal of consent, or death. PROs are assessed using validated instruments including the EORTC quality of life and EuroQol questionnaires. AEs are graded according to NCI CTCAE v5.0. Enrollment is ongoing worldwide. Clinical trial information: NCT05224141. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

TPS8607 **Poster Session**

Phase II study of KN046 in patients with thymic carcinoma who failed immune checkpoint inhibitors. *First Author: Barbara Ting-wen Ma, Weill Cornell Medicine, New York-Presbyterian Hospital, New York, NY*

Background: Thymic carcinomas are the most aggressive form of thymic epithelial tumors. They are often not operable and are more resistant to chemotherapy than thymomas. Thymic carcinoma is sensitive to pembrolizumab. However, most patients who respond to pembrolizumab eventually recur. Recently, molecules that combine PD(L)1 and CTLA-4 have been developed for solid tumor patients, with the hope that targeted therapy will be more effective than standard of care. KN046 is a bi-specific antibody against PD-L1 and CTLA-4 with a much higher affinity of the anti-PD-L1 portion and a weaker affinity for anti-CTLA-4, potentially leading to less autoimmune disorders and toxicities. We developed a Phase II study to test the hypothesis that dual PD-L1 and CTLA-4 inhibition with KN046 may represent a safe and tolerable option for patients with advanced thymic carcinoma who have progressed on prior treatment with immune checkpoint inhibitors. **Methods:** Key eligibility criteria include thymic carcinoma with progression after treatment with an immune checkpoint inhibitor with no limit to prior lines of therapy, adequate organ function and performance status. History of prior or current autoimmune disorders are not allowed and history of baseline positive anti-acetylcholine receptor (AChR) autoantibody are not allowed. KN046 will be administered intravenously at 5 mg/kg every 2 weeks until progression or excessive toxicity for up to 2 years. A cycle is defined as 2 treatments (28 days). The primary objective is to evaluate the antitumor activity of KN046 in patients with thymic carcinoma as measured by overall response rate defined by RECIST 1.1 criteria. The secondary objectives are to assess the safety and tolerability of KN046 including safety as measured by the number of adverse events (CTCAE 5.0), duration of response (RECIST 1.1) from first documented response to the date of first documented disease progression, progression-free survival, and overall survival. Exploratory objectives include the association of biomarkers (PD-L1 expression, tumor immune microenvironment determined by multiplex IHC, tumor mutational burden, T-cell inflamed gene expression profile) and clinical efficacy parameters. We will also characterize the safety laboratory results (AChR autoantibodies and creatinine kinase) and the occurrence of adverse events of interest. Simon's two-stage design will be used. The null hypothesis that the true response rate is 5% will be tested against a one-sided alternative of target response rate ≥20%. In the first stage, 10 patients will be accrued. If there are no responses in the first stage, then the study will be stopped. Otherwise, 19 additional patients will be accrued for a total of 29 patients. The null hypothesis will be rejected if ≥4 responses are observed in 29 patients, with a type 1 error rate of 0.05 and power of 80%. The study was activated at Weill Cornell Medicine in December 2021. Clinical trial information: NCT04925947. Research Sponsor: Jiangsu Alphamab Biopharmaceuticals.

9000 **Oral Abstract Session**

Outcomes of anti–PD-(L)1 therapy with or without chemotherapy (chemo) for first-line (1L) treatment of advanced non–small cell lung cancer (NSCLC) with PD-L1 score ≥ 50%: FDA pooled analysis. *First Author: Oladimeji Akinboro, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD*

Background: FDA-approved 1L treatment options for patients with PD-L1-high advanced NSCLC (PD-L1 score ≥50%) include IO ± chemo (± anti-angiogenics) but it is unclear if chemo substantially improves efficacy outcomes when added to IO in this patient population. **Methods:** Data was pooled from 12 randomized controlled trials that investigated anti-PD-(L)1 regimens ± chemo for the 1L treatment of patients with advanced NSCLC. PD-L1 score was defined as the proportion of tumor cells stained by the assay and analysis was conducted for patients with tumor PD-L1 score ≥50%. OS, PFS, and ORR were compared between chemo-IO and IO alone via a pooled analysis. Median survival times were estimated using Kaplan-Meier methods. Hazard ratios were estimated using Cox proportional hazards models stratified by trial; odds ratios were estimated using a logistic regression model with trial as a covariate. All analyses were adjusted for age, sex, race, ECOG, histology and smoking status. **Results:** A total of 3,189 patients with NSCLC and PD-L1 score ≥50% were identified for this analysis. Baseline characteristics were: 38% ages 65-74 years and 11% ages ≥75 years; 69% male; 80% White; 66% ECOG ≥1; and 89% former/current smokers. Median OS in the pooled chemo-IO (*N*=455) and IO-only (*N*=1,298) arms was 25.0 vs 20.9 months (HR 0.82; 95% CI: 0.62, 1.08); median PFS was 9.6 vs 7.1 months, respectively (HR 0.69; 95% CI: 0.55, 0.87). ORR was higher with chemo-IO than with IO alone (61% vs 43%; Odds ratio 1.2, 95% CI: 1.1, 1.3). **Conclusions:** This exploratory, hypothesis-generating pooled analysis suggests that most subgroups of patients with advanced NSCLC with PD-L1 score ≥50% receiving FDA-approved chemo-IO regimens may have OS and PFS outcomes that are comparable with or better than IO-only regimens. Patients ≥75 years of age receiving chemo-IO may not have improved outcomes over IO. These results support shared decision-making that balances potential benefits and risks of adding chemo to IO regimens based on patient factors that may impact tolerability. Research Sponsor: None.

Efficacy outcomes of chemo-IO versus IO alone by subgroup.

			OS		PFS		ORR	
	Subgroup	N[1]	Median, months	HR (95% CI)	Median, months	HR (95% CI)	%	Odds ratio (95% CI)
Age, years	<65	898	25.0 vs 23.3	0.67 (0.46, 0.99)	9.4 vs 7.7	0.54 (0.39, 0.75)	62 vs 43	2.2 (1.3, 3.7)
	65-74	642	22.2 vs 18.6	0.83 (0.54, 1.28)	9.7 vs 6.8	0.80 (0.56, 1.13)	62 vs 43	1.9 (1.1, 3.4)
	≥75	185	NE vs 18.9	1.68 (0.69, 4.06)	11.8 vs 7.2	1.22 (0.58, 2.57)	52 vs 45	1.2 (0.4, 3.8)
ECOG	0	602	NE vs 31.8	0.70 (0.40, 1.21)	13.7 vs 8.5	0.61 (0.40, 0.92)	66 vs 47	2.6 (1.5, 4.7)
	1+	1148	17.7 vs 18.0	0.87 (0.64, 1.19)	8.2 vs 6.3	0.75 (0.57, 0.98)	58 vs 41	1.7 (1.1, 2.6)
Smoking	Never	197	NE vs 14.4	0.39 (0.15, 0.98)	10.2 vs 3.7	0.46 (0.23, 0.92)	69 vs 28	4.6 (1.5, 14.5)
	Ever	1549	23.0 vs 22.1	0.92 (0.69, 1.22)	9.3 vs 8.2	0.75 (0.59, 0.95)	60 vs 45	1.7 (1.2, 2.5)

[1] Patients in the pooled chemo-IO and IO-only arms.

9001 **Oral Abstract Session**

Outcomes of first-line immune checkpoint inhibitors with or without chemotherapy according to KRAS mutational status and PD-L1 expression in patients with advanced NSCLC: FDA pooled analysis. *First Author: Erica C. Nakajima, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD*

Background: While existing data suggest a detriment of immune checkpoint inhibitors (ICI) in other targetable mutations in non-small cell lung cancer (NSCLC), limited retrospective analyses suggest patients with *Kirsten rat sarcoma oncogene* (*KRAS)*-mutated NSCLC benefit from ICI in the front-line (1L). To better define this benefit, pooled data from 12 registrational clinical trials investigating 1L ICI with or without chemotherapy (chemo) in patients with documented *KRAS* status (mutant or wildtype) was evaluated for efficacy of ICI+chemo, ICI alone, and chemo alone. **Methods:** Pooled data was evaluated for objective response rate (ORR) and overall survival (OS) by *KRAS* status (mutant, G12C, or wildtype). ORR and 95% confidence intervals (CI) were estimated using Clopper-Pearson method; median OS was estimated using Kaplan-Meier methods. Subgroup analyses were performed using Cox model stratified by KRAS status and PD-L1 status (Positive (combined positive score (CPS) ≥1), Negative (CPS<1), High (CPS≥50), Low (CPS<50)). **Results:** *KRAS* mutational status was reported in 1430 patients (61% wildtype, 39% mutated). *KRAS G12C* was reported in 11% of patients with a *KRAS* mutation (157/555). Demographics were similar between KRAS mutated, G12C, and wildtype patients. Amongst all patients, 60% were male, 89% white, 60% positive PD-L1, 67% former or current smokers. Table 1 shows outcomes of chemo+ICI, ICI alone, and chemo alone in each population. **Conclusions:** This retrospective, pooled analysis suggests that patients with *KRAS*-mutated NSCLC benefit from 1L chemo-ICI similarly to those with *KRAS* wild-type NSCLC, and should receive combination therapy upfront. Patients with *KRAS*-mutated NSCLC derived the greatest benefit from the combination of chemo-ICI as compared to ICI or chemo alone. The small number of patients with documented KRAS G12C mutation limits interpretation of the data for this subgroup. Clinical trials investigating targeted therapies for *KRAS*-mutated NSCLC in the 1L should include a chemo-ICI comparator arm. Research Sponsor: U.S. Food and Drug Administration.

Median OS and ORR in patients with *KRAS* mutated, *G12C*, or wildtype NSCLC treated with chemo+ICI, ICI alone, or chemo alone.

KRAS status (n)	Median OS (months): chemo+ICI (95% CI)	Median OS (months): ICI alone (95% CI)	Median OS (months): chemo alone (95% CI)	ORR: chemo+ICI (95% CI)	ORR: ICI alone (95% CI)	ORR: chemo alone (95% CI)
Mutated (555)	22.4 (18.2, NE) (n=219)	16.2 (11.1, NE) (n=135)	17.1 (12.3, 18.9) (n=201)	46 (39, 53)	37 (29, 46)	35 (28, 42)
G12C (157)	20.8 (11.3, NE) (n=58)	11.8 (8.2, NE) (n=45)	17.5 (10.7, 21.1) (n=54)	47 (33, 60)	33 (20, 49)	44 (31, 59)
Wildtype (875)	18.7 (16.0, 25.2) (n=313)	16.4 (13.4, 19.7) (n=240)	14.9 (12.2, 16.6) (n=322)	51 (46, 57)	33 (27, 40)	32 (27, 37)

NE = Not estimable.

9002 **Oral Abstract Session**

KRYSTAL-1: Activity and safety of adagrasib (MRTX849) in patients with advanced/metastatic non–small cell lung cancer (NSCLC) harboring a KRAS^{G12C} mutation. *First Author: Alexander I. Spira, Virginia Cancer Specialists Research Institute, Fairfax, VA*

Background: KRAS is a key mediator of the RAS/MAPK signaling cascade that promotes cellular growth and proliferation. KRAS^{G12C} mutation occurs in ~14% of NSCLC. Adagrasib, an investigational agent, is a KRAS^{G12C} inhibitor that irreversibly and selectively binds KRAS^{G12C}, locking it in its inactive state. Adagrasib is optimized for favorable pharmacokinetic (PK) properties, including long half-life (~24 h), dose-dependent PK, and central nervous system penetration; it has demonstrated objective response and favorable tolerability in the Phase 1/1b setting. **Methods:** KRYSTAL-1 (NCT03785249) is a multicohort Phase 1/2 study evaluating adagrasib as monotherapy or in combination regimens in patients with advanced solid tumors harboring a KRAS^{G12C} mutation. Here we report the first disclosure from all patients enrolled in Cohort A, a Phase 2 cohort with registrational intent, evaluating adagrasib given 600 mg orally BID in patients with NSCLC previously treated with platinum-based chemotherapy and anti-PD-1/L1 therapy. Study objectives include evaluating efficacy (objective response rate [ORR], duration of response [DOR], progression-free survival [PFS], overall survival [OS]), safety, PK, and exploratory correlative analyses. Objective tumor response was assessed per RECIST v1.1 by blinded independent central review (BICR). **Results:** As of the 15 October 2021 data cutoff, 116 patients with NSCLC harboring a KRAS^{G12C} mutation were enrolled and treated, with a median follow-up of 12.5 months. Baseline characteristics include median age 64 years, 65% female, and 15.5%/83.6% with ECOG PS 0/1; 98.3% of patients received adagrasib following prior treatment with immunotherapy and chemotherapy, with a median of 2 prior systemic therapies. The ORR (by BICR) was 42.9% (48/112) and the disease control rate was 79.5% (89/112); 31 patients remain on treatment. Median DOR was 8.5 months (95% CI 6.2–13.8), median PFS was 6.5 months (95% CI 4.7–8.4), median OS was 12.6 months (95% CI 9.2–NE). Treatment-related AEs (TRAEs) of any grade occurred in 97.4% of patients, grade ≥3 TRAEs in 45.7%, 2 grade 5 TRAEs, and 8 (6.9%) TRAEs led to discontinuation. The most commonly reported (≥25%) TRAEs (any grade) were diarrhea (62.9%), nausea (62.1%), vomiting (47.4%), fatigue (40.5%), ALT/AST increased (27.6%/25%), blood creatinine increased (25.9%); the most commonly reported (≥5%) TRAEs (grade 3/4) were lipase increased (6%) and anemia (5.2%). Additional subgroup analyses will be presented, including selected demographics, molecular markers and sites of metastases. **Conclusions:** Adagrasib is well tolerated and demonstrates promising efficacy in pretreated patients with NSCLC harboring a KRAS^{G12C} mutation. A Phase 3 trial evaluating adagrasib monotherapy versus docetaxel in previously treated patients with KRAS^{G12C}-mutant NSCLC is ongoing (NCT04685135). Clinical trial information: NCT03785249. Research Sponsor: Mirati Therapeutics Inc.

9003 **Oral Abstract Session**

A phase II study (TACTI-002) in first-line metastatic non–small cell lung carcinoma investigating eftilagimod alpha (soluble LAG-3 protein) and pembrolizumab: Updated results from a PD-L1 unselected population. *First Author: Enriqueta Felip, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain*

Background: Eftilagimod alpha (E) is a soluble LAG-3 protein binding to a subset of MHC class II molecules to mediate antigen presenting cell (APC)/CD8 T-cell activation. Stimulation of the APCs and subsequent T cell recruitment with E may lead to stronger anti-tumor responses than observed with pembrolizumab (P) alone. We hereby report results of the extended first-line non-small cell lung carcinoma (NSCLC) cohort of the TACTI-002 ("Two ACTive Immunotherapies") phase II trial. **Methods:** Pts with untreated metastatic NSCLC, unselected for PD-L1 expression were recruited. Objective response rate (ORR) by iRECIST was the primary endpoint (EP) and secondary EPs include ORR by RECIST 1.1, tolerability, disease control rate (DCR), progression free survival (PFS), overall survival (OS) and exploratory biomarker. Pts received 30 mg E SC q2w for 8 cycles (1 cycle= 3 weeks) and then q3w for up to 1 year with P (200 mg IV q3w for up to 2 years). Imaging was done every 8 weeks. PD-L1 was assessed centrally. This has been approved by relevant CAs, ECs, and IRBs. **Results:** From Mar 2019 to Nov 2021 114 pts were enrolled. Median age was 67 years (44-85) and 74% were male. ECOG PS was 0 and 1 in 37% and 63% of pts, respectively. Pts presented squamous (35%) or non-squamous (62%) NSCLC with 88% of pts at stage IV at the time of study entry. All PD-L1 subgroups were represented (Table). Pts received median 6.0 (range 1–35) P and 7.0 (1-22) E administrations. 19 (17%) pts discontinued treatment due to adverse events (AEs). The most common (≥15%) AEs were dyspnea (33%), asthenia (30%), decreased appetite (22%), cough (20%), anemia (20%), fatigue (19%), pruritus (18%), constipation (17%) and diarrhea (15%). At data cut-off (Jan 2022), 75 pts with a minimum follow-up of 6 months were evaluated for efficacy. ORR (iRECIST) was 37.3% in the ITT and 41.8%% in the evaluable pts assessed by local read. DCR 73.3% was reported. Response rate for squamous and non-squamous pathology were 33.3 % and 40.3 %, respectively. Results according to RECIST 1.1 were comparable. Responses were observed in all PD-L1 subgroups (Table). 24/28 (86%) responses were already confirmed while median duration of response was not yet reached (5 events). **Conclusions:** E + P is safe and shows encouraging antitumor activity in first-line metastatic NSCLC patients unselected for PD-L1, warranting further investigation. Clinical trial information: NCT03625323. Research Sponsor: Immutep S.A.

ORR/DCR by iRECIST and PD-L1 subgroup.

ORR / DCR by iRECIST	N (%) [95 % CI[&]]
ORR ITT* (N=75)	28 (37.3) [26.4-49.3]
DCR ITT* (N=75)	55 (73.3) [61.9-82.9]
ORR evaluable[$] (N=67)	28 (41.8) [29.8-54.5]
ORR ITT*[#] (TPS < 1%); n=22	6 (27.3) [10.7-50.2]
ORR ITT*[#] (TPS ≥ 1%); n=50	22 (44.0) [30.0-58.8]
ORR ITT*[#] (TPS < 50%); n=50	16 (32.0) [19.5-46.7]
ORR ITT*[#] (TPS ≥ 50%); n=22	12 (54.5) [32.2-75.6]

* - intent to treat population; $ - ≥ 1 post baseline tumor imaging.
& - Clopper-Pearson; # - ITT with available PD-L1 results (n=72).

9004 **Oral Abstract Session**

Overall survival from a phase II randomized study of ramucirumab plus pembrolizumab versus standard of care for advanced non–small cell lung cancer previously treated with immunotherapy: Lung-MAP nonmatched substudy S1800A. *First Author: Karen L. Reckamp, Cedars-Sinai Medical Center, Los Angeles, CA*

Background: Resistance to immune checkpoint inhibitor (ICI) therapy develops in most patients (pts) with advanced non-small cell lung cancer (NSCLC). Tumors that develop resistance to ICI constitute a major unmet need. Combined ICI and VEGF/VEGF receptor inhibition have shown benefit in multiple tumor types through immune modulation. We evaluated pembrolizumab and ramucirumab (P+R) in advanced, ICI-exposed NSCLC, under the aegis of Lung-MAP, a master protocol for pts with stage IV, previously treated NSCLC. Pt characteristics and treatment toxicities were presented at ASCO 2021. **Methods:** S1800A was a randomized phase II trial for pts ineligible for a biomarker-matched substudy with acquired resistance to ICI defined as previous ICI therapy for at least 84 days with progressive disease (PD) on or after therapy. Eligibility stipulated PD on prior platinum-based doublet therapy (sequential or in combination with ICI) and ECOG PS of 0-1. Pts were stratified by PD-L1 expression, histology, and intent to receive ramucirumab in the standard of care (SOC) arm and were randomized to P+R or SOC (investigator's choice of docetaxel+R; docetaxel, pemetrexed, gemcitabine). With a goal of 144 total/130 eligible pts, the primary objective was to compare overall survival (OS) between the arms using a 1-sided 10% level log-rank test upon 90 deaths. Secondary endpoints included response, duration of response, investigator assessed-progression free survival and toxicity. **Results:** From May 17, 2019 to November 16, 2020, 166 pts were enrolled with 137 eligible (69 P+R; 68 SOC [45 +R, 23 w/o R]). Main causes for ineligibility were lack of PD on ICI or chemotherapy (6 SOC, 6 P+R), > 1 line of ICI (2 P+R), ICI discontinued due to toxicity (2 SOC), or lack of measurable disease (2 SOC, 1 P+R). OS was significantly improved with P+R (HR: 0.61 [0.38-0.97], 1-sided p-value = 0.019; median [95% CI] OS of 15.0 (13.2-17) months (mo) for P+R and 11.6 (8.5-13.8) mo in SOC arm). Progression-free survival (PFS) was not different between the arms (HR: 0.86 [0.57-1.31], 1-sided p-value=0.25; median PFS (95% CI) of 4.5 (4.0-6.9) mo for P+R and 5.2 (4.0-6.6) mo in SOC arm). ORR was not different between the arms (p=0.28). OS benefit for P+R was seen in most subgroups. Analysis of survival based on genomic alterations, tumor mutational burden and PD-L1 will be presented. **Conclusions:** Pembrolizumab + ramucirumab in pts with advanced NSCLC previously treated with chemotherapy and immunotherapy led to improved OS compared to SOC. Discordance of ORR and PFS from OS has been reported in prior ICI trials (Rittmeyer et al. Lancet 2017). This is the first trial in the 2nd line setting without a chemotherapy backbone to demonstrate a potential survival benefit compared to SOC regimens including docetaxel and ramucirumab using the Lung-MAP platform. Clinical trial information: NCT03971474. Research Sponsor: NIH/NCI U10CA180888, U10CA180819, U10CA180821, Other Foundation, in part by Eli Lilly and Company and Merck & Co., Inc.

9005 **Oral Abstract Session**

Cabozantinib (C) plus atezolizumab (A) or C alone in patients (pts) with advanced non–small cell lung cancer (aNSCLC) previously treated with an immune checkpoint inhibitor (ICI): Results from Cohorts 7 and 20 of the COSMIC-021 study. *First Author: Joel W. Neal, Stanford University, Stanford Cancer Institute, Palo Alto, CA*

Background: C, a multitargeted receptor tyrosine kinase inhibitor (TKI), promotes an immune-permissive environment that may enhance ICI activity. COSMIC-021 (NCT03170960) is a multicenter phase 1b study evaluating C + A in advanced solid tumors. In COSMIC-021, C + A demonstrated encouraging clinical activity in the cohort of pts with aNSCLC previously treated with ICIs (cohort 7 [C7]) (Neal. ASCO 2020. Abstr 9610). Updated outcomes of C + A in expanded C7 and outcomes for C alone in exploratory cohort 20 (C20) are presented. **Methods:** Pts with stage IV nonsquamous NSCLC without mutations in EGFR, ALK, ROS1, or BRAF V600E who progressed on one prior ICI and ≤2 prior lines of systemic anticancer therapy but no prior VEGFR TKI were eligible. Cohorts were not accrued contemporaneously. Pts received C 40 mg PO QD plus A 1200 mg IV Q3W (C7) or C alone 60 mg PO QD (C20). Primary endpoint was objective response rate (ORR) per RECIST v1.1 by investigator. Other endpoints included safety, duration of response (DOR), progression-free survival (PFS), and overall survival (OS). CT/MRI scans were performed Q6W for the first year and Q12W thereafter. **Results:** A total of 81 and 31 pts received C + A and C, respectively; baseline characteristics were as follows: median age, 67 y, 70 y; male, 57%, 58%; ECOG PS 1, 64%, 71%; liver metastasis, 21%, 23%; refractory to prior ICI (progressive disease [PD] as best response), 32%, 45%; median number of prior systemic therapies, 3 and 3. As of Nov 30, 2021, median follow-up (range) (mo) was 24.7 (10.7, 42.8) and 21.5 (17.3, 27.6) for C + A and C, respectively, with 6 (7%) and 1 (3%) on study treatment. Clinical activity was observed for C + A and C alone (Table). Most common treatment-related adverse events (TRAEs) of any grade for C + A and C, respectively, included diarrhea (40%, 42%), nausea (22%, 45%), decreased appetite (25%, 26%), vomiting (14%, 23%), and fatigue (28%, 19%); grade 3/4 TRAEs occurred in 44% and 52% and one grade 5 TRAE occurred in each cohort (pneumonitis [C + A] and gastric ulcer hemorrhage [C]). **Conclusions:** C + A and C demonstrated encouraging clinical activity with manageable toxicity in pts with aNSCLC previously treated with ICIs. A phase 3 trial (CONTACT-01; NCT04471428) of C + A vs docetaxel is ongoing in NSCLC previously treated with an ICI and platinum-containing chemotherapy. Clinical trial information: NCT03170960. Research Sponsor: Exelixis, Ipsen, Takeda.

	C + A (C7) (N = 81)	C (C20) (N = 31)
ORR, % (95% CI)	19 (11, 29)	6 (1, 21)
Best overall response, n (%)		
Complete response (CR)	0	0
Partial response (PR)	15 (19)	2 (6)
Stable disease (SD)	50 (62)	18 (58)
PD	13 (16)	6 (19)
Disease control rate, % (95% CI)*	80 (70, 88)	65 (45, 81)
Median DOR, mo (95% CI)	5.8 (4.2, 6.9)	10.6 (6.3, NE)
Median PFS, mo (95% CI)	4.5 (3.5, 5.6)	3.4 (1.4, 5.6)
Median OS, mo (95% CI)	13.8 (7.2, 15.7)	9.4 (4.5, 11.7)

*CR + PR + SD.

9006 **Oral Abstract Session**

Amivantamab and lazertinib in patients with EGFR-mutant non–small cell lung (NSCLC) after progression on osimertinib and platinum-based chemotherapy: Updated results from CHRYSALIS-2. *First Author: Catherine A. Shu, Columbia University Medical Center, New York, NY*

Background: Initial results with the amivantamab (ami) and lazertinib (laz) regimen showed encouraging efficacy in patients (pts) whose disease progressed after standard-of-care osimertinib (osi) and platinum-based chemotherapy (pt-chemo; Shu *Ann Oncol* 2021; 32:S949-1039; 1193MO). We present updated results of this population (Cohort A) from the CHRYSALIS-2 study (NCT04077463). **Methods:** Cohort A evaluated ami and laz in pts with EGFR exon 19 deletion or L858R NSCLC whose disease progressed on 1st/2nd-line osi followed by pt-chemo as last line of therapy (target population, n=106) and among a more heavily-pretreated population (n=56) whose disease progressed after osi and pt-chemo ± other therapies without regard to number and sequence of these therapies. Pts received 1050 mg IV ami (1400 mg, ≥80 kg) + 240 mg oral laz. Investigator (INV)- and blinded independent central review (BICR)-assessed response per RECIST v1.1 is reported for efficacy-evaluable pts, defined as pts who initiated study treatment on or before 17 Mar 2021, allowing for ≥6 mo of follow-up for response durability. **Results:** As of 6 Nov 2021, 162 pts were enrolled in Cohort A (median 62 y, 65% women, 61% Asian, median 3 [range, 2–14] prior lines). Median time between last osi treatment to first dose of ami + laz was 6.3 mo and 2.0 mo for the target and heavily-pretreated populations, respectively. Of 50 efficacy-evaluable pts in the target population, the overall response rate (ORR) by BICR was 36% (95% CI, 23–51), with 1 complete response (CR) and 17 partial responses (PRs), and the clinical benefit rate (CBR) was 58% (95% CI, 43–72); full results for all enrolled pts will be reported at the meeting. Median duration of response (mDOR) was not reached based on BICR. At a median follow-up of 8.3 mo, 7 responders (39%) have achieved a DOR lasting ≥6 mo by BICR. INV-assessed responses were consistent with BICR. Of 56 efficacy-evaluable pts in the heavily-pretreated population (8.7-mo median follow-up), ORR by INV was 29% (95% CI, 17–42), with 1 CR and 15 PRs. CBR was 55% (95% CI, 42–69) and mDOR was 8.6 mo (95% CI, 4.2–NR). BICR results are pending. Preliminary evidence of CNS antitumor activity was reported among 8 pts with baseline brain lesions (7 non-target, 1 target) who had not received radiation within 1 year prior to study enrollment. Most frequent adverse events (AE) were infusion-related reaction (65%), paronychia (49%), rash (41%), and stomatitis (39%). Most common grade ≥3 treatment-related AEs (TRAEs) were infusion-related reactions (7%), acneiform dermatitis (5%), and hypoalbuminemia (4%). TRAEs leading to discontinuation of either or both ami and laz occurred in 12% and 7%, respectively. **Conclusions:** Among an unselected population that has exhausted SOC osi and pt-chemo, ami and laz demonstrates encouraging antitumor activity with a manageable safety profile. Clinical trial information: NCT04077463. Research Sponsor: Janssen.

9007 **Oral Abstract Session**

Phase (Ph) 1/2a study of CLN-081 in patients (pts) with NSCLC with EGFR exon 20 insertion mutations (Ins20). *First Author: Helena Alexandra Yu, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: EGFR ins20-mutant NSCLC has historically been challenging to treat. While new agents targeting EGFR ins20 have recently been approved, adverse events (AEs), particularly wild type (WT) EGFR-related AEs are common. CLN-081 is a novel EGFR tyrosine kinase inhibitor (TKI) with broad activity against *EGFR* mutations, including ins20, and increased selectivity for ins20 versus WT EGFR. CLN-081 has been granted FDA Breakthrough Therapy Designation for the treatment of pts with EGFR ins20 NSCLC. We present updated results of the initial multicenter Ph1/2a study of CLN-081 in pts with advanced, EGFR ins20-mutant NSCLC, including 39 pts treated in an expanded cohort at the dose of 100 mg twice daily (BID). **Methods:** Ph1 dose escalation utilized an accelerated titration (AT) and rolling six design. Individual cohorts were expanded in Phase 1 and 2a based on prespecified protocol criteria. Pts were required to have received prior platinum-based chemotherapy. Stable, treated brain metastasis (mets) were allowed. CLN-081 is dosed in 21-day cycles. **Results:** As of 13 December 2021, 73 pts [median age: 65 (36-82), median lines of prior therapy: 2 (1-9), 28 (39%) with a history of brain mets] received CLN-081 at 30 mg (8), 45 mg (1), 65 mg (14), 100 mg (39), and 150 mg (11), all BID. Treatment-related AEs in ≥ 15% of pts were rash (74%), diarrhea (27%), paronychia (25%), fatigue (19%), anemia (18%), dry skin (18%), nausea (16%). Treatment-related Gr ≥ 3 AEs in ≥ 4 % of pts included anemia (10%), increased ALT (4%), and increased AST (4%). Gr 3 rash and Gr 3 diarrhea were observed in 1 and 2 pts, respectively, at 150 mg BID, while no pts treated at ≤ 100 mg BID experienced Gr 3 rash or diarrhea. Treatment-related dose reductions and discontinuations across all dose levels occurred in 10 pts (14%) and 5 pts (7%) respectively. Among 70 response-evaluable pts across all dose levels, 25 (36%) had a confirmed partial response (PR), 34 (49%) had stable disease (SD), and 3 (4%) had progressive disease as a best response. Seven pts (10%) had a PR that remained unconfirmed; 1 (1%) pt was pending a confirmatory scan. Of 36 response-evaluable pts at 100 mg BID, 14 (39%) had a confirmed PR, 17 (47%) had SD, and 1 (3%) had PD. Three pts had a PR that remained unconfirmed (8%); 1 (3%) pt was pending a confirmatory scan. Notably, among Ph1 pts treated at 100 mg BID (N = 13) in whom longer follow-up is available, the mDOR and mPFS (estimated by Kaplan-Meier) was > 15 months and 12 months, respectively. Disease control (SD ≥ 6 months or any PR) was observed in 12/13 pts (92%). Updated data with additional follow-up will be presented. **Conclusions:** In pts with heavily-pretreated advanced EGFR ins20 NSCLC, CLN-081 has a manageable safety profile, with anti-tumor activity across the range of doses tested. Further, CLN-081 has demonstrated a favorable clinical profile at the dose of 100 mg BID, with an encouraging objective response rate, response durability, and no Gr 3 rash or diarrhea. Clinical trial information: NCT04036682. Research Sponsor: Cullinan Oncology, LLC.

9008 **Oral Abstract Session**

Amivantamab in patients with NSCLC with MET exon 14 skipping mutation: Updated results from the CHRYSALIS study. *First Author: Matthew Krebs, The University of Manchester and The Christie NHS Foundation Trust, Manchester, United Kingdom*

Background: Amivantamab, a fully human bispecific antibody targeting epidermal growth factor receptor (EGFR) and MET, is approved for the treatment of non-small cell lung cancer (NSCLC) with EGFR exon 20 insertion after prior platinum-based chemotherapy. Given its bispecific nature, amivantamab is being explored in patients (pts) with primary MET exon 14 skipping mutation (METex14) in the MET-2 cohort of the CHRYSALIS study. **Methods:** CHRYSALIS (NCT02609776) is an ongoing phase 1 dose escalation/dose expansion study of amivantamab in pts with advanced NSCLC. Pts with primary METex14 whose disease progressed on or who declined current standard of care therapy were treated with amivantamab 1050 mg (pts <80 kg) or 1400 mg (pts ≥80 kg) weekly in cycle 1 and biweekly thereafter. Response was assessed by investigators using RECIST v1.1. **Results:** As of 2 Dec 2021, 43 pts with METex14 had received amivantamab. Median age was 70 y (range, 43-88), 58% were women, median prior lines of therapy was 2 (range, 0-10) [eg, crizotinib (n=13), capmatinib (n=11), tepotinib (n=5), anti-MET antibody (n=1)], and 23% had history of brain metastases at baseline. In 36 pts with ≥1 postbaseline disease assessment, median duration of follow-up was 5.8 months (range, 0.3-15.8); 6 pts had no prior treatment, 11 had no prior MET inhibitor, and 19 had a prior MET inhibitor. Overall response rate was 33% (50% [3/6] in treatment-naïve pts, 46% [5/11] in pts with no prior MET inhibitor, and 21% [4/19] in pts with prior MET inhibitor therapy). Clinical benefit rate was >54% regardless of prior treatment (Table). Median duration of response (DOR) was not reached (range, 2.1-12.2 months); 67% (8/13) had DOR ≥6 months. Ten of the 12 responders remain on treatment (6.0-14.4 months) with ongoing responses; 2 discontinued after 2 and 12 months, respectively. Safety profile was consistent with previously reported experience of amivantamab (Sabari 2021 *JTO* 16(3):S108-109). Treatment-related adverse events leading to dose reduction or discontinuation occurred in 3 pts, each. **Conclusions:** Amivantamab demonstrates anti-tumor activity in primary METex14 NSCLC including after prior MET inhibitor treatment. Enrollment is ongoing and updated data will be shown. Clinical trial information: NCT02609776. Research Sponsor: None.

Best overall response.

	No Prior treatment (n=6)	No prior MET inhibitor (n=11)	Prior MET inhibitor (n=19)	Total (n=36)
Complete response (CR), n (%)	0	0	0	0
Partial response (PR), n (%)	3 (50.0)	5 (45.5)	4 (21.1)	12 (33.3)
Stable disease (SD), n (%)	2 (33.3)	4 (36.4)	11 (57.9)	17 (47.2)
Progressive disease, n (%)	0	2 (18.2)	3 (15.8)	5 (13.9)
Not evaluable/unknown, n (%)	1 (16.7)	0	1 (5.3)	2 (5.6)
Overall response rate (Confirmed CR + Confirmed PR), n (%) [95% CI]	3 (50.0) [11.8, 88.2]	5 (45.5) [16.7, 76.6]	4 (21.1) [6.1, 45.6]	12 (33.3) [18.6, 51.0]
Clinical benefit rate (Confirmed CR + Confirmed PR + SD ≥11 weeks), n (%) [95% CI]	4 (66.7) [22.3, 95.7]	6 (54.5) [23.4, 83.3]	11 (57.9) [33.5, 79.7]	21 (58.3) [40.8, 74.5]

LBA9009 **Clinical Science Symposium**

Activity of adagrasib (MRTX849) in patients with KRAS^{G12C}-mutated NSCLC and active, untreated CNS metastases in the KRYSTAL-1 trial. *First Author: Joshua K. Sabari, Perlmutter Cancer Center, New York University Langone Health, New York, NY*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

9010 **Clinical Science Symposium**

Updated analysis from the ATEZO-BRAIN trial: Atezolizumab plus carboplatin and pemetrexed in patients with advanced nonsquamous non–small cell lung cancer with untreated brain metastases. *First Author: Ernest Nadal, Institut Català d'Oncologia, L'Hospitalet, Barcelona, Spain*

Background: Atezolizumab plus chemotherapy was safe and yielded promising clinical outcome as frontline therapy for patients (pts) with advanced NSCLC with untreated brain metastases (BM) in the ATEZO-BRAIN study (NCT03526900). **Methods:** A multicenter single-arm phase II trial with a Bayesian design for evaluating the safety and efficacy of atezolizumab plus carboplatin with pemetrexed every 3 weeks for 4-6 cycles, followed by maintenance with pemetrexed plus atezolizumab in pts with stage IV non-squamous NSCLC without EGFR or ALK genetic alterations and untreated BM. Pts not presented neurologic symptoms at baseline; but anticonvulsants and dexamethasone (DXM) ≤ 4mg qd were allowed. Co-primary endpoints were safety and investigator-assessed progression-free survival (PFS) at 12 weeks according to RANO-BM and RECIST v1.1 for brain and systemic disease, respectively. Here we present the final data and an exploratory analysis based on PD-L1 expression and corticosteroid treatment at baseline. **Results:** Out of 40 pts included in the study, 22 (55%) were receiving DXM at baseline and 20 (50%) had positive expression of PD-L1. Sixteen (40%) pts had confirmed intracranial response based on RANO-BM (12 PR, 4 CR) and 19 (47.5%) pts achieved systemic response (all PR). Only 4 pts had discordant responses between the body and the brain. No differences were observed in the overall systemic and intracranial response rate according to the PD-L1 expression or the use of corticosteroids at baseline. As of December 31, 2021 (median follow-up, 20 months), the updated median (95% CI) systemic PFS was 8.9 (6.7 to 13.8) and intracranial PFS was 6.9 (4.7 to 11.9). Median (95% CI) OS was 13.6 (9.72 to not reached) and estimated 2-year OS rate (95% CI) was 30.5% (18.4 to 50.4). Median (95%CI) OS was longer for PD-L1 positive pts (16.2; 10.3 to not reached) compared to PD-L1 negative pts (10.7; 7.6 to not reached) but differences were not statistically significant due to the limited statistical power (HR = 0.99; 95% CI 0.35 to 2.12). No significant differences in OS were observed between pts receiving or not baseline DXM treatment. Treatment was well tolerated and no grade 5 toxicities were observed. **Conclusions:** In this updated analysis, treatment with atezolizumab plus carboplatin and pemetrexed yields a promising 2-year OS rate and intracranial response rate in patients with untreated BM from NSCLC, regardless of treatment with corticosteroids at baseline and PD-L1 expression. Clinical trial information: NCT03526900. Research Sponsor: ROCHE.

9011 **Clinical Science Symposium**

Randomized phase III study of nivolumab and ipilimumab versus carboplatin-based doublet in first-line treatment of PS 2 or elderly (≥ 70 years) patients with advanced non–small cell lung cancer (Energy-GFPC 06-2015 study). *First Author: Herve Lena, Centre Hospitalier Universitaire de Rennes, Rennes, France*

Background: Combination of anti-PD1 and CTLA4 have showed superiority to chemotherapy (CT) in advanced non–small cell lung cancer (NSCLC), but data for fit elderly or PS2 patients are scarce. **Methods:** eNErgy compared the combination of nivolumab ipilimumab (N-I) to a platinum doublet in elderly or PS2 patients with advanced NSCLC. Primary endpoint was overall survival (OS), secondary endpoints included progression-free survival (PFS), objective response rate (ORR), and safety. Main inclusion criteria were: stage IV histologically proven NSCLC, age ≥ 70 y, and PS 0/1/2 or age < 70 and PS2, EGFR ALK/ROS1 negative, judged fit enough to receive a platinum doublet. The main exclusion criteria were active cerebral metastasis or contraindication to N-I. Patients were randomly selected 1/1, stratified by age (≥ 70 vs. < 70 y), PS (0/1 vs. 2), and histology (squamous vs. no-squamous). Nivolumab (240 mg, 2w), ipilimumab, 1 mg/kg, 6w, was administrated until progression or unacceptable toxicity. CT was planned for 4 cycles, with carboplatin (AUC5) and pemetrexed (500 mg/m2, 3w) or paclitaxel (90 mg/m2, d1,d8, d15); 242 patients had to be randomized to detect a treatment effect hazard ratio (HR) on OS of 0.65, with a 85% power at a 2-sided alpha level of 5%. **Results:** A preplanned interim analysis carried out after observation of 33% of deaths, out of 174 randomized patients, showed a risk of futility especially for PS 2 patients, HR: 1.8 (95% CI, 0.99-3.3). This led to a halt in randomization but continued follow-up of the 204 patients randomized at the time of the decision. The current final analysis is carried out 18 months after the inclusion of the last patient: men, 71%, median age 74 (51-89, PS 0/1/2 in 30%, 37.5%, and 36.6% respectively), smokers or former smokers in 25.5 and 64.4%, with 62% adenocarcinoma. The median OS of N-I and chemo arms were 14.7 (95% CI, 8.0-19.7) and 9.9 (95% CI, 7.7-12.3) months, HR 0.85, 95% CI, 0.62-1.16. The subgroup analyses showed a significant benefit of the association N-I compared to CT for elderly PS 0/1 patients, with median OS of 22.6 (95% CI, 18.1-36) vs. 11.8 (95% CI, 8.9-20.5) months, p = 0.02. In PS2 patients, median OS of N-I and CT arms was 2.9 (1.4-4.8) vs. 6.1 (3.5-10.4) months (p = 0.22). Median PFS was significantly in favor of N-I arm in the entire population: 5.5 (2.8-8.7) vs. 4.6 (3.5-5.6); p = 0.015. Safety was similar with 31.4% of patients with grade ≥ 3 related SAES in N-I arm vs. 49.5% for CT. Treatment was discontinued for toxicity in 28.6% in N-I arm vs. 22.3% of patients in CT arm. **Conclusions:** Despite no statistically significant benefit in OS observed in the entire population, there was a clinical signal of efficacy of N-I combination over platinum doublet in elderly NSCLC patients PS 0-1 with a significant benefit of OS of 22.6 months vs. 11.8 for CT arm. Clinical trial information: NCT03351361. Research Sponsor: Bristol Myers Squibb, Groupe Français de PneumoCancerologie.

9012 **Clinical Science Symposium**

Checkpoint inhibitor accessibility in 15,000+ Indian patients. *First Author: Madala Ravikrishna, Tata Memorial Hospital, Mumbai, India*

Background: Access to newer therapies is an issue in low and low middle income countries. Hence we decided to audit our practice in the head and neck and thoracic medical oncology unit from 2015 to 2019 to study the accessibility of checkpoint inhibitors and factors influencing them. **Methods:** All patients who were registered in the head and neck and thoracic medical oncology unit between 2015-2019 were included in the study. The number of patients who received immunotherapy among them was identified from the prospective database of immunotherapy maintained in the department. We made a list of patients who were eligible for immunotherapy per year and identified how many of them received recommended immunotherapy. The indication for eligibility of immunotherapy was based on published pivotal data and its date of publication of the study online. For nominal and ordinal variable percentage with 95% CI was provided. Factors impacting the accessibility of immunotherapy were identified. **Results:** A total of 15,674 patients were identified who required immunotherapy; out of them only 444 (2.83%, 95% CI, 2.58-3.1) received it. The distribution of patients eligible as per cancer disease management group and time period is shown in the Table. Among head and neck cancer patients 4.5% (156 out of 3,435) received immunotherapy versus 2.35% (288 out of 12,239) among thoracic cancer patients ($p < 0.0001$). Among the general category (low socioeconomic), 0.29% (28 out of 9,405) versus 6.6% (416 out of 6,269) among the private category (high socioeconomic) received immunotherapy ($p < 0.0001$). While 3.7% (361 out of 9,737) among males versus 1.39% (83 out of 5,937) females received immunotherapy ($p < 0.0001$). There was also a temporal trend seen in the accessibility of immunotherapy ($p < 0.0001$, Table). **Conclusions:** The accessibility of immunotherapy is below 3% in India. Patients with head and neck cancers, those with private category and with male gender had higher access to this therapy. There was also a temporal trend observed suggesting increased accessibility over the years. Research Sponsor: None.

Disease Site	Years→	2015	2016	2017	2018	2019	p Value
Head and neck cancer	Number of patients with indication for immunotherapy	-	776	773	750	1136	< 0.0001
	Number of patients who received immunotherapy	-	2	27	43	84	
	Percentage of patients receiving immunotherapy	-	0.25	3.49	5.7	7.3	
	95% CI of the percentage of patients receiving immunotherapy	-	0.01-1	2.4-5.1	4.3-7.7	6-9.1	
Thoracic cancer	Number of patients with indication for immunotherapy	1,365	1,844	2,730	3,000	3,300	< 0.0001
	Number of patients who received immunotherapy	1	3	44	110	130	
	Percentage of patients receiving immunotherapy	0.07	0.16	1.6	3.6	3.9	
	95% CI of the percentage of patients receiving immunotherapy	0-0.4	0.03-0.5	1.2-2.1	3.1-4.4	3.3-4.7	

Both the cites significantly different increases in rates are observed.

9013 **Poster Discussion Session**

Phase 1/1b study of telisotuzumab vedotin (Teliso-V) + osimertinib (Osi), after failure on prior Osi, in patients with advanced, c-Met overexpressing, *EGFR*-mutated non-small cell lung cancer (NSCLC). *First Author: Jonathan W. Goldman, David Geffen School of Medicine at UCLA, Los Angeles, CA*

Background: Osi (third-generation tyrosine kinase inhibitor) is a standard frontline treatment (Tx) for advanced/metastatic *EGFR*-mutated NSCLC. However, tumors invariably progress after an initial response, with c-Met protein overexpression (OE) often associated with acquired resistance. Second- and third-line Tx options are limited to chemotherapy-based regimens with limited efficacy and significant toxicities. Teliso-V (ABBV-399), an anti–c-Met antibody-drug conjugate, delivers a cytotoxic payload (monomethyl auristatin E) into c-Met OE tumor cells. In a phase 1/1b study (NCT02099058) in patients (pts) with c-Met OE NSCLC, Teliso-V alone or in combination with erlotinib demonstrated an acceptable safety profile and antitumor activity. Interim safety and efficacy data from the Teliso-V + Osi cohort (arm E) of this trial are presented. **Methods:** Pts (≥18 yr) with metastatic *EGFR*-mutated, c-Met OE (by central immunohistochemistry) NSCLC who had progressed on a prior Osi regimen were eligible. Pts received Teliso-V (IV Q2W) + Osi (oral; 80 mg QD). Teliso-V was evaluated at 1.6 mg/kg and, after review of safety data, escalated to 1.9 mg/kg (safety evaluation). An expansion cohort was opened at 1.9 mg/kg for pts who had received ≤2 prior lines of systemic therapy. Pharmacokinetics (PK) were assessed throughout the study. Pts received study Tx until disease progression, unacceptable toxicity, or for up to 24 months. **Results:** As of 20 Dec 2021, 25 pts received Teliso-V (1.6 mg/kg, n = 7; 1.9 mg/kg, n = 18) + Osi. Median age was 60.0 yr; 14 (58%) pts were on prior Tx with Osi for > 12 mo. No dose-limiting toxicities (grade [Gr] ≥3 non-hematologic or Gr 4 hematologic Tx-related adverse events [AEs]) were reported during the safety lead-in or evaluation phases. All-Gr AEs considered possibly related to Teliso-V occurred in 22/25 (88%) pts: the most common (≥20%) were peripheral sensory neuropathy (36%), nausea, and peripheral edema (20% each); Gr ≥3 AEs (> 5%) were anemia (12%) and peripheral motor neuropathy (8%). No Gr 5 events related to Tx were reported. PK of Teliso-V + Osi was similar to single-agent Teliso-V. Efficacy data (19/25 pts) are in the table. The overall objective response rate (ORR) was 58% (67% at 1.9 mg/kg). **Conclusions:** Teliso-V + Osi is well tolerated with an ORR of 58% (67% at 1.9 mg/kg) in pts with c-Met OE NSCLC who progressed on prior Osi. Clinical trial information: NCT02099058. Research Sponsor: AbbVie.

		N	ORR,* n (%) [95% CI]
Dose	1.6 mg/kg	7	3 (43) [10, 82]
	1.9 mg/kg	12	8 (67) [35, 90]
	Total	19	11 (58) [34, 80]
c-Met level	High (≥50%, 3+ staining)	10	5 (50) [19, 81]
	Intermediate (25–49%, 3+ staining)	8	5 (63) [25, 92]
	Total	18†	10 (56) [31, 79]
EGFR mutation	L858R	9	5 (56) [21, 86]
	Del19	9	6 (67) [30, 93]
	Total	19‡	11 (58) [34, 80]

*RECIST v1.1; data not mature for duration of response and progression-free survival. †c-Met IHC score < 25% 3+, n = 1. ‡G719S mutation, n = 1.

9014 **Poster Discussion Session**

Osimertinib plus necitumumab in EGFR-mutant NSCLC: Final results from an ETCTN California Cancer Consortium phase I study. *First Author: Jonathan W. Riess, University of California Davis Comprehensive Cancer Center, Sacramento, CA*

Background: Osimertinib (Osi) is standard of care in 1st line (1L) EGFR mut NSCLC and TKI resistant T790M^{pos} NSCLC but acquired resistance emerges; outcomes are less robust in T790M^{neg}, C797X^{pos} and EGFR exon 20 insertion (ex20ins) disease. We examined Osi with the EGFR monoclonal antibody Necitumumab (Neci) in select settings of EGFR TKI resistance. **Methods:** Pts were accrued to 5 expansion cohorts (ExC) at recommended phase 2 dose (RP2D) of Osi 80 mg daily and Neci 800 mg D1 + D8 of q21d cycle. ExC (18 pts/cohort): A) T790M^{neg} progressive disease (PD) on 1st/2nd gen TKI as last therapy, B) T790M^{neg} PD on 1st/2nd gen TKI and PD on 3rd gen TKI, C) T790M^{pos} PD on 1st/2nd gen TKI and PD on 3rd gen TKI, D) EGFR ex20ins PD on chemotherapy, E) PD on 1L osi. In ExC A-C, T790M was confirmed centrally (tissue) by ddPCR. Additional correlative studies include: tissue NGS (> 400 gene panel), EGFR FISH, plasma for PK and serial EGFR ctDNA by ddPCR. Adverse events were graded (Gr) by CTCAEv5; ORR, PFS by RECIST 1.1. Primary pre-specified efficacy endpoint ≥3/18 pts responding per cohort. **Results:** 101 patients accrued (100 evaluable). Efficacy is summarized in the Table. Drug related Gr 3 AEs were seen in 38% of pts, mainly rash (21%). ORR among all pts was 19% (95% CI 12-28%) that varied across cohorts (Table). In ExC A-C, 69% pts had detectable EGFR activating mutations in ctDNA, with decline in mutant allele frequency (AF) on treatment in 80% and ctDNA clearance in 33%. **Conclusions:** Osi/Neci is feasible and tolerable at the RP2D. EGFR ctDNA was detectable at baseline in the majority of pts with decrease in AF on treatment. Osi/Neci was active in select settings of EGFR-TKI resistance, meeting its prespecified efficacy endpoint in T790M^{neg} PD on 1st/2nd gen TKI as last therapy (ExC A), EGFR ex20ins post-chemo (ExC D) and PD on 1L osimertinib (ExC E). mPFS in the EGFR ex20ins cohort was within the range of current EGFR Exon 20 ins agents in development. EGFR monoclonal antibodies with osimertinib warrant further study in settings of de novo and acquired EGFR dependent resistance to EGFR-TKI. Clinical trial information: NCT02496663. Research Sponsor: U.S. National Institutes of Health.

Summary of Response and Progression-Free Survival.

Cohort	# Patients	Response	Median PFS in Months (90% confidence interval)*
Dose Escalation	10	5 PR (3 cPR)	9.7 (5.3, 13.7)
(A) T790M^{neg} PD on 1st/2nd gen TKI as last therapy	18	4 PR (3 cPR)**	3.9 (1.3, 5.7)
(B) T790M^{neg} PD on 1st/2nd gen TKI and PD on 3rd gen TKI	18	0	1.5 (1.2, 2.6)
(C) T790M^{pos} PD on 1st/2nd gen TKI and PD on 3rd gen TKI	18	2 PR (both cPR)	3.9 (2.4, 5.6)
(D) EGFR ex20ins PD on chemotherapy	18	4 PR (3 cPR)**	6.9 (4.1, 11.4)
(E) PD on 1L osimertinib	18	4 PR (3 cPR)**	2.3 (1.4, n/a)

*n/a means that the upper limit of the confidence interval was not reached at the time of the analysis;
** cohort met pre-specified efficacy endpoint
cPR = confirmed partial response.

9015 **Poster Discussion Session**

Antitumor activity of sunvozertinib in NSCLC patients with EGFR Exon20 insertion mutations after platinum and anti-PD(L)1 treatment failures. *First Author: Pasi A. Janne, Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, MA*

Background: Platinum-based chemotherapy is the 1st line standard of care for NSCLC patients with EGFR exon 20 insertion mutations (Exon20ins), with anti-PD(L)1 frequently used as well. Here we present anti-tumor activity of sunvozertinib in these patients whose disease had progressed on these therapies from two ongoing phase 1/2 studies (WK-KONG1, NCT03974022 and WU-KONG2, CTR20192097). Based on these data, sunvozertinib was granted the Breakthrough Therapy Designation by both US FDA and China NMPA. **Methods:** The objective of this study is to characterize the safety and efficacy of sunvozertinib in platinum-pretreated advanced NSCLC patients harboring EGFR Exon20ins, with or without anti-PD(L1) treatment. In addition, the effect of prior treatment on sunvozertinib's safety and efficacy were explored. **Results:** As of July 30, 2021, a total of 52 locally advanced or metastatic NSCLC patients harboring EGFR Exon20ins post platinum treatment were enrolled into WU-KONG1 and WU-KONG2 studies, and included in the efficacy analysis set (dose range: 50 mg to 400 mg, once daily). Male/Female: 21/31; Median age 59; Asian/White: 44/8; Prior therapies: median 2.5 (range 1-10); 31% received prior anti-PD(L)1 treatment (all in £ 300 mg cohorts); 40% of the subjects with baseline brain metastasis. Partial response was observed at ≥ 100 mg. At the dose level of 100 mg, 200 mg, 300 mg and 400 mg, confirmed ORR was 50% (1/2), 55.6 % (5/9), 44.8% (13/29) and 22.2% (2/9), respectively. With a median follow-up time of 10.5 months, median DoR was not reached for 200 mg cohort; with a median follow-up of 7 months, median DoR of 300 mg group was 5.6 months. Progression free survival (PFS) rate at 6 months for 100 mg, 200 mg, 300 mg and 400 mg cohorts was 50%, 53.3%, 44.6% and 44.4%, respectively. In patients with/without prior anti-PD(L)1 treatment, comparable efficacy and safety profiles were observed. **Conclusions:** The data suggest sunvozertinib is active in platinum-pretreated patients with EGFR Exon20ins, irrespective of prior or after anti-PD(L)1 treatment. The updated data will be presented at the meeting. Sunvozertinib is currently in phase 2 pivotal clinical development (NCT03974022 and China CTR20211009). Clinical trial information: NCT03974022. Research Sponsor: None.

9016 **Poster Discussion Session**

Telisotuzumab vedotin (Teliso-V) monotherapy in patients (pts) with previously treated c-Met–overexpressing (OE) advanced non-small cell lung cancer (NSCLC). *First Author: D. Ross Camidge, University of Colorado Cancer Center, Aurora, CO*

Background: Teliso-V is an antibody-drug conjugate composed of a c-Met antibody (ABT-700) and a microtubule inhibitor (monomethyl auristatin E). The phase 2 M14-239 trial (LUMINOSITY, NCT03539536) aims to identify the c-Met OE NSCLC populations best suited to Teliso-V (Stage 1) and expand selected groups for further evaluation of efficacy (Stage 2). In Stage 1, pts were enrolled into cohorts defined by histopathology (non-squamous [NSQ] or squamous [SQ]) and *EGFR* mutation status (mutant or wild type [WT]); NSQ cohorts were further divided in groups on the basis of c-Met expression (high or intermediate). Updated data from the fourth interim analysis (IA4) are presented. **Methods:** Pts had locally advanced/metastatic NSCLC, ≤2 prior lines of systemic therapy, ≤1 line of chemotherapy, and tumors that were c-Met OE by central immunohistochemistry (IHC; Ventana; Tucson, AZ). c-Met OE was defined for the NSQ cohort as ≥25% 3+ by IHC (high, ≥50% 3+; intermediate, 25 to <50% 3+) and for the SQ cohort as ≥75% 1+ by IHC. The planned enrollment was up to approximately 150 pts in Stage 1 and 160 pts in Stage 2. Teliso-V was dosed at 1.9 mg/kg IV Q2W. The primary endpoint is objective response rate (ORR) by independent central review. Secondary endpoints include duration of response (DOR). **Results:** As of data cutoff (27 May 2021), 136 pts were treated with Teliso-V; 122 were evaluable for ORR. ORR was 36.5% in the NSQ *EGFR* WT cohort (52.2% in c-Met high group and 24.1% in c-Met intermediate group), but was modest in the NSQ *EGFR* mutant and SQ cohorts. Efficacy data in groups/cohorts are in the Table. The most common any-grade adverse events (AEs) were peripheral sensory neuropathy (25.0%), nausea (22.1%), and hypoalbuminemia (20.6%). Grade 5 AEs considered possibly related to Teliso-V occurred in 2 pts (sudden death and pneumonitis in 1 pt each in the SQ cohort). **Conclusions:** Teliso-V demonstrated a promising ORR in pts with previously treated c-Met OE NSQ *EGFR* WT NSCLC; this cohort is currently expanding in Stage 2. ORR was modest in the cohorts of pts with c-Met OE NSQ *EGFR* mutant NSCLC and with c-Met OE SQ NSCLC; both cohorts have now met the protocol-specified stopping criteria and are no longer enrolling. The safety profile observed was consistent with IA3. Clinical trial information: NCT03539536. Research Sponsor: AbbVie.

NSCLC Group	Confirmed Responses (n/N)	ORR,% (95% CI)	Events/Responders	Median DOR, mo (95% CI)
c-Met OE NSQ *EGFR* WT	19/52	36.5 (23.6, 51.0)	8/19	6.9 (4.1, –)
c-Met high	12/23	52.2 (30.6, 73.2)	5/12	6.9 (2.4, –)
c-Met intermediate	7/29	24.1 (10.3, 43.5)	3/7	– (4.1, –)
c-Met OE NSQ *EGFR* mutant	5/43	11.6 (3.9, 25.1)	2/5	– (3.0, –)
c-Met high	5/30	16.7 (5.6, 34.7)	2/5	– (3.0, –)
c-Met intermediate	0/13	0 (–, –)	0	Not applicable
c-Met OE SQ	3/27	11.1 (2.4, 29.2)	2/3	4.4 (3.0, –)

9017 **Poster Discussion Session**

Efficacy and safety of patritumab deruxtecan (HER3-DXd) in advanced/metastatic non-small cell lung cancer (NSCLC) without *EGFR*-activating mutations. *First Author: Conor Ernst Steuer, Winship Cancer Institute of Emory University, Atlanta, GA*

Background: Patients (pts) with advanced NSCLC without *EGFR*-activating mutations (*EGFR*m) have limited treatment options after failure of molecularly targeted therapies or platinum-based chemotherapy (PBC) with or without immunotherapy (IO). HER3-DXd is an antibody drug conjugate consisting of a fully human monoclonal antibody to HER3 attached to a topoisomerase I inhibitor payload via a tetrapeptide-based cleavable linker. We previously published efficacy and safety data from a study of HER3-DXd in *EGFR*m NSCLC after failure of EGFR tyrosine kinase inhibitor (TKI) therapy. Here we present results in pts without *EGFR*m who progressed after PBC ± IO treatment. **Methods:** This ongoing phase 1 dose expansion study included a cohort of pts with advanced NSCLC without *EGFR*m who received prior PBC ± IO (NCT03260491). Pts with stable brain metastases were eligible, as were pts with non-*EGFR* oncogenic alterations and prior targeted therapy. The primary endpoint was confirmed ORR by blinded independent central review (BICR) per RECIST v1.1; secondary endpoints included DOR, PFS, and safety. **Results:** At the Mar 26, 2021, data cutoff, 47 pts had been treated with HER3-DXd 5.6 mg/kg IV every 3 wk; 17 pts had an identified driver genomic alteration (4 *KRAS* and 1 *NRAS* mutations, 4 *EGFR* Ex20ins, 3 *ROS1* and 2 *ALK* fusions, and 3 other). Median age was 62 y (range, 29-79 y); 53% of pts were female; 17% had squamous NSCLC. Median follow-up was 9.5 mo (range, 3.7-19.1 mo). Median number of prior anticancer regimens in the advanced setting was 3 (range, 0-8). Median treatment duration on study was 4.1 mo (range, 0.7-13.6 mo); treatment was ongoing in 11 pts (23%) at data cutoff. Confirmed ORR by BICR was 28% (13/47 pts; 95% CI, 16%-43%; 13 PRs, 22 SD). Median DOR was 5.7 mo (95% CI, 3.7-10.7 mo) and median PFS was 5.4 mo (95% CI, 3.9-12.7 mo). Among pts with identified driver genomic alterations, 35% (6/17) had a confirmed response by BICR, including 3 of 5 pts with *KRAS/NRAS* mutations and 2 of 2 with *ALK* fusions. Among pts without identified driver genomic alterations, 23% (7/30) had a confirmed response by BICR. The most common grade ≥3 treatment-emergent adverse events (TEAEs) were neutropenia (26%), thrombocytopenia (15%), and fatigue (15%). Drug-related interstitial lung disease by central adjudication occurred in 4 pts (9%; 0 grade ≥3). Four pts (9%) had TEAEs associated with treatment discontinuation. No drug-related deaths occurred. **Conclusions:** These data show promising clinical activity in pts with NSCLC without *EGFR*m, including pts with other identified driver genomic alterations. Updated results from this study will be presented. The overall safety profile was similar to that previously reported in pts with *EGFR*m NSCLC. A phase 2 study of HER3-DXd in pts with *EGFR*m NSCLC after failure of EGFR TKI and PBC is ongoing (NCT04619004). Clinical trial information: NCT03260491. Research Sponsor: Daiichi Sankyo, Inc.

9018 **Poster Discussion Session**

Phase I trial of the RAF/MEK clamp VS-6766 in combination with everolimus using an intermittent schedule with expansion in NSCLC across multiple *KRAS* variants. *First Author: Anna Rachel Minchom, The Institute of Cancer Research and The Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom*

Background: VS-6766 is a small molecule RAF/MEK clamp that results in the reduction of p-MEK and p-ERK. Preclinical data show synergy of VS-6766 with the mTOR inhibitor everolimus across a panel of *KRAS* mutated (mt) NSCLC cell lines. This clinical trial evaluated the safety and efficacy of a novel intermittent regimen of VS-6766 and everolimus with an expansion in *KRAS* mt NSCLC (NCT02407509). **Methods:** The trial used a 3+3 dose escalation design with an intermittent once a week schedule A, and if tolerated, twice a week schedule B (Mon-Thu or Tue-Fri) for both drugs on a 3 weeks on/1 week off, 28 day cycle. Patients with *RAS* or *RAF* mt cancers were eligible for the dose escalation cohort, and 20 patients with *KRAS* mt NSCLC will be treated in the dose expansion cohort. Toxicity was evaluated by NCI CTC V4 and efficacy was evaluated using RECIST 1.1. **Results:** A total of 28 patients have been treated; median age 60 yrs (range 36-78), and median lines of previous treatment 3 (range 0-7). Sixteen patients have been treated in the dose escalation (3 in schedule A and 13 in the schedule B). The doses of 4 mg of VS-6766 and 5 mg everolimus (once weekly) were tolerated with no dose limiting toxicities (DLTs) and the dose intensity escalated to schedule B (twice weekly). At 4 mg VS-6766 twice weekly, DLTs were observed in two out of six patients and included grade 4 CPK elevation and grade 3 rash. Thus, the dose in schedule B (twice weekly) was de-escalated to 3.2 mg VS-6766 and the dose of everolimus was kept at 5 mg. No DLTs were reported in 6 patients and thus this was declared as the recommended phase 2 dose (RP2D). At the RP2D, the grade 3-4 drug related AE were rash (18%) and pruritus (7%). In the dose escalation cohorts, 3 partial responses (PRs) were reported (2 *KRAS G12D* low grade serous ovarian cancer and 1 *NRAS Q61K* mt thyroid cancer). In the *KRAS* mt NSCLC expansion cohort, 10 patients are evaluable for efficacy and 2 confirmed responses were reported (*KRAS* mutations G12V and G13A) with an objective response rate (ORR) 20% to date. The disease control rate (PR + SD) at the first scheduled evaluation was 90%. The median progression free survival (PFS) in the *KRAS* mt NSCLC cohort is 6.35 months (95% CI 3.52 – not reached). Updated ORR and PFS data will be presented. **Conclusions:** A tolerable intermittent dosing schedule targeting both the MAPK and PI3K pathways has been established. The combination of VS-6766 with everolimus has shown activity in patients with a variety of *KRAS* mutation variants including responses in *KRAS* mt NSCLC. Research Sponsor: tbc.

9019 **Poster Discussion Session**

A phase II study of AK112 (PD-1/VEGF bispecific) in combination with chemotherapy in patients with advanced non-small cell lung cancer. *First Author: Yuangyuan Zhao, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Based on IMPOWER 150, atezolizumab in combination with bevacizumab and platinum-based chemotherapy has been the first-line treatment for advanced non-squamous NSCLC with negative driver genes. AK112 is a global first-in-class anti-PD-1/VEGF bi-specific antibody developed by Akesobio. Preclinical and clinical studies have indicated that AK112 possess potential anti-tumor efficacy in solid tumors. Therefore, we aimed to assess the efficacy and safety of AK112 in combination with chemotherapy for patients with advanced NSCLC. **Methods:** This was an open-label, multi-center phase II study evaluating the efficacy and safety of AK112 in combination with chemotherapy in pts with advanced NSCLC. Enrolled pts were divided into three cohorts: Previously untreated advanced NSCLC pts with wide-type EGFR/ALK (Cohort 1), pts with EGFR mutations who had failed prior EGFR-TKI therapies without T790M mutation or failed osimertinib treatment (Cohort 2), and pts who progressed after anti-PD-1/L1 and platinum-based chemotherapy (Cohort 3). Pts were treated with 10mg/kg or 20mg/kg AK112 once every 3 weeks in combination with carboplatin and pemetrexed or carboplatin and paclitaxel for Cohort 1/2, and docetaxel for Cohort 3. Primary endpoint was ORR as assessed by investigator per RECIST v1.1. **Results:** 133 pts were enrolled from Feb 03, 2021 to Dec 31, 2021 and received AK112 plus chemotherapy (44 received AK112 10 mg/kg and 89 received AK112 20 mg/kg). As of Dec 31, 2021, in cohort-1, among 26 evaluable pts with squamous cell carcinoma, 20 partial response and 6 stable disease were observed for a 76.9% ORR and a 100.0% DCR, median DOR and median PFS was not reached while 6-month PFS rate was 86.2%. In Cohort-2, among 19 evaluable pts, 13 partial response and 5 stable disease were observed for a 68.4% ORR and a 94.7% DCR while median DOR was 5.5 months, and median PFS was 8.3 months. In Cohort-3, among 20 evaluable pts, 8 partial response and 8 stable disease were observed for a 40.0% ORR and a 80.0% DCR, median DOR and median PFS was not reached while 6-month PFS rate was 71.1%. Treatment emergent adverse events (TEAE) occurred in 86.5% (115/133) of the pts, and grade ≥3 AEs occurred in 28.6% (38/133) of pts including two deaths. Most common AE (incidence ≥ 5%) included alanine/aspartate aminotransferase increased, epistaxis, anemia, vomiting, nausea, rash, leukopenia, thrombocytopenia, and neutropenia. Treatment discontinuation due to AE occurred in 3.0% (4/133) of the pts. **Conclusions:** AK112 plus chemotherapy has shown a promising anti-tumor efficacy in each cohort and warrants potentially superior safety in comparison to anti-PD-(L)1 and anti-VEGF combination therapies in advanced NSCLC. PFS and ORR were also significantly improved with AK112 plus chemotherapy. Therefore, phase III registration studies of AK112 plus chemotherapy in advanced NSCLC will be initiated in 2022. Clinical trial information: NCT04736823. Research Sponsor: Akeso Biopharma Co.,Ltd.

9020 **Poster Discussion Session**

Phase 1/2a trial of nadunolimab, a first-in-class fully humanized monoclonal antibody against IL1RAP, in combination with cisplatin and gemcitabine (CG) in patients with non-small cell lung cancer (NSCLC). *First Author: Astrid Paulus, CHU de Liège, Liège, Belgium*

Background: Interleukin-1 Receptor Accessory Protein (IL1RAP) is expressed by cancer and stromal cells of many solid tumors. The IL-1 pathway is active in tumors and upregulated in response to chemotherapy. IL1RAP interacts with IL-1R1 and modulates downstream factors (e.g. IL-6, IL-8) and CRP level. Nadunolimab (CAN04), a fully humanized ADCC-enhanced IgG1 antibody, targets IL1-RAP and blocks IL-1α and IL-1β signaling. Here, results are reported from the phase 1/2a clinical trial CANFOUR evaluating nadunolimab combined with CG in NSCLC. **Methods:** Patients (pts) with unresectable, locally advanced or metastatic NSCLC, progressed on pembrolizumab or in first line for advanced disease, were eligible. Pts received 1 (n =17), 2.5 (n = 3) or 5 mg/kg (= 13) nadunolimab given Q1W in Cycle 1 and Q2W from Cycle 2, combined with standard CG. Due to risk of infusion-related reactions, a priming dose of 0.5 mg/kg nadunolimab was given one week before CG. Primary objective was safety; secondary objectives included ORR, PFS and OS, and exploratory objectives included effects on serum and tumor tissue biomarkers. **Results:** Thirty-three pts were enrolled: median age 64 years (39-77), 30% female, 42% ECOG 0, 55% non-squamous histology, 82% stage IV, 45% received previous pembrolizumab monotherapy. Treatment-related adverse events of grade≥3 were observed in 73% of pts, including neutropenia (58%), febrile neutropenia (9%), thrombocytopenia (30%) and anemia (18%). Neutropenia could be managed by G-CSF. Thirty pts received combination therapy and were included in the efficacy analysis. Three pts did not receive chemotherapy due to clinical deterioration (n = 2) or consent withdrawal (n = 1). ORR was 53% (95% CI 34-72%), disease control rate 80% (61-92%) and median duration of response 5.5 months (3.7-7.0) with 23% of pts still on treatment. The lower limit of the 95% CI for the observed ORR excludes the pre-specified 30%. ORR in pts with squamous histology was 46% and non-squamous 56%. Median PFS was 6.7 months (5.5-7.3) and median OS 13.7 months. The neutrophil-lymphocyte ratio was reduced throughout the trial and was driven by the reduction in circulating neutrophil numbers. IL1RAP expression on both cancer and stromal cells was confirmed in tumor biopsies. **Conclusions:** Nadunolimab combined with CG shows manageable safety and promising efficacy with a response rate of 53% in NSCLC pts. Nadunolimab is currently evaluated in several clinical trials investigating chemotherapy or IO combinations, including carboplatin and pemetrexed in non-squamous NSCLC. Clinical trial information: NCT03267316. Research Sponsor: Cantargia AB.

9021 **Poster Discussion Session**

Genomic correlates of acquired resistance to PD-(L)1 blockade in patients with advanced non-small cell lung cancer (NSCLC). *First Author: Biagio Ricciuti, Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, MA*

Background: Despite improvements in survival with immune checkpoint inhibition (ICI), the majority of patients develop acquired resistance to ICI after an initial benefit. However, the mechanisms underlying acquired resistance to ICI in NSCLC are largely unknown. **Methods:** Patients with advanced NSCLC treated with ICI at the Dana-Farber Cancer Institute (DFCI), and whose tumors underwent genomic profiling before and after ICI, with no intervening therapies, were included. Mutations, tumor mutational burden (TMB), copy number variations (CNVs), and PD-L1 tumor proportion score (TPS) were compared between pre- and post-ICI samples. Acquired resistance was defined as the development of disease progression after an initial objective response, or stable disease ≥3 months with PD-(L)1 blockade. **Results:** Among 1763 patients with advanced NSCLC who received ICI, 45 had matched pre- and post-ICI tissue samples available for genomic profiling. Putative mechanisms of resistance were identified in 55% of cases (N = 25). Five patients (20%) acquired an *STK11* mutation, one patient (4%) acquired a *KEAP1* mutation, and another patient (4%) developed concurrent *KEAP1* and *SMARCA4* mutations. A patient (4%) with *KRAS* G12C-mutant NSCLC developed concurrent *STK11* and *KEAP1* mutations at resistance. In 3 cases (12%) with pre-existing *STK11* or *KEAP1* mutations prior to ICI administration, we identified acquired copy losses of *STK11* and *KEAP1*, respectively, resulting in bi-allelic inactivation of these genes. Acquired beta-2-microglobulin (*B2M*) mutations were detected in 3 patients (12%), one of whom developed concurrent *B2M* copy loss, indicating bi-allelic inactivation. Eight additional patients (32%) developed *B2M* gene deletions. Other acquired alterations that have been implicated in ICI resistance included *CDKN2A/B* loss (N = 10, 40%), including 5 with bi-allelic deletion, acquired *PTEN* deletions (N = 5, 20%), and *MDM2* amplification (N = 2, 8%). When we examined alterations in immune checkpoint genes, we identified acquired *CD274* (PD-L1) and *PDCD1LG2* (PD-L2) loss in 8% of cases (N = 2), and bi-allelic deletion in one case (4%). Intervening ICI did not affect TMB (median TMB: 8.7 [pre-ICI] vs 9.1 [post-ICI] mut/Mb, P = 0.6), PD-L1 expression (median PD-L1 TPS: 3% [pre-ICI] vs 5.0% [post-ICI] mut/Mb, P = 0.5), or aneuploidy levels (as fraction of genome altered [FGA]) (median FGA: 18.4% [pre-ICI] vs 21.1% [post-ICI], P = 0.2), indicating that acquired gene level CNVs were not a reflection of increased cancer aneuploidy. In a control cohort of 30 patients with pre- and post-chemotherapy matched samples which underwent genomic profiling, no acquired mutations in *STK11*, *KEAP1*, *SMARCA4*, or *B2M* were detected. **Conclusions:** Mechanisms of acquired resistance to PD-(L)1 blockade are heterogenous, and new therapeutic strategies are required to delay and overcome ICI resistance in patients with NSCLC. Research Sponsor: Society of Immunotherapy for Cancer.

9022 **Poster Discussion Session**

Association of comprehensive molecular genotyping and overall survival in patients with advanced non-squamous non-small cell lung cancer. *First Author: Charu Aggarwal, University of Pennsylvania, Philadelphia, PA*

Background: Current guidelines recommend comprehensive molecular genotyping for newly diagnosed patients (pts) with metastatic non-squamous (non-Sq) NSCLC. We have previously demonstrated that concurrent plasma (P) and tissue (T) based next-generation sequencing (NGS) improves detection of clinically actionable mutations in pts with advanced NSCLC. We analyzed the impact of concurrent T+P NGS on comprehensiveness of molecular genotyping and on overall survival (OS). **Methods:** A retrospective cohort study of pts with newly diagnosed stage IV non-Sq NSCLC who received therapy at our institution between 01/2019 and 12/2020 was performed. Categories of NCCN guideline testing were defined, i) comprehensive: *EGFR, ALK, BRAF, ROS1, MET, RET,* and *NTRK* testing, ii) incomplete: 2-6 genes tested, and iii) no testing performed. The proportion of pts with comprehensive molecular testing performed, prior to 1st-line therapy and by detection modality (T NGS vs. T+P NGS), were compared using Fisher's exact test. Median OS was estimated using Kaplan-Meier methodology from diagnosis to death or censored at most recent follow-up. **Results:** 335 patients were included in this analysis, 98.5% (330/335) underwent molecular testing: either comprehensive: n = 291 (86.9%), incomplete testing: n = 39 (11.6%); or no testing n = 5 (1.5%). Testing with T NGS was completed in 32.7% (108/330); 67.2% (222/330) underwent concurrent T+P NGS. These groups were well balanced for baseline characteristics, with the exception of a higher number of never smokers in T+P vs. T NGS (30.2% vs. 14.8%, p < 0.0001). Proportion of pts with comprehensive molecular testing was higher among pts with T+P NGS: 99.5% (221/222) vs. T NGS: 64.8% (70/108), p < 0.0001. All pts with T+P NGS testing had results available prior to 1st line therapy; 100% (204/204) compared to 60.7% (51/84) for T NGS, p < 0.0001. With median follow up of 20.5 months (mos, range 0.3 - 33.1), median OS was 18.6 mos. Median OS for pts tested with T+P NGS vs T alone was numerically longer at 23.2 vs. 14.1 mos, but not statistically significant (p = 0.078). However, regardless of testing modality, patients with comprehensive molecular genotyping had superior OS compared to those with incomplete or no testing (22.1 mos vs. 11.6 mos, p = 0.017). The institution of oral targeted therapy had no bearing on this difference in OS (test for interaction, p = 0.6509). **Conclusions:** Performance of concurrent T+P NGS testing was associated with a higher likelihood of comprehensive molecular genotyping, as well as improved availability of results, including prior to first line therapy. Patients with comprehensive genotyping have improved OS compared to patients with incomplete or no testing. These results support implementation of a concurrent T+P NGS approach upon initial diagnosis of metastatic non-Sq NSCLC. Research Sponsor: National Comprehensive Cancer Network, Pharmaceutical/Biotech Company.

LBA9023 **Poster Discussion Session**

Efficacy/safety of entrectinib in patients (pts) with *ROS1*-positive *(ROS1+)* advanced/metastatic NSCLC from the Blood First Assay Screening Trial (BFAST). *First Author: Solange Peters, Lausanne University Hospital, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

9024 **Poster Discussion Session**

Updated efficacy and safety of larotrectinib in patients with tropomyosin receptor kinase (TRK) fusion lung cancer. *First Author: Alexander E. Drilon, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY*

Background: Neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions have been identified as oncogenic drivers in a variety of tumor types, including lung cancer. Larotrectinib is a highly selective, central nervous system (CNS)-active TRK inhibitor that demonstrated an objective response rate (ORR) of 73% across 15 investigator-assessed patients (pts) with lung cancer (Drilon et al, *JCO Precis Oncol* 2022). We report data on an expanded cohort of pts with TRK fusion lung cancer treated with larotrectinib. **Methods:** Pts with TRK fusion lung cancer enrolled in two larotrectinib clinical trials (NCT02576431 and NCT02122913) were included for this analysis. Larotrectinib was administered at 100 mg twice daily. Response was assessed by independent review committee (IRC) per RECIST v1.1. **Results:** As of July 20, 2021, a total of 26 pts with TRK fusion lung cancer (24 non-small cell lung cancer, 1 atypical carcinoid, 1 neuroendocrine) were enrolled, including 10 pts with CNS metastases at baseline. Median age was 51.5 years (range 25.0–76.0). The gene fusions involved *NTRK1* (n =21; 81%) or *NTRK3* (n =5; 19%). Pts received a median of 2 prior lines of systemic therapies with 19 (73%) receiving ≥2. Among 23 pts evaluable per IRC, the ORR was 83% (95% confidence interval [CI] 61–95): two complete responses, 17 partial responses (PR), and four stable disease (SD). The median time to response was 1.8 months. Among 10 evaluable pts with baseline CNS metastases, the ORR was 80% (95% CI 44–97): eight PR and two SD. Median duration of response (DoR) and progression-free survival (PFS) were not reached; median follow-up was 12.9 and 14.6 months, respectively. The 24-month rates for DoR and PFS were 72% and 67%, respectively. Median follow-up for overall survival (OS) was 12.9 months. The 24-month and 36-month rates for OS were both 72%. For the 10 evaluable pts with CNS metastases, the 12-month DoR, PFS, and OS rates were 26%, 22%, and 78%, respectively. Duration of treatment for all pts evaluable per IRC ranged from 2.1 to 52.7+ months. At data cut-off, six pts had progressed, with all six continuing treatment post-progression for ≥4 weeks. Treatment-related adverse events (TRAEs) were predominantly Grade 1–2. Grade 3–4 TRAEs were reported in five pts (increased alanine aminotransferase, increased aspartate aminotransferase, hypersensitivity, myalgia, and increased weight). There were no treatment discontinuations due to TRAEs. **Conclusions:** In this larger dataset, larotrectinib demonstrated rapid and durable responses, extended survival, and a favorable long-term safety profile in pts with advanced lung cancer harboring *NTRK* gene fusions, including in pts with CNS metastases. These results support testing for *NTRK* gene fusions in pts with lung cancer. Clinical trial information: NCT02576431, NCT02122913. Research Sponsor: Bayer HealthCare and Loxo Oncology.

LBA9025 **Poster Session**

Five-year survival outcomes with nivolumab (NIVO) plus ipilimumab (IPI) versus chemotherapy (chemo) as first-line (1L) treatment for metastatic non–small cell lung cancer (NSCLC): Results from CheckMate 227. *First Author: Julie R. Brahmer, Bloomberg-Kimmel Institute for Cancer Immunotherapy, Johns Hopkins Kimmel Cancer Center, Baltimore, MD*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

LBA9026 **Poster Session**

First-line (1L) nivolumab (NIVO) + ipilimumab (IPI) + 2 cycles of chemotherapy (chemo) versus chemo alone (4 cycles) in patients (pts) with metastatic non–small cell lung cancer (NSCLC): 3-year update from CheckMate 9LA. *First Author: Luis G. Paz-Ares, Hospital Universitario 12 de Octubre, Universidad Complutense de Madrid, Madrid, Spain*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

9027 **Poster Session**

A protocol pre-specified interim overall survival (OS) analysis of GEMSTONE-302: A phase 3 study of sugemalimab (suge) versus placebo plus platinum-based chemotherapy (chemo) as first-line (1L) treatment for patients (pts) with metastatic non–small cell lung cancer (NSCLC). *First Author: Caicun Zhou, Oncology Department, Shanghai Pulmonary Hospital, Shanghai, China*

Background: GEMSTONE-302, a randomized, double-blind, phase 3 study, previously met its primary endpoint and demonstrated statistically significant and clinically meaningful prolongation of progression-free survival (PFS) with suge+chemo vs placebo+chemo as a 1L treatment in pts with metastatic NSCLC. PFS benefit was observed in both squamous (sq) and non-squamous (nsq) NSCLC, regardless of PD-L1 expression levels. Here we report the data from a protocol pre-specified interim OS analysis. **Methods:** Pts with systemic treatment-naïve stage IV NSCLC, measurable disease per RECIST v1.1, ECOG PS 0-1, and no known EGFR, ALK, ROS1 and RET alterations were randomized 2:1 to receive suge (1200 mg, IV) or placebo plus chemo (sq-NSCLC: carboplatin+paclitaxel; nsq-NSCLC: carboplatin+pemetrexed) every 3 weeks for up to 4 cycles, followed by maintenance therapy (sq-NSCLC: suge/placebo; nsq-NSCLC: suge/placebo+pemetrexed) for up to 35 cycles. The primary endpoint was investigator assessed PFS (INV-PFS). Key secondary endpoints included OS, INV-PFS in pts with tumor PD-L1 expression ≥1%, and ORR. Pts in the placebo group could cross over to receive suge monotherapy upon disease progression. **Results:** As of 22 Nov 2021, among all 479 enrolled pts, 51 (15.9%) and 7 (4.4%), respectively, remained on treatment with suge+chemo or placebo+chemo. The median follow-up was 25.4 and 24.9 months, respectively. Following treatment discontinuation, 17.8% and 43.4% of the pts, respectively, received cross-over suge or other non-study anti-PD-(L)1-containing therapies. Median OS was 25.4 months in suge+chemo group vs 16.9 months in placebo+chemo group (HR = 0.65 [95%CI, 0.50-0.84], p = 0.0008), and 2-year OS rate was 51.7% vs 35.6%. OS benefits were observed across all subgroups including different tumor histologies (sq: HR = 0.56; nsq: HR = 0.72) and PD-L1 expression levels (≥1%: HR = 0.64; < 1%: HR = 0.66). In the intent-to-treat population, median PFS was 9.0 months with suge+chemo vs 4.9 months with placebo+chemo (HR = 0.49 [0.40-0.61]), and 2-year PFS rate was 20.8% vs 7.3%. In pts with PD-L1≥1%, the median PFS was 10.9 vs 4.9 months (HR = 0.48 [0.36-0.63], p < 0.0001). ORR was 63.4% vs 40.3% (p < 0.0001). Among pts with baseline brain metastases, suge+chemo improved their OS (HR = 0.45) and intracranial INV-PFS (post-hoc analysis, HR = 0.33) vs placebo+chemo. Safety profile was consistent with previously reported results. **Conclusions:** Suge plus chemo demonstrated statistically significant and clinically meaningful OS improvement compared with placebo plus chemo, irrespective of tumor histology or PD-L1 expression levels, in pts with newly diagnosed metastatic NSCLC, offering a new 1L treatment option for this group of pts. Clinical trial information: NCT03789604. Research Sponsor: CStone Pharmaceuticals.

9028 **Poster Session**

Final progression-free survival, interim overall survival, and biomarker analyses of CHOICE-01: A phase 3 study of toripalimab versus placebo in combination with first-line chemotherapy for advanced NSCLC without EGFR/ALK mutations. *First Author: Jie Wang, State Key Laboratory of Molecular Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: Toripalimab (anti-PD-1) in combination with chemotherapy showed significant improvement in progression-free survival (PFS) and overall survival (OS) in the first-line treatment of advanced NSCLC regardless of tumor PD-L1 expression. Whole exome sequencing (WES) was performed to identify correlative biomarkers for survival. **Methods:** Patients (n = 465) with treatment-naïve, advanced NSCLC without EGFR/ALK mutations were randomized 2:1 to receive toripalimab 240 mg (n = 309) or placebo (n = 156) in combination with chemotherapy for 4-6 cycles, followed by maintenance of toripalimab or placebo plus standard care until disease progression, intolerable toxicity, or completion of 2 years of treatment. Stratification factors included PD-L1 expression status, histology, and smoking status. The primary endpoint was PFS by investigator per RECIST v1.1. Secondary endpoints included PFS by a blinded independent review committee (BIRC), OS and safety. **Results:** At the prespecified final PFS analysis (cutoff date Oct 31, 2021), a significant improvement in PFS as assessed by investigator was observed for the toripalimab arm over the placebo arm: HR = 0.49 (95% CI: 0.39-0.61), two-sided $p < 0.0001$, median PFS 8.4 vs 5.6 months. The 1-year PFS rates were 36.7% vs 17.2%. PFS as assessed by BIRC was also significantly longer in the toripalimab arm. The improvements of PFS were observed across key subgroups, including histology and PD-L1 expression. At the interim OS analysis, the toripalimab arm had a significantly longer OS than the placebo arm: HR = 0.69 (95% CI: 0.52-0.92), two-sided p = 0.0099, median OS not reached vs 17.1 months. The incidence of Grade ≥3 adverse events (AEs) (78.6% vs 82.1%) was similar between the two arms. AEs leading to discontinuation of toripalimab/placebo (14.3% vs 3.2%) and fatal AEs (5.5% vs 2.6%) were more frequent in the toripalimab arm. WES results from 394 available patients revealed that patients with high tumor mutational burden (TMB) (≥10 mutations per million base pairs) were associated with significantly better PFS in the toripalimab arm over the placebo arm (median PFS 13.1 vs 5.5 months) (interaction P = 0.026). In addition, patients with mutations in the FAK-PI3K-Akt pathway or IL-7 signaling pathways achieved significantly better PFS and OS from the toripalimab chemotherapy combination (interaction P values ≤ 0.01). **Conclusions:** The addition of toripalimab to chemotherapy in patients with advanced NSCLC provided superior PFS and OS when compared to chemotherapy alone with a manageable safety profile. These results support the use of toripalimab with chemotherapy as 1st line therapy for advanced NSCLC patients without EGFR/ALK mutations. Clinical trial information: NCT03856411. Research Sponsor: Shanghai Junshi Biosciences.

9029 **Poster Session**

Association of progression-free survival and overall response rate with overall survival in first-line randomized trials of immune checkpoint inhibitor–based regimens for metastatic non–small cell lung cancer (NSCLC): An FDA pooled analysis. *First Author: Bernardo Haddock Lobo Goulart, U.S. Food & Drug Administration, Silver Spring, MD*

Background: Overall Survival (OS) has represented the endpoint of choice to support approvals of Immune Checkpoint Inhibitors (ICIs) in first-line metastatic NSCLC. Despite continued interest in the use of earlier clinical endpoints as true surrogates for OS in this setting, the correlation of Progression-Free Survival (PFS) and Overall Response Rate (ORR) with OS remain an area of active investigation. We conducted a patient-level and trial-level pooled analysis of first-line randomized trials of ICI-based regimens to assess correlations of early clinical endpoints of PFS and ORR with OS in first-line metastatic NSCLC. **Methods:** The analysis included randomized trials comparing ICI-based regimens (anti-PD-(L)1 with or without anti-CTLA4 antibodies, with or without platinum-based chemotherapy) to platinum-based chemotherapy alone for the first-line treatment of patients with metastatic NSCLC that were submitted to the U.S. Food and Drug Administration between July 2016 to March 2021 to support a marketing application. Patient-level associations were estimated using Spearman (rs) correlation coefficients for PFS and OS, and Cox Proportional Hazards models in RECIST response-based subgroups for ORR and OS. At the trial level, associations were estimated using R2 coefficients from weighted linear regression models, using the log of hazard-ratio (HRs) for PFS and OS and log-odds ratio for ORR. **Results:** The pooled analysis included 13 trials enrolling 9,285 patients total. Seven trials compared ICIs combined with chemotherapy vs chemotherapy; 6 trials compared ICIs alone vs chemotherapy. Among all patients, the distribution of PD-L1 expression was 31%, 66%, and 32% for PD-L1 <1%, ≥1%, and ≥50%, respectively. The table shows the correlation coefficients for PFS and OS, and ORR and OS at the patient and trial levels. At the patient level, the OS HR comparing ICI-based regimens to chemotherapy was 0.54 (95% CI: 0.48, 0.61) for RECIST responders and 0.96 (95% CI: 0.90, 1.02) for non-responders. **Conclusions:** This pooled analysis did not indicate a strong correlation between endpoints of PFS and ORR with OS at the patient and trial levels in first-line randomized trials of ICI-based regimens for metastatic NSCLC, potentially because of use of subsequent therapies, cross-over to ICIs, and continuation of ICIs beyond progression. Future research will explore the correlation of alternative endpoints with OS, such as time to treatment discontinuation. Our analysis supports the continued importance of OS as an endpoint for first-line NSCLC trials of ICI-based regimens. Research Sponsor: U.S. Food & Drug Administration.

Correlation of PFS and ORR with OS.

Endpoints	All Patients	PD-L1 ≥1%	PD-L1 ≥50%
Patient level			
PFS and OS (Spearman)	0.64	0.62	0.63
Trial level			
R2 (PFS and OS)	0.69	0.70	0.60
R2 (ORR and OS)	0.61	0.54	0.31

9030 **Poster Session**

A randomized phase II/ III trial of nivolumab versus nivolumab plus docetaxel for previously treated advanced or recurrent non–small cell lung cancer: TORG1630. *First Author: Yosuke Kawashima, Department of Pulmonary Medicine, Sendai Kousei Hospital, Sendai, Japan*

Background: Immuno-checkpoint inhibitor (ICI) monotherapy is a standard second-line treatment for non-small-cell lung cancer (NSCLC). Addition of a cytotoxic agent to ICI may enhance the benefits. **Methods:** This multi-institutional open-label randomized phase II/III study compared the arm A consisting of nivolumab (NIV) monotherapy and arm B consisting of NIV + docetaxel (DTX) for patients with previously treated ICI-naïve NSCLC, prestratified by PS/histological types/sex/driver-mutations. The primary endpoint was superiority of arm B in OS in the phase III part. Assuming a HR of 0.75 for OS with the estimated mOS of arm A/B as 10.5/14.0 mo, a total 350 patients would be required to provide 80% power at a one-sided α of significance being 0.05. It was started at Nov. 2017, however, the patients' accrual was discontinued due to the approval of ICI in the first-line setting in late 2018. Eventually, a total of 131 patients were enrolled for analysis. **Results:** 128 patients (64 in each arm) were eligible and included in full analysis set (FAS), and the patients' demographics were well-balanced in each arm. The mOS was 14.7 mo (95%CI, 11.4-18.7) in arm A, and 23.1 mo (95%CI, 16.7-NR) in arm B. The HR of OS was 0.63 (90%CI, 0.42-0.95; p = 0.0310). The mPFS was 3.1 mo (95%CI, 2.0-3.9) and 6.7 mo (95%CI, 3.8-9.4) in arm A and B, respectively. The HR for PFS was 0.58 (95%CI, 0.39-0.88; p = 0.0095). The ORR was 14.0% (95%CI, 6.3-25.8) in arm A, and 41.8% (95%CI, 28.7-55.9) in arm B, with a statistical significance (p = 0.0014). Subgroup analyses for OS disclosed that the HRs favored arm B over arm A across all prespecified subgroups. The mOS of EGFR-mutant subgroup also showed better tendency in arm B than A (11.0 mo in arm A; 95%CI, 3.5-14.0; vs 20.6 mo in B; 95%CI, 5.8-NR; HR 0.45; 95%CI, 0.17-1.17). The hematological toxicity and gastrointestinal adverse events were more common in arm B than in A. Six (9.4%) in arm A and 25 patients (39.1%) in arm B discontinued protocol treatment due to adverse events. Overall, two treatment-related deaths were observed; one from pneumonitis in arm A, and one from myocarditis in arm B. **Conclusions:** Although the resulting statistical power was limited because of reduced sample size, the addition of DTX to NIV in the second-line NSCLC therapy significantly improved OS, PFS, and ORR, despite slightly elevated risk of toxicity. This is the first randomized clinical trial that confirmed significant survival benefit of ICI + chemotherapy over ICI alone in any cancer type. Clinical trial information: UMIN000021813. Research Sponsor: Ono Pharmaceutical Co. Ltd, Bristol-Myers Squib K.K.

9031 **Poster Session**

Three days of CIV rh-Endostatin in combination with PD-1 antibody plus chemotherapy as first-line regimen for EGFR/ALK-negative, advanced or metastatic, non-squamous non–small cell lung cancer (NSCLC): A open label, multicenter, phase II and cohort study (ENPOWER). *First Author: Dong Wang, Third Military Medical University, Chongqing, China*

Background: rh-Endostatin, an antiangiogenic agent, in combination with chemotherapy is recommended by the CSCO guideline as the first-line treatment for EGFR/ALK-negative, advanced or metastatic, non-squamous non–small-cell lung cancer (NSCLC). However, evidence supporting the application of rh-Endostatin plus PD-1 antibody in clinical settings has been limited. The ENPOWER study is an open-label, multicenter, phase II and cohort study to evaluate the efficacy and safety of three days of continuous intravenous infusion (CIV) of rh-Endostatin in combination with PD-1 antibody plus chemotherapy as the first-line regimen for EGFR/ALK-negative, advanced or metastatic, non-squamous NSCLC. **Methods:** ENPOWER was an open label, multicenter, phase II and cohort study. Patients with EGFR/ALK-negative, advanced or metastatic, non-squamous NSCLC were enrolled and assigned into the following two cohorts. Patients in Cohort 1 (PD-1 combination) received rh-Endostatin plus PD-1 antibody plus standard chemotherapy (Carboplatin or Cisplatin plus Pemetrexed) during the induction period up to 4 - 6 cycles and rh-Endostatin plus PD-1 antibody during the maintenance period until disease progression or intolerable adverse events. Those in cohort 2 different from in cohort 1 was not subject to PD-1 antibody. **Results:** 43 subjects were evaluable for efficacy analysis, with 15 in Cohort 1 (PD-1 combination) and 28 in Cohort 2. ORR and DCR was 53% and 93% in Cohort 1 (CR, 0; PR, 8; SD, 6; PD,1) and 39% and 86% in Cohort 2 (CR 0; PR 11; SD, 13; PD, 4), respectively. 50 subjects were included in safety analysis. The overall incidence of AEs of any grade was 89%. 92% of the patients in the cohort 1 and 85% in the cohort 2. The majority of AEs was grade 1 or 2. Adverse events of any grade that occurred in at least 10% of patients were neutropenia（76%）, nausea/vomiting (61%), AST/ALT abnormal (33%), palpitate (28%), anemia (22%) and skin hypersensitivity (11%) in the cohort 1 and neutropenia（68%）, nausea/vomiting (59%), AST/ALT abnormal (21%), palpitate (16%), anemia (40%) in the cohort 2, respectively. Adverse events of grade 3 or higher found in the cohort 1 were neutropenia (23%) and those were neutropenia (19%), AST/ALT abnormal (3%) and anemia (3%) in the cohort 2. Seemingly, Adverse events that occurred more frequently in the cohort 1 than in the cohort 2 were AST/ALT abnormal, palpitate and skin hypersensitivity. **Conclusions:** Three days of CIV rh-Endostatin in combination with PD-1 antibody plus chemotherapy for the first line treatment of EGFR/ALK negative, advanced or metastatic, non-squamous NSCLC could obtain the better improvement in the efficacy and result in the higher frequent in some of AEs. Clinical trial information: NCT: 04063449. Research Sponsor: None.

9032 **Poster Session**

Sintilimab versus pembrolizumab in monotherapy or combination with chemotherapy as first-line therapy for advanced non–small cell lung cancer: Results from phase 2, randomized clinical trial (CTONG1901). *First Author: Si-Yang Maggie Liu, Department of Hematology, First Affiliated Hospital, Institute of Hematology, School of Medicine, Key Laboratory for Regenerative Medicine of Ministry of Education, Jinan University; Chinese Thoracic Oncology Group (CTONG), Guangzhou, China*

Background: Immunotherapy has become standard therapy for untreated advanced NSCLC. However, no direct comparison between anti-PD-1 inhibitors has been reported. **Methods:** CTONG1901 is an open label, randomized, phase II clinical trial to compare sintilimab and pembrolizumab in monotherapy or combination with chemotherapy for advanced NSCLC at first-line setting. The primary endpoint was objective response rate (ORR). Patient without *EGFR* and *ALK* alteration were enrolled. Patients with PD-L1 tumor proportion score (TPS) ≥50% were randomly to receive sintilimab (A) or pembrolizumab (B) ; and with TPS<50% were randomly to receive sintilimab (C) or pembrolizumab (D) combined with chemotherapy. Sample size was calculated by Optimal Two-Stage Designs. 20 patients were enrolled in 1st stage. When ≥4 patients achieve partial response (PR) in sintilimab arms, the study will enter into 2nd stage and the sample size will be calculated based on the ORR results of the 1st stage. **Results:** The ORR was 57.1% in sintilimab and 33.3% in pembrolizumab arms at the 1st stage. The study successfully entered into the 2nd stage. 48 additional patients should be enrolled after calculation. When 15 PR in sintilimab arms achieved, the primary endpoint will be reached. From Mar. 2020 to Jan. 2022, 71 patients were screened and 68 patients were enrolled in two stages. Histologic subtypes and brain metastasis were well balanced between arms. As of Dec. 31st 2021, the median follow-up was 5.6 months. The confirmed ORR was 45.5% (15/33) in sintilimab vs. 28.6% (10/35) in pembrolizumab arms (A vs. B: 30.8% [4/13] vs. 28.6% [4/14]; C vs. D: 55.0% [11/20] vs. 28.6% [6/21]). Unconfirmed ORR was 57.6% vs. 42.9% and disease control rate (DCR) was 87.9% vs. 91.4% in sintilimab and pembrolizumab arms. The primary endpoint was reached. Survival data was immature. Any grade and 3-4 grade treatment-related adverse events (TRAEs) were comparable in sintilimab and pembrolizumab arms (Table). **Conclusions:** This is the first head-to-head phase II study to directly compare two anti-PD-1 antibodies as first-line treatment in advanced NSCLC. The result suggested comparable tumor response and similar safety profile between sintilimab and pembrolizumab. Clinical trial information: NCT04252365. Research Sponsor: CTONG1901.

Pathological and clinical efficacy of CTONG1901 in sintilimab and pembrolizumab arms.

	Arm A (Sintilimab) N=13	Arm B (Pembrolizumab) N=14	Arm C (Sintilimab + chemo) N=20	Arm D (Pembrolizumab + chemo) N=21
Histology (SQ/NSQ)	3/10	3/11	5/15	2/19
Brain metastasis (Y/N)	3/10	5/9	1/19	3/18
Confirmed PR	4	4	11	6
Unconfirmed PR	2	1	2	4
SD	5	8	5	8
Confirmed ORR	30.8%	28.6%	55.0%	28.6%
Unconfirmed ORR	46.2%	35.7%	65.0%	47.6%
DCR	84.6%	100%	90.0%	85.7%
Any Grade TRAEs	100%	100%	100%	100%
3-4 Grade TRAEs	6 (46.15%)	5 (35.71%)	15 (78.95%)	15 (75%)

SQ: squamous carcinoma; NSQ: non-squamous carcinoma; SD: stable disease.

9033 **Poster Session**

PEOPLE (NTC03447678), a phase II trial of first-line, single-agent pembrolizumab in advanced NSCLC with low PD-L1: Clinical outcomes and association with circulating immune biomarkers. *First Author: Giuseppe Lo Russo, Thoracic Oncology Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy*

Background: In advanced NSCLC (aNSCLC) with PD-L1 < 50% chemo-immunotherapy is the standard of care. Although the activity of single agent pembrolizumab was reported, no biomarkers have been identified able to select patients who mostly benefit. The trial aimed to identify immune biomarkers associated with PFS in aNSCLC patients with PD-L1 levels < 50% treated with first-line pembrolizumab. Here we reported for the first time the clinical outcomes of the trial and circulating immune profiling (CIP) biomarkers correlated to PFS. **Methods:** This phase II trial was conducted at Fondazione IRCCS Istituto Nazionale dei Tumori of Milan. Eligible patients were previously untreated stage IIIB-IV NSCLC, EGFR and ALK wild type with PD-L1 < 50%, PS 0-2. PD-L1 was assessed with 22-C3 antibody (Dako). Patients received pembrolizumab 200 mg every 3 weeks until 35 cycles, disease progression or unacceptable toxicity. The primary endpoint was the association of immune biomarkers with PFS. OS, ORR, DCR, DoR and safety were secondary endpoints. CIP was performed by determination of absolute cell counts for 36 innate and adaptive immunity subsets through multiparametric flow cytometry on freshly isolated whole blood samples at baseline. An orthoblique principal components-based clustering approach and multivariable Cox regression model adjusted for clinical variables were used to analyse CIP variables and their correlation with clinical endpoints. **Results:** From May 2018 to October 2020, of 87 screened, 65 patients were enrolled. The median age was 70.9 years, most patients were male (67.7%), smoker (87.7%), non-squamous (83.1%), PDL1 + (70.8%). 12 patients (18.5%) had PS 2. During a median follow-up of 26.4 months (mo), 51 radiological progressions, 46 deaths and 60 PFS events were observed. The median PFS was 2.9 mo (95%CI 1.8 - 5.6) and the median OS was 12.1 mo (95%CI 8.7 - 17.1). The ORR was 24.1% (2 complete and 12 partial responses), DCR was 53.4% and median DoR was 14.5 mo (95%CI 6.4 - 24.9). Drug related G3-G4 adverse events were: 2 hyponatremia, 2 lipase increased, 1 pneumonitis. Out of 7 CIP clusters identified, 2 were statistically significant at multivariable analysis on 57 patients. Higher baseline counts of 8 subsets within these two clusters were associated with better PFS (HR values range: 0.88-0.98; p values range: 0.001- 0.016). The significant subsets included lymphocytes (cells expressing CD3, or CD19 or CD56, but lacking granulocyte and monocyte markers) and main NK subsets (including CD56dim CD16+, CD56dim CD16- and HLA-DR+ NK cells). **Conclusions:** This trial confirmed that pembrolizumab as first-line single agent is safe and active also in a subgroup of aNSCLC patients with PD-L1 < 50%. CIP biomarkers can be useful to identify patients with a favourable outcome, thus avoiding the adding toxicity of chemotherapy. Clinical trial information: NTC03447678. Research Sponsor: Merck Sharp & Dohme.

9034 **Poster Session**

Platinum-free chemotherapy in the new era of immunotherapy: A phase II study of camrelizumab combined with apatinib and albumin paclitaxel in advanced non-squamous NSCLC (CAPAP-lung). *First Author: Lin Wu, Department of Thoracic Medicine, Hunan Cancer Hospital, The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, China*

Background: Cytotoxic chemotherapy and anti-angiogenic therapy may enhance the therapeutic efficacy of immune checkpoint inhibitors (ICIs). Platinum-containing dual-agent chemotherapy combined with ICIs is the standard first-line treatment for non-small cell lung cancer (NSCLC), however, the optimal combination regimen remains unclear. The adverse effects of platinum-based chemotherapy are relatively serious, whether platinum chemotherapy can be eliminated in the first-line treatment of non-small cell lung cancer is a hotspot and difficulty in current research. Based on these results, we initiated CAPAP-lung study, which is a single-arm, multicenter Phase II trial to evaluate the efficacy and safety of Camrelizumab in combination with apatinib and albumin paclitaxel without platinum as the first-line therapy for non-squamous non-small cell lung cancer. **Methods:** Patients diagnosed with IIIB-IV non-squamous NSCLC without EGFR and ALK sensitive mutations received Camrelizumab (200mg/3w) in combination with Albumin Paclitacxel (135mg/m^2, d1, d8/3w, 4-6 cycles) and Apatinib (250mg Qd po for 5 days, resting for 2 days every week). From August 2020 to February 2022, 54 of the planned 63 patients have been enrolled. The primary endpoint is progression-free survival(PFS), and secondary endpoints were overall survival (OS), duration of Response (DOR), objective response rate (ORR), and disease control rate (DCR) assessed by RECIST v1.1. This study is registered with ClinicalTrials.gov, NCT04459078 (follow-up is ongoing). **Results:** The data for a total of 38 patients out of 54 enrolled patients were evaluable. Median PFS was 10.97 mo (95%CI 7.1-NR).The objective response rate (ORR) and disease control rate (DCR) were 71.1% (27/38, 95%CI 53.9-84.0) and 97.4% (37/38, 95%CI 84.6-99.9), respectively. The incidence of grade 3 and worse treatment-related adverse events was acceptable, with grade 3 events in 25(46.3%) patients and grade 4 events in 3(5.6%) patients. The most common grade 3 treatment-related adverse events were decreased neutrophil count (8 [14.8%]), liver function damage (9 [16.7%]), rash (3 [5.6%]), and decreased white blood cell count (3 [5.6%]). **Conclusions:** Camrelizumab combined with albumin paclitaxel and apatinib showed encouraging antitumor activity with an acceptable safety profile for the first-line treatment of advanced lung adenocarcinoma. Clinical trial information: NCT04459078. Research Sponsor: Suzhou Sheng Diya Biomedical Co., Ltd.

9035 **Poster Session**

Durvalumab (D) +/- tremelimumab (T) + chemotherapy (CT) in first-line (1L) metastatic (m) NSCLC: AE management in POSEIDON. *First Author: Byoung Chul Cho, Yonsei Cancer Center, Seoul, South Korea*

Background: In the Phase 3 POSEIDON study in 1L mNSCLC, adding T to D+CT resulted in statistically significant improvements in PFS and OS vs CT. No new safety signals were identified and treatment discontinuations due to treatment-related AEs (TRAEs) were similar for the T+D+CT and D+CT arms (15.5% and 14.1%). Here we present details of AEs and their management. **Methods:** 1013 pts with *EGFR*/*ALK* wild-type mNSCLC were randomized 1:1:1 to 1L T+D+CT, D+CT or CT. Safety was assessed in all treated pts. **Results:** 330, 334 and 333 pts received T+D+CT, D+CT and CT; 78%, 82% and 74% received at least 4 cycles of platinum-based CT. The most common grade 3/4 TRAEs were hematologic (anemia in 17%, 15% and 20% of pts in the T+D+CT, D+CT and CT arms and neutropenia in 16%, 13% and 12%) and most were managed using standard approaches per local practice; 22%, 18% and 16% of pts received colony stimulating factors and 22%, 21% and 26% received blood transfusions. All grade immune-mediated AEs (imAEs) occurred in 34%, 19% and 5% of pts in the T+D+CT, D+CT and CT arms; a higher incidence of diarrhea/colitis, dermatitis/rash and endocrinopathies was seen with the addition of T to D+CT (Table). Grade 3/4 imAEs occurred in 10%, 7% and 2% of pts in the T+D+CT, D+CT and CT arms, and serious imAEs in 10%, 6% and 1%; imAEs led to discontinuation of any study treatment in 6%, 4% and 0.6%, and led to death in 0.6%, 0.3% and 0%. Most imAEs were low grade and manageable with systemic corticosteroids (received by 26%, 13% and 4% of pts in the T+D+CT, D+CT and CT arms) or endocrine therapy (12%, 8% and 1%). Median time from first dose to onset of imAEs (TTO) was generally > 60 days and the majority of non-endocrine imAEs resolved (Table). **Conclusions:** In POSEIDON, the safety profile of all regimens was manageable per standard guidelines and in line with the known profiles of D, T+D and CT; the most common grade 3/4 TRAEs were those typically associated with CT. As expected, more imAEs occurred with T+D+CT than D+CT, but the incidence of grade 3 or 4 imAEs, imAE-related deaths and treatment discontinuations due to imAEs was generally similar in the IO arms. T+D did not compromise the ability to administer planned CT. Clinical trial information: NCT03164616. Research Sponsor: AstraZeneca.

	T+D+CT (n = 330)			D+CT (n = 334)			CT (n = 333)		
imAE (grouped term) with incidence ≥2% in any arm	**n (%)**	**Median TTO, days (range)**	**% of n resolved**	**n (%)**	**Median TTO, days (range)**	**% of n resolved**	**n (%)**	**Median TTO, days (range)**	**% of n resolved**
Any imAE	111 (34)	–	52	64 (19)	–	50	17 (5)	–	71
Hypothyroid	27 (8)	105(8–596)	19	20 (6)	129(3–659)	40	3 (0.9)	115 (1–195)	33
Dermatitis/rash	24 (7)	64.5(1–913)	67	9 (3)	183(2–856)	56	7 (2)	7 (3–16)	86
Diarrhea/colitis	17 (5)	62(13–476)	88	6 (2)	158.5(6–369)	67	2 (0.6)	50.5(30–71)	100
Pneumonitis	12 (4)	191.5 (43–665)	75	10 (3)	104.5(19–479)	60	2 (0.6)	76.5 (68–85)	100
Hepatic	12 (4)	102.5(6–970)	58	11 (3)	22 (6–173)	91	0	–	–
Hyperthyroid	9 (3)	47(22–147)	78	4 (1)	95.5(21–136)	0	1 (0.3)	351 (351–351)	0
Adrenal insufficiency	8 (2)	118 (42–189)	13	4 (1)	125.5 (102–739)	0	0	–	–

9036 **Poster Session**

Association between immune-related adverse events and microbiome composition in patients with advanced non–small cell lung cancer treated with immunotherapy. *First Author: Marion Tonneau, Centre de Recherche du Centre Hospitalier de l'Université de Montréal (CRCHUM), Montréal, QC, Canada*

Background: Despite immune-checkpoint inhibitors (ICI) achieving high response rates in patients (pts) with advanced non-small cell lung cancer (NSCLC), immune-related adverse events (irAE) remain an important therapeutic hurdle. The gut microbiome represents a novel prognostic marker of ICI response and early clinical evidence suggests that the microbiome may also regulate the development of irAE. We aimed to assess the association between irAE and the gut microbiome composition in advanced NSCLC pts amenable to ICI. **Methods:** In this study, we enrolled 464 pts from two independent cohorts (Montreal and Tokyo) with advanced NSCLC treated with ICI monotherapy or combination with chemotherapy. Fecal samples were collected prior to ICI initiation. Metagenomics microbiome profiling and 16S rRNA microbiome sequencing were performed for 81 pts and 133 pts respectively. The irAE were classified as CTCEA grade 0-1 (G0-1 irAE) and grade > 2 (G2-5 irAE). Microbiome composition of both groups was represented using alpha diversity, beta diversity indexes and LEfSe relative abundances. **Results:** Median follow-up was 28.3 months (mos) and the incidence of G2-5 irAE was 25.1% in the Montreal cohort. For the Tokyo cohort, the median follow-up was 19.6 mos and 30.8% pts developed G2-5 irAE. First, in both cohorts, overall survival (OS) and progression-free survival (PFS) were significantly improved for pts with G2-5 irAE compared to G0-1 irAE (OS: HR: 1.71, $p = 0.008$ and PFS: HR: 1.65, $p < 0.001$) and (OS: HR: 2.34, $p = 0.001$, and PFS: HR = 2.34, $p = 0.006$) respectively. Second, metagenomics analysis of 81 pts demonstrated a numerical decrease of the alpha diversity in terms of observed species in the G2-5 irAE. *Dorea sp CAG 31, Anaerosporobacter mobilis, Butyricicoccus,* and *Enterococcus faecium* were overrepresented in pts with G2-5 irAE. Conversely, *Gordonibacter* was increased in G0-1 irAE. Next, 16S rRNA profiling from the Tokyo cohort revealed an enrichment of *Dorea, Butyricicoccus,* and *Eubacterium ventriosum* in G2-5 irAE. Finally, we observed an enrichment in *Dorea* and *Butyricicoccus* in the pts with PFS > 6 months, as observed in the G2-5 irAE group. **Conclusions:** IrAE correlated with clinical outcome and microbiome composition in two independent cohorts of pts with advanced NSCLC. These results prompt further research on the potential mechanism underling the role of the microbiome in the development of irAE. Research Sponsor: None.

9037 **Poster Session**

First report of safety/tolerability and preliminary antitumor activity of CAN-2409 in inadequate responders to immune checkpoint inhibitors for stage III/IV NSCLC. *First Author: Charu Aggarwal, University of Pennsylvania, Philadelphia, PA*

Background: Immune checkpoint inhibitors (ICI) are standard of care for advanced NSCLC. Even among patients with initial response, a majority ultimately progress, and rational combination approaches are needed to improve outcomes. CAN-2409 is a replication-deficient adenoviral gene construct that delivers the thymidine kinase gene, resulting in local conversion of a prodrug (valacyclovir) into a toxic metabolite. This leads to tumor cell lysis and immunization against the injected tumor and uninjected metastases. We have previously shown that monotherapy intra-tumoral (IT) delivery of CAN-2409 followed by oral valacyclovir in NSCLC patients is safe and results in CD8+ T cell infiltration in the injected tumor and activation of this cell population in tissue and peripheral blood. **Methods:** This open-label Ph2 experimental medicine clinical trial evaluates safety and clinical activity of IT CAN-2409 combined with ICI (± chemo) for stage III/IV NSCLC. Three cohorts are defined based on response to ICI at enrollment: stable disease (SD; Cohort 1; C1), progressive disease (PD) after ≥18 weeks (w) of ICI (Cohort 2; C2), or ICI refractory disease (RD; Cohort 3; C3). Two doses of CAN-2409 ($5x10^{11}$ vp) are given 5-7w apart via bronchoscopic or percutaneous injection into a lung tumor, disease-positive lymph node or peripheral metastasis, followed by valacyclovir. Patients are assessed for safety, immunologic biomarkers (analysis in progress), and clinical response. **Results:** As of data cutoff (10Jan22), 28 patients received ≥1 dose of CAN-2409 (safety population). Median age was 70 years; 86% stage IV; 32% squamous; 11% PD-L1 >50%; 82% receiving pembrolizumab and 18% nivolumab. Study treatment and procedures were generally well tolerated. The most common TRAEs were Gr1/2, with fatigue, fever, and chills in 18-39% of patients; 1 patient had Gr3 fever. Twenty-two patients are alive and 6 patients died due to disease. Of the 14 RECIST evaluable patients who received 2 doses of CAN-2409, clinical response was seen in 4 patients (Table 1). Two PRs are ongoing (6w, 24w) and reduction in tumor size was observed in non-injected lesions. In C2, 6 of 7 patients achieving SD are ongoing with median duration of 13w (range 10-40w). **Conclusions:** The addition of CAN-2409 for patients with advanced NSCLC and inadequate response to front-line ICI (± chemo) appears to be well tolerated. Preliminary clinical data suggest that CAN-2409 induced a clinical response in 4/14 evaluable patients and produced disease stabilization in most patients entering the trial with PD, with evidence of abscopal effect in a subset of patients. Clinical trial information: NCT04495153. Research Sponsor: Candel Therapeutics, Inc, Partnership for Accelerating Cancer Therapies (PACT).

Cohort	Disease status at study entry	Enrolled	Completed 12-week Treatment	PR	SD	PD
1	SD	2	2	1	1	0
2	PD	20	12*	3	7	1
3	RD	6	1	0	0	1
Totals		**28**	**15**	**4**	**8**	**2**

*1 pending RECIST.

9038 **Poster Session**

A phase 2 study of an off-the-shelf, multi-neoantigen vector (ADXS-503) in patients with metastatic non–small cell lung cancer either progressing on prior pembrolizumab or in the first-line setting. *First Author: Gregory James Gerstner, Illinois Cancer Care, Peoria, IL*

Background: ADXS-503 (A503) is an off-the-shelf, attenuated Listeria monocytogenes (Lm)-based immunotherapy bioengineered to elicit potent T-cell responses against 22 tumor antigens commonly found in non-small-cell lung cancer (NSCLC, i.e. 11 hotspot mutations and 11 tumor-associated antigens, TAAs). Pembrolizumab (pembro) is a programmed death receptor-1 (PD-1)-blocking antibody approved for the treatment of advanced lung cancer. A503 and pembro have complementary mechanisms of immune activation and reversal of immune tolerance. **Methods:** A phase 2 study of A503 ± pembro is being conducted in patients with metastatic squamous or non-squamous NSCLC. In Part B of the study, A503 was added-on to pembro within 12 weeks of the first scan showing disease progression following pembro (per RECIST criteria v1.1). In Part C of the study, A503 and pembro were administered to previously untreated patients. Both A503 ($1x10^8$ CFU) and pembro (200 mg) were infused by IV every 3 weeks until disease progression or limiting toxicity. **Results:** A total of 17 patients have been treated/evaluated from Part B (n = 14/13) and Part C (n = 3/3). Pembro + A503 was well tolerated in both parts of the study, with mostly grade 1–2, transient and reversible treatment-related adverse events, the most common being fever (47%), chills (35%), fatigue (29%) and nausea (21%). There have been no added immune-related toxicities associated with the combination. Of the 13 evaluable patients in Part B, 2 achieved partial response (PR) and 4 achieved stable disease (SD), yielding an objective response rate (ORR) of 15.4% and a disease control rate (DCR) of 46.2%. Two patients from Part C also achieved SD (DCR 67%). The 2 PRs in Part B have been durable (i.e. 710 and 189 days) as were 5 of the SDs: 3 in Part B (i.e. 448, 175, 117 days) and 2 in Part C (i.e. 322 and 175 days). Both patients with PR in Part B are still undergoing therapy in addition to the other patients who achieved SD. Patients who seem to achieve clinical benefit in both parts of the study include those with PD-L1 expression ≥ 50% and those who show proliferation and/or activation of NK and CD8+ T cells within the first weeks of therapy. In addition, patients with prior pembro exposure ≥ 6 months and DCR > 6 months seem to have clinical benefit when A503 is added to pembro (Part B). **Conclusions:** The addition of A503 to pembro after disease progression on pembro appears to be well tolerated and induced antigen-specific T-cell responses and durable disease control in 46% of patients in Part B and 67% of patients in Part C. Additional patients are currently being enrolled into both parts of the study to further explore the potential of A503 to restore or enhance sensitivity to checkpoint inhibitors. Clinical trial information: NCT03847519. Research Sponsor: Advaxis Inc.

9039 **Poster Session**

Safety and efficacy of tusamitamab ravtansine (SAR408701) in long-term treated patients with nonsquamous non–small cell lung cancer (NSQ NSCLC) expressing carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5). *First Author: Charles Ricordel, Service de Pneumologie, CHU Rennes, Rennes, France*

Background: Tusamitamab ravtansine (tusa) is a novel antibody-drug conjugate that selectively targets CEACAM5, a cell surface glycoprotein highly expressed in several tumor types. In previously reported results from an open-label Phase 1/2 study (NCT02187848), tusa showed promising antitumor activity in patients (pts) with heavily pretreated NSQ NSCLC and high CEACAM5 expression (Gazzah A et al. *J Clin Oncol.* 2020;38[15 suppl]:9505). Herein we report results for pts treated for ≥ 12 mo with NSQ NSCLC and high or moderate CEACAM5 expression. **Methods:** In the Phase 1/2 study, 92 pts with heavily pretreated NSQ NSCLC and high (n = 64) or moderate (n = 28) CEACAM5 expression (≥ 2+ intensity in ≥ 50% of tumor cells or in ≥ 1% to < 50% of tumor cells, respectively) were treated with tusa 100 mg/m^2 Q2W. As of Jan 2020, among CEACAM5 high expressors, 13 had confirmed partial response (PR) and 28 had stable disease (SD); among moderate expressors, 2 had PR and 15 had SD. We focus here on pts treated ≥ 12 mo as of Dec 2021. **Results:** A total of 24 pts were treated for ≥ 6 mo, 15 pts for ≥ 9 mo, 11 pts for ≥ 12 mo, 6 pts for ≥ 24 mo, and 2 pts for ≥ 42 mo. At the data cutoff, 5 pts remained on treatment, 1 for > 3.5 y. For pts treated ≥ 12 mo median (range) treatment duration was 26.6 (12.1–45.3) mo. Of 15 pts with PR in the prior analysis, as of Dec 2021 PR was still observed in 10 pts (67%) treated for ≥ 6 mo, 8 pts (53%) for ≥ 9 mo, and 7 pts (47%) for ≥ 12 mo. For the 11 pts treated ≥ 12 mo, 7 had PR and 4 had SD. Of the 11 pts treated ≥ 12 mo, 9 had high CEACAM5 expression and 2 had moderate CEACAM5 expression; most had prior treatment with an anti-PD1/PD-L1. Pts treated for ≥ 12 mo had better ECOG performance status and fewer prior treatments than the overall group. Of pts treated for ≥ 12 mo, PR occurred irrespective of CEACAM5 expression level. Only 1 pt treated for ≥ 12 mo discontinued due to a treatment emergent adverse event (TEAE) (breast cancer). Corneal events (keratitis/keratopathy) were the most frequent TEAEs, occurring in 8 pts (73%); 4 pts (36%) with Grade ≥ 3; 7 pts had subsequent treatment modification (delay or delay/reduced dose). No corneal TEAE was serious or led to treatment discontinuation. **Conclusions:** Almost half (47%) of pts who achieved a PR were treated for ≥ 1 y, suggesting that response to tusa in heavily pretreated pts was durable and frequently sustained. No patient discontinued long-term treatment because of drug-related toxicity. Corneal toxicity in these pts was manageable with dose modification (delay/reduction). The observed long-term clinical benefit and safety profile of tusa support its further clinical development; a Phase 3 study is ongoing to evaluate tusa monotherapy in previously treated pts with high CEACAM5 expressing NSQ NSCLC. Clinical trial information: NCT02187848. Research Sponsor: The study was funded by Sanofi. Editorial support was provided by Zeshan Mahmood, PharmD, and Elizabeth Strickland, PhD of inScience Communications (Philadelphia, PA, USA), funded by Sanofi.

9040 **Poster Session**

A phase Ib/II study of AK112, a PD-1/VEGF bispecific antibody, as first- or second-line therapy for advanced non–small cell lung cancer (NSCLC). *First Author: Caicun Zhou, Shanghai Pulmonary Hospital, Shanghai, China*

Background: Besides the well-known antiangiogenic effects, anti-VEGF agents also modulate the tumor immune micro-environment, leading to synergic anti-tumor effects. AK112 is a humanized IgG1 bispecific antibody against PD-1 and VEGF. Here, we reported results of an ongoing phase Ib/II trial of AK112 in advanced NSCLC pts. **Methods:** Pts with stage IIIB/IIIC/IV NSCLC, ECOG PS 0-1 and negative oncogenic drivers were enrolled and given AK112 (10 mg/kg Q3W, 20 mg/kg Q2W, 20 mg/kg Q3W or 30 mg/kg Q3W) intravenously. The primary endpoints were ORR per RECIST v1.1 and safety. **Results:** At data cutoff (January 5, 2022), 94 pts were enrolled: median age 66.0 years (range: 48-75), PS 1 90.4%, male 85.1%, non-squamous 48.9%, PD-L1 positive (TPS ≥1%) 70.2% and treatment-naïve 84.0%. Of 83 pts evaluable for efficacy, ORR (unconfirmed, similarly hereinafter) and DCR were 22.2%/88.9%, 44.0%/92.0%, 37.9%/93.1% and 100%/100% at doses of 10 mg/kg Q3W, 20 mg/kg Q2W, 20 mg/kg Q3W and 30 mg/kg Q3W, respectively. When doses of AK112 > 10mg/kg Q3W, ORR and DCR were 42.9% (24/56) and 92.9% (52/56) in 56 evaluable pts, 56.3% (18/32) and 100% (32/32) in pts with TPS≥1% at 1st line setting, and 23.5% (4/17) and 76.5% (13/17) in pts with PD-L1 TPS < 1%, respectively. Grade≥3 treatment-related adverse events (TRAEs) occurred in 10.6% (10/94) pts, in which the most common event (occurring in > 1 pt) was pneumonia (2.1%, 2/94). No TRAEs led to permanent treatment discontinuation. Most frequent TRAEs (incidence ≥10%) were proteinuria (17.0%), hypertension (16.0%), lipase increase (12.8%), alanine aminotransferase increase (12.8%), blood urea increase (10.6%), apolipoprotein E increase (10.6%) and hyperglycaemia (10.6%). No significant difference in the incidences of TRAEs were observed between non-squamous and squamous pts. **Conclusions:** In advanced NSCLC, AK112 was well-tolerated and presented remarkable anti-tumor efficacy. Further phase III studies are planned to validate the findings of this study. Clinical trial information: NCT04900363. Research Sponsor: Akeso Biopharma, Inc.

9041 **Poster Session**

Clinical efficacy and safety of the BAT1706 (proposed bevacizumab biosimilar) compared with reference bevacizumab in patients with advanced nonsquamous NSCLC: A randomized, double-blind, phase III study. *First Author: Likun Chen, Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: A Randomized, Double-blind, Phase III Study was conducted to confirm clinical similarity between BAT1706, a proposed biosimilar to reference bevacizumab, and EU-bevacizumab in patients with advanced non-squamous non-small cell lung cancer (NSCLC). **Methods:** Patients were randomized 1:1 to BAT1706 plus paclitaxel and carboplatin (Arm A) or EU-bevacizumab plus paclitaxel and carboplatin (Arm B) given three weeks for 6 cycles, followed by maintenance therapy with BAT1706 or EU- bevacizumab. The primary endpoint was overall response rate at Week 18 (ORR_{18}). Secondary endpoints included ORR at Week 6 and 12, best ORR, duration of response (DoR), progression-free survival (PFS), and overall survival (OS). **Results:** A total of 651 patients were randomized: BAT1706 (n = 325) or EU- bevacizumab (n = 326). In total, 649 randomized patients (BAT1706 (n = 325) or EU- bevacizumab (n = 324)) received at least one cycle of combination treatment. The median duration of therapy was 29.1 weeks (ranging from 3.0 to 62.1 weeks) in the Arm A and 27.0 weeks (ranging from 3.0 to 53.9 weeks) in the Arm B. The extent of exposure to BAT1706 and EU- bevacizumab was similar between these two arms. Overall, the proportion of patients achieving an ORR by Week 18 was comparable across Arm A and B (48.0% and 44.5%). The ORR risk ratio of 1.08 with 90% CI (0.94, 1.24) and the ORR risk difference of 0.03, with 95% CI (-0.04, 0.11) were within pre-specified equivalence margin. In addition, the multivariate-adjusted risk ratio was 1.07, with a 90% CI (0.93, 1.22). The ORR_{18} risk difference between BAT1706 and EU- bevacizumab was 0.03, with the 2-sided 95% CI (-0.04, 0.11) that fell entirely within pre-specified equivalence margin. In addition, the multivariate-adjusted risk difference was 0.03, with a 95% CI (-0.04, 0.11). The hazard ratio stratified for time to PFS was 0.915 and the PFS rate at 12 months was 20.7% versus 21.8%. At the end of the study, there were no significant differences between both the treatments. The incidence of treatment-emergent adverse events (TEAEs) and study drug-related TEAEs was similar between these two arms. Overall, the safety profiles of BAT1706 were consistent with that of EU- bevacizumab, no new safety signals or noticeable trends were observed. The mean serum concentrations were comparable between BAT1706 and EU- bevacizumab over the entire sampling interval both in pre-dose and post-dose. The incidence of positive anti-drug antibodies results was low (≤5%) and decreased over time in both treatment arms. No patient was detected to have positive neutralizing anti-drug antibody result during the study. **Conclusions:** BAT1706 demonstrated clinical equivalence to reference EU-bevacizumab in terms of efficacy, safety, pharmacokinetics, and immunogenicity. Clinical trial information: NCT03329911. Research Sponsor: Bio-Thera Solution.

9042 **Poster Session**

Immunogenicity and disease control induced by a multineoantigen vaccine (ADXS-503) in patients with metastatic non–small cell lung cancer who have progressed on pembrolizumab. *First Author: Aaron E. Lisberg, Department of Medicine, Division of Hematology/Oncology, UCLA, Los Angeles, CA*

Background: The administration of a lung cancer-specific immunotherapy with 22 tumor-associated antigens (ADXS-503, A503), has been evaluated as an add-on therapy for patients (pts) with metastatic non-small-cell lung cancer (NSCLC) who have progressed on pembrolizumab (pembro) as last therapy [Haigentz M et al. ASCO 2021]. The present study explores the immunogenicity and potential reversal of immune resistance with A503 when added-on to pembro at the time of progressive disease (PD). **Methods:** A phase 2 study of A503 + pembro is being conducted in pts with metastatic squamous or non-squamous NSCLC. In Part B of the study, A503 was added-on to pembro within 12 weeks after the first scan showing disease progression following pembro therapy (per RECIST criteria v1.1). Both A503 ($1x10^8$ CFU) and pembro (200 mg) were infused by IV every 3 weeks until disease progression or dose-limiting toxicity. Immunogenicity assays included serum cytokine and chemokine levels; flow cytometry; and in-vitro stimulation FluoroSpot assay with 4 different antigen-pools represented in A503 [i.e., hot spot mutations, heteroclitic/wild-type tumor-associated antigens and other antigens not included in the A503 construct (antigen spreading)]. **Results:** A total of 14 pts have been treated in Part B, of which 13 are clinically evaluable and up to 11 have immune assessments. Combination therapy was well tolerated with transient increased secretion of cytokines for several hours after infusion of A503 consistent with the expected immune activation and transient 'flu-like' syndrome. The objective response rate (16%) and disease control rate (46%) were encouraging with 2 partial responses (PR), 4 stable diseases (SD) and 7 pts with PD. Pts with disease control, in particular, generated CD8+ T cells reactive to neoantigens in 1 or more of the 4 antigen pools tested in FluoroSpot. Also, activation of NK cells and of cytotoxic- and memory-CD8+ T cells was mainly observed in pts with PR or SD, but not in those with PD, as shown in the table. **Conclusions:** Adding A503 to pembro after PD appears to induce innate and adaptive immune responses that may restore or enhance sensitivity to checkpoint inhibitors in pts with clinical benefit. Clinical trial information: NCT03847519. Research Sponsor: Advaxis Inc.

Cell count change from baseline (%).

Patient	1	2	3	4	7	8	9
Baseline	0 / 0 / 0	–100 / 0 / NA	0 / 0 / 0	0 / 0 / 0	0 / 0 / 0	0 / 0 / 0	0 / 0 / 0
W2	15 / 10 / 70	0 / 60 / –10	200 / –20 / 130	170 / 110 / 110	–50 / –40 / –90	–50 / 10 / –90	–30 / –20 / –60
W5	–5 / 70 / 40	100 / 60 / 70	0 / 20 / 70	210 / 190 / 180	0 / 120 / –50	–50 / –20 / –80	–20 / –70 / –70
W8	0 / 20 / 40	200 / 40 / 100	200 / 20 / 30	–50 / 260 / –50	–10 / 80 / –60	–50 / –20 / –90	– / – / –
W25	200 / 200 / 140	220 / 10 / 120	380 / 200 / 110	380 / 300 / 140	–20 / 0 / –70	– / – / –	– / – / –
EOT	Ongoing	350 / –10 / 160	– / – / –	590 / 110 / 250	–50 / –60 / –80	–50 / –30 / –90	– / – / –
BOR	PR	SD	SD	SD	PD	PD	PD

Cell types: CD8+ PD1+ TIGIT+ cells / Total NK cells / CD8+ central memory cells.

9043 **Poster Session**

Three-year outcomes and correlative analyses in patients with non–small cell lung cancer (NSCLC) and a very high PD-L1 tumor proportion score (TPS) ≥ 90% treated with first-line pembrolizumab. *First Author: Biagio Ricciuti, Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, MA*

Background: Although 1st-line PD-1 monotherapy has improved survival in advanced NSCLC with a PD-L1 TPS ≥50%, responses occur in ~45% of patients (pts). We previously showed that among pts treated with 1st-line pembrolizumab, clinical outcomes were significantly improved in those with a PD-L1 TPS of ≥90% compared to a TPS of 50-89%. Here, we report the 3-year survival analysis to 1st-line pembrolizumab in pts with a PD-L1 TPS ≥90% vs 50-89%, and characterize genomic and immunophenotypic differences between these PD-L1 expression groups. **Methods:** Pts with stage IV *EGFR/ALK* wild-type NSCLC and PD-L1 TPS ≥50% who received 1st-line pembrolizumab at the Dana-Farber Cancer Institute (DFCI) and Memorial Sloan Kettering Cancer Center (MSKCC), with a minimum follow-up of 3 years were included. Comprehensive tumor genomic profiling and multiplexed immunofluorescence (mIF) were performed to examine genomic and immunophenotypic correlates of very high PD-L1 expression on separate cohorts of NSCLC at the DFCI. **Results:** Among 396 pts, median age was 69, 53.3% were women, 90.1% had a history of tobacco use, 83.6% had a ECOG performance status of 0-1, and 28.8% had a *KRAS* mutation. At a median follow-up of 42.6 months, median progression-free (mPFS) and overall survival (mOS) in the entire cohort were 5.1 months, and 19.0 months, respectively. When compared to pts with a PD-L1 TPS of 50-89% (N = 252), those with PD-L1 TPS ≥90% (N = 144) had a significantly longer mPFS (6.0 vs 4.5 months, HR 0.67, p < 0.001), and longer mOS (30.2 vs 16.9 months, HR 0.66, p < 0.01). Kaplan-Meier estimates of the 3-year PFS and OS were 24.9% and 47.0% in the PD-L1 TPS ≥90% groups, and 9.4% and 27.7% in the PD-L1 TPS 50-89% group, respectively. A PD-L1 TPS ≥90% was confirmed to be an independent predictor of improved PFS (HR 0.68, p < 0.01) and OS (HR 0.67, p < 0.01) in multivariable analysis. Tumor genomic profiling from a separate cohort of 500 NSCLC samples revealed that mutations in *STK11*, *KEAP1*, *FBXW7*, and *CTNNB1* were significantly more frequent in tumors with a PD-L1 TPS of 50-89% compared to those with a PD-L1 TPS ≥90% (q < 0.05). mIF on 91 NSCLCs identified significantly higher CD8+PD1+ T cells and PD-L1+ immune cells in tumors with PD-L1 TPS ≥90% vs 50-89% (p < 0.05). **Conclusions:** Pembrolizumab monotherapy continues to demonstrate a meaningful long-term survival benefit in pts with advanced NSCLC and a PD-L1 TPS ≥90%. NSCLCs with very high PD-L1 TPS may have a more favorable genomic and immunophenotypic profile. These findings have implications for treatment selection and clinical trial interpretation and design. Research Sponsor: None.

9044 **Poster Session**

Dynamic changes in serum analyte levels associated with clinical outcome in squamous cell lung cancer trial SWOG Lung-MAP S1400I of nivolumab ± ipilimumab. *First Author: Edgar Gonzalez-Kozlova, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: *While* Immune checkpoint blockade (ICB) is standard treatment for lung cancer there are limited biomarkers that predict benefit, pharmacokinetic on-treatment activity or explain progression. S1400I was a randomized Phase III trial of nivolumab(N)+ipilimumab(I) versus N (NCT02154490, PMID 34264316) for ICB naïve, previously treated stage IV or recurrent squamous cell lung cancer. We performed circulating serum protein analysis of serial blood specimens from patients enrolled in S1400I to evaluate if serum proteins levels changed over time, changes differed by treatment arm, and if they were associated with overall survival. **Methods:** 561 serial blood specimens (baseline, weeks (wk) 3, 7, 9, and progression [PD]) from 160 of 252 eligible patients enrolled to S1400I were analyzed for 92 immuno-oncology analytes with the Olink proximity extension assay. Protein levels were normalized with use of internal controls and quantified as log2 protein expression (denoted as NPX). Linear mixed models evaluated change in expression from baseline at each time point (wks 3,7,9 and PD), and NPX differences at baseline, wk3, and PD depending on best objective response. A Cox model was used to evaluate the association between baseline NPX and survival. Overall survival and longitudinal cytokine expression were jointly modeled using a linear mixed model to estimate dynamic biomarker changes in NPX and a Cox model for survival. The joint models for time-varying NPX values included a random intercept and modeled time using a natural spline with three knots. Significance was defined as $P < 0.05$. **Results:** Serum proteins PCDC1, CXCL9, and CXCL10 were increased from baseline at wks 3,7,9 and at PD. CCL19 was increased at wks 3 and 7 but not at wk 9 and PD. IL10 and IFNγ were increased at wk 3 but subsequently returned to baseline. Change in CXCL13 from baseline to PD was larger for N+I versus N. Baseline CCL23, CSF-1, IL6, and MUC-16 were associated with shorter survival (HR > 1). Joint modeling of survival with cytokines showed an increased risk of death (HR > 1) with higher longitudinal serum levels of CXCL13, MMP12, CSF-1, and IL8. Patients achieving objective response had higher IL4 and LAMP3 and lower IL6 and IL8 at baseline and wk 3 compared to non-responders. **Conclusions:** Measurements of blood circulating soluble proteins represent easily accessible biomarkers that may be useful as indicators of outcome, and that will need to be prospectively confirmed. Clinical trial information: NCT02154490. Research Sponsor: U.S. National Institutes of Health.

9045 **Poster Session**

CtDNA shed as a tool to select immune checkpoint inhibitors (ICPI) with or without chemotherapy for patients (pts) with advanced non–small cell lung cancer (aNSCLC). *First Author: Benjamin Besse, Cancer Medicine Department, Gustave Roussy, Villejuif, France*

Background: ICPI are compelling therapies for pts with aNSCLC given the potential for durable benefit and limited toxicity. Even in tumors with biomarkers associated with ICPI response, early progression (eP) can be seen, leading to chemotherapy combination approaches. We hypothesize that ctDNA tumor fraction (TF) may identify pts at risk of eP on ICPI, helping to select the optimal first-line regimen. **Methods:** This study used the nationwide (US-based) de-identified Flatiron Health-Foundation Medicine NSCLC clinico-genomic database (FH-FMI CGDB). The de-identified data originated from ~280 US cancer clinics (~800 sites of care). Real-world overall survival (rwOS) accounting for delayed entry and real-world progression free survival (rwPFS) were estimated with Kaplan-Meier analysis. Hazard ratios (HR) were calculated using multivariate Cox proportional hazard models adjusting for relevant covariates. TF was calculated using an aneuploidy-based measure plus variant-based estimate and was categorized as follows: ≥10%: elevated, 1-10%: intermediate, < 1%: low. eP was defined as rw progression within 8 weeks of starting therapy. **Results:** 426 pts with documented aNSCLC initiated 1st or 2nd line ICPI (128 ICPI, 298 ICPI+chemo) within 60 days of liquid biopsy. 88 (21%) pts had elevated TF, 193 (45%) had intermediate, and 145 (34%) had low. Pts with elevated TF had higher frequency of liver involvement (elevated: 27%; intermediate: 12%; low: 8%) and had worse performance status (ECOG 2+) near the start of therapy (elevated: 33%; intermediate 22%; low: 17%). PD-L1 was unknown for most pts (elevated: 44%; intermediate: 53%; low: 57%); elevated TF was associated with high PD-L1 positivity (elevated: 22%; intermediate: 17%; low: 12%). In pts with elevated TF, eP was more frequent (elevated: 26%, intermediate: 22%, low: 15%). Amongst all patients treated with either ICPI ± chemo, low TF was associated with better median rwPFS (low 6.7m [ref]; intermediate 5.1m, HR: 1.39 [1.11-1.74]; elevated 3.4m, HR: 1.74 [1.31-2.31]) and median rwOS: (low 14.2m [ref]; intermediate 8.4m, HR: 1.52 [1.10-2.09]; elevated 4.6m, HR: 2.17 [1.47-3.21]). In pts with elevated TF, the addition of chemo to ICPI was associated with favorable rwPFS and rwOS compared to pts who received ICPI alone (Table). **Conclusions:** ctDNA TF identifies pts with aNSCLC with an increased risk of eP on ICPI who may benefit from ICPI+chemo. In pts with low TF, outcomes on ICPI alone are favorable and similar to those receiving ICPI+chemo, suggesting low TF may be a non-invasive tool for identifying pts for single-agent ICPI. Research Sponsor: Foundation Medicine, Inc.

	ICPI [ref]			ICPI + chemo			HR	
TF	N	rwPFS	rwOS	N	rwPFS	rwOS	rwPFS	rwOS
Low	50	6.8 m	12.0 m	95	6.6 m	15.3 m	1.11 [0.73-1.70]	1.32 [0.71-2.45]
Intermediate	62	5.5 m	8.0 m	131	5.0 m	9.6 m	0.94 [0.66-1.35]	0.86 [0.52-1.41]
Elevated	16	1.9 m	2.1 m	72	4.3 m	6.9 m	0.26 [0.12-0.56]	0.24 [0.09-0.60]

9046 **Poster Session**

Multiomics profiling and association with molecular and immune features in association with benefits from immunotherapy for patients with previously treated stage IV or recurrent squamous cell lung cancer from the phase III SWOG LungMAP S1400I trial. *First Author: Edwin R. Parra, Department of Translational Molecular Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Immune checkpoint blockade (ICB) has become a standard pillar of treatment for lung cancer. However, only ~20% of unselected patients can achieve durable clinical benefits. We performed immunogenomic profiling of tissue specimens from a randomized Phase III trial S1400I on metastatic lung squamous cell carcinoma (SCC) to evaluate if there were factors associated with better prognoses with ICB from single-agent versus combined targeting PD-1/CTLA-4 and evaluate if any differentiated between the treatments. **Methods:** We utilized FFPE tumor tissue submitted for Lung-MAP screening provided by the SWOG bank. SCC samples from 82 eligible patients treated with combined nivolumab+ipilimumab (N+I) or single agent nivolumab (N) were subjected to multiplex immunofluorescence (mIF, n = 82) and NanoString (ncounter Pan-Cancer Immune Profiling Panel, n = 32). Cell density phenotypes (cells/mm2) were defined using image analysis of staining for cytokeratin, CD3, CD8, granzyme B, CD45RO, FOXP3, PD1, PD-L1, and CD68. Immunogenomic features were associated with response, PFS, and OS derived from data provided by the LungMap team to the CIDC portal. For statistical analyses, non-parametric tests were utilized to assess associations of cell phenotypes versus continuous or categorical variables, and log-rank test analysis was performed to identify cell phenotypes or genes correlated with survival. **Results:** In both arms higher densities of total CD3+CD45RO+ T cells (P= 0.041), CD3+PD-1+ T cells (P= 0.024) and CD3+CD8+PD-1 T cells in stroma (P= 0.042) and CD3+CD8+GZMB+ T cells in the tumor compartment (P= 0.011) were positively associated with PFS. In the N+I arm but not in the N arm, higher densities of CD3+CD8+GZMB+ T cells in the tumor compartment were associated with better PFS (P= 0.015) and higher densities of stroma CD3+CD8-FOXP3+ T cells with worse OS. Spatial analysis showed that the presence of CD8+GZMB+ T cells close to malignant cells (median, ≤19.27 μm) was associated with better PFS (P= 0.037) in N+I arm and cluster analysis showed low clustering of cells in TMB-high vs. TMB-low tumors ($P < 0.01$). Gene expression profiling demonstrated that myeloid infiltration, immune recruitment, and inflammation genes were associated with a positive clinical outcome (P< 0.05). In both arms, *BLNK, CD163, FCGR2A* were associated with better OS (P< 0.01), *IRF1* and *BLNK* were associated with increased PFS (P< 0.01). In the N+I arm but not in the N arm, we observed significantly higher CD45 immune cell scores, including CD8 T cells and neutrophils, in responders versus non-responders. **Conclusions:** Our findings suggest a potential advantage in PFS and OS with an increased presence of cytotoxic immune cells and genes associated with the recruitment and proliferation of these cell types before therapy. Research Sponsor: The Foundation for the National Institutes of Health (FNIH), U.S. National Institutes of Health.

9047 **Poster Session**

Identifying prognostic and predictive value of mutations associated with clinical outcomes in first line (1L) patients with advanced or metastatic non–small cell lung cancer (aNSCLC). *First Author: Diego Perez Parente, Lung Cancer Squad, Roche Farma, Madrid, Spain*

Background: Whilst the impact of certain mutations on aNSCLC survival outcomes has been evaluated, real-world (rw) evidence on its predictive and prognostic value remains limited. We aimed to identify the predictive and prognostic value of non-driver mutations that are deemed to be clinically relevant in aNSCLC. **Methods:** This retrospective cohort study analysed de-identified electronic medical records from the Flatiron Clinico-Genomic (FCGD) and FoundationCORE™ databases of aNSCLC patients who have initiated 1L cancer immunotherapy (CIT, alone or in combination) or chemotherapy (chemo) under routine care between 2016 and 2021. Propensity-based multivariable models were used to determine associations between mutational status and progression-free survival (rwPFS), overall survival (rwOS) and overall response (rwR). **Results:** Of 10,795 patients identified, 2,999 met inclusion criteria (1,042 chemo, 1,957 CIT). Among these, 53% were men and 65% were ≥65 years old. Patients mostly had non-squamous histology (68%), a previous history of smoking (95%) and ECOG ≤1 (61%). 58% of patients were diagnosed as *de novo*. A total of 185 different mutations were identified in this population, and variants of the same mutation were grouped, identifying 58 mutation families. *STK11*, *KEAP1* and *CDKN2A/B* mutations were significantly associated with all effectiveness outcomes (Table), indicating lower response (rwR OR<1) and shorter survival (rwOS and rwPFS HR>1) in patients harbouring mutated vs. wild type genes. *APC* and *KRAS* mutations were only significantly associated with lower rwR, while *FGRF* and *HRAS* mutations were related to worse rwPFS and rwOS, respectively. In contrast, a significantly higher likelihood of response or PFS was associated with *ATM/R/RX* and *GATA3* mutations, respectively. Moreover, our results suggest that *KRAS* mutations potentially have predictive value for PFS in CIT-treated patients. Mutations with prognostic value on clinical outcomes (overall population). HR, hazard ratio; PFS, progression-free survival; OR, odds ratio; OS, overall survival; rw, real-world. **Conclusions:** *STK11*, *KEAP1* and *CDKN2A/B* mutations were significantly associated with poor prognosis in all effectiveness outcomes. In addition, *KRAS* mutations resulted in clinically significant differences in terms of PFS. Further analyses should be conducted to confirm this clinical significance and to evaluate the relevance of these mutations in future clinical trials design. Research Sponsor: Roche.

Mutation	rwR		rwPFS		rwOS	
	OR [95% CI]	p	HR [95% CI]	p	OR [95% CI]	p
STK11	0.49 [0.39, 0.62] n = 365	<0.001	1.6 [1.39, 1.84] n = 639	<0.001	1.38 [1.19, 1.59] n = 639	<0.001
CDKN2A/B	0.78 [0.64, 0.96] n = 544	0.019	1.18 [1.07, 1.3] n = 938	0.001	1.19 [1.07, 1.32] n = 938	0.001
KEAP1	0.62 [0.47, 0.82] n = 222	0.001	1.35 [1.14, 1.59] n = 391	<0.001	1.33 [1.13, 1.58] n = 391	0.001

9048 **Poster Session**

Clinical and genomic characteristics of pts with durable benefit from immune checkpoint inhibitors (ICI) in advanced non-small cell lung cancer (aNSCLC). *First Author: Jacob Sands, Dana-Farber Cancer Institute, Boston, MA*

Background: The 2-year mark has become a new milestone in pts with aNSCLC receiving immunotherapy. In pts who are progression free at that point, a subset experience ongoing disease control even after stopping active treatment. Some pts experience such impressive durability beyond 2 years, raising a question about potential cure. We queried a real-world (RW) clinico-genomic database (CGDB) to better understand these pts with durable benefit and their clinical and genomic features. **Methods:** Using the nationwide (~280 US cancer clinics) de-identified EHR-derived Flatiron Health-Foundation Medicine aNSCLC CGDB linked to genomic data, pts treated with ICI (+/- chemotherapy) from 01/2011-06/2021 were selected. RW progression (rwP) was obtained via technology-enabled abstraction of EHR data. Durable benefit was classified as absence of rwP, death or treatment failure (indicated by switch to a new line of therapy) within 24 mos of beginning ICI therapy. **Results:** In a cohort of 4,030 evaluable aNSCLC pts, 184 (4.6%) were free of rwP or treatment failure at 24 mos. Of these 184 pts with durable benefit, 84% received ICI monotherapy and 16% received ICI with chemotherapy; ICI treatment was more often first line (1L, 43%) or 2L (38%). 59% with durable benefit were still on ICI at the 2-year mark, whereas 41% had stopped a median of 11.4 mos after therapy start. Of 109 pts remaining on ICI for 2-years, median time on ICI was 36.3 mos from therapy start. Overall, pts with durable benefit had a median rwPFS of 37.1 mos and median rwOS of 58.8 mos from start of ICI. Compared to pts with rwP on ICI before 24 mos, those with durable benefit were more likely to have history of smoking (94% vs 86%) and absence of liver, brain or bone metastases (all $p < 0.001$). High tumor mutational burden (TMB ≥10) was more common (62% vs 35%, $p < 0.001$) and *STK11, CDKN2B, PIK3CA,* and *EGFR* alterations were less common in pts with durable-benefit vs those with rwP on ICI before 24 mos. In a multivariate cox model of rwPFS beyond 24 mos in pts with durable benefit, TMB ≥20 was significantly associated with longer rwPFS (HR 0.45 95% CI 0.24-0.83, $p = 0.01$) while TMB ≥10 was marginally significant (HR 0.65 95% CI 0.40-1.03, $p = 0.07$); treatment with ICI with chemotherapy was significantly associated with worse rwPFS (HR 1.84 95% 1.093.12, $p = 0.02$). High PD-L1 > 50% was noted in 728 (19%) of those without durable benefit and 38 (21%) of those with durable benefit, though many in the data set had unknown PD-L1 status. **Conclusions:** Pts with durable benefit > 2 years after starting ICI therapy for aNSCLC represent a unique population of immune survivors with a median OS of almost 5 years; 41% of pts stopped ICI before the 2-year mark. Elevated TMB was associated with durable benefit on ICI as well as prolonged rwPFS after the 2-year mark and deserves further investigation as a biomarker for prolonged benefit to ICI in aNSCLC. Research Sponsor: Foundation Medicine.

9049 **Poster Session**

Clinical outcome and potential benefits of post-progression immunotherapy for patients with metastatic NSCLC with primary resistance to ipilumumab and nivolumab in the LONESTAR phase III study. *First Author: Mehmet Altan, MD Anderson Cancer Center, Houston, TX*

Background: Primary resistance to immune checkpoint inhibitor (ICI) therapy remains a major challenge in clinical oncology. Here, we describe the clinical outcome of patients who experienced radiologic progression within 12 weeks of therapy with nivolumab and ipilimumab (I+N) for metastatic non-small cell lung cancer (mNSCLC). **Methods:** The LONESTAR study is an ongoing phase III study (NCT03391869). Study enrolls patients with immunotherapy naïve mNSCLC (prior chemotherapy is allowed). All patients receive I+N for 12 weeks and are randomized to experimental therapy vs. control arm if they did not have disease progression. Patients who experience radiologic progression per RECIST v1.1 are not randomized and removed from the study. Treatment beyond progression is allowed if they clinically benefit from the systemic therapy. We prospectively collected clinicopathologic and radiologic outcome data from patients who experienced radiologic progression within 12 weeks of I+N therapy and have not randomized to investigational therapy. We described the primary progression pattern. We collected subsequent treatment, radiologic, and toxicity data and calculated clinical outcomes, including progression-free survival (PFS) and overall survival (OS). **Results:** Of the 194 patients who received at least one dose of I+N therapy, 72 patients had clinical and/or radiologic progression at ≤ 12 weeks. Thirty-five (35; 48%) patients did not receive subsequent treatment, 21 (29%) patients received subsequent 2nd line systemic therapy, and 16 (22%) patients were continued on I+N beyond radiologic progression due to ongoing clinical benefit. Among patients treated with 2nd line therapy, 13 patients were treated with platinum doublet +/- anti-PD-(L)1, seven (7) patients were treated with single-agent chemotherapy +/- VEGF inhibitor, and one (1) patient was treated with targeted therapy. The PFS for the 2nd line therapy was 6.5 months (95%CI: 4.8, 8.9), and OS was 10.4 months (95%CI: 6.6, 16.1). Among the 16 patients treated with I+N beyond progression, 13 had a mixed response to induction therapy, where primary progression was most frequently observed in mediastinal lymph nodes. LCT with radiotherapy was utilized with I+N in 10 patients. The median duration of post-progression treatment with I+N plus LCT was 8.7 months (95%CI: 5.9, 22.3) and 5.6 months (95%CI 4.4, 11.5) with I+N alone. The OS was 19.5 months (95% CI: 6.2,18.7). **Conclusions:** In this study cohort, primary resistance to I+N was observed in 37% of the patients, and in a subset of these patients treated with post-progression I+N, either alone or in combination with LCT, durable clinical benefit was observed. Further studies are warranted to identify which patients are most likely to benefit from post-progression I+N. Clinical trial information: NCT03391869. Research Sponsor: Bristol Myers Squibb.

9050 **Poster Session**

Association between lung immune prognostic index, microbiome, and immunotherapy outcomes in non–small cell lung cancer. *First Author: Edouard Auclin, CRCHUM, Montreal, QC, Canada*

Background: Host-related inflammatory biomarkers and gut microbiome are two major prognostic factors for non-small cell lung cancer (NSCLC) patients (pts) treated with immune checkpoint inhibitors (ICI). In this study, we aimed to assess an association between the Lung Immune Prognostic Index (LIPI) and the microbiome composition on ICI outcomes in two independent cohorts of NSCLC pts. **Methods:** We included 205 patients with advanced NSCLC treated with ICI (monotherapy or in combination with chemotherapy) from two independent cohorts. Metagenomics microbiome profiling was performed on the Canadian discovery cohort of 72 pts while 16S rRNA microbiome sequencing was used in the Japanese validation cohort of 133 pts. The LIPI score was calculated using the dNLR (neutrophils/[leucocytes-neutrophils]) and lactate deshydrogenase (LDH). Pts were classified as Good (G: 0 high factor), Intermediate (I: 1 high factor) and Poor (P: 2 high factors). Median overall survival (OS) was estimated using the Kaplan-Meier method. Microbiome diversity indexes and bacterial relative abundances were compared according to LIPI groups. **Results:** Among the 72 pts included in the discovery cohort, the median follow-up of 20.6 months (mos). The LIPI was distributed as follows: G (n = 31, 43.1%), I (31, 43.1%), P (10, 13.8%) and baseline characteristics were well balanced between the 3 groups. When segregating pts according to LIPI, the OS was 25.6 mo, 19.8 mo, and 5.7 mo in the G, I (HR: 1.71, 95%CI: 0.80-3.65) and P (HR: 3.97, 95%CI: 1.60-9.82) groups, respectively ($p = 0.003$). The microbiome alpha diversity was lower in the P group compared with the G group ($p = 0.03$), and there was a trend towards different microbiome composition in beta diversity ($p = 0.055$) between both groups. Pts in the G group had a favorable microbiome (enriched in *Ruminococcus* and *Anaerostipes*), while pts from the P group had an unfavorable microbiome (enriched in *Enterobacteriaceae* and *Clostridium symbiosum and lavalense*). Next, in the validation cohort of 133 pts, LIPI was distributed as follows: G (n = 62, 46.6%), I (51, 38.3%), P (20, 15%). Pts with G LIPI had not reached their median OS compared to pts in the I [15.7 mo HR: 1.60 (0.88-2.94)] and P [8.8 mo groups, HR: 2.02 (0.98-4.19)], $p = 0.03$. Similar to the discovery cohort, at the genus level, G LIPI group had enrichment of *Ruminococcus* as well as *Anaerostipes* compared with pts in the P and I groups with an overrepresentation of *Hungatella*. **Conclusions:** Host-related inflammatory biomarkers, represented by the LIPI, seemed to be associated with microbiome and ICI outcomes in pts treated with NSCLC. This observation was validated in an external validation cohort. This link could be in relation to the presence of proinflammatory bacteria in pts with poor LIPI. Research Sponsor: Nuovo Soldati Institute.

9051 **Poster Session**

PEOPLE (NTC03447678), a phase II trial to test pembrolizumab as first-line treatment in patients with advanced NSCLC with PD-L1 < 50%: A multiomics approach. *First Author: Marina Chiara Garassino, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: Chemo-immunotherapy is the standard of care for patients with advanced NSCLC and PD-L1 < 50%. Efficacy has been reported in this setting with single agent pembrolizumab, but no reliable biomarkers yet exist for selecting patients likely to respond to single agent immunotherapy. The aim of this trial was to identify potential new immune biomarkers associated with PFS in NSCLC patients with PD-L1 < 50% treated with first line pembrolizumab. **Methods:** Advanced EGFR and ALK wild type treatment-naïve NSCLC patients with PD-L1 < 50% were enrolled. Gene expression profile was performed using nCounter PanCancer IO 360 Panel (Nanostring) on baseline tissue. Circulating immune profiling was performed by determination of absolute cell counts with multiparametric flow cytometry on freshly isolated whole blood samples at baseline and at first radiological evaluation. Gut bacterial taxonomic abundance was obtained by shotgun metagenomic sequencing of stool sample at baseline. Pembrolizumab was administered at 200 mg flat dose every 3 weeks until 35 cycles, disease progression or unacceptable toxicity. Omics data was analyzed with sequential univariate Cox Proportional Hazards regression predicting PFS, with Benjamini-Hochberg multiple comparisons correction. Biological features significant with univariate analysis were analyzed with multivariate Least Absolute Shrinkage and Selection Operator (LASSO). **Results:** From May 2018 to October 2020 65 patients were enrolled. Main characteristics were: male 67.6%, smokers 87.7%, PD-L1 positive 70.8%. Median follow up and PFS were 26.4 and 2.9 months, respectively. Gene expression profile was performed in 48 patients, microbiome in 54 patients and circulating immune profiling in 56 patients at baseline and in 46 patients at first radiologic evaluation. LASSO multivariate analysis with optimal lambda of 0.28 showed high expression levels of IRF9 and COMP genes was associated with an unfavorable PFS (HR 3.03, 1.52 – 6.02, $p = 0.08$ and HR 1.22, 1.08 – 1.37, corrected $p = 0.06$, respectively). High expression levels of CD244 (HR 0.74, 0.62- 0.67, $p = 0.05$), PTPRC (HR 0.55, 0.38 – 0.81, $p = 0.098$), KLRB1 (HR 0.76, 0.66 – 0.89, $p = 0.05$) in tissue samples and NK cells/CD56dimCD16+ (HR 0.56, 0.41 – 0.76, $p = 0.006$) in peripheral blood at baseline and non classical CD14dim CD16+ monocytes (HR 0.52, 0.36 – 0.75, $p = 0.004$), eosinophils (CD 15+CD16-) (HR 0.62, 0.44 – 0.89, $p = 0.003$) lymphocytes (HR 0.28, 0.15 – 0.5, $p < 0.001$) in peripheral blood after first radiologic evaluation were associated to a favorable PFS. No microbiome features were selected by LASSO. **Conclusions:** To the best of our knowledge, this is the first prospective trial in NSCLC with PD-L1 < 50% performed with a multi-omic approach able to identify immune cell subsets and expression levels of genes associated to PFS under first line treatment with pembrolizumab. Clinical trial information: NTC03447678. Research Sponsor: Merck & Sharp Dohme.

9052 **Poster Session**

Outcomes of single-agent PD-(L)-1 versus combination with chemotherapy in patients with PD-L1-high (≥ 50%) lung cancer. *First Author: Arielle Elkrief, Human Oncology & Pathogenesis Program, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Single agent PD-(L)-1 blockade (IO) and PD-(L)-1 blockade combined with chemotherapy (ChemoIO) are both standard first-line treatments for patients with PD-L1-high (≥ 50%) metastatic non-small cell lung cancer (NSCLC). These regimens have not been compared prospectively, so comparative effectiveness is unclear. It is also unknown if clinical and molecular tumor characteristics differentially associate with benefit to IO vs ChemoIO in patients with NSCLC with high PD-L1 tumor expression. **Methods:** All patients with metastatic NSCLC treated with IO or ChemoIO at two institutions (Memorial Sloan Kettering Cancer Center and Dana-Farber Cancer Institute) were reviewed. Patients with *EGFR* or *ALK* alterations, PD-L1 expression < 50%, treated with IO or ChemoIO in > 1st line setting were excluded. Overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) were compared between the IO vs ChemoIO groups and association with clinical, pathologic, and molecular features was examined. To account for NGS panel differences, tumor mutational burden (TMB) values were harmonized using a z-score conversion as previously described (Vokes et al, 2019). **Results:** Of 639 patients with stage IV *EGFR*/*ALK* wild-type NSCLC and PD-L1 ≥50% treated in the 1st line setting, 504 received IO and 135 received ChemoIO. Baseline ECOG performance status (p = 0.3), median PD-L1 % (p > 0.9) and TMB (p = 0.2) were similar between the IO and ChemoIO groups. For patients receiving IO vs ChemoIO, there was no significant difference in OS (HR 0.8, 95% CI 0.6 to 1.08; p = 0.2). Median PFS was shorter (HR 0.7, 95% CI 0.6 to 0.9; p = 0.004) and ORR was lower (40% IO vs 55% ChemoIO, p = 0.002) in the IO group. Among patients with durable responses (> 6 months), never smokers were less common in the IO group (6% vs 18%, p < 0.001), but there was no difference in PD-L1 expression, TMB, or mutational (*KRAS*, *STK11*, or *KEAP1*) profile to suggest differential predictors of benefit to IO or ChemoIO. **Conclusions:** In patients with PD-L1 high NSCLC, there was no survival benefit associated with the addition of chemotherapy to IO. There were also no clear differences in PD-L1 expression or molecular features associated with durable response to IO vs ChemoIO. These findings have implications for treatment selection in this population. Research Sponsor: Memorial Sloan Kettering Cancer Center Support Grant/Core Grant (P30 CA008748) and the Druckenmiller Center for Lung Cancer Research at MSK.

9053 **Poster Session**

Impact of performance status on survival outcomes and health care utilization in patients with advanced non–small cell lung cancer treated with immune checkpoint inhibitors. *First Author: Daniel E. Meyers, Department of Medicine, University of Calgary, Calgary, AB, Canada*

Background: Immune checkpoint inhibitors (ICIs) have revolutionized the treatment paradigm of non-small cell lung cancer (NSCLC). Despite the high prevalence of patients with poor Eastern Cooperative Oncology Group (ECOG) performance status (PS ≥2) in real-world practice, landmark studies have typically excluded this patient group from enrolment. The primary objective of this study was to evaluate the impact of ECOG PS on clinical outcomes and health care utilization in a large cohort of NSCLC patients treated with ICI in real-world practice. **Methods:** Using the Alberta Immunotherapy Database, we identified consecutive patients who received at least one dose of Pembrolizumab or Nivolumab for the treatment of advanced NSCLC between 1/1/2010 and 12/30/2019. The data cut-off date was 10/1/2020. Baseline clinical, pathological, and laboratory-based data were collected retrospectively. The primary outcome was median overall survival (mOS), as stratified by ECOG PS. The secondary outcomes were median time-to-treatment failure (mTTF) and metrics of health care utilization, including emergency department (ED) visits, hospitalizations, and death in hospital. Kaplan-Meier survival curves were used to determine survival outcomes, and compared with the log-rank test. The association between ECOG PS and healthcare utilization were represented with risk ratios and evaluated using chi-square tests. **Results:** A total of 790 patients were included. Median follow-up time was 20.6 months. 29.2% (n = 231) had PS ≥2 at the time of ICI initiation. As compared with the favorable PS group (PS < 2), patients with PS ≥2 had significantly lower mOS - 3.3 months (95% CI 2.5-4.0) versus 13.4 months (95% CI 11.7-16.0) (HR, 3.0; 95% CI 2.5-3.6, p < 0.0001), and mTTF – 1.4 months (95% CI 0.9-1.8) versus 4.9 months (95% CI 4.4-5.6) (HR, 2.2; 95% CI 1.9-2.6, p < 0.0001). 3- and 12-month survival rates were also significantly lower in the PS ≥2 group as compared with the PS < 2 group (52.8% versus 86.4% and 13.4% versus 41.0%, p < 0.0001 for both comparisons). Patients with PS ≥2 were also significantly more likely to present to the ED (RR 1.6; 95% CI, 1.3-2.0, p < 0.001) and be admitted to hospital (RR 2.3; 95% CI 1.7-3.0, p < 0.0001) within the first month after treatment initiation. These patients were also significantly more likely to die in hospital during their first admission (RR 2.7; 95% CI 1.8-4.1, p < 0.0001), as well as at any point during treatment (RR 2.2; 95% CI 1.60-3.0, p < 0.0001). **Conclusions:** NSCLC patients with poor ECOG PS at the time of ICI initiation had significantly worse survival outcomes and were significantly more likely to utilize health care services than those with favorable ECOG PS. The large proportion of patients with poor ECOG PS further justifies the urgent need for randomized trials evaluating the efficacy of ICI in this high-risk population. Research Sponsor: None.

9054 **Poster Session**

Immunophenotypic correlates and response to first-line pembrolizumab among elderly patients with PD-L1-high (≥ 50%) non–small cell lung cancer. *First Author: Adriana Paula de Castro Barrichello, Lowe Center For Thoracic Oncology, Dana-Farber Cancer Institute, Boston, MA*

Background: Older age is associated with increased levels of systemic inflammation and altered immunosurveillance in cancer. Whether aging correlates with a distinct immunophenotype or impacts clinical outcomes to first-line pembrolizumab in patients with advanced non-small-cell lung cancer (NSCLC) and a PD-L1 tumor proportion score (TPS) of ≥50% is unclear. **Methods:** We performed a retrospective analysis of patients with NSCLC. Multiplexed immunofluorescence (mIF) for CD8+, PD-1+, PD-1+CD8+ and FOXP3+ was performed to explore tumor immunophenotype. Clinical outcomes were analyzed on a separate cohort of patients with PD-L1-high (TPS of ≥50%) NSCLC (negative for sensitizing genomic alterations in *EGFR* and *ALK*) who received treatment with first-line pembrolizumab. Variables demonstrating a univariate signal of association of p < 0.1 were included in the multivariate model. The results were compared in patients < 80 vs ≥80 years old. **Results:** Among 541 patients with NSCLCs profiled by mIF, the median age was 67 (28-90). When comparing patients < 80y (n = 497) to ≥80y (n = 44), there was no difference in median CD8+ T cells/mm2 (171 vs 148; p = 0.69), PD-1+ immune cells/mm2 (81.1 vs 87.2; p = 0.95), or PD-1+CD8+ T cells/mm2 (18.0 vs 13.1; p = 0.56). NSCLCs from patients ≥80y had a higher median of intratumoral-associated FOXP3+ T cells/mm2 (63.6 vs 91.1; p = 0.03). In a cohort of 271 patients with PD-L1 ≥50% who received first-line pembrolizumab, baseline clinicopathological characteristics were balanced in the < 80y (n = 225) vs ≥80y (n = 46) groups in terms of sex, tobacco use, Eastern Cooperative Oncology Group-Performance Status (ECOG-PS), histology, presence of potentially targetable driver mutations (KRAS, MET, BRAF, HER2, RET), and PD-L1 TPS distribution (50-89% vs ≥90%). Compared to patients < 80y, patients ≥80y had no difference in objective response rate (ORR 39.1% vs 28.2%; p = 0.22) or median progression-free survival (mPFS 6.0 vs 3.0 months; p = 0.16). However, patients ≥80y had a shorter median overall survival (mOS 25.7 vs 7.6 months; p = 0.02), and this result remained significant after adjusting for ECOG-PS. Among those who experienced disease progression on pembrolizumab, patients ≥80y were significantly less likely to receive any second-line systemic therapy compared to patients < 80y (55.6% vs 30.8%; p = 0.008). **Conclusions:** In patients with NSCLC and PD-L1 ≥50%, the ORR and mPFS to first-line pembrolizumab were similar between patients < vs ≥80 years old. OS was shorter among patients ≥80y, potentially reflecting lower use of second-line therapy in elderly patients after progression on pembrolizumab. The immunophenotypic correlates of NSCLC in older patients need further investigation. Research Sponsor: None.

9055 **Poster Session**

Real-world effectiveness of immune checkpoint inhibitors alone or in combination with chemotherapy in metastatic non–small cell lung cancer. *First Author: Lingzhi Hong, Department of Thoracic and Head and Neck Medical Oncology, Department of Imaging Physics, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The benefit of combination immune checkpoint inhibitor (ICI) with chemotherapy over ICI monotherapy in non-small cell lung cancer (NSCLC) remains underexplored. **Methods:** This retrospective cohort included patients with metastatic NSCLC from a single-institution database treated with ICI monotherapy or with chemotherapy between 1/2014-2/2020. Clinical progression-free survival (PFS) and overall survival (OS) were the primary outcomes. Propensity score adjustment for clinical and sociodemographic characteristics was used for analysis of first-line treatment outcomes. **Results:** A total of 1,139 patients (54% male; median age, 64.9) were included. Adenocarcinoma histology, smoking history, higher PD-L1 expression, and lower metastatic stage associated with improved PFS. However, PD-L1 expression and smoking associated with PFS only in adenocarcinoma (LUAD); squamous (LUSC) patients had shorter PFS independent of PD-L1 and smoking history (PD-L1 > 50% vs 1-49%: LUAD $P < 0.001$; LUSC $P = 0.69$; Former vs never smoker: LUAD $P = 0.008$; LUSC $P = 0.89$). In first-line patients (n = 680), treatment with ICI plus chemotherapy (ICI-chemo) associated with higher progression-free rates at 3 and 6 months compared with ICI-monotherapy (ICI-chemo vs ICI-mono: 3-month PFS, 85.2% vs 68.8%, $P = 0.001$; 6-month PFS, 66.4% vs 52.6%, $P = 0.008$). However, there was no difference overall in PFS or OS in either the full or propensity-matched cohort. Treatment with ICI and chemotherapy concurrently vs sequentially was associated with similar PFS (log-rank $P = 0.12$). **Conclusions:** In this real-world cohort, the addition of chemotherapy to ICIs may protect against early progression but does not influence long-term outcomes. Treatment with sequential vs concurrent ICI and chemotherapy produced similar outcomes. These findings suggest that combination therapy may maximally benefit patients at risk of early progression. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology, The University of Texas MD Anderson Lung Moon Shot Program and the MD Anderson Cancer Center Support Grant P30 CA01667.

9056 **Poster Session**

Differential prognostic effect of systemic inflammation in patients with NSCLC treated with immunotherapy or chemotherapy: A post hoc analysis of the phase III OAK trial. *First Author: Alessio Cortellini, Department of Surgery and Cancer, Imperial College London, London, United Kingdom*

Background: A pro-inflammatory diathesis as measured by the neutrophil-to-lymphocyte ratio (NLR) heralds an adverse disease course in non-small cell lung cancer (NSCLC). Whether the NLR identifies patients who derive a differential degree of benefit from immunotherapy versus chemotherapy is not known. **Methods:** This post hoc analysis used data from the phase III OAK trial, which randomized previously treated patients with NSCLC to receive atezolizumab or docetaxel. The main objective was to assess the differential impact of pre-treatment NLR on overall survival (OS) depending on the treatment modality. In addition, we assessed patients genomic characteristics according to inflammatory status using circulating free (cf)DNA NGS analysis. **Results:** A total of 600 and 575 patients with an available NLR were included in the atezolizumab and docetaxel cohort, with a median NLR of 4 (IQR: 2.6-6.7) for the pooled population. NLR $\geq$ 4 was associated with positive smoking status (88.6% vs 78.1%, $p < 0.01$), male sex (66.4% vs 57.6%, $p = 0.01$), worse performance status (71.3% vs 55.2%, $p < 0.01$), higher number of metastatic sites (63.2% vs 51.6%, $p = 0.01$), squamous histology (32.1% vs 21.4%, $p < 0.01$), and tissue KRAS mutation (30% vs 18.7%, $p = 0.02$), but not with PD-L1 expression, nor with tissue EGFR/ALK status. Pre-treatment NLR of $\geq$ 4 was more strongly associated with mortality following atezolizumab with an adjusted hazard ratio (HR) of 1.64 (95%CI:1.35-2.01) compared to docetaxel (HR 1.32, 95%CI: 1.08-1.60, multivariable (MVA) interaction $p = 0.08$. Exclusion of EGFR/ALK positive patients further increased the prognostic ability of baseline NLR in favor of atezolizumab (HR 1.67, 95%CI: 1.35-2.06), as compared with the docetaxel arm (HR 1.24, 95%CI: 1.02-1.52, MVA interaction $p = 0.02$). The HR for the risk of death for patients with NLR$\geq$ 4/PD-L1 negative tumours (compared to NLR < 4/PD-L1 positive) was significantly higher in the atezolizumab cohort (HR 2.28, 95%CI: 1.72-3.03) than in the docetaxel cohort (HR 1.42, 95%CI: 1.08-1.86, MVA interaction $p = 0.01$). NGS pretreatment cfDNA data showed that patients with a high blood tumor mutational burden (cut-off 16 Mut/Mb) had a higher median NLR (4.6 vs 3.7, $p = 0.01$). After adjusting for multiple comparisons, none among the selected variants of interest (EGFR, KRAS, TP53, KEAP1, STK11, SMARCA4, ARID1A and targeted DDR genes), were significantly associated with the NLR. **Conclusions:** In this post-hoc analysis, a baseline low NLR identifies patients with NSCLC who derive a greater survival benefit from atezolizumab as compared to those identified in the docetaxel cohort, irrespective of genomic features. Patients with a low NLR and PD-L1 positive tumors derive the greatest benefit with immunotherapy and the NLR could complement PD-L1 expression in tailoring treatment in this setting. Clinical trial information: NCT02008227. Research Sponsor: None.

9057 **Poster Session**

Immunotherapy and chemo-immunotherapy for non–small cell lung cancer with novel actionable oncogenic driver alterations. *First Author: Laura Mazzeo, Medical Oncology Department, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy*

Background: Immune checkpoint inhibitors (IO) single agent or in combination with platinum chemotherapy (CT-IO) are standard of care for Stage IV non-small cell lung cancer (NSCLC) according to PD-L1 expression. While the efficacy of IO among patients (pts) with common EGFR and ALK alterations appears to be limited, its activity in pts with novel oncogenic drivers alterations is not well characterized. Compared to non-oncogene-addicted NSCLC, the overall response rate (ORR) seems to be similar in BRAF and c-MET altered NSCLC, lower in RET altered NSCLC, while data are less consistent in HER2 and EGFR exon 20 (EGFRex20) altered NSCLCs. **Methods:** From January 2016 to January 2022, we retrospectively enrolled pts with Stage IV NSCLC that received IO or combination CT– IO in any line, ECOG PS 0 - 2 and detection of MET exon 14 skipping mutations (METex14), BRAF mutations (V600E or non-V600E), RET rearrangement, HER2 point mutations (HER2mut)/exon 20 insertions (HER2ex20) or uncommon EGFR mutations (uEGFRmut)/EGFRex20. A review of clinicopathologic and molecular features and an analysis of response to combination or single-agent IO were conducted. **Results:** Among sixty-four pts enrolled, 20 (31%) had METex14, 19 (30%) had EGFR alterations [12 (19%) EGFRex20, 7 (11%) uEGFRmut], 8 (12%) had BRAF mutation (3 V600E and 5 non-V600E), 13(20%) had HER2 alterations [7 (11%) HER2ex20, 6 (10%) HER2mut] and 4 (6%) were RET rearranged. 43 received IO single agent and 21 received CT-IO. With a median follow up of 22 months (m), median progression free survival (mPFS) was 5.40 m (0.95 CI 4.73-6.9) overall, 6.77m in CT-IO arm (0.95 CI 5.37-NA) and 5.10m in IO arm (0.95 CI 2.60-6.7), with a trend to better mPFS for CT-IO (p 0.054). Regarding specific mutations irrespectively from treatment arm, NSCLC harboring METex14 showed a mPFS of 5.33 m (0.95 CI, 2.30-13.9), BRAF 9.9 m (0.95 CI, 6.70-NA), EGFR 4.93 m (0.95 CI, 1.80-6.9), HER2 11.4 (0.95 CI, 4.2-NA), RET 5.28 (0.95 CI, 1.42-NA). Disease control rate (DCR) was better in the CT-IO arm vs IO one in the overall population (84.2% vs 50%, p 0.013). **Conclusions:** Novel driver alterations seem to show a benefit from IO treatments. CT-IO seems to have a better outcome in terms of DCR. Therefore, IO-based treatment should be evaluated also in tumors harboring novel driver alterations. Research Sponsor: None.

Driver alteration	n(%)	Gender n M/F	Treatment type IO n(%) - CT-IO n(%)	DCR n(%)	PFS m(95%CI)
METex14	20(31)	13/7	15(75)-5(25)	11(55)	5.33(2.30-13.9)
EGFRex20	12(19)	4/8	8(67)-4(33)	6(50)	5.05(2.73-NA)
BRAF V600E	3(5)	1/2	3(100)-0(0)	1(33)	2.63(1.6-NA)
BRAF non-V600E	5(8)	4/1	4(80)-1(20)	5(100)	29.3(9.9-NA)
uEGFRmut	7(11)	4/3	6(86)-1(14)	1(14)	2.1(0.7-NA)
HER2ex20	7(11)	2/5	1(14)-6(86)	5(71)	4.2(2.8-NA)
HER2mut	6(9)	3/3	4(67)-2(33)	5(83)	15.67(11.4-NA)
RET	4(6)	4/0	2(50)-2(50)	3(75)	5.28 (1.42-NA)

9058 **Poster Session**

Nivolumab timing as a major survival predictor in patients with stage IV non–small cell lung cancer. *First Author: Abdoulaye Karaboué, Medical Oncology Unit, GHT Grand Paris Est, Montfermeil Hospital, Montfermeil, France*

Background: Functional activity and trafficking of T(CD8) and other immune cells are regulated over the 24 hours by the circadian timing system. Nivolumab (NIV) binds to PD-1 receptors and targets T(CD8). These pharmacologic effects could be regulated by circadian clocks, hence suggesting possible daily changes in its efficacy, as substantiated for immune checkpoint inhibitors (ICIs) in two prior reports. **Methods:** Here we searched whether increasing the proportion of morning NIV infusions could critically improve efficacy in consecutive metastatic Non-Small Cell Lung Cancer (NSCLC) patients (pts). Pts received NIV (240 mg iv q 2 weeks) at a daily time that was 'randomly' allocated for each course by the day-hospital coordinators. The median time of actual NIV infusions was computed for each pt. The study population was split into three timing-groups: a 'morning' one, where the pts received at least 2/3 of NIV infusions before 12:54, i.e. the median time of all NIV infusions; an intermediate group, where the pts received at least 1/3 of NIV infusions before and 1/3 after 12:54; and an 'evening' group, where pts received at least 2/3 of NIV infusions after 12:54. CTCAE-toxicity rates, iRECIST-tumor responses, progression-free survival (PFS), and overall survival (OS) were computed according to NIV timing group. **Results:** 95 previously-treated stage IV NSCLC pts (M/F,79/16; PS 0-1, 96%; 41-83 years old) were retrospectively allocated to a 'morning' group (36 pts), an 'intermediate' group (24 pts), and an 'evening' group (35 pts). Pts received NIV as 2nd line (76%). Tumor PD-L1 status was positive for 39 of 72 pts (54%). Main metastatic sites were bone (52% of the pts), pleura (41%), liver (25%), brain (24%), and adrenal gland (20%). Pt characteristics were similar in the 3 groups, except for liver metastases (41.7%, 8.3% and 25.7% for 'morning', 'intermediate' and 'evening' groups respectively, $p = 0.010$). Grade 2-4 fatigue was least in the 'morning' group (28%) vs 62% ('intermediate') and 40% ('evening') ($p = 0.027$). Median PFS (months) was 11.1 for the 'morning' group, 5.9 for the 'intermediate' group, and 3.1 for the 'evening' group ($p = 0.002$). Median OS (months) [95% C.L.] was 34.2 [-] for the 'morning' group, 15.3 [8.0 – 22.7] for the 'intermediate' group, and 12.4 [4.0 – 20.7] for the 'evening' group ($p = 0.023$). Respective 2-years survival rates were was 52.6%, 26.2% for the and 15.0% ($p = 0.002$). Multivariable analysis confirmed that the administration of >2/3 NIV in the morning predicted for longer PFS (Hazard ratio, 0.26 [0.14-0.51], $p < 0.001$) and OS (0.22 [0.10-0.51], $p < 0.001$). **Conclusions:** NIV was largely more effective in the 'morning' as compared to the 'intermediate' or 'evening' groups, with no apparent bias. Randomized and translational circadian timing studies are needed to unravel the mechanisms at work in the chronopharmacology of ICI's, so as to minimize the risk of resistance and to maximize therapeutic benefits. Research Sponsor: None.

9059 **Poster Session**

Impact of *STK11* copy loss on clinical outcomes to PD-(L)1 blockade in non–small cell lung cancer. *First Author: Catherine Gutierrez, Harvard Medical School, Brookline, FL*

Background: *STK11* is among the most commonly altered genes in non-squamous lung cancers. While *STK11* mutation is associated with diminished efficacy of immune checkpoint inhibition (ICI), particularly in *KRAS* mutated tumors, it is not known whether *STK11* copy deletion influences outcomes to ICI. **Methods:** Patients with advanced non-squamous non-small cell lung cancer (NSCLC) treated with ICI whose tumors underwent genomic profiling were included. Clinical outcomes to ICI were analyzed according to *KRAS* mutation and *STK11* deletions. *STK11* copy number variations (CNVs) were determined using an internal informatic pipeline. Kaplan-Meier methodology was used to estimate event-time distributions. **Results:** Of 559 patients with non-squamous NSCLCs (Nsq-NSCLC), 40.4% (N = 226) had a *KRAS* mutation (*KRAS*^{mut}), 18.4% (N = 103) had an oncogenic *STK11* mutation (*STK11*^{mut}), and 22.5% had either single (N = 123), or bi-allelic (N = 3) deletion (*STK11*^{del}). Given that 32.5% of *STK11*^{del} cases had a concurrent oncogenic *STK11* mutation in our cohort, to isolate the impact of *STK11*^{del} on ICI outcomes we excluded samples with *STK11*^{mut} from this analysis. In all comers with NSCLC, *STK11*^{del} had no impact on objective response rate (22.2% versus 23.8%, P = 0.8), progression-free (PFS, HR 0.90, P = 0.30), and overall survival (OS, HR 0.96, P = 0.79) to ICI. When we examined the impact of *STK11*^{del} on clinical outcomes to PD-(L)1 blockade among *KRAS*^{mut} cases we found that *STK11*^{del} was associated with a numerically lower ORR (13.3% versus 30.0%, P = 0.12), and a significantly shorter PFS (HR 0.57, P = 0.018) compared to cases without *STK11*^{del}. No difference in OS were observed between these groups (HR 0.77, P = 0.39). Among *KRAS*^{wt} NSCLCs, *STK11*^{del} cases had a similar ORR (22.6% versus 22.9%, P = 0.99), PFS (HR 0.92, P = 0.63), and OS (HR 1.18, P = 0.32) to PD-(L)1 inhibition compared to cases without *STK11*^{del}. Among *KRAS*^{mut} but not *KRAS*^{wt} NSCLCs, cases with *STK11*^{del} had significantly lower PD-L1 expression compared to those without *STK11* deletions (27.5% versus 70%, P = 0.01). **Conclusions:** *STK11* deletion is associated with low response rate and short progression-free survival among *KRAS* mutant NSCLCs. Future analyses will incorporate additional cases to increase sample size and immunopathologic findings to assess impact of mono and bi-allelic deletion on protein expression. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

9060 **Poster Session**

A phase II study of talazoparib plus avelumab in patients with stage IV or recurrent nonsquamous non–small cell lung cancer bearing pathogenic *STK11* genomic alterations (SWOG S1900C, LUNG-MAP sub-study, NCT04173507). *First Author: Ferdinandos Skoulidis, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Inactivating *STK11* genomic alterations are prevalent in non-squamous (nsq) NSCLC and define a patient (pt) subgroup with poor prognosis and inferior response to immune checkpoint inhibitors (CPIs). PARP inhibitors (PARPi) can potentiate response to CPIs in preclinical models. We conducted a single arm Phase II study within Lung-MAP to evaluate the efficacy and safety of talazoparib in combination with avelumab in patients (pts) with previously treated nsq NSCLC harboring pathogenic *STK11* genomic alterations. **Methods:** Eligibility: *STK11* pathogenic somatic mutation or bi-allelic loss on tumor identified via LUNGMAP screening; stage IV or recurrent nsq NSCLC, receipt of one prior line of anti-PD-1/anti-PD-L1 therapy and platinum-based chemotherapy for stage IV or recurrent disease (sequentially or in combination) and disease progression > 42 days following treatment initiation, a ECOG PS of 0-1, adequate organ function and no previous PARPi exposure. Pts received talazoparib (1000 mg PO daily) plus avelumab (800 mg IV Q2W). Co-primary objectives were to evaluate the best objective response rate (ORR) and disease control rate at 12 weeks (DCR12) after study registration, assessed by RECISTv1.1. Rejection of an ORR of 10% required ≥ 8 responses or rejection of a DCR12 of 30% required ≥18 w/ disease control at 12 weeks and ≥4 responses. **Results:** 47 pts enrolled from January 16 - November 16, 2020; 42 pts met eligibility (50% male, 50% female). 54% of pts had PD-L1 TPS < 1%. The median TMB was 8.83 Mut/Mb and 45% of pts had *KRAS* mutations. 52% of the pts had received ≥2 prior lines of treatment for stage IV disease. As of the November 24, 2021 data cutoff, 3 pts remain on treatment, the ORR was 2% (n = 1) and the DCR12 was 40% (n = 17). 26 pts (62%) had SD as best objective response. One responding pt remained on treatment for > 14 mo. The median progression-free survival (39 events) was 2.7 mo (95% CI, 1.6-3.9 mo) and the median overall survival (30 events) was 7.6 mo (95% CI, 6.3-12.2 mo). There were no reported grade 5 treatment toxicities and most grade 3-4 toxicities were hematologic. Additional biomarker analysis to assess effects of key co-mutations on clinical outcomes will be presented. **Conclusions:** Treatment with talazoparib and avelumab did not meet the pre-specified threshold for efficacy in previously treated *STK11*-mutant NSCLC in this biomarker-driven Phase II study, though durable disease stabilization was observed. Further studies are required to determine optimal therapeutic approaches for this challenging subset of NSCLC pts. Funding: NIH/NCI grants U10CA180888, U10CA180819. Talazoparib was provided by Pfizer. Avelumab was provided by Pfizer, as part of an alliance between Pfizer and the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100004755). Clinical trial information: NCT04173507. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

9061 **Poster Session**

Deep learning signature from chest CT and association with immunotherapy outcomes in EGFR/ALK-negative NSCLC. *First Author: Maliazurina B Saad, Department of Imaging Physics, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Many clinicopathological and molecular features are associate with clinical benefit from immune checkpoint inhibitors (ICIs) for patients with non-small-cell lung cancer (NSCLC), yet none was exclusive underscoring the heterogeneity of lung cancers. As images may provide a holistic view of cancer, we attempted deep learning to chest CT scans to derive a predictor of response to ICIs and test its benefit relative to known clinicopathological factors. **Methods:** 928 stage IV, EGFR/ALK-negative NSCLC patients treated with ICIs alone or in combination (MD Anderson GEMINI Database) were divided into training (CT^{tr} = 572), validation (CT^{va} = 78), and testing (CT^{te} = 278) cohorts, balancing the distribution of clinicopathological and radiological factors. Progression-free (PFS) and overall survival (OS) were defined as outcomes. We analyzed whole lung, including tumor and normal parenchyma of chest CT images ≤ 3 months prior to ICI treatment. An ensemble learning model (CT-deep-learning) to clustering patients into high vs low risk groups of PFS or OS was developed by fusing risk scores from four independent deep learning networks (supervised, unsupervised, and hybrid). This CT-deep-learning model was further evaluated in different clinicopathological subgroups. Finally, a composite model (CT-Clinic-path) was built by combining image model with clinicopathological factors. Antolini's concordance index (C-index) was used to assess model performance. **Results:** Median PFS and OS were shorter in the high-risk vs low-risk group as defined by CT-deep-learning: PFS (CT^{tr}: 4.2 vs 9.6 mons; HR 1.96; 95% CI 1.62-2.38; P < 0.0001; CT^{va}: 3.7 vs 10.2 mons; HR 2.32; 95% CI 1.32-4.07; P = 0.0025; CT^{te}: 3.6 vs 9.1 mons; HR 1.89; 95% CI 1.39-2.56; P < 0.0001) and OS (CT^{tr}: 16.0 vs 31.4 mons; HR 2.19; 95% CI 1.72-2.79; P < 0.0001; CT^{va}: 12.7 vs 28.6 mons; HR 2.01; 95% CI 1.04-3.88; P = 0.035; CT^{te}: 14.8 vs 32.0 mons; HR 1.84; 95% CI 1.31-2.60; P = 0.0004). CT-deep-learning outperformed clinicopathologic features known to associate with ICI benefit, such as histology, smoking status, PD-L1 expression, and remained to be an independent (P < 0.001) prognostic factor on multivariate analysis. Furthermore, integrating CT-deep-learning to clinicopathological variables improved prediction performance with a net reclassification up to 7% (Clinic-path model, C-indices 0.60 – 0.62 vs CT-clinic-path model, 0.64 - 0.65 for PFS; Clinic-path model 0.64 – 0.67 vs CT-clinic-path model 0.69 – 0.71 for OS). **Conclusions:** We have developed and validated a deep learning signature associated with PFS and OS in ICI-treated NSCLC patients, which appears to be independent of and superior to known clinicopathological biomarkers. If validated, this signature may strengthen the predictive value of clinicopathological factors and facilitate selecting appropriate patients for ICI-based therapies. Research Sponsor: The University of Texas MD Anderson Lung Moon Shot Program and the MD Anderson Cancer Center Support Grant P30 CA016672.

9062 **Poster Session**

18F-FDG PET–derived parameter total lesion glycolisis (TLG) as a tool to stratify patients (pts) with advanced non–small cell lung cancer (aNSCLC) treated with immunotherapy. *First Author: Filippo Gustavo Dall'Olio, Cancer Medicine Department, Institut Gustave Roussy, Villejuif, France, Villejuif, France*

Background: Upfront Immune Checkpoint Blockers (ICB) alone or in combination with chemotherapy (CT) have become the backbone treatment of non-oncogene addicted aNSCLC. PD-L1 remains the only predictive biomarker, but additional biomarkers are mandatory to better discriminate the population more suitable for the combination approach (CT-ICB). We hypothesized that TLG, a parameter that measure tumor burden and metabolic activity, may help to select the optimal first-line regimen. **Methods:** We performed a multicentric (n = 5) retrospective study including pts treated either with ICB alone, CT-ICB or CT alone. Overall survival (OS) and progression-free survival (PFS) were estimated with Kaplan-Meier analysis. Hazard ratios (HR) were calculated using multivariate Cox proportional Hazard models adjusting for relevant covariates (neutrophil/lymphocyte ratio, ECOG PS, liver, bone metastases). TLG was calculated on PET scans as the product of metabolic tumor volume (with a threshold of 42% of SUV max) and SUV mean. **Results:** 250 pts with aNSCLC initiated first-line treatment (94 ICB, 102 CT-ICB and an hystorical control group of 54 CT) within 42 days from PET. Median follow up was 22 months for ICB, 16 for CT-ICB and 47 for CT. 170 pts were male (68%), 210 had non-squamous histology (84%), 110 (44%)and 38 (15%) had bone and liver metastasis, respectively. On the 194 pts with PD-L1 status available: 20%, 29% and 50% had PD-L1 < 1%, 1-49% and > 50%, respectively. No correlation was seen between PD-L1 and TLG. Presence of liver metastases (13% vs 2%) and ECOG PS > 1 (16% vs 3%) were associated with elevated TLG. PFS correlated with TLG, with longer median PFS in the lower quartile (TLG < 380) either with ICB (12.4 vs 4.7 months, HR 1.9, 95% CI1.1 – 3.35, p 0.025) and CT-ICB (17.9 vs 7.3, HR 1.9, 95% CI1.1 – 3.7, p 0.032) but not with CT (4.2 vs 3.5, p 0.986), whereas OS was correlated with TLG < 380 in all 3 groups. The risk of progression under ICB was lower in tumors with TLG < 380 (15% vs.29%, p = 0.02), but no difference was seen in other 2 groups. In PD-L1 ≥50% pts with elevated TLG, treatment with CT-ICB (n = 20) increased the PFS respect with ICB (n = 55) (10.7 vs 3.9, HR 0.54, 95% CI 0.29 – 0.99, p = 0.048).The analysis was underpowered to find a difference in OS (HR 0.49, 95% CI 0.21 - 1.12, p = 0.092). **Conclusions:** TLG retains a prognostic validity in aNSCLC identifying pts with an increased rate of early progression on ICB, who may benefit from CT-ICB. Further analyses are required to compare CT-ICB and ICB in PD-L1 ≥50% according to TLG. Enrollement from other centers is ongoing, an update will be presented. Research Sponsor: None.

9063 **Poster Session**

Association of early tumor growth rate and survival outcomes in first-line metastatic non–small cell lung cancer (mNSCLC). *First Author: Antonio Tito Fojo, Columbia University College of Physicians and Surgeons, New York, NY*

Background: Tumor growth rates (*g*) estimated using imaging measurements, have been associated with overall survival (OS) and progression-free survival (PFS) in patients with mNSCLC, including those treated with first-line immunotherapy (1L IO) or chemotherapy (chemo). Here, we evaluated whether early *g* estimates within 18 weeks of first treatment dose are associated with survival outcomes for 1L treatment in mNSCLC. **Methods:** This was a retrospective analysis of data from patients randomized to either nivolumab+ipilimumab (NIVO+IPI) or chemo in CheckMate 227 Part 1 (NCT02477826), or NIVO+IPI+chemo or chemo alone in CheckMate 9LA (NCT03215706). Tumor assessments were performed by blinded independent central review using RECIST v 1.1 at baseline, every 6 weeks for the first 48 weeks and then every 12 weeks until disease progression. The analysis included patients with at least 3 measurable timepoints, including baseline, week 6, week 12, and/or week 18. If a patient did not have a week 18 measurement, the first three measurements alone were used. To derive the median early *g*, sum of longest diameters (SLD), based on baseline, weeks 6, 12 and/or 18 assessments, and time relative to baseline were fitted to the model defined by sum of exponential growth (g) and decay (d): SLD (t) = exp (–d x t) + exp (g x t) – 1. OS and PFS were estimated using Kaplan-Meier methodology. **Results:** In the two studies, 865/1166 (75%) of randomized patients in CheckMate 227 Part 1 and 562/719 (78%) in CheckMate 9LA had evaluable tumor growth rate data (Table). The median early *g* at weeks 12 and 18 was numerically lower for the IO-containing arm vs chemo arm in both studies (Table). Patients with lower growth rate at week 12 or week 18 (*g* in first quartile [Q1]) had better OS relative to those with higher rate (*g* in fourth quartile [Q4]) across all treatment arms (Table). A similar trend was observed for PFS. **Conclusions:** Early *g* estimates based on 2 or 3 post-baseline tumor assessment timepoints were associated with longer-term survival outcomes for 1L treatment of mNSCLC and could discern efficacy outcomes. These findings provide the foundation for further research, which may incorporate volumetric segmentations of measurable lesions and radiomic feature changes to further explore indicators of patient outcomes that could inform future clinical trials and clinical practice. Research Sponsor: Bristol Myers Squibb.

Tumor growth rates (*g*) at weeks 12 (W12) and 18 (W18) and associated OS.

	NIVO + IPI (CM 227)	Chemo (CM 227)	NIVO + IPI + chemo (CM 9LA)	Chemo (CM 9LA)
Number of patients	418	447	299	263
W12: Median (IQR) *g*, x 10^3/day	1.9 (0.0-3.6)	2.8 (0.7-4.1)	2.6 (0.014-4.1)	2.9 (1.1-4.1)
W12: Median OS, *g* in Q1, mo	30.0	17.5	22.8	16.3
W12: Median OS, *g* in Q4, mo	20.2	16.0	17.0	11.8
W18: Median (IQR) *g*, x 10^3/day	1.5 (0.0-2.6)	2.6 (1.1-3.7)	1.8 (0.0-3.1)	2.7 (1.2-3.6)
W18: Median OS, *g* in Q1, mo	30.7	19.0	24.1	17.9
W18: Median OS, *g* in Q4, mo	20.0	14.8	15.5	11.3

9064 **Poster Session**

Multimodal integration of radiology, pathology, and genomics for prediction of response to PD-1 blockade in patients with non–small cell lung cancer. *First Author: Jia Luo, Dana-Farber Cancer Institute, Boston, MA*

Background: Immunotherapy is now given to almost all patients with advanced non-small cell lung cancer (NSCLC). However, developing robust biomarkers to predict benefit remains challenging. We set out to evaluate the predictive capacity of integrating medical imaging, histopathologic, and genomic features to develop a multimodal biomarker for immunotherapy response. **Methods:** We used baseline data that is routinely obtained during diagnostic clinical workup at a single center in patients with NSCLC and known outcomes following immunotherapy. The multimodal dataset included DNA alterations from NGS, CT scan images, and digitized PD-L1 immunohistochemistry (IHC) slides. Guided by experts in each field, we developed a workflow to extract data for each patient and used an attention-gated machine learning approach to integrate the features into a risk prediction model. **Results:** Our cohort included 247 patients with advanced NSCLC who received immunotherapy and had complete radiology, pathology, genomic, and clinical data. The patient cohort was 54% female, had a median age of 68 years (range 38-93), and 88% patients had a smoking history. Responders (CR/PR) vs non-responders (SD/PD) showed a median PFS and OS of 2.7 months (95% CI 2.5-3.0) and 11.4 months (95% CI 10.3-12.8), respectively. Of all patients, 187 (76%) had segmentable disease on chest CT scans. We used a radiomics approach and aggregated the average individual lesion predictions to construct patient-level response predictions which resulted in an overall AUC = 0.65, 95% CI 0.57-0.73. We next studied digitized FFPE slides of pre-treatment PD-L1 IHC staining of tumor specimens. Overall, 52% of slides showed PD-L1 tumor proportion score (TPS) ≥ 1% and were used to extract IHC-texture, a novel spatial characterization of PD-L1 staining. Logistic regression modeling on IHC-texture resulted in prediction accuracy of AUC = 0.62 (95% CI 0.51-0.73) which was inferior to the pathologist-assessed PD-L1 TPS (AUC = 0.73, 95% CI 0.65-0.81). We next implemented a dynamic deep attention-based multiple instance learning model with masking to evaluate the impact of combining features from all modalities. Our multimodal model (AUC = 0.80, 95% CI 0.74-0.86) outperformed unimodal measures, including tumor mutational burden (AUC = 0.61, 95% CI 0.52-0.70) and PD-L1 TPS (AUC = 0.73, 95% CI 0.65-0.81). **Conclusions:** Our study is a proof of concept for using multimodal features to improve prediction of immunotherapy response over standard-of-care approaches in patients with NSCLC using expert-guided machine learning. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

9065 **Poster Session**

Artificial intelligence in digital pathology approach identifies the predictive impact of tertiary lymphoid structures with immune-checkpoints therapy in NSCLC. *First Author: Mehrdad Rakaee, UiT The Arctic University of Norway, Tromsø, Norway*

Background: The presence of Tertiary Lymphoid Structures (TLS) in multiple cancer types has been recognized as a potential predictive biomarker for response to immune-checkpoint blockade. However, there is no standardized method to quantify their presence. In this context, Artificial Intelligence (AI)-based assessment of histology images may well contribute to improve reproducibility, accuracy and speed of TLS quantification. **Methods:** We developed an automated workflow for quantification of TLS on digitized H&E slides through A) pixel-level classification of tissue using supervised artificial neural networks model, B) object-level cell classification of candidate TLS regions, C) merging the two approaches for curation and validation of TLS *versus* non-TLS regions. 433 advanced stage non-small cell lung cancer (NSCLC) patients treated with first or subsequent line of anti-PD-(L)1 single agent at DFCI were included in this study. **Results:** TLS were detected in 37% (n = 161) of the patients H&E slides, with the highest score of 4.7 TLS per mm2 (interquartile range: Q1 = 0, Q2 = 0, Q3 = 0.03 TLS/mm2). TLS density (per mm2) was significantly higher in surgically resected (n = 246; TLS^{POS}= 49%) compared to bioptic samples (n = 187; TLS^{POS}= 21%). No association was observed between TLS and tumor mutational burden (TMB) or PD-L1 protein expression as continuous variables. Among clinically actionable mutations, EGFR (all subtypes) mutated patients (n = 38) had a significantly lower number of TLS compared to patients without EGFR mutations. Patients with ≥ 0.01 TLS/mm2 had a significantly higher objective response rate (32% *vs* 22%, p = 0.03), a significantly longer median progression-free survival (PFS, 4.8 *vs* 2.7 months, HR: 0.73, 95% CI: 0.59-0.90, p = 0.004), and a significantly improved median overall survival (OS, 16.5 *vs* 12.5 months, HR: 0.72, 95% CI: 0.57-0.92, p = 0.008). In multivariable analysis, after adjusting for PD-L1 (≥ *vs* < 50%), TMB (≥ *vs* < 10 mu/Mb), sex, age, ECOG score, smoking and line of treatment, TLS/mm2 (≥ *vs* < 0.01) levels were found to be an independent positive predictive factor for both PFS (HR:0.69, 95% CI: 0.54-0.88, p = 0.003) and OS (HR: 0.70, 95% CI: 0.52-0.93, p = 0.01). **Conclusions:** These findings suggest that TLS status is an independent predictor of immunotherapy effectiveness in NSCLC, with predictive value similar to that of PD-L1 expression and TMB. This novel AI system has potential for automated identification and quantification of the TLS on digital histopathological slides, and could be utilized in a standard pathology workflow with relative ease. These findings are currently being validated in other solid tumors and cohorts. Research Sponsor: None.

9066 **Poster Session**

Digital quantification of lymphocytic infiltration on routine H&E images and immunotherapy response in non–small cell lung cancer. *First Author: Mehrdad Rakaee, Brigham and Women's Hospital, Harvard Medical School, Boston, MA*

Background: Current biomarker(s) for immuno-oncology (IO) therapy response prediction in lung cancer are limited. Additional predictive biomarkers are useful to help refine patient selection and guide precision therapy. **Methods:** Biopsy and surgical specimens stained with hematoxylin-eosin (H&E) were subjected to whole-slide scanning for 446 advanced stage non-small cell lung cancer (NSCLC) treated with single agent immune check point inhibitors (ICI). A machine learning model was trained on H&E images for classification of tumor infiltrating lymphocytes (TILs), tumor cells, and stromal cells in specific tissue types. **Results:** TIL levels were found to be highly variable, with a range of 12 to 4270 cells/mm2, and median of 319 (Q1 = 159, Q3 = 681). TIL levels were assessed on tissue samples from multiple organs which had shown primary or metastatic NSCLC, and were similar across all specimen sites except the liver, for which median TIL levels were significantly lower, at 90 cells/mm2. There was no correlation between tumor mutational burden (TMB) and TIL levels, while high TIL levels were correlated with high PD-L1 (≥ 50%) expression. Patients who experienced a partial/complete response to ICI therapy had a trend to higher median TILs compared to those who had progressive/stable disease (350 versus 310 cells/mm2, P = 0.09). In a multivariable analysis after controlling for covariates (incl. sex, age, cigarette smoking, ECOG, PD-L1, TMB & treatment line), a higher TIL level (≥ 250 cells/mm2) was an independent predictor of IO response for both progression-free survival (PFS; HR_{adj} 0.70; 95% CI, 0.55 - 0.89; P = 0.003) and overall survival (HR_{adj} 0.73; 95% CI, 0.56 - 0.95; P = 0.02). In a ROC analysis considering single biomarkers, PD-L1 had the highest AUC (0.68, P < 0.001), while TIL (AUC = 0.53, P = 0.08) and TMB (AUC = 0.55, P = 0.05) had similar AUC values for classifying responders from non-responders based on objective response rate. Using weighted linear regression approach to combine the biomarkers, paired PD-L1/TMB had the greatest AUC (0.70, P < 0.001) compared to PD-L1 single assay. In the PD-L1 negative (< 1%, N = 50) subgroup, TIL levels had superior predictive performance for classification of IO responders (AUC = 0.77, P = 0.02) compared to TMB (AUC = 0.57, P = 0.3), such that patients with a high TIL level (≥ 250 cells/mm2) had an improved PFS (median PFS: 2.7 vs 2.2 months; HR = 0.48; 95% CI, 0.26 - 0.87; P = 0.02). **Conclusions:** Digital TIL quantification with use of machine learning is feasible. TIL levels appear to be a robust and independent biomarker of likelihood of response to IO treatment in NSCLC, especially in the PD-L1 negative subgroup. The findings of this study are under validation in additional lung cancer cohorts. Research Sponsor: None.

9067 **Poster Session**

Effect of bone metastasis on outcomes in the CCTG BR.34 phase II randomized trial of dual immune checkpoint inhibitor (ICI) treatment with or without chemotherapy in high-risk, stage IVA/B NSCLC. *First Author: Kim Leitzel, Penn State Hershey Medical Center, Hershey, PA*

Background: Bone metastasis (BM) occurs in about 40% of patients with metastatic lung cancer. Recently, BM was associated with decreased OS to nivolumab in previously-treated NSCLC (Landi L et al, P1.01.53, 19th WCLC, 2018). CCTG BR.34 (NCT03057106) was an open-label, randomized phase II clinical trial that randomized 301 patients with treatment-naïve, high-risk, stage IVA/B NSCLC without sensitizing EGFR or ALK alterations (1:1) to durvalumab plus tremelimumab with or without platinum doublet chemotherapy. First, 109 patients accrued with stage IVB, or selected IVA disease. Then 192 patients accrued with any stage IVA/B disease. In CCTG BR.34, median OS was not significantly different: 16.6 mo in the chemotherapy plus immunotherapy (C+IO) arm, vs 14.1 mo in the IO alone arm (HR 0.88, p = 0.46) (Leighl NB et al, J Thor Oncol, 2021). However, in BR.34 PFS was significantly longer in the C+IO arm (7.7 mo) compared to the IO alone arm (3.2 mo) (HR 0.67, 95% CI, 0.52 0.88). Here we analyzed the effect of BM on outcomes in BR.34. **Methods:** The 301 patients in the trial were characterized by the presence of BM at study entry (129-yes, 172-no). BM effect was evaluated on trial outcomes (OS, PFS, and ORR) using Cox/logistic regression analysis. Multivariable analysis was performed adjusting for the clinical and molecular covariates available. **Results:** In univariate analysis of the entire study population, median OS was significantly shorter for patients with BM vs those without BM (10. 9 vs 18.7 mos, HR 1.68, p = 0.001), as was median PFS (3.4 vs 7.2 mos, HR 1.82, p < 0.0001), and lower ORR (29.5% vs 45.9%, OR 0.52, p = 0.003), respectively. There was no evidence of differential association of BM with treatment arms for OS (p = 0.23), PFS (p = 0.84), and ORR (p = 0.25, Breslow-Day test). In multivariate analysis (MVA), BM remained significantly associated with worse OS (HR 1.44, p = 0.026), PFS (HR 1.69, p < 0.0001), and ORR (OR 0.52, p = 0.01). In MVA for OS: TMB, histology type, race, and ECOG were also significant; but age, smoking history, and PD-L1 IHC status were not significant. **Conclusions:** In CCTG BR.34 the presence of BM at trial entry was associated with significantly shorter OS, PFS, and lower ORR. BM is therefore a significant adverse prognostic factor in high-risk, stage IVA/B NSCLC treated with durvalumab and tremilimumab (with or without platinum doublet chemotherapy). If confirmed in a larger phase III trial, BM should be considered as an important new stratification factor in all clinical trials of immune checkpoint inhibitor (ICI) therapy. We and others have reported that molecules arising in the bone microenvironment (e.g: IL-8, PTHrP, TGF-b, sclerostin, and activin A) cause immunosuppression in cancer, and future trials should evaluate the addition of targeted therapies against these factors in combination with the ICIs in patients with BM. Research Sponsor: None.

9069 **Poster Session**

Progression-free survival with subsequent anticancer therapies from a phase 3 trial of lorlatinib in treatment-naive patients (pts) with *ALK*+ advanced non–small cell lung cancer (NSCLC). *First Author: Benjamin J. Solomon, Department of Medical Oncology and Research Division, Peter MacCallum Cancer Centre & Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, VIC, Australia*

Background: Lorlatinib, a brain-penetrant, third generation ALK tyrosine kinase inhibitor (TKI), demonstrated statistically significant and clinically meaningful improvement in progression-free survival (PFS) vs crizotinib in a phase 3 study in pts with previously untreated *ALK*+ advanced NSCLC (CROWN; NCT03052608). This study investigated the efficacy of treatments following progression on lorlatinib or crizotinib from the CROWN trial. **Methods:** Pts were randomized 1:1 to receive oral lorlatinib 100 mg daily or crizotinib 250 mg twice daily. The primary endpoint was PFS assessed per blinded independent central review, and secondary endpoints included time from randomization to the date of progression of disease on first subsequent systemic anticancer therapy or death (PFS2). **Results:** As of September 20, 2021, 91 of 149 patients (61.1%) vs 12 of 147 patients (8.2%) were still receiving lorlatinib vs crizotinib, respectively. In the lorlatinib arm, 33 of 149 patients (22.1%) received ≥1 subsequent systemic anticancer therapy vs 103 of 147 patients (70.1%) in the crizotinib arm. Among the patients who received subsequent systemic anticancer therapy, most patients in both treatment arms received ALK TKIs as first subsequent treatment: 63.6% and 93.2% in the lorlatinib and crizotinib arms. Chemotherapy was administered as first subsequent therapy to 36.3% and 2.9% of the patients, respectively. Median duration of treatment on first subsequent anticancer therapy was 9.6 months (IQR, 2.9-18.1 months) for lorlatinib arm and 13.3 months (IQR, 4.8-21.2 months) for crizotinib arm. Median PFS2 was not reached (NR; 95% CI, NR-NR) in the lorlatinib arm and was 39.6 months (95% CI, 27.4-NR) in the crizotinib arm, with a hazard ratio for lorlatinib vs crizotinib of 0.45 (95% CI, 0.30-0.67). **Conclusions:** While subsequent anticancer therapies offered clinical benefit in both treatment arms, PFS2 results indicated that clinical benefit was prolonged with lorlatinib vs crizotinib. Clinical trial information: NCT03052608. Research Sponsor: Pfizer Inc.

9070 **Poster Session**

Phase 3 trial of lorlatinib in treatment-naive patients (Pts) with *ALK*-positive advanced non–small cell lung cancer (NSCLC): Comprehensive plasma and tumor genomic analyses. *First Author: Alessandra Bearz, CRO Centro di Riferimento Oncologico di Aviano, Aviano, Italy*

Background: Lorlatinib, a third-generation ALK tyrosine kinase inhibitor, has shown overall and intracranial activity in *ALK*+ advanced NSCLC. In the randomized, multicenter, phase 3 study in pts with previously untreated *ALK*+ advanced NSCLC (CROWN; NCT03052608), lorlatinib showed a statistically significant and clinically meaningful improvement in progression-free survival (PFS) vs crizotinib (Shaw AT, et al. *N Engl J Med.* 2020;383:2018-2029). Comprehensive molecular profiling of circulating tumor DNA (ctDNA) and tumor tissue was performed to identify molecular correlates of response. **Methods:** At baseline (BL), plasma samples were available from 134 and 129 pts in the lorlatinib and crizotinib arms, respectively. Analyses returned results for tumor tissue (archived or new biopsy) from 147 pts across both arms. Plasma and tumor DNA were analyzed by next-generation sequencing (NGS; Guardant360 and TissueNext, respectively, Guardant Health, Inc.). Objective response rate (ORR), duration of response, and PFS based on the September 20, 2021, cutoff, all assessed by blinded independent central review, were summarized according to mutation and tumor mutation burden (TMB) status. **Results:** At BL, 22% of pts had no detectable ctDNA. *ALK* missense mutations (n=19) or deletion (n=1) were detected in plasma of 12 pts (n=5 and 7 in the lorlatinib and crizotinib arms, respectively). Most pts harbored 1 mutation, but 3 pts harbored ≥3 mutations. In tumor samples, no somatic *ALK* mutation was detected. *ALK* fusions were detected in plasma of 48% of pts and in tumor of 80%. *EML4-ALK* variant (v) subtypes were highly concordant between ctDNA and tumor tissue. Based on ctDNA, ORRs were generally higher in the lorlatinib vs crizotinib arm, reaching 80% and 72% for *EML4-ALK* v1 and v3, respectively, in the lorlatinib arm, and 50% and 74% in the crizotinib arm. Median PFS was not reached for v1 in the lorlatinib arm and was 7.4 mo in the crizotinib arm; for v3, mPFS was 33.3 and 5.5 mo, respectively. *TP53* mutations were found in 42% of pts with detectable ctDNA, and their presence did not seem to influence lorlatinib activity. In the crizotinib arm, absence of *TP53* mutations led to longer PFS. These findings are being verified in tumor tissue. A pt treated with lorlatinib with an ongoing partial response in tumor lesions at the data cutoff date was found to have a *KRAS* G12V mutation and the presence of *ALK* fusion in tumor tissue but had no ctDNA detected at BL. **Conclusions:** Pts with untreated *ALK*+ advanced NSCLC had higher ORRs and potentially longer PFS across predefined biomarker subgroups when treated with lorlatinib compared with crizotinib in the phase 3 CROWN study. Based on pretreatment ctDNA and tumor tissue analyses, lorlatinib led to strong clinical benefit regardless of the type of *ALK* rearrangement or presence of potential driver co-mutation. Clinical trial information: NCT03052608. Research Sponsor: Pfizer.

9071 **Poster Session**

First-in-human phase I results of APG-2449, a novel FAK and third-generation ALK/ ROS1 tyrosine kinase inhibitor (TKI), in patients (pts) with second-generation TKI-resistant ALK/ROS1$^+$ non–small cell lung cancer (NSCLC) or mesothelioma. *First Author: Hongyun Zhao, State Key Laboratory of Oncology in South China Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Investigational agent APG-2449 is a novel, orally active FAK inhibitor and a third-generation ALK/ROS1 TKI that has shown potent activity against a range of ALK-resistant mutations, including *G1202R, L1196M*, *V1180L*, *E1210K*, *S1206F*, *G1269A*, *F1174L*, *I1171S,* and *C1156Y* in preclinical NSCLC, mesothelioma, and other solid tumor models. **Methods:** This dose escalation and dose expansion study evaluated APG-2449 in patients with second-generation TKI-resistant ALK/ROS1$^+$ NSCLC or mesothelioma. APG-2449 was administered orally once daily at the assigned doses on a 28-day cycle using a "3+3" dose escalation design under fasted/fed conditions. Study aims were to assess safety/tolerability, recommended phase 2 dose (RP2D), pharmacokinetics (PK), pharmacodynamics (PD), and efficacy. **Results:** As of the data cutoff date of December 30, 2021, 84 pts (median age 52 [range 21-78] years; 42% female) with NSCLC or mesothelioma enrolled were treated with APG-2449 at doses ranging from 150 to 1,500 mg. PK analyses indicated an approximately dose-proportional increase in plasma exposure under fed conditions across dose levels tested. Cerebrospinal fluid PK analyses showed that APG-2449 was brain-penetrant. Low-fat meals increased APG-2449 C_{max} and AUC by approximately 40% to 80% compared to fasting conditions. Based on PK, biomarker, efficacy, and safety results, the RP2D was determined to be 1,200 mg. Four partial responses (PRs) were observed in 14 ALK$^+$ pts resistant to second-generation TKIs treated at the RP2D. Another pt with the *G1202R* mutation following alectinib treatment had tumor shrinkage of 27.9%. Among 8 pts with brain metastases, 1 complete response and 3 PRs were observed intracranially. In 10 TKI-naïve pts, the overall response rate was 80% (ALK$^+$, 6/8; ROS1$^+$, 2/2) and the disease control rate (DCR) was 100%. Preliminary biomarker data showed decreased FAK phosphorylation in peripheral blood mononuclear cells and increased IFN-γ levels in serum after multiple doses of APG-2449. No dose-limiting toxicity was observed. A total of 66 (78.6%) pts experienced treatment-related adverse events (TRAEs). The most frequent TRAEs included elevated blood creatinine (33.3%), ALT (25.0%), and AST (19.0%) levels and gastrointestinal disorders: nausea (22.6%), vomiting (17.9%), and diarrhea (13.1%). Only 6 (7.1%) TRAEs were grade ≥ 3. **Conclusions:** APG-2449 has a favorable safety and PK profile and was well tolerated in 84 subjects. Preliminary efficacy was observed in pts whose disease was resistant to second-generation TKIs, especially among those with brain metastases, and in TKI-naïve pts. Biomarker data indicated potential target engagement on FAK and immunomodulatory effects of APG-2449. Clinical trial information: NCT03917043. Research Sponsor: Ascentage Pharma Group Corp Ltd (Hong Kong).

9072 **Poster Session**

Association of depth of target lesion response to brigatinib with outcomes in patients with ALK inhibitor-naive *ALK*+ NSCLC in ALTA-1L. *First Author: D. Ross Camidge, University of Colorado Cancer Center, Aurora, CO*

Background: In patients (pts) with crizotinib (CRZ)-refractory advanced *ALK+* NSCLC in the phase 2 ALTA trial (NCT02094573), the depth of target lesion response to brigatinib (BRG) correlated with PFS and OS. Here, we examine the association of maximum decrease in target lesions with PFS and OS in ALTA-1L (NCT02737501), a randomized phase 3 trial of BRG vs CRZ in pts with ALK inhibitor-naive advanced *ALK+* NSCLC. **Methods:** Pts were randomized 1:1 to receive BRG 180 mg qd (7-day lead-in at 90 mg; n=137) or CRZ 250 mg bid (n=138). Pts with target lesion assessment by blinded independent review committee (BIRC) were grouped based on greatest decrease from baseline per RECIST v1.1: none–50%, 51%–75%, and 76%–100% shrinkage. Outcomes in the ≤50% target lesion shrinkage group served as the comparator for outcomes in the 51%–75% and 76%–100% groups. **Results:** At study end (last pt contact: Jan 29, 2021), 124/137 pts in the BRG arm and 125/138 pts in the CRZ arm had ≥1 evaluable target lesion assessment; female (BRG/CRZ), 51%/59%; median age, 57.5/60.0 years. Median follow-up was 40.8/15.7 months. In BRG/CRZ arms, 76%-100% shrinkage was observed in 56%/34% of pts, 51%-75% shrinkage in 27%/30%, and ≤50% shrinkage in 16%/35%, respectively. BRG was associated with significantly more pts with target lesion shrinkage >75% vs CRZ (P=0.0005), and a Cochran-Armitage trend analysis demonstrated significantly deeper response across all shrinkage groups for BRG compared with CRZ (P<0.0001). A majority of pts in the BRG arm experienced 76%–100% target lesion shrinkage in all subgroups analyzed. Pts treated with BRG or CRZ with target lesion shrinkage >50% had lower risk of a PFS event (BRG HR [95% CI]: 51%–75% shrinkage, 0.58 [0.29–1.18]; 76%–100%, 0.23 [0.12–0.46]; CRZ: 51%–75% shrinkage, 0.68 [0.41–1.12]; 76%–100%, 0.26 [0.15–0.45]) or an OS event (BRG: 51%–75% shrinkage, 0.39 [0.17–0.89]; 76%–100%, 0.15 [0.07–0.35]; CRZ: 51%–75% shrinkage, 0.43 [0.21–0.85]; 76%–100%, 0.23 [0.10–0.50]) than pts with ≤50% shrinkage. Longer median time to PFS and OS and higher 4-year estimated OS rates were associated with depth of response in both arms (Table). **Conclusions:** In this exploratory post hoc analysis, BRG demonstrated significantly deeper target lesion response vs CRZ. Pts with >75% shrinkage had significantly reduced risk of a PFS or OS event vs pts with ≤50% target lesion shrinkage. Clinical trial information: NCT02737501. Research Sponsor: ARIAD Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

Best Target Lesion Shrinkage	n (%)[a]	Median PFS,[b,c] Months (95% CI)	Median OS,[b] Months (95% CI)	4-year OS,[b] % (95% CI)
None–50%				
BRG	20 (16)	3 (2–17)	28 (7–NE)	NE (NE–NE)
CRZ	44 (35)	4 (4–9)	38 (19–NE)	NE (NE–NE)
51%–75%				
BRG	34 (27)	11 (7–19)	NE (35–NE)	61 (41–76)
CRZ	38 (30)	9 (7–13)	NE (41–NE)	65 (46–79)
76%–100%				
BRG	70 (56)	44 (25–NE)	NE (NE–NE)	81 (68–89)
CRZ	43 (34)	27 (13–NE)	NE (NE–NE)	81 (65–90)

NE, not estimable. [a]Evaluable pts. [b]Kaplan-Meier estimate. [c]BIRC-assessed.

9073 **Poster Session**

A phase II trial of ALK/ROS1 tyrosine kinase inhibitor WX-0593 (iruplinalkib) in *ALK*-positive and crizotinib-resistant advanced non–small cell lung cancer. *First Author: Yuankai Shi, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, Beijing, China*

Background: This single-arm, multicenter phase II trial aimed to evaluate the efficacy and safety of second generation ALK/ROS1 TKI WX-0593 (iruplinalkib) in advanced *ALK*/*ROS1*-positive non-small cell lung cancer (NSCLC). We reported the results from the crizotinib-resistant *ALK*-positive cohort. **Methods:** Patients aged ≥18 years, with histologically or cytologically confirmed *ALK*-positive NSCLC, progression on ≥12-week crizotinib treatment, ≥one measurable lesion according to RECIST v1.1, and ECOG PS of 0 to 2 were eligible. Patients received oral WX-0593 180 mg once daily (with a 7-day lead-in period at 60 mg once daily). The primary endpoint was confirmed overall response rate (ORR) by independent review committee (IRC) per RECIST v1.1. Secondary endpoints included confirmed disease control rate (DCR) by IRC, ORR, DCR, duration of response (DoR), progression-free survival (PFS), time to progression (TTP), intracranial ORR (iORR) per RANO-brain metastases criteria by investigator (INV), overall survival (OS), safety, and $C_{max,ss}$. **Results:** Between August 7, 2019 and October 30, 2020, totally 146 patients were enrolled. The data cutoff date was March 10, 2021. The median follow-up was 9.3 months (IQR 6.3-14.1). 90 (61.6%) patients had brain metastases, of which 41 (46%) had measurable intracranial lesions and 20 (22%) received prior radiotherapy to brain. 56 (38.4%) patients received prior chemotherapy. The IRC-assessed ORR was 67.8% (95% CI 59.6%-75.3%). Efficacy data were detailed in the Table. Additionally, subgroup analyses indicated IRC-assessed ORR were slightly higher in the patients without brain metastases (79% vs 61%) or prior radiotherapy to brain (66% vs 45%). Patients with prior chemotherapy or not had similar results (71% vs 66%). The iORR was 63% (95% CI 47%-78%) in pts with measurable intracranial lesions. OS data were immature. 134 (91.8%) of 146 experienced treatment-related adverse events (TRAEs). The most common TRAEs were AST increased (60 [41.1%]), ALT increased (52 [35.6%]), and blood creatine phosphokinase increased (49 [33.6%]). Dose reduction and discontinuation due to TRAE, and serious TRAEs occurred in 15 (10.3%), three (2.1%), and six (4.1%), respectively. No treatment-related death was reported. Drug concentration reaches steady state at Day 21 ($C_{max,ss}$ =255.4 ng/mL). **Conclusions:** WX-0593 showed promising activity against *ALK*-positive NSCLC after crizotinib resistance and favorable safety profile, demonstrating WX-0593 could be a new treatment option for this patient population. Clinical trial information: NCT04641754. Research Sponsor: Qilu Pharmaceutical Co., Ltd.

Endpoints	Results (n =146)
IRC ORR, % (95% CI)	67.8% (59.6%-75.3%)
IRC DCR, % (95% CI)	96.6% (92.2%-98.9%)
INV ORR, % (95% CI)	61.6% (53.2%-69.6%)
INV DCR, % (95% CI)	94.5% (89.5%-97.6%)
Median INV DoR, mo (95% CI)	13.1 (8.3-NE)
Median INV PFS/TTP, mo (95% CI)	14.4 (9.7-NE)
18-month OS rate, % (95% CI)	81.9% (69.8%-89.4%)

9074 **Poster Session**

A phase II study of alectinib in combination with bevacizumab as first-line treatment in advanced NSCLC with confirmed ALK fusion: ALEK-B trial. *First Author: Oscar Gerardo Arrieta, Instituto Nacional De Cancerologia, Mexico DF, Mexico*

Background: Alectinib is one of the standard treatment options as an upfront therapy in advanced ALK-rearranged non-small-cell lung cancer. However, all patients will eventually progress to target therapy, developing resistance mechanisms. Preclinical data have demonstrated an enhanced activity combining an anti-vascular endothelial growth factor blockade to ALK tyrosine inhibitors. Hence, this study assesses the safety and efficacy of adding bevacizumab to alectinib. **Methods:** ALEK-B is an open-label phase II trial investigating the efficacy and safety of combined alectinib 600mg daily and bevacizumab 15mg/kg every three weeks in untreated patients with advanced ALK fusion-positive NSCLC. Every patient had confirmed molecular diagnosis by next-generation sequencing (Foundation One CDx) at baseline and progression. The primary endpoint was investigator progression-free survival (PFS). Secondary endpoints were investigator-assessed objective response rate (ORR), intracranial response (ICR), time to central nervous system (CNS) progression, and overall survival. Hence, we present the first interim analysis. **Results:** Between April 2020 and October 2021, 37 patients were recruited. At the data cut-off of January 31st, 2022, the median follow-up was 15.6 months (IQR 12.5), and an event of disease progression or death occurred in 1 of 36 patients (2.7%). The 12-month event-free survival rate was 97.1% (95% CI 91 to 99), and median PFS was not reached (95% IC 8.9 to NR). Of 36 evaluable patients, 35 had an objective response [ORR 97.2% (95% CI 91 to 99)], and 3 (8.3%) experienced a complete response. Five patients had brain metastases at baseline; among those with measurable disease (n = 4), the ICR was 100%, one complete response, and median duration of response of 11.4 months (IQR 13.1). The 12-month CNS event-free rate was 100%. Any grade adverse events occurred in 86.4% of patients; most common were AST/ALT increase (40.5%), diarrhea (32.4%), blood bilirubin increase (21.6%), anemia (18.9%), and peripheral edema (18.9%). Grade 1-2 hypertension and proteinuria occurred in five (13.5%) patients, and no > G3 occurred. Grade ≥3 treatment-related AEs (TRAEs) occurred in 32.4%; most frequent were AST/ALT increase (27%) and creatinine increase (5.4%). **Conclusions:** The combination of Alectinib and bevacizumab demonstrated to be a safe and highly effective treatment in terms of response in the first-line setting. Moreover, it seems promising for patients with brain metastases. These results warrant the design of larger confirmatory trials, ideally a randomized phase III study. Clinical trial information: NCT03779191. Research Sponsor: Roche.

9075 **Poster Session**

Brigatinib in Japanese patients (pts) with *ALK*+ NSCLC: Final results from the phase 2 J-ALTA trial. *First Author: Pingkuan Zhang, Takeda Development Center Americas, Inc., Lexington, MA*

Background: In previous J-ALTA (NCT03410108) analyses, brigatinib demonstrated substantial efficacy and manageable safety in pts with TKI-refractory and TKI-naive *ALK*+ NSCLC. We report the final J-ALTA results. **Methods:** J-ALTA was a single arm, multicenter, open-label study that included ALK TKI-naive and -refractory NSCLC expansion parts. The main cohort within the refractory part was a group with alectinib-refractory NSCLC. Primary endpoints: IRC-assessed confirmed ORR in the alectinib-refractory cohort; IRC-assessed 12-month PFS in the TKI-naive cohort. Secondary endpoints included confirmed ORR (IRC-assessed in the total refractory cohort; investigator-assessed in all cohorts); DoR, PFS, DCR, and iPFS by IRC; and safety. Final analyses were performed following last pt last contact. **Results:** A total of 104 pts were enrolled; 72 had TKI-refractory (56% female; median age, 53.0 y) and 32 had TKI-naive (53% female; median age, 60.5 y) NSCLC. As of 28 July, 2021 (last pt last contact), median follow-up was 24.2 mo in the refractory cohort (alectinib-refractory subgroup [n = 47], 23.0 mo) and 22.1 mo in the TKI-naive cohort. Confirmed ORR was 34% (95% CI: 21–49) by IRC with 16 partial responses (PR) in the alectinib-refractory cohort and 32% (21–44; 22 PR) in the total refractory cohort. In the TKI-naive cohort, IRC-assessed 24-mo PFS was 73% (90% CI: 55–85); median PFS was not mature. Additional efficacy analyses are reported in Table. TEAEs were reported in all 104 pts (most common: increased CPK, 79%; hypertension, 48%; diarrhea, 47%). Grade ≥3 TEAEs were reported in 68% and 91% of pts in the TKI-refractory and -naive cohorts, respectively; most commonly (TKI-refractory/naive) elevated CPK, 24%/50%; elevated lipase, 15%/19%; hypertension, 11%/34%. Pneumonitis was mandated to be reported as an SAE regardless of severity and was the only SAE reported in > 5% of pts (refractory, n = 5 [7%; early onset, 1]; naive, n = 4 [13%; early onset, 0]). TEAEs led to dose interruption/reduction/discontinuation in 63%/31%/7% of pts in the TKI-refractory cohort and 94%/69%/0% in the TKI-naive cohort. **Conclusions:** Final efficacy and safety results in pts with TKI-refractory and -naive NSCLC were consistent with previous J-ALTA analyses. No new safety signals were observed in either cohort. Brigatinib demonstrated a favorable benefit-risk profile and is an important option for Japanese pts with *ALK*+ NSCLC regardless of TKI treatment history. Clinical trial information: NCT03410108. Research Sponsor: This study was funded by Takeda Pharmaceutical Company Limited.

IRC-Assessed Efficacy (95% CI)	Alectinib-Refractory[a] n = 47	All TKI-Refractory n = 72	TKI-Naive n = 32
ORR, %	34 (21–49)	32 (21–44)	97 (84–100)
Investigator-assessed ORR, %	38 (25–54)	–	94 (79–99)
12-mo PFS, %	36 (21–51)[b]	41 (29–53)[b]	90 (75–96)[b]
Median PFS, mo	7 (4–13)	8 (6–16)	NR (NR–NR)
Median DoR[c], mo	15 (6–19)	15 (6–19)	NR (19–NR)
DCR, %	79 (64–89)	74 (62–83)	97 (84–100)
Median iPFS, mo	21 (9–NR)	21 (13–NR)	NR (NR–NR)

[a]With/without prior crizotinib; [b]90% CI; [c]Confirmed responders. NR, not reached.

9076 **Poster Session**

SAF-189s in advanced, ALK-positive, non–small cell lung cancer: Results from a first-in-human phase 1/2, multicenter study. *First Author: Jin-Ji Yang, Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital and Guangdong Academy of Medical Sciences, Guangzhou, China*

Background: SAF-189s is a potent, brain-penetrant, next-generation anaplastic lymphoma kinase (ALK) inhibitor with preclinical activity against most known resistance mutations of ALK. We investigated safety, population pharmacokinetics, efficacy, and antitumor activity of SAF-189s in advanced, ALK-positive (ALK+) non-small cell lung cancer (NSCLC). **Methods:** In this first-in-human phase 1/2 trial (NCT04237805), patients aged ≥18 years with histologically or cytologically confirmed, advanced, ALK+ NSCLC (with or without brain metastases) and an Eastern Cooperative Oncology Group performance status of 0–2 were recruited from 41 hospitals in China. Oral SAF-189s was given in escalating doses of 20–210 mg once daily in continuous, 21-day cycles until disease progression, unacceptable toxicity, consent withdrawal, or death. Phase 1 data were presented at ASCO 2020. Here, we report updated phase 1 results and preliminary phase 2 data. **Results:** At a clinical cutoff date of January 18, 2022, 45 patients with prior systemic therapy enrolled in phase 1 and 150 were enrolled in phase 2. SAF-189s was well tolerated, the most common grade 3–4 treatment-related adverse events were hyperglycemia (7%), hypertension (6%) and diarrhea (3%). No treatment-related death was reported. 160 mg was chosen as the recommended phase 2 dose. In phase 1, 11 (24%) patients were ALK inhibitor (ALKi)-naive and 34 (76%) were ALKi-pretreated. Median progression-free survival (PFS) was 33.1 and 22.1 months (95% CI 6.9–not reached: 13.8–26.6) in ALKi-naive and ALKi-pretreated patients, respectively. Disease control rates (DCRs) were 100% in both ALKi-naive and ALKi-pretreated patients. Most patients in phase 2 were ALKi-naive (n=104, 69%), 26 (17%) received prior crizotinib only and 20 (12%) were pretreated with ≥1 non-crizotinib ALKi. The median duration of follow-up was 11.7 months (range 10.3–16.8), ORRs were comparable between the full analysis set and the 71 patients with brain metastases at 78.7% (95% CI 71.2–84.9) and 74.6% (95% CI 62.9–84.2) respectively. ALKi-naive patients had ORR of 92.3% (95% CI 85.4–96.6), compared to 65.4% (95% CI 44.3–82.8) in the crizotinib-pretreated group. DCR was 98.1% in ALKi-naive and 88.5% in crizotinib-pretreated patients. PFS data are not mature. **Conclusions:** SAF-189s showed clinical antitumor activity and was well tolerated in patients with advanced, ALK+ NSCLC, including those with brain metastases and pretreated with crizotinib. SAF-189s represents a promising, next-generation, targeted therapy for patients with ALK+ NSCLC. Clinical trial information: NCT04237805. Research Sponsor: Wanbang Biopharmaceuticals.

Objective response for ALK inhibitor naïve patients in phase 2.

	80 mg (N=15)	120 mg (N=33)	160 mg (N=52)	210 mg (N=4)	Total (N=104)
ORR (confirmed CR/PR)*	14 (93.3) [68.1–99.8]	31 (93.9) [79.8–993]	47 (90.4) [79.0–96.8]	4 (100.0) [39.8–100.0]	96 (92.3) [85.4–96.6]

*Expressed as n (%) [95% CI].

9077 **Poster Session**

Treatment patterns and outcomes in *ALK* or *ROS1* altered NSCLC: An ATOMIC Registry Study. *First Author: Melina Elpi Marmarelis, University of Pennsylvania, Philadelphia, PA*

Background: New tyrosine kinase inhibitors (TKIs) targeting *ALK* and *ROS1* alterations in non-small cell lung cancer (NSCLC) have emerged over the last decade. Given the rarity of these genetic changes in NSCLC, data on long term outcomes with sequential therapies are limited. **Methods:** We conducted a multicenter retrospective cohort study of patients with metastatic NSCLC and *ALK* or *ROS1* alterations across 12 Academic Thoracic Oncology Medical Investigators Consortium (ATOMIC) sites between 1/29/2007 and 3/31/2021. Data were abstracted from the electronic medical record. Median time to treatment discontinuation (TTD) of 1st TKI, overall survival (OS), and time to brain metastases were estimated using Kaplan-Meier methodology from start date of 1st TKI. **Results:** 566 patients with *ALK* (n = 464) or *ROS1* (n = 102) were included. The majority (ALK: 426/464, 92%; ROS1: 88/102, 86%) received a TKI at some point during therapy (1st line TKI n = 262 ALK, 48 ROS1). Crizotinib was the most common 1st TKI (ALK: 57%; ROS1: 88%). Following crizotinib, alectinib (64%) and lorlatinib (41%) were the most common subsequent TKIs for *ALK* and *ROS1*, respectively. Alectinib (38%) and entrectinib (10.2%) were the 2nd most common initial TKIs used in *ALK* and *ROS1*, respectively. Additional treatment patterns presented in table. With a median follow up time of 31.1 (ALK, 95% CI, 27.6-35.0) and 32.6 (ROS1, 95% CI, 25.7-39.6) months, median OS from start of 1st TKI was 53.3 (ALK, 95% CI, 40.0-68.9) and 42.0 (ROS1, 95% CI, 31.8-NA) months. Out of the 321 patients with brain imaging prior to 1st line therapy, 40% (105/262, ALK) and 39% (23/59, ROS1) had CNS disease. Median time to development of brain metastases from start of 1st TKI in those without previous CNS disease (ALK: 278; ROS1: 58) was 30.0 (ALK, 95% CI, 25.3-39.1) and 27.0 (ROS1, 95% CI, 18.2-NA) months. Median TTD of 1st TKI was 11.2 (ALK) and 10.8 (ROS1) months. **Conclusions:** This is the largest retrospective cohort of NSCLC patients with *ALK* or *ROS1* rearrangements treated in the real world setting. CNS metastases are common and subset analyses by agent and by year of diagnosis will be presented. Median time to CNS metastasis of > 2 years supports revision of the NCCN guidelines to include regular surveillance brain MRIs in this population. Research Sponsor: Takeda, Other Foundation.

ALK 1st TKI (n)	2nd TKI	% among those who switch to a 2nd TKI	ROS1 1st TKI (n)	2nd TKI	% among those who switch to a 2nd TKI
Crizotinib (243)	Alectinib	64% (121)	Crizotinib (77)	Lorlatinib	41% (15)
	Ceritinib	22% (41)		Entrectinib	24 % (9)
	Brigatinib	7% (14)		Ceritinib	16% (6)
Alectinib (162)	Lorlatinib	49% (17)	Entrectinib (9)	Repotrectinib	66% (2)
	Brigatinib	29% (10)		Crizotinib	33% (1)
			Lorlatinib (2)	Crizotinib	(1)
Ceritinib (9)	Alectinib	75% (6)			
	Crizotinib	25% (2)			

9078 **Poster Session**

Crizotinib in *ROS1*-rearranged lung cancer (EUCROSS): Updated overall survival. *First Author: Sebastian Yves Friedrich Michels, University of Cologne, Department I of Internal Medicine, Faculty of Medicine and University Hospital Cologne Center for Integrated Oncology Aachen Bonn Cologne Düsseldorf, Lung Cancer Group, Cologne, Germany*

Background: *ROS1* rearrangements are found in approximately 1% of non-small cell lung cancer (NSCLC) patients. Prospective clinical trials showed high efficacy of crizotinib in this molecular subset. Lately, we reported an overall response rate (ORR) of 70% and a median progression-free survival (PFS) of 19.4 months for patients treated within the EUCROSS trial (Michels et al. Clin Oncol, 37(15_suppl):9066-9066, 2019). Here we present an updated analysis of the overall survival. **Methods:** EUCROSS is a European multi-centre, single arm phase 2 trial (Clinicaltrial.gov identifier: NCT02183870). Key eligibility criteria were ≥18 years of age, advanced/metastatic lung cancer, centrally confirmed *ROS1*-rearranged (fluorescence-in situ hybridisation) and no or stable brain metastases at baseline. Crizotinib was given at a dose of 250 mg twice daily. Primary endpoint of the trial was investigator-assessed ORR in the response-evaluable population (Response Evaluation Criteria in Solid Tumors, version 1.1), with secondary endpoints of PFS and overall survival (OS). **Results:** Of the 34 patients who received at least one dose of crizotinib (intention-to-treat population, ITT), 30 were included the primary efficacy analysis set (PAS). After a median follow-up of 55.9 months, 13 (43%) patients in the PAS and 15 (44%) in the ITT had died. Median OS was not reached in either group (95% CI, 17.1-NR and 20.3-NR, respectively). OS was negatively correlated with the presence of brain metastases (Log-rank p = 0.1805) and *TP53* mutations (Log-rank p = 0.015). Detailed listings of the survival rates are depicted in Table. No new safety signals were observed. Owing to the approval of crizotinib by the European Medicines Agency, all patients who were still on treatment by January 24th 2018 (n=8), were prescribed crizotinib outside the trial. **Conclusions:** Updated OS highlights the efficacy of crizotinib in patients with *ROS1*-rearranged lung cancer. Patients with co-occurring *TP53* mutations or brain metastases had worse outcomes and represent challenging populations. Clinical trial information: NCT02183870. Research Sponsor: Pfizer.

OS rates in the PAS.

Overall survival (OS)	
Median (months, 95% CI)	NR (17.1-NR)
Events censored	17/30 (56.6%)
OS rate at 24 months (%; 95% CI)	65.6 (45.5-79.8)
OS rate at 36 months (%; 95% CI)	58.7 (38.9-74.0)
OS rate at 48 months (%; 95% CI)	55.0 (35.4-70.9)

9079 **Poster Session**

Use of RET inhibitors among patients with advanced NSCLC: A real-world evidence analysis. *First Author: Shaheenah S. Dawood, Mediclinic City Hospital, Dubai, United Arab Emirates*

Background: *RET* rearrangements are found in approximately 1% to 2% of patients with NSCLC. Two selective RET inhibitors have been FDA approved based on phase 1/2 data showing significant activity among patients with advanced NSCLC that have *RET*rearrangements. The objective of this retrospective analysis was to look at the prognostic outcome associated with the use of selective RET inhibitors (sRETi) and multikinase inhibitors (MKIs) that have been used to target RET fusions among pts with NSCLC in the real-world setting. **Methods:** We utilized a federated network of de-identified health data representing approximately 84 million pt lives available through the TriNetX Research Network. We identified 1,215 pts with metastatic NSCLC treated with selpercatinib, praseltinib, cabozantanib or vandetanib. Overall survival (OS) was evaluated with Kaplan Meier statistics and compared between patients treated with either sRETi (selpercatinib or pralsetinib) vs either MKI (cabozantanib or vandetanib). **Results:** Mean age among all anti-RET treated patients was 67.6 years. 518 pts (43%) were female and 697 (57%) were male. 531 (39.6%), 205 (15.3%) and 605 (45.1%) pts had received selpercatinib, pralsetinib, and either cabozantinib or vandetinib, respectively. 56.6% of pts receiving pralsetinib received prior selpercatinib. Among pts receiving sRETi, 39.7%, 6.4%, 11.2%, and 32.4% received sRETi in the 0-3, 3-6, 6-12, and 12+ months after metastatic diagnosis, respectively. Among pts receiving MKIs, 17.0%, 8.4%, 13.3%, and 44.9% received MKIs in the 0-3, 3-6, 6-12, and 12+ months after metastatic diagnosis. Median OS after treatment with MKIs and sRETi during any time frame was 16.3m and 25.0m, respectively (p < 0.01). Among pts treated with MKIs vs sRETi during the 0-3, 3-6, 6-12, and 12+ months after metastatic diagnosis, 1-year survival probability after treatment was 59.7% vs 55.9% (p = 0.39), 45.0% vs 83.1% (p < 0.01), 53.9% vs 82.2% (p < 0.01), and 57.7% vs 87.1% (p < 0.01), respectively. 30% of pts of all anti-RET treated patients had brain metastases, and median OS from index metastasis among pts with and without brain metastases was 31.4m and 63.1m respectively (p < 0.01). **Conclusions:** To our knowledge this is the first real world data set to show a > 8m improvement in OS with the use of sRETi compared to MKIs among pts with metastatic NSCLC. OS improvements may be more significant in pts treated in later lines of therapy with sRETi. Research Sponsor: None.

9080 **Poster Session**

Chylothorax and chylous ascites during RET tyrosine kinase inhibitor therapy. *First Author: Or Kalchiem-Dekel, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Spontaneous, atraumatic chylous effusions are rare. Investigators have observed a higher than anticipated incidence of chylothorax and chylous ascites in patients (pts) treated with RET tyrosine kinase inhibitors (TKIs). A systematic analysis of the occurrence of chylous effusions during RET TKI therapy and management strategies was thus performed. **Methods:** In this multicenter, retrospective study, the frequency of biochemically confirmed chylothorax or chylous ascites in pts treated with multikinase inhibitors (MKIs) with anti-RET activity or selective RET TKIs was determined. Clinicopathologic features and management of pts with chylous effusions were assessed. **Results:** A pan-cancer cohort of 7517 pts treated with at least 1 of 17 MKIs and selective RET TKIs and an independent cohort of 96 pts treated with the selective RET TKIs, selpercatinib or pralsetinib, were identified. Across cohorts, chylous effusions were identified in 22 pts and were most common with selpercatinib (7%; 15/217), followed by the MKIs agerafenib (4%; 1/24), cabozantinib (0.3%; 3/918), and lenvatinib (0.3%; 3/1185). Chylous effusions were not noted in 28 pts treated with pralsetinib. The distribution of malignancies included lung adenocarcinoma (54%) medullary thyroid carcinoma (23%), renal cell carcinoma (19%), and desmoplastic small round cell tumor (4%). Of the 22 pts, 12 had chylothorax, 5 had chylous ascites, and 5 had both. The cumulative incidence of chylous effusions from TKI initiation at 12 months was 3.09%. Median fluid triglyceride level was lower in chylothorax than in chylous ascites [397 mg/dL (IQR 282-4000) vs. 3786 mg/dL (IQR 676-6596), p = 0.035]. Median pleural fluid triglyceride level was higher with selpercatinib compared to MKIs [4,000 mg/dL (IQR 356-4425) vs. 287 mg/dL (IQR 216-395); p = 0.017]. Malignant cells were identified in the effusions from 12% (2/17) and 10% (1/10) of pts with chylothoraces and chylous ascites, respectively. Median time to disease progression from radiographic index and biochemical index across the full cohort was 1.5 years (IQR: 0.6-2.4) and 1.0 year (IQR: 0.1-1.2), respectively. Anatomic chyle leak was not identified in 6 pts who underwent lymphangiography. After initial drainage, additional drainage procedures were required in all cases with chylothorax and 50% of cases with chylous ascites. Chylous effusions prompted TKI dose reduction in 47% (7/15) of pts treated with selpercatinib and 14% (1/7) treated with MKI; none discontinued TKI due to chylous effusions. **Conclusions:** Chylous effusions can emerge on treatment with certain MKIs or selective RET TKIs. Recognition of this potential side effect is key to prevent misattribution of worsening effusions to progressive malignancy and to motivate a better understanding of its biology and management. Research Sponsor: U.S. National Institutes of Health.

9081 **Poster Session**

Phase 1 dose escalation and expansion study of bemcentinib (BGB324), a first-in-class, selective AXL inhibitor, with docetaxel in patients with previously treated advanced NSCLC. *First Author: Sheena Bhalla, University of Texas Southwestern Medical Center, Dallas, TX*

Background: AXL, a transmembrane receptor tyrosine kinase, is overexpressed and associated with poor prognosis and treatment resistance in non-small cell lung cancer (NSCLC). Bemcentinib (BGB324) is a selective orally bioavailable small molecule inhibitor of AXL, currently in phase 2 clinical development, that has demonstrated synergistic activity with docetaxel in *in vivo* models of NSCLC. This phase I dose escalation and expansion trial assessed the safety, tolerability, and preliminary efficacy of bemcentinib in combination with docetaxel in previously treated advanced NSCLC. **Methods:** Dose escalation of daily bemcentinib in combination with docetaxel (60 or 75 mg/m^2 every 3 weeks) followed a standard 3+3 design. Bemcentinib monotherapy was administered for one week prior to docetaxel initiation to assess pharmacodynamic effects alone and in combination. Plasma protein biomarker levels were measured using the DiscoveryMap v3.3 panel (Myriad RBM) pre-dose (C1D-7), C1D1, and C2D1. **Results:** A total of 21 patients (pts) were enrolled with median age 62 (range 39-84) and 67% male. A median of 3 (range 1-13) cycles of therapy were administered. Principal treatment-related adverse events were neutropenia (86%, 76% ≥G3), diarrhea (57%, 0% ≥G3), fatigue (52%, 5% ≥G3), and nausea (52%, 0% ≥G3). Neutropenic fever ≥G3 occurred in 7 (33%) pts. The maximum tolerated dose was 60 mg/m^2 docetaxel plus 200 mg bemcentinib daily with prophylactic G-CSF support. Pharmacokinetics of bemcentinib alone and in combination with docetaxel were highly similar. Among 15 evaluable pts, 4 (27%) pts had partial response and 9 (60%) pts had stable disease as the best radiographic response. Bemcentinib treatment resulted in changes in plasma levels of proteins associated with regulation of sterol synthesis and AKT signaling. **Conclusions:** Bemcentinib in combination with docetaxel and prophylactic G-CSF support has a manageable safety profile, leads to decreases in systemic factors associated with tumor growth and metastasis, and demonstrates evidence of anti-tumor activity in previously treated, advanced NSCLC. Further studies to identify the patient population most likely to benefit from this regimen are warranted. Clinical trial information: NCT02922777. Research Sponsor: BerGenBio ASA, South Plains Oncology Consortium (SPOC).

9082 **Poster Session**

Efficacy of dabrafenib-trametinib combination in *BRAF* V600E-mutated metastatic non–small cell lung cancer: Results of the IFCT-2004 BLaDE cohort. *First Author: Aurélie Swalduz, Department of Medical Oncology, Centre Léon Bérard, Lyon, France*

Background: *BRAF* V600E mutations occur up to 2% of advanced non-small cell lung (NSCLC). Dabrafenib-trametinib (D-T) combination was associated with improved OS rates in phase II study and was approved in the 1st-line setting and further. The IFCT-2004 BLaDE study reports the D-T combination efficacy in a large French real-world multicenter cohort of advanced *BRAF V600E*-mutated NSCLC. **Methods:** Patients (pts) with advanced NSCLC harboring *BRAF V600E* mutation diagnosed between 01.01.2016 and 31.12.2019 and treated with D-T combination (D 300 mg + T 2 mg daily) whatever the treatment line were included. Demographic, clinical, pathological data were collected as well as data of efficacy and reason of treatment discontinuation. The primary endpoint was 12 months-OS rate in pts receiving the D-T as 2nd-line or subsequent treatment (L2+). **Results:** 163 pts were included in 54 centers through 32 national testing labs: 50.3 % were female, 30.2% never-smokers, 95.1 % had adenocarcinoma and PDL1 was > 1% in 78.2%. Median age was 68.3 years. At D-T initiation, 80.8 % of pts were PS 0/1, 93.9 % were stage IIIB/C ineligible for surgery or local therapy and IV, 20.9% had brain metastases and 27% received D+T as 1st line treatment (L1). At the data cutoff (30.06.2021), median (m) follow-up was 27.4 months [95% CI 22.2-31.9] and 47 pts (28.8%) remained on study treatment. 12 months-OS rate in pts receiving D+T in L2+ (n = 119) was 67.4% [95% CI 57.8-75.3] with a median progression-free survival (mPFS) of 10.4 months [95% CI 7.3-13.1]. In the 44 pts receiving D+T in L1, 12 months-OS rate was also 67.4% [95% CI 51.2-79.3] with a mPFS of 18.2 months [95% CI 7.7-21.3]. Objective response rates were 73.8% [95% CI 65.5 - 82.2] and 82.9% [95% CI 71.4 - 94.4], disease progression was observed as best response in 3.7% [95% CI 0.1 - 7.3] and 0% in L2+ and L1, respectively. Other efficacy results are detailed in the table. D-T discontinuation for toxicity was reported in 10.3% of pts. 51.2% and 43.7% of pts received subsequent treatment in L2+ and L1 respectively. For L2+ pts, subsequent treatments were immunotherapy (IO)-based in 37.2 % and chemotherapy in 58.3%. For L1 pts, subsequent treatments were (IO)-based in 42.9% and chemotherapy in 42.7%. **Conclusions:** Our series confirms significant efficacy of D-T combination in *BRAF* V600E-mutated metastatic NSCLC. These results in real-world conditions are consistent with registration studies but also support its use in 1st line setting. Research Sponsor: NOVARTIS.

	L2+ (n = 119)	L1 (n = 44)
PFS rates, % [95% CI]		
6 months	65.4 [55.7-73.5]	70.4 [54.6-81.6]
12 months	43.7 [33.9-53.1]	55.5 [39.3-68.9]
mOS, months [95% CI]	19.7 [15.7-26.9]	24.1 [12.3-37.9]
OS rates, % [95% CI]		
18 months	55.2 [44.9-64.3]	62.6 [46.3-75.2]
24 months	44.7 [34.3-54.6]	53.0 [36.1-67.3]

9083 **Poster Session**

***BRAF* mutation classes and co-occurring mutations in NSCLC.** *First Author: Jiaxin Niu, Banner MD Anderson, Phoenix, AZ*

Background: Targeted therapy against unique molecular drivers has revolutionized non-small cell lung cancer (NSCLC) treatment. *BRAF* mutations, present in 2%-5%, have emerged as therapeutic targets, and can be divided into three classes: kinase-activating monomers (class I, V600) or dimers (class II), or kinase-inactivating dimers (class III). Most studies have focused on *BRAF* V600E NSCLC. Limited clinical data suggest classes II and III may not respond well to chemo- or targeted therapy and tend to have a poorer prognosis. Little is known about co-occurring mutations. This study examines *BRAF* classes and co-occurring mutations in NSCLC. **Methods:** Between October 2018 and October 2021, data from 3009 NSCLC Oncotype MAP test results were analyzed. This test utilizes tumor DNA to identify single nucleotide variants, indels, copy number alterations, and select structural variants/fusions by next generation sequencing with a 257 gene panel. Tumor mutational burden and microsatellite instability are also assessed. Pathogenic/likely pathogenic mutations were identified, *BRAF* mutations assigned to 3 different classes based on current understanding, and associations of other mutated genes with *BRAF* class examined. **Results:** Among samples, 133 (4.4%) had *BRAF* mutations: 30 class I (1%); 42 class II (1.4%); 36 class III (1.2%); and 25 unclassified (0.8%) (Table). Two genes showed associations with *BRAF* class: *STK11* was significantly overrepresented in class II and III, and *SETD2* in class I ($p<0.05$ for both). *BRAF* class II mutations were further divided into subclasses, IIa (n= 5) and IIb (n= 35); two could not be assigned. The lack of a positive association between *KRAS* (and *NF1*) and *BRAF* class III was unexpected since class III is RAS-dependent while class I and II are RAS-independent. The overrepresentation of *STK11* in classes II (with 11/12 events in IIb) and III might explain, at least in part, the poor prognosis relative to class I. By contrast, *SETD2* is overrepresented in class I, which might help explain its better response to immunotherapy. **Conclusions:** For the first time we report the incidence of *BRAF* mutation classes and associated co-mutations in NSCLC. These associations may help to explain therapeutic outcomes. The impact of coexisting STK11 mutations in class II subclasses warrants further investigation. Research Sponsor: Exact Sciences Corporation.

The most frequent co-occurring mutations in 133 mutant *BRAF* NSCLC samples.

Gene	n	Class I n=30	Class II (n=42)			Class III n=36	Unclassified n=25
			NA (n=2)	IIa (n=5)	IIb (n=35)		
TP53 (p53)	88	13 (43.3%)	2 (100.0%)	4 (80.0%)	22 (62.9%)	26 (72.2%)	21 (84.0%)
STK11*	22	1 (3.3%)	0	1 (20.0%)	11 (31.4%)	7 (19.4%)	2 (8.0%)
KRAS	21	1 (3.3%)	1 (50.0%)	1 (20.0%)	6 (17.1%)	8 (22.2%)	4 (16.0%)
SETD2*	19	10 (33.3%)	0	0	4 (11.4%)	1 (2.8%)	4 (16.0%)
CDKN2A (p16)	14	4 (13.3%)	0	0	2 (5.7%)	4 (11.1%)	4 (16.0%)
DNMT3A	12	3 (10.0%)	1 (50.0%)	1 (20.0%)	1 (2.9%)	4 (11.1%)	2 (8.0%)
NF1	11	1 (3.3%)	0	0	5 (14.3%)	2 (5.6%)	3 (12.0%)

(*$p<0.05$, Chi-squared test for three *BRAF* classes).

9084 **Poster Session**

Clinicopathologic and mutational landscape of *BRAF*^{V600E}-mutant non–small cell lung carcinoma. *First Author: Jane Sze Yin Sui, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: *BRAF* mutations (mts) occur in 2-5% of non-small cell lung cancers (NSCLC) with approximately 50% being *BRAF*^{V600E}. Limited data is known regarding the mutational landscape (ML) and prognostic role of co-mutations in *BRAF*^{V600E} NSCLC. We performed this study to evaluate clinicopathological characteristics and the impact of ML in *BRAF*^{V600E} NSCLC. **Methods:** Patients (pts) with *BRAF*^{V600E}mutant NSCLC were identified using MSK-IMPACT at Memorial Sloan Kettering Cancer Center between January 2014 to October 2021. Baseline clinicopathological characteristics and treatment outcomes were annotated. Due to the enrichment of *SETD2* in *BRAF*^{V600E} NSCLC, we conducted further analyses using cbioportal to identify co-mutations of *SETD2* with other actionable mutations in NSCLC. Overall survival (OS) was assessed from the date of metastatic disease until death using the log-rank test. **Results:** *BRAF* mutations were detected in 5% of NSCLC samples (512/10220) with 22% (97/435 pts) being *BRAF*^{V600E}. Of the 97 pts with *BRAF*^{V600E} NSCLC identified: 57 pts (59%) were females, median age of 68 (range: 38-93 years), 58 pts (60%) were former smokers. All *BRAF*^{V600E} tumors were adenocarcinoma and the median tumor mutational burden was 5 mt/Mb (range: 0-40). 46 pts (48%) with *BRAF*^{V600E} NSCLC were diagnosed with de novo metastatic disease. Pts receiving targeted therapy at first, second, and subsequent lines of therapy numbered 17 (29%), 18 (31%), and 10 (17%) respectively. Co-alterations of *BRAF*^{V600E} with *TP53* and *SETD2* were found in 45% (44/97) and 42% (41/97), respectively. There is a much lower prevalence of concurrent inactivating *SETD2* mutations than with other actionable alterations in NSCLC: *ROS1* (9%), *ALK* (8%), *RET* (8%), *HER2* (6%), *MET* (5%), *KRAS* (5%), *EGFR* (2.9%) and *BRAF*$^{non\text{-}V600E}$ (2%). Median OS in *BRAF*$^{V600E+}$/*TP53*$^{+}$ vs *BRAF*$^{V600E+}$/*SETD2*$^{+}$ were 35 vs 36 mos (HR 0.88m 95% CI 0.45-1.75, *P*= 0.71) and *BRAF*$^{V600E+}$/*TP53*$^{+}$/*SETD2*$^{+}$ vs *BRAF*$^{V600E+}$/*TP53*$^{-}$/*SETD2*$^{-}$ were 19 vs 39 mos (HR 0.37, 95% CI 0.09-1.50, *P*= 0.06). **Conclusions:** Among the *BRAF*^{V600E} lung adenocarcinomas, concurrent *TP53* mutation and *SETD2* inactivation define a patient subset with significantly shorter overall survival. Further studies are warranted to investigate the role of *SETD2* mutations in the context of *BRAF*^{V600E} in NSCLC pts. Research Sponsor: None.

9085 **Poster Session**

A first-in-human, phase 1 study of ASTX029, a dual-mechanism inhibitor of ERK1/2, in relapsed/refractory solid tumors. *First Author: Patricia LoRusso, Yale University, New Haven, CT*

Background: Aberrant activation of the RAS-RAF-MEK-ERK pathway is common in human cancers. This is an open-label Phase 1 study of ASTX029, a dual-mechanism extracellular signal-regulated kinase 1/2 (ERK1/2) inhibitor, in subjects with relapsed/refractory solid tumors (NCT03520075). **Methods:** The primary objective is to identify a recommended Phase 2 dose. Subjects with relapsed/refractory solid tumors were eligible for Phase 1A with any molecular feature and for Phase 1B if the tumor demonstrated RAS or BRAF mutations. ASTX029 was administered orally daily on a continuous basis in 21-day cycles. Phase 1A was a modified 3+3 dose-escalation design based on dose-limiting toxicity (DLT) events. Phase 1B subjects were treated at the recommended dose for expansion (RDE) based on emerging safety, pharmacokinetic (PK), and pharmacodynamic (PD) data. Disease response was evaluated by RECIST v1.1. **Results:** 76 subjects were treated with at least one dose of ASTX029 in Phase 1A (n = 56) and Phase 1B (n = 20). In Phase 1A, ASTX029 was evaluated from 10 mg to 280 mg daily. Two subjects experienced grade 2 central serous retinopathy (CSR) within a few days of dosing at the 280 mg daily dose level (one event was declared a DLT). Both subjects recovered to baseline within days of dose interruption. CSR is an expected AE based on the class of drugs. At the selected RDE dose level of 200 mg daily, the mean PK exposure was 109% of target exposure (13,022 ng*hr/ml), defined as the level expected to have biological activity based on mouse models. As of the data cut-off of February 7, 2022, the most frequent grade ≥2 AEs experienced by subjects (≥5%) assessed as related to ASTX029 included ocular AEs (n = 6: all Grade 2); nausea (n = 7: all Grade 2); diarrhea (n = 6: 5 Grade 2, 1 Grade 3); fatigue (n = 4: all Grade 2); rash (n = 4, 3 Grade 2, 1 Grade 3). There were 52 serious AEs, all unrelated to ASTX029 except for one subject with Grade 3 malaise. Four subjects had a partial response, including *KRAS*-G12A *BRAF*-D549N non-small cell lung cancer (NSCLC; Phase 1A: 120 mg treated 20.0 months); *KRAS*-G12D pancreatic cancer (Phase 1A: 200 mg treated 2.1 months); *KRAS*-G13D NSCLC (Phase 1B; treated 10.6 months); *KRAS*-G12S NSCLC (Phase 1B; treated 10.4 months and ongoing). In all, two partial responses were observed out of 3 NSCLC subjects enrolled in Phase 1B. Phospho-ERK and phospho-RSK were evaluated for PD effect on fresh tumor biopsies obtained at baseline and cycle 2. A PD effect and decreased cell proliferation (Ki-67) were observed in 6 of 9 and 3 of 8 evaluable Phase 1B samples, respectively. The most common reason for ASTX029 discontinuation was disease progression. **Conclusions:** This Phase 1 study of the ERK1/2 inhibitor ASTX029 has identified a dose level of 200 mg daily continuously for investigation in the Phase 2 study. PK and PD data suggest target exposures are achieved with preliminary clinical activity, especially in KRAS-mutated NSCLC. Clinical trial information: NCT03520075. Research Sponsor: Astex Pharmaceuticals, Inc.

9086 **Poster Session**

Molecular characterization of NF1-mutated NSCLC and clinical outcomes. *First Author: Christopher Gates, West Virginia University Health Sciences Center, Morgantown, WV*

Background: *NF1* is a tumor suppressor gene that regulates the RAS-MAPK and mTOR pathways. Co-mutations previously observed with *NF1*-mutations (mt) include *TP53, KRAS, EGFR* and rarely *HER2, STK11,* and *PIK3CA* mutations. We report a comprehensive molecular characterization with clinical outcomes analyses for *NF1*-mt non-small cell lung cancer (NSCLC). **Methods:** Next-generation sequencing (NGS) of DNA (592-gene or whole exome) and RNA (whole transcriptome) was performed for NSCLC patient (pt) samples (n = 10,310) submitted to a CLIA-certified laboratory (Caris Life Sciences, Phoenix, AZ). . RAS-MAPK and PI3K-AKT-MTOR signaling were assessed by transcriptional signatures of pathway activation (MAPK pathway Activation Score [MPAS], Wagle, 2018; and GSEA Hallmarks collection, respectively)., PD-L1 by immunohistochemistry (IHC, positive: TPS ≥1%), high tumor mutational burden (TMB) defined as ≥10 mut/Mb, and deficient mismatch repair/high microsatellite instability (dMMR/MSI-High) was assessed by IHC/NGS. Overall survival (OS) was obtained from insurance claims. Statistical significance was determined using Chi-square & Wilcoxon rank sum tests. P-value adjust for multiple hypothesis testing (Benjamini-Hochberg). **Results:** *NF1*-mt were identified in 1,045 NSCLC samples (10.1%). Concurrent *KRAS, EGFR, ERBB2, BRAF* or *MET* alterations are noted in Table 1, with no *ROS1, RET or ALK* fusions identified. Compared to *NF1*-wt, *NF1*-mt NSCLC was associated with increased RAS-MAPK expression (3.0-fold, P < 0.0001), while PI3K-AKT-MTOR-signaling was not significantly increased (2.1-fold, P = 0.12). Rates of TMB-High (51.7% vs 32.5%, P < 0.0001), PD-L1+ (69.1% vs 58.8%, P = 0.06), and dMMR/MSI-High (1.7 vs 0.7%, P < 0.05) were higher in *NF1*-mt samples. OS and duration on treatment from the start of Pembrolizumab (HR: 1.0 and 1.0, respectively) or other IOs (HR: 0.9 and 1.0, respectively) were not significantly different between *NF1*-mt and *NF1*-wt patients, However, among *NF1-mt* samples, high TMB and *TP53*-wt were associated with better OS (HR 0.6, P < 0.05 each). **Conclusions:** *NF1*-mt patients rarely harbored actionable NSCLC driver co-alterations. *NF1*-mt cases showed increased activation of RAS-MAPK axis, which may represent a potential pathway to target with MEK inhibitors. *NF1-mt* are responsive to immunotherapy and better outcomes are seen with high TMB and absence of TP53 mutations. Further work is warranted to determine the influence of actionable drivers on targeted therapy outcomes in *NF1*-mt NSCLC. Research Sponsor: None.

Molecular Alteration	Percentage (NF1-mt)	Percentage (NF1-wt)	p-value
KRAS mt	14.6974	29.0946	6.99E-23
MET amplification	1.2821	0.9761	0.355
MET exon 14 skipping	2.027	2.9268	0.402
NRG1 fusion	0.2632	0.2722	1
NTRK1 Fusion	0.1776	0.0932	0.444
NTRK3 Fusion	0.1776	0.0466	0.285
BRAF mt	4.9133	4.2721	0.336
EGFR mt	1.3397	11.656	1.01E-24
ERBB2 mt	0.1918	1.7053	0.000178

9087 **Poster Session**

A multicenter real-world study of tumor-derived DNA from cerebrospinal fluid in genomic profiling of NSCLC with central nervous system metastases. *First Author: Yongping Mu, Inner Mongolia Autonomous Region Cancer Hospital, Hohhot, China*

Background: Genomic profiling of cerebrospinal fluid (CSF) could be used to detect actionable mutations to guide the clinical treatment of NSCLC patients with central nervous system (CNS) metastases. Examining the performance of CSF samples in a real-world setting can further confirms the potential of CSF in genotyping for guiding therapy in clinical practice. **Methods:** A total of 1097 samples were collected from 773 treated NSCLC patients with CNS metastases in a real-world setting, including 117(10.67%) CSF samples, 287(26.16%) tissue samples and 693(63.17%) plasma samples. All samples were subjected to the targeted next-generation sequencing of 1021 cancer-relevant genes. **Results:** Of these 1097 treated samples, somatic alterations were identified in 112 (95.72%) of the CSF samples, comparing with 287 (100%) of tumor tissue samples and 592 (85.43%) of plasma**.** Among the tumor tissue samples, 242 were non-intracranial tissues, which could not reveal the unique genetic profiles of intracranial metastases. The median of maximal somatic allele frequency of CSF samples (72.35%) was significantly higher than those of plasma (1.30%) and tumor tissues (37.30%) (all p<0.001). In the thirty-two pairs CSF and plasma samples tested simultaneously, 442 alterations were detected, of which 377 were detected in CSFs and 92 in plasma. 27 alterations could be detected in both plasma and CSF, 65 were not detected in CSFs and 350 were not in plasma, the same alterations were 10.91% (27/442). For SNV or InDel, 220 mutations were detected, of which 155 were detected in CSFs and 89 in plasma, the same mutations were 10.91% (24/220)**.**For CNVs, 216 CNV alterations were detected, of which 216 were detected in CSFs and only one in plasma**.** We compared actionable mutation of these 1097 treated samples to further analyze the detection capability of actionable mutations of CSF samples in this real-world setting (Table). Compared with plasma, the detection rates of all actionable mutation and actionable *EGFR* in CSF were significantly higher than those in plasma samples (93.16% vs. 53.97% for all actionable mutation, 83.76% vs. 39.54% for *EGFR*, all p<0.001). **Conclusions:** This real-world large cohort study verified that CSF had higher sensitivity than plasma for identifying actionable mutations. In the process of multiple comparison, it can be seen that CSF is better than plasma in detecting alterations, especially in detecting CNV alteration. CSF can be used as a substitute in genomic profiling for NSCLC patients with CNS metastases when there is no intracranial tumor tissue. Research Sponsor: None.

Actionable mutations detected in different samples from treated NSCLC patients with CNS metastases.

	CSF (Sample=117)	Tissue (Sample=287)	Plasma (Sample=693)
All actionable mutations	109	276	374
EGFR	98	171	274
ALK fusion	4	18	17
ROS1 fusion	1	8	4
BRAF	0	5	4
KRAS	2	24	25
MET	16	33	17
RET	0	2	3
ERBB2	8	25	11

9088 **Poster Session**

Evaluation of weight gain and overall survival of patients with advanced non–small cell lung cancer (NSCLC) treated with first-line platinum-based chemotherapy. *First Author: Eric Roeland, Oregon Health and Sciences University Knight Cancer Institute, Portland, OR*

Background: Cachexia is a multifactorial syndrome frequently associated with cancer characterized by anorexia and unintentional weight loss, including skeletal muscle loss, fatigue, functional impairment, poor quality of life, and worse survival. The objective of this post-hoc analysis was to examine the relationship between weight gain and overall survival (OS) in patients with NSCLC treated with first-line platinum-based regimens. **Methods:** Data were pooled from three phase 3 clinical trials (NCT00254891, NCT00254904, and NCT00596830) conducted between Nov 2005 and Mar 2011 in patients with advanced NSCLC (stage IIIB or stage IV) treated with first-line standard-of-care (SOC) chemotherapy (control arm). Weight was recorded at baseline, prior to dosing on day 1 of each 3-week treatment cycle (up to 6 cycles), and post-treatment according to each study's schedule. Weight gain was categorized as > 0%, > 2.5%, and > 5% increase from baseline up to 4.5 months. Cox Proportional Hazards modeling of OS including time to weight gain and time to confirmed objective response (RECIST v1.0) and baseline covariates were used to estimate hazard ratios (HR) for each category. **Results:** The total 1,030 patients from the SOC control arms were predominantly male (70.5%) with Stage IV NSCLC (88.5%) and a mean age (SD) of 60.9 (9.4) years and BMI 24.6 (4.4) kg/m^2. Overall, 486 (47.2%), 299 (29.0%), and 164 (15.9%) patients experienced weight gain from baseline of > 0%, > 2.5%, and > 5%, respectively. Median time to > 0%, > 2.5%, and > 5% weight gain was 24, 43, and 64 days, respectively. After adjusting for statistically significant time-dependent confirmed objective response, the risk of death was significantly less for patients with weight gain. For patients with > 0% vs. ≤0% weight gain, HR was 0.70 (95%CI 0.61, 0.82) with median OS of 13.6 vs. 8.3 months. For patients with > 2.5% vs. ≤2.5% weight gain, HR was 0.70 (95%CI 0.59, 0.83) with median OS of 15.3 vs. 9.1 months. For patients with > 5% vs. ≤5% weight gain, HR was 0.76 (95%CI 0.61, 0.94) with a median OS of 14.4 vs. 9.8 months. **Conclusions:** In this pooled analysis, weight gain during treatment with first-line platinum-based chemotherapy was associated with a significantly reduced risk of death in patients with advanced NSCLC, independent of tumor response defined by RECIST criteria. The survival benefit was comparable for > 2.5% vs. > 5% weight gain. Weight gain of 2.5% may be an earlier predictor of survival outcomes and may have implications for the design of cancer cachexia trials. Clinical trial information: NCT00254891, NCT00254904, and NCT00596830. Research Sponsor: Pfizer.

9089 **Poster Session**

Nedaplatin plus pemetrexed or cisplatin plus pemetrexed as first-line chemotherapy for EGFR/ALK-negative advanced lung adenocarcinoma (NACA): A multicenter, open-label, non-inferiority, randomized, phase III trial. *First Author: Xue Hou, Department of Medical Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, China*

Background: Platinum-based chemotherapy is the backbone of treatment for advanced non-small cell lung cancer. Cisplatin has well-known side effects such as gastrointestinal reaction and fatigue, and nedaplatin was developed to be an alternative platinum with less toxicity. We aimed to compare nedaplatin plus pemetrexed was non-inferior to cisplatin plus pemetrexed as first-line chemotherapy for advanced EGFR/ALK-negative lung adenocarcinoma. **Methods:** We did an open-label, randomized, phase III trial at 15 centers in China. Advanced lung adenocarcinoma patients with EGFR/ALK-negative status were randomly assigned to receive nedaplatin 90 mg/m^2 or cisplatin 75 mg/m^2 plus pemetrexed 500 mg/m^2 for 6 cycles as first-line treatment, and pemetrexed maintenance for those without progressive disease. The primary endpoint was progression-free survival (PFS), non-inferiority was shown if the upper limit of the 95% CI for the hazard ratio (HR) of PFS did not exceed 1.30. Secondary endpoints included objective response, overall survival and toxicity. This trial is registered with ClinicalTrials.gov, number NCT02607592. **Results:** Between Sep 2015 and May 2021, 218 patients were randomized to nedaplatin group (n = 111) or cisplatin group (n = 107). In the intention-to-treat population, median PFS time was 6.87 months (95%CI, 5.25 to 8.49) in the nedaplatin group and 5.53 months (95%CI, 4.57 to 6.50) in the cisplatin group, with a HR of 0.76 (95%CI, 0.56 to 1.03, p= 0.078). In the per-protocol population (nedaplatin group, n = 105; cisplatin group, n = 94), median PFS time was 6.87 months (95%CI, 5.36 to 8.37) and 5.20 months (95%CI, 4.03 to 6.37) respectively, with a HR of 0.76 (95%CI, 0.56 to 1.03, p= 0.082). Overall response rate was 41.9% in nedaplatin group and 26.6% in cisplatin group (p= 0.026). A significantly higher frequency of any grade nausea and vomiting (51[53.68%] of 95 in the cisplatin group *vs* 30[28.04%] of 107 in the nedaplatin group, p< 0.001), fatigue (37[38.95%] *vs* 27[25.23%], p= 0.037), and constipation (15[15.79%] *vs* 5[4.67%], p= 0.008) were reported in the cisplatin group compared with the nedaplatin group. Higher rate of grade 3/4 nausea and vomiting was observed in cisplatin group (10[10.53%] *vs* 0, p= 0.001). Patients in the nedaplatin group had higher frequency of thrombocytopenia but without statistical significance (any grade: 28[26.17%] of 107 in the nedaplatin group *vs*17[17.89%] of 95 in the cisplatin group, p= 0.158; grade 3/4: 8[7.48%] in the nedaplatin group *vs* 3[3.16%] in the cisplatin group, p= 0.177). **Conclusions:** Our findings show that nedaplatin plus pemetrexed is not inferior to cisplatin plus pemetrexed in progression-free survival, with less toxicities, which represents an alternative chemotherapy regimen for EGFR/ALK-negative advanced lung adenocarcinoma. Clinical trial information: NCT02607592. Research Sponsor: None.

9090 **Poster Session**

Subgroup analysis in patients (pts) with non-squamous (N-Sq), EGFR-wild type (wt), second/third-line NSCLC from the global phase (Ph) 3 trial DUBLIN-3 (BPI-2358-103) with the plinabulin/docetaxel (Plin/Doc) combination versus Doc alone. *First Author: Baohui Han, Department of Pulmonary Medicine, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China*

Background: With PD-1/PD-L1 inhibitors moving to first line in NSCLC, 2nd/3rd line NSCLC is a severe unmet medical need, dominated by docetaxel-based therapies with > 40% severe neutropenia and limited survival. Plin, a novel immune-enhancing small molecule, enhances dendritic cell maturation and T-Cell proliferation. In the ITT population, the Plin/Doc combination had superior Efficacy (mOS; HR = 0.82, p = 0.0399), Safety (lower Gr3/4 AE rate/pt/year (yr); p = 0.038) and better Quality of Life (QTWiST; p = 0.026) versus (vs) standard of care (SoC) Doc alone in advanced and metastatic NSCLC pts in DUBLIN-3 (Han, ESMO 2021) who failed platinum therapy. Here we report on the N-Sq pts subgroup. **Methods:** DUBLIN-3(NCT02504489) was a randomized, single-blind (pts only), active controlled Ph3 study in 2nd/3rd line stage IIIB/IV, EGFR wt NSCLC pts with a measurable lesion (RECIST 1.1) in the lung, and ECOG ≤ 2, conducted in US, Australia and China. Pts (n = 559) were randomized 1:1 to Plin/Doc or Doc/Placebo (21-day (D) cycle (C)). Doc (75 mg/m^2 on D1 and Plin 30 mg/m^2 on D1 and D8 were given by IV infusion. A post-hoc analysis of median Overall Survival (mOS) and restricted mean survival time (RMST) from K-M curves, OS rate at 24,36 and 48 month (Mo), and grade 4 neutropenia (Gr4N) rates was performed for the N-Sq patients (n = 153 for Plin/doc and n = 178 for Doc). **Results:** Baseline characteristics were balanced between both groups. Primary and key secondary objectives in the ITT population were met (Han, ESMO 2021). Plin/Doc was well tolerated. Estimated Adverse Event Rate per Year [95% CI] was 1.43 [1.13,1.81] for Plin/Doc versus 2.77 [2.33,3.28] for Doc alone (p < 0.001). The median OS benefit is 2.6 months (p = 0.023). The table below summarizes the results for the N-Sq subgroup. **Conclusions:** The addition of Plin to Doc was superior to SoC Doc alone for efficacy and safety in the clinically relevant subgroup of non-squamous EGFR-wild type, 2nd/3rd line NSCLC pts. Clinical trial information: NCT02504489. Research Sponsor: BeyondSpring Pharmaceuticals Inc.

N-Sq subset	mOS Mo [95% CI]	RMST Mo [SE]	24 Mo OS-Rate (%)	36 Mo OS-Rate (%)	48 Mo OS-Rate (%)	Gr4N Rate (%)
Plin/Doc (n = 153)	11.4 [9.37;12.4]	16.1 [1.188]	24.9%	14.2%	11.85%	13.9
Doc (n = 178)	8.8 [8.05;10.9]	12.8 [0.845]	14.1%	4.68%	0%	37.9
HR	0.75	NA	NA	NA	NA	
P value	0.023	0.025	0.025	0.03	NA	< 0.001

9091 **Poster Session**

DUBLIN-3 results on quality of life (QoL) in second/third-line EGFR-wild type NSCLC patients (pts) receiving docetaxel (Doc) with or without plinabulin (Plin) using the validated EORTC QLQ C30 and QLQ LC13 questionnaires. *First Author: Trevor Feinstein, Piedmont Cancer Institute, Fayetteville, GA*

Background: Plin, a novel immune-enhancing small molecule, enhances dendritic cell maturation and T-cell proliferation. In the ITT population, the Plin/Doc combination had superior Efficacy (mOS; p = 0.0399), Safety (Gr3/4 AE rate/pt/year; p = 0.038) and QTWiST (p = 0.026) vs standard of care (SoC) Doc alone in NSCLC pts in DUBLIN-3 (Han, ESMO 2021). Here we report DUBLIN-3 QoL results. **Methods:** DUBLIN-3(NCT02504489) was a randomized, single-blinded (pts only), active-controlled Ph3 study in 2nd/3rd line stage IIIB/IV, EGFR wt NSCLC pts with a measurable lesion (RECIST 1.1) in the lung, and ECOG ≤ 2, conducted in US, Australia, and China. Pts (n = 559) were randomized 1:1 to Plin/Doc or Doc/Placebo (21-day (D) cycle). Doc (75 mg/m^2 on D1 and Plin 30 mg/m^2 on D1 and D8 were given by IV infusion. QoL was evaluated by the validated questionnaires EORTC QLQ C30 and QLQ LC13 (which is specific for Lung Cancer), and patient-reported scores were collected at baseline and D1, D8 of each cycle (C). **Results:** Baseline characteristics and QLQ C30 and LC13 scores were comparable between both groups. Plin/Doc was well tolerated. Cumulative C30 sand LC13 scores were calculated for each patient. Mean (SEM) change from baseline in cumulative C30 and LC13 scores were comparable for Plin/Doc and Doc in the first 10 cycles, however separated after C10 in favor of Plin/Doc (table). LC13 items in favor of Plin/Doc vs Doc alone, were items 31 (Coughing; p < 0.05), 36 (Sore Mouth; p < 0.01), 37 (Dysphagia; p < 0.01). **Conclusions:** We previously reported an OS, Safety, and QTWiST benefit with Plin/Doc vs Doc alone (ESMO 2021) in EGFR wild type 2nd/3rd line NSCLC pts from DUBLIN-3. Here, we report statistically significant QoL benefits with Plin/Doc vs Doc alone, as assessed with EORTC QLQ C30 and LC13, which may be relevant to guide treatment decisions in this generally sick patient population. Clinical trial information: NCT02504489. Research Sponsor: BeyondSpring pharmaceuticals, Inc.

	C10	C20	C30	C40	C50	C60
Plin/Doc C30	440 (15.6)	499 (23.7)	515 (27.0)	518 (28.1)	519 (28.3)	519 (28.3)
Doc C30	423 (13.2)	457 (18.6)	467 (21.6)	473 (24.4)	479 (27.5)	480 (27.7)
Plin/Doc LC13	93 (4.2)	106 (6.1)*	110 (6.9)*	110 (7.1)*	111 (7.1)	111 (7.1)
Doc LC13	87 (4.3)	93 (5.1)	94 (5.3)	95 (5.6)	96 (5.9)	96 (5.9)

*p < 0.05

9092 **Poster Session**

Effect of performance status (ECOG PS) on treatment outcome with second-line (2L) nintedanib (NIN) + docetaxel (DOC) for patients (pts) with lung adenocarcinoma after first-line (1L) immune checkpoint inhibitor (ICI) combination therapy. *First Author: Christian Grohé, Department of Respiratory Diseases, ELK Berlin, Berlin, Germany*

Background: ICIs with or without chemotherapy represent 1L standard of care for patients with advanced non-small cell lung cancer (NSCLC) without targetable driver mutations. Given the paucity of prospective randomized trials assessing second-line treatment options post-immunochemotherapy, non-interventional data may help support clinical decision making. Patients with ECOG PS > 1 are generally underrepresented in clinical trials relative to routine clinical practice. We therefore examined treatment outcomes with 2L NIN + DOC after 1L ICI combination therapy with respect to ECOG PS at baseline. **Methods:** In this analysis of Cohort C of the ongoing, non-interventional VARGADO study (NCT02392455), eligible pts had locally advanced, metastatic or locally recurrent adenocarcinoma NSCLC and received 2L NIN+DOC in routine clinical practice after failure on 1L ICI in combination with chemotherapy. The primary endpoint is 1-year survival rate (not yet mature). Tumor response was according to investigator review. **Results:** In 164 pts enrolled in Cohort C, median age was 63 years (range: 37 – 84), 100 pts (61.0%) were men, and 123 pts (75.0%) were ECOG PS 0–1. 146 pts (89.0%) had received prior 1L pembrolizumab-based combination therapy. Objective response rate (ORR) with 2L NIN+DOC was 35.4% (40/113 pts) in the overall population and 41.2%, 30.8% and 28.6% for pts with ECOG PS 0, 1 and > 1, respectively. Disease control rate (DCR) was 67.3% (76/113 pts) in the overall population and 76.5%, 65.4% and 50.0% for pts with ECOG PS 0, 1 and > 1, respectively. Median PFS was 4.7 months (95% CI: 3.4 – 5.3) in the overall population and 5.1 months (95% CI: 2.8 – 8.3), 3.7 months (95% CI: 2.5 – 5.3) and 2.1 months (95% CI: 1.3 – 6.5) for pts with ECOG PS 0, 1 and > 1, respectively. The median OS was 8.1 months (95% CI: 6.3 – 11.2) in the overall population and 9.1 months (95% CI: 5.4 – 14.5), 10.5 months (95% CI: 6.3 – 14.9) and 4.0 months (95% CI: 2.5 – 6.3) for pts with ECOG PS 0, 1 and > 1, respectively. **Conclusions:** Our results support 2L NIN+DOC as an effective treatment option in pts with advanced adenocarcinoma NSCLC following 1L ICI in combination with chemotherapy. ECOG PS > 1 was associated with lower ORR, DCR and shorter PFS and OS. These findings warrant further evaluation of the effect of ECOG PS on 2L treatment outcomes in patients after 1L ICI combination therapy. Clinical trial information: NCT02392455. Research Sponsor: Boehringer Ingelheim Pharma GmbH & Co. KG.

9093 **Poster Session**

Capecitabine in pretreated metastatic pulmonary lymphoepithelioma-like carcinoma: A retrospective study. *First Author: Gavin Tin Chun Cheung, Department of Clinical Oncology, Queen Elizabeth Hospital, Kowloon, Hong Kong*

Background: Pulmonary lymphoepithelioma-like carcinoma (LELC) is a rare disease, sharing common histological features with the undifferentiated subtype of nasopharyngeal carcinoma (NPC), and being under-represented in non-small cell lung cancer trials and clinical guidelines. While gemcitabine-based platinum doublet chemotherapy is more established in 1st line treatment of stage IV disease, there is limited evidence for subsequent treatment strategy. Oral capecitabine is one of the active agents in metastatic NPC, and was observed to have encouraging outcomes in pulmonary LELC. **Methods:** All consecutive patients with pulmonary LELC in 2010 – 2019 treated in a tertiary institution were reviewed. Patients with metastatic disease who progressed after gemcitabine-based platinum doublets and treated with capecitabine were included. Capecitabine was given at 1250 mg/m^2 twice daily for 14 days followed by 7 days of rest in each cycle. Treatment response was monitored by clinical history, physical examination and imaging. Treatment was continued till drug holiday, intolerance or disease progression. Progression-free survival (PFS) and overall survival (OS) were estimated by the Kaplan-Meier method. Clinical predictors for PFS and OS were analyzed using log-rank test and the Cox proportional hazard model. **Results:** Of the 140 LELC patients identified, 36 patients satisfied the above inclusion criteria (14 male, 22 female). Median age was 58.6 years old (range 41.5 – 75.6). All patients had an ECOG performance score of 0 or 1. 16 patients (44.4%) received 2 or more lines of prior systemic treatment. Median capecitabine cycles received was 5 (range 2 – 68). Objective response rate was 27.8% (complete response: 5.6%; partial response: 22.2%), disease control rate was 75.0%. With a median follow-up of 15.3 months (range 1.8 – 82.6), the median PFS and OS were 5.4 months (95% CI, 2.1 – 8.8) and 15.4 months (95% CI, 10.0 – 20.7) respectively. Capecitabine was generally well tolerated, with 22.2% grade 3 or above side effects, and 5.6% treatment termination due to intolerance. Bone and distant lymph node (LN) involvement were significant predictors of poorer PFS on multivariate analyses (bone: HR 3.24, 95% CI 1.44 – 7.29, p=0.004; distant LN: HR: 2.62, 95% CI 1.14 – 6.02, p=0.024). Age, sex, smoking history, number of treatment lines, and other sites of disease involvement were not significant predictors. **Conclusions:** This is to date the largest reported cohort of capecitabine in pre-treated metastatic pulmonary LELC. Capecitabine is effective and well tolerated, and should be considered as a treatment option after 1st line platinum-based chemotherapy. Future studies are warranted to delineate the optimal treatment pathway of this rare disease entity. Research Sponsor: None.

9094 **Poster Session**

Quality of life (QoL) of OSE2101 in patients with HLA-A2+ non–small cell lung cancer (NSCLC) after failure to immune checkpoint inhibitors (IO): Final data of phase 3 Atalante-1 randomized trial. *First Author: Benjamin Besse, Gustave Roussy Institute, Villejuif, France*

Background: OSE2101 (Tedopi) is an anticancer vaccine increasing overall survival (OS) versus Standard of Care (SoC docetaxel or pemetrexed) in HLA-A2+ NSCLC patients with secondary resistance after sequential Chemo (CT)-IO (ESMO 2021 #47LBA). Here we present the QoL analysis. **Methods:** EGFR and ALK negative NSCLC patients who failed prior IO, ECOG PS 0-1 were randomized 2:1 to receive either OSE2101 or SoC (docetaxel or pemetrexed). Primary endpoint was OS; secondary endpoints included time to ECOG PS deterioration and QoL by EORTC QLQ-C30/LC13 questionnaires at baseline and before each treatment administration until the end of treatment (EOT). Changes in QLQ-C30/LC13 scores from baseline to EoT were assessed using mixed-effects model for repeated measures (MMRM). Overall treatment effect and associated p value were estimated using MMRM. **Results:** 95 out of 118 (81%) patients with secondary resistance to IO completed baseline and ≥ one follow-up questionnaire. Median OS was 11.1 mo for OSE2101 vs 7.5 mo for SoC [HR 0.59; p = 0.02]. Median time to ECOG PS deterioration was 9.0 mo for OSE2101 vs 3.3 mo for SoC [HR: 0.43; p = 0.004]. Global Health Status remained stable with OSE2101 whereas it deteriorated from the 1st cycle with SoC (p = 0.045). Most pronounced effects were observed in the physical (ability to perform activities that require physical effort; p = 0.07) and the role (ability to work and carry out daily activities; p = 0.03) functioning scores (refer table below). Patients had less mouth soreness (p = 0.01), dysphagia (p = 0.01), peripheral neuropathy (p = 0.03), alopecia (p < 0.001) and fatigue (p = 0.06) with OSE2101 than with SoC. The change from baseline of dyspnea, coughing, hemoptysis, and pain were not significantly different between the 2 groups. **Conclusions:** In advanced HLA-A2+ NSCLC patients with secondary resistance to IO after sequential CT-IO, OSE2101 improves OS and maintains QoL vs. SoC, especially global health status, physical and role functioning scores. Patients presented fewer symptoms typically related to adverse effects of chemotherapy as compared to SoC. Clinical trial information: NCT02654587. Research Sponsor: OSE Immunotherapeutics.

QLQ-C30 Domain Least square mean [95%CI]	OSE2101 (n = 70)	SoC (n = 25)	p value
Global Health Status	0.77 [-2.92,4.47]	-6.19 [-11.83,-0.55]	0,045
Physical functioning	-2.74 [-6.21,0.73]	-8.75 [-14.17,-3.33]	0,069
Role functioning	-5.09 [-10.60,0.43]	-16.78 [-25.29,-8.28]	0,025
Emotional functioning	0.50 [-3.29,4.28]	-2.75 [-8.63,3.12;	0,358
Cognitive functioning	-3.20 [-7.18,0.78]	-7.64 [-13.86,-1.43]	0,235
Social functioning	-3.82 [-8.30,0.66]	-10.43 [-17.23,-3.64]	0,111

9095 **Poster Session**

Gefitinib plus chemotherapy versus gefitinib alone in untreated patients with *EGFR*-mutated non–small cell lung cancer and brain metastases (GAP Brain): An open-label, randomized, multicenter, phase 3 study. *First Author: Likun Chen, Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Combination of tyrosine kinase inhibitor (TKI) and chemotherapy has shown improved clinical outcomes in advanced epidermal growth factor receptor (*EGFR*) mutated non-small cell lung cancer (NSCLC) patients. We conducted this phase 3, randomized, controlled trial to further investigate the clinical efficacy and safety of gefitinib combined with chemotherapy in *EGFR* mutated NSCLC patients with brain metastases. **Methods:** Treatment-naïve, confirmed brain metastases and *EGFR* sensitive mutated NSCLC patients were screened from six centers in China. The eligible patients were randomly assigned (1:1) to receive gefitinib alone or gefitinib plus pemetrexed-platinum chemotherapy until intracranial progressive diseases, unacceptable adverse, or any cause of death. Theprimary endpoint was intracranial progression-free survival (iPFS), secondary endpoints were PFS, overall survival, intracranial objective response rate, overall objective response rate, and safety. This study is registered at ClinicalTrials.gov, number NCT01951469. **Results:** From January 2017 to June 2021, 161 patients were randomly assigned to receive gefitinib (n = 81) or gefitinib plus pemetrexed-platinum chemotherapy (n = 80), the median follow-up time was 18.2 (IQR 11.8-29.7) months. The median intracranial PFS was 15.6 (14.3-16.9) months in gefitinib plus chemotherapy group versus 9.1 (8.0-10.2) months in gefitinib group (HR = 0.36, 95% CI, 0.25-0.53, P < 0.001). Similarly, the median PFS was also significantly longer in gefitinib plus chemotherapy than gefitinib alone (16.3 months vs 9.5 months, P < 0.001). In addition, gefitinib plus chemotherapy had better intracranial objective response rate (85.0% versus 63.0%, P = 0.002) and overall objective response rate (80.0% versus 64.2%, P = 0.035) than gefitinib alone. At the data cutoff, 50.3% of patients (35 patients in gefitinib plus chemotherapy group and 46 patients in gefitinib group) had died. The 3-year OS rate was significantly higher in gefitinib plus chemotherapy group (47.4%, 95% CI 36.3-58.7) than in gefitinib group (24.9%, 95% CI 15.1-34.3, P = 0.003). And median overall survival was 35.0 months (95% CI, 28.8-41.3 months) in gefitinib plus chemotherapy group versus 28.9 months (95% CI, 23.4-34.4 months) in gefitinib group (HR = 0.66, 95% CI, 0.42-1.03, P = 0.065). Grade 3 or worse adverse events were more common in gefitinib plus chemotherapy group (40.0% versus 21.0%, P = 0.010), but most of them were manageable. **Conclusions:** Inuntreated EGFR mutated NSCLC patients with brain metastases, gefitinib plus chemotherapy significantly improved intracranial PFS, PFS and a tendency of OS than gefitinib alone, and could be the optional first-line treatment. Clinical trial information: NCT01951469. Research Sponsor: None.

9096 **Poster Session**

Aumolertinib activity in patients with CNS metastases and EGFR-mutated NSCLC treated in the randomized double-blind phase III trial (AENEAS). *First Author: Shun Lu, Shanghai Chest Hospital, Jiao Tong University, Shanghai, China*

Background: We previously reported (Lu, ASCO 2021, abstract # 9013) that treatment with aumolertinib (Au), a 3rd generation EGFR TKI, led to robust improvement in progression free survival (PFS) (median PFS 19.3 to 9.9 months, HR = 0.46, p < 0.0001) when compared to gefitinib (G) with a predictable and encouraging safety profile. This benefit was maintained across all prespecified stratification factors including the subset of ~ 27% of patients (pts) with CNS metastases (HR = 0.38). Here we undertook this analysis to more fully characterize the activity and benefit of Au as compared to G in this clinically important subset of EGFR mutant NSCLC pts. **Methods:** Pts with previously untreated metastatic or locally advanced NSCLC with EGFR sensitizing mutations were enrolled and randomly assigned in a 1:1 ratio to receive either Au (110 mg QD) or G (250 mg QD). Predefined stratification factors were EGFR-mutated status (Ex19del vs L858R) and CNS metastases (yes vs no). Patients with stable, asymptomatic CNS metastases were eligible for enrollment. All pts had baseline brain imaging by magnetic resonance imaging or computed tomography. The primary endpoint was PFS assessed by investigator per RECIST v1.1 in full analysis set (systemic analysis). Independent CNS efficacy was performed both in pts with baseline CNS metastases (CNS full analysis set, cFAS) and in pts with baseline CNS target lesions (CNS evaluable-for-response set, cEFS) by blinded independent central neuroradiology review (BICR) per RECIST v1.1. **Results:** Of 429 pts, 106 pts (Au, n = 51; G, n = 55) were found to have CNS metastases (cFAS) and 61 pts (Au, n = 29; G, n = 32) had CNS target lesions as defined by RECIST 1.1 (cEFS) at baseline by BICR. At the cutoff date (Aug 6, 2021), based on cEFS, CNS PFS events were observed in 11 pts (38%) treated with Au versus 20 pts (63%) who were randomized to receive G. Treatment with Au significantly prolonged CNS median PFS compared with G (29.0 vs 8.3 months; HR = 0.300; 95% CI, 0.137-0.657; *P* = 0.0015). Estimated CNS PFS rate at 12 and 18 months were 71% and 62% in Au arm compared with 23% and 0% in G arm. The confirmed CNS ORR were 82.8% and 75.0% in pts treated with Au and G, respectively (odds ratio = 1.600; 95% CI, 0.457-5.597; *P* = 0.4621). Au also achieved longer CNS median PFS over G in cFAS (29.0 vs 8.3 months; HR = 0.323; 95% CI, 0.181-0.576; *P* < 0.0001). No new safety findings were observed. **Conclusions:** Au demonstrated superior clinical efficacy against CNS metastases over G as first-line therapy in EGFR-mutated advanced NSCLC, and the safety profile was consistent with that reported previously. Additional randomized studies of Au in pts with CNS metastases are ongoing (NCT04870190). Clinical trial information: NCT03849768. Research Sponsor: Hansoh Pharmaceutical Group Co. Ltd.

9097 **Poster Session**

A phase II study of osimertinib in combination with platinum plus pemetrexed in patients with EGFR-mutated, advanced non–small cell lung cancer: The OPAL study (NEJ032C/LOGIK1801). *First Author: Atsushi Nakamura, Department of Pulmonary Medicine, Sendai Kousei Hospital, Sendai, Japan*

Background: Osimertinib (OSI), a third-generation EGFR-tyrosine kinase inhibitor (EGFR-TKI), is now a standard treatment for previously untreated EGFR-mutated (EGFRm) advanced non-small cell lung cancer (NSCLC). In the two randomized phase 3 studies, progression-free survival (PFS) and overall survival were statistically significant and clinically longer with gefitinib and platinum-based chemotherapy compared with gefitinib monotherapy. Based on these data, we have planned this phase 2 study to evaluate the safety and efficacy of OSI combined with platinum-based chemotherapy. **Patients and Methods:** This multicenter phase 2 study enrolled patients (pts) with clinical stage IIIB, IIIC, IVA, IVB or postoperative recurrent, previously untreated EGFRm NSCLC. Pts received oral OSI 80mg once daily (QD), with either cisplatin 75mg/m2 (arm A) or carboplatin [area under the curve (AUC) = 5, arm B], plus pemetrexed (PEM) 500 mg/ m2 every 3 weeks (Q3W) for four cycles. In both arms, maintenance was OSI 80mg QD with PEM 500 mg/ m2 Q3W until disease progression or discontinuation. The co-primary endpoints were the safety and the objective response rate (ORR), and the secondary endpoints included the complete response rate (CRR), disease control rate (DCR), and PFS. **Results:** From July 2019 to February 2020, 67 pts (34 pts in Arm A; 33 pts in arm B) were enrolled: median (range) age 67 (26-75) years; 43 (64.2%) female; 46 (68.7%) ECOG PS 0; 66 (98.5%) adenocarcinoma; 31 (46.3%) EGFR exon19 deletion, 35 (52.2) L858R, and 1 (1.5%) both. One pt did not comply with the eligibility criteria and was excluded from the efficacy analysis. At data cut off (August 31, 2021), 27 (40.3%) pts [15 (44.1%) in arm A and 12 (36.4%) in arm B] had discontinued the protocol treatment, including 9 (13.4%) pts [5 (14.7%) in arm A and 4 (12.1%) in arm B] due to the adverse event (AE). The rate of grade (G) ≥ 3 AEs were 91.0% (88.2% in arm A and 93.9% in arm B). For the safety, neutropenia, anemia and thromobocytopenia were numerically higher in arm B and the rates of G ≥ 3 were 29.4%/60.6%, 14.7%/27.3% and 0.0%/42.4% in arm A/B, respectively. G ≥ 3 QTc interval prolonged and G ≥ 2 anorexia were observed in 14.7%/21.2% and 26.5%/24.2%, respectively. For the efficacy, the ORR was 90.9% [95% confidence interval (CI); 84.0-97.8%]. The CRR/DCR were 3.0%/97.0% (95% CI; 0.0-7.2%/92.8%-100.0%), respectively. At a median follow-up time of 21.4 months (range, 18.2-25.7), median PFS was not reached in both A and B, with an estimated 12-/24-months PFS rate of 90.4%/70.0%. **Conclusions:** OSI combined with platinum-based chemotherapy for previously untreated EGFRm advanced NSCLC showed the excellent efficacy with tolerable toxicity. This combination treatment is highly promising and should be validated in the phase 3 study. Clinical trial information: jRCTs031180226. Research Sponsor: Astrazeneca.

9098 **Poster Session**

Efficacy and safety of rezivertinib (BPI-7711) in patients with locally advanced or metastatic/recurrent EGFR T790M-mutated NSCLC: A phase IIb, multicenter, single-arm, open-label study. *First Author: Shiman Wu, The First Hospital of Shanxi Medical University, Taiyuan, China*

Background: Rezivertinib (BPI-7711) is a third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) targeting both EGFR-sensitizing mutations and EGFR T790M mutation. This study aimed to evaluate the efficacy and safety of Rezivertinib in patients with locally advanced or metastatic/recurrent EGFR T790M mutated non-small cell lung cancer (NSCLC). **Methods:** Locally advanced or metastatic/recurrent NSCLC patients with histologic or cytologic or plasmatic confirmation of EGFR T790M mutations who progressed after first/second generation EGFR-TKIs therapy or primary EGFR T790M mutations were enrolled. Patients received Rezivertinib at 180mg orally once daily until disease progression, unacceptable toxicity, or withdrawal of consent. The primary endpoint was objective response rate (ORR) assessed by blinded independent central review (BICR) per RECIST1.1. The efficacy for patients with central nervous system (CNS) metastases was measured by BICR according to the Response Assessment in Neuro-Oncology Brain Metastases. Secondary endpoints included disease control rate (DCR), duration of response (DoR), progression-free survival (PFS), overall survival (OS) and safety. Safety was assessed as per CTCAE 4.03. **Results:** A total of 226 patients were enrolled from Jul 5, 2019, to Jan 22, 2020. 91 (40.3%) patients had brain metastases. The tissue sample and plasma sample were positive for *EGFR* T790M in 120 (53.1%) and 116 (51.3%) patients, respectively. By the data cut-off date on Dec 23, 2021, the ORR by BICR was 64.6% (95%CI:58.0-70.8) and DCR was 89.8% (95%CI:85.1-93.4). The median DoR was 12.5 (95%CI:10.0-13.9) months and median PFS was 12.2 (95%CI:9.6-13.9) months. The median OS was 23.9 (95%CI:20.0-NC) months. Subgroup ORR: exon 19 deletion 72.4% (95%CI:64.4-79.5), L858R 51.9% (95%CI:40.4-63.3), tissue T790M positive 70% (95%CI:61.0-78.0), plasma T790M positive 56.9% (95%CI:47.4-66.1). Subgroup PFS: exon 19 deletion 12.4 (95%CI:8.8-15.1) months, L858R 10.3 (95%CI:8.3-13.9) months, tissue T790M positive 13.9 (95%CI:11.3-17.9) months, plasma T790M positive 9.6 (95%CI:7.0-11.0) months. Among 91 patients with CNS metastases, 29 patients had at least one brain target lesion whose CNS-ORR and CNS-DCR were 69.0% (95%CI:49.2-84.7) and 100% (95%CI:88.1-100), respectively. Time to progression of CNS was 16.5 (95%CI:9.7-NC) months. 188 of 226 (83.2%) patients had at least one adverse drug reaction, with the most common being white blood cell count decreased (27.9%), platelet count decreased (23.0%), anemia (22.6%). No interstitial lung disease was reported. **Conclusions:** Rezivertinib demonstrated promising efficacy and favorable safety for locally advanced or metastatic/recurrent NSCLC patients with EGFR T790M mutation. Clinical trial information: NCT003812809. Research Sponsor: Beta Pharma (Shanghai) Co., Ltd.

9099 **Poster Session**

Mobocertinib (TAK-788) in *EGFR* exon 20 insertion (ex20ins)+ metastatic non–small cell lung cancer (mNSCLC): Treatment (tx) beyond progressive disease (PD) in platinum-pretreated patients (pts) with and without intracranial PD. *First Author: Pasi A. Janne, Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, MA*

Background: Mobocertinib is a potent, irreversible, oral tyrosine kinase inhibitor selectively targeting *EGFR* ex20ins in NSCLC. Mobocertinib demonstrated clinical efficacy in 114 platinum-pretreated pts (PPP) with *EGFR* ex20ins+ mNSCLC in a phase 1/2 study. **Methods:** In this study (NCT02716116), pts with ECOG status 0–1 and ≥1 prior therapy line for locally advanced/metastatic *EGFR* ex20ins+ NSCLC received mobocertinib 160 mg QD. Pts were allowed to continue tx beyond PD at the discretion of the investigator (INV) if evidence of clinical benefit existed. We present data on continuation of mobocertinib tx beyond PD in the PPP cohort by site of first PD (brain vs extracranial). **Results:** At the November 1, 2020, data cutoff, among PPP (n=114; median age 60 y, 66% female, 60% Asian), 59% had ≥2 prior systemic anticancer lines; 35% had baseline brain metastases (Zhou C, et al. *JAMA Oncol.* 2021;7(12):e214761. doi:10.1001/jamaoncol.2021). Confirmed objective response rate (cORR) per independent review committee (IRC) was 28%; median duration of response was 17.5 mo. IRC-assessed cORR was 34% among PPP with no baseline brain metastases versus 18% among PPP with baseline brain metastases (Zhou C, et al. *JAMA Oncol.* 2021;7(12):e214761. doi:10.1001/jamaoncol.2021); median progression-free survival was 9.2 and 3.7 mo, respectively. Per INV assessment, 64 pts had PD. Duration of mobocertinib tx beyond PD is summarized in the Table. Among pts with first site of PD in brain per INV (n=21), 17 (81%) pts remained on mobocertinib tx beyond PD; 7 (33%) received radiotherapy to brain and remained on mobocertinib tx, of whom 3 pts remained on mobocertinib tx for ≥6 mo and 1 pt for ≥12 mo. Among pts with first site of PD outside the brain per INV (n=43), 28 (65%) pts continued tx beyond PD and 4 (9%) pts remained on mobocertinib tx for ≥6 mo. **Conclusions:** These results suggest that mobocertinib may have limited intracranial activity given the high frequency of first PD in brain (25%) and numerically lower IRC-assessed cORR in pts with baseline brain metastases. Per INV assessment, pts may derive ongoing systemic benefit from mobocertinib. Duration of time to next progression based on local therapy continues to be investigated. Clinical trial information: NCT02716116. Research Sponsor: Sponsored by Takeda Development Center Americas, Inc.

INV Assessment	First Site of PD in Brain (n=21)	Extracranial First Site of PD (n=43)
Pts remaining on tx after PD per INV, n (%)	17 (81)	28 (65)
Median time on tx after PD, mo (range)	2.8 (0.2, 15.4)	1.0 (0.1, 18.4)
≥3 mo, n (%)	8 (38)	7 (16)
≥6 mo, n (%)	4 (19)	4 (9)

INV, investigator; PD, progressive disease.

9100 **Poster Session**

Identification of pretreatment genomic biomarkers and mechanisms of acquired resistance to first-line osimertinib in advanced *EGFR*-mutant lung cancers. *First Author: Noura J. Choudhury, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Despite its widespread use, few series explore genomic biomarkers that impact progression-free survival (PFS) for first line osimertinib use and how mechanisms of acquired resistance impact post-osimertinib progression survival. **Methods:** All pts treated with first line osimertinib at Memorial Sloan Kettering Cancer Center were identified; available pre-osimertinib and post-progression tumor samples underwent next-generation sequencing (NGS) using MSK-IMPACT. Real-world (rw)PFS was estimated with Kaplan-Meier methods from start of osimertinib to progression, defined using interpretation of imaging reports. Post-baseline factors were evaluated using time-dependent covariate Cox model. **Results:** We identified 331 pts, of which 67 had paired tumor samples and 28 had post-progression tumor samples that underwent MSK-IMPACT. Most pts with biopsies were women (68%), never smokers (83%) and did not have baseline brain metastases (56%). With median follow-up of 24 months (mo), median rwPFS was 14 mo (95% confidence interval (CI) 13 -17 mo, n = 331). *EGFR* driver alterations (n = 40 atypical, n = 108 L858R, n = 182 exon 19 deletion) were associated with distinct rwPFS (median 8 (95% CI 6-12), 14 (12-18) and 16 mo (13-21), respectively, $p < 0.001$ logrank test). Pts with concurrent pre-treatment *TP53* (14 mo,12-17) or *TP53/RB1* (12 mo, 9-15) alterations had shorter median rwPFS compared to pts without these alterations (20 mo,16-24, $p < 0.001$, logrank test). Fifty patients (53%) had an identified mechanism of resistance. Off target mechanisms (n = 9 *MET* amplification (amp), n = 3 *HER2* amp, n = 3 *PIK3CA* mutations, n = 3 acquired fusions, n = 2 *RB1* loss and n = 1 *CCND1* amp, *MYC* amp, *CDK4* amp, *KRAS* G12A, respectively) and histological transformation (n = 7 small cell, n = 5 squamous and n = 2 large cell neuroendocrine) were detected. On target acquired mechanisms were *EGFR* amplification (n = 7), and G724S (n = 2) and C797S (n = 3) mutations. Pts with an identified mechanism of resistance did not have improved post-progression survival (12 mo HR 1.6, p = 0.09), but receiving next line of therapy based on post-progression tumor biopsy results (including platinum-etoposide for transformation) did improve post-progression survival (12 mo HR 0.4, p = 0.01). **Conclusions:** Pts with atypical *EGFR* drivers or concurrent *TP53+/-RB1* alterations have significantly shorter rwPFS on first line osimertinib, highlighting need for additional interventions for these patients. Given the high frequency of transformation and improvement in post-progression survival by tailoring next line of therapy to the identified mechanism, pts with *EGFR*-mutant lung cancer on first line osimertinib may benefit from tissue biopsies at progression. For pts without an identified resistance mechanism by NGS, additional methods of interrogating tumors at progression are needed. Research Sponsor: LUNGevity EGFR Resisters Award, U.S. National Institutes of Health.

9101 **Poster Session**

Central nervous system efficacy of furmonertinib versus gefitinib in patients with non–small cell lung cancer with epidermal growth factor receptor mutations: Results from FURLONG study. *First Author: Gongyan Chen, Department of Respiration, Harbin Medical University Cancer Hospital, Harbin, China*

Background: Furmonertinib (AST2818) is a third-generation epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitor (TKI) with central nervous system (CNS) penetration. Here we report the CNS response to furmonertinib versus gefitinib as first-line therapy in *EGFR*-mutated non-small cell lung cancer (NSCLC) patients in the FURLONG study. **Methods:** FURLONG was a randomized, double-blind, multi-center phase III study. Patients were randomized 1:1 to receive first-line furmonertinib 80mg/d or gefitinib 250mg/d. Brain scan was mandatory at screening. Patients with asymptomatic CNS metastases who did not require steroid treatment for 28 days or more were enrolled. A pre-planned CNS efficacy analysis was done using RECIST v1.1 in patients with measurable or non-measurable CNS lesions (cFAS) and patients with only measurable CNS lesions (cEFR). **Results:** Of 358 enrolled patients in the FURLONG study, 133 (37%) patients were defined as cFAS and 60 (17%) were defined as cEFR according to baseline brain scan judged by a blinded independent review committee (IRC). At the cut-off date of Sep 15, 2021, CNS progression-free survival (PFS) assessed by IRC in the cFAS population was significantly longer in the furmonertinib group than in the gefitinib group (20.8 vs 9.8 months, HR 0.40 [95% 0.23-0.71]; p = 0.0011). CNS PFS rate at 6, 12, 18 months were 91%, 77%, 63% in the furmonertinib group, and 76%, 46%, 34% in the gefitinib group. In the cEFR set, confirmed CNS objective response rate was 91% in patients with furmonertinib and 65% in patients with gefitinib (p = 0.0277), and CNS disease control rate were 100% vs 84% (p = 0.9420), respectively. The mean best percentage change in the sum of target CNS lesion size from baseline in cEFR was -61.8% in the furmonertinib group versus -38.7% in the gefitinib group (p = 0.0011). **Conclusions:** Furmonertinib showed CNS efficacy as first-line therapy in EGFR-mutated NSCLC patients with CNS lesions. Patients treated with furmonertinib had a reduced risk of CNS progression or death, a higher CNS ORR and a deeper CNS response compared with gefitinib. Clinical trial information: NCT03787992. Research Sponsor: Shanghai Allist Pharmaceuticals Co., Ltd, China National Major Project for New Drug Innovation (2017ZX09304015).

9102 **Poster Session**

Mefatinib as first-line treatment of patients with advanced non–small cell lung cancer harboring rare EGFR mutations. *First Author: Pingli Wang, Department of Respiratory Medicine, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China*

Background: Mefatinib is a novel, second-generation, irreversible epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI). A Phase Ib/II study has showed promising efficacy in patients with advanced EGFR (19del/L858R) mutant non-small cell lung cancer (NSCLC). This study is aimed to assess the efficacy and safety of mefatinib as first-line therapy for advanced rare EGFR mutations (G719X/S768I/L861Q) NSCLC. **Methods:** In this phase II study, we enrolled patients with stage IIIB-IV lung adenocarcinoma with at least one mutation in G719X, L861Q, and S768I who hadn¡t received front-line anticancer therapy. Other concurrent EGFR mutations were allowed with the exception of Ex19del, L858R, and exon 20 insertions. Eligible patients were treated with mefatinib 80 mg orally once daily. The primary endpoint was objective response rate (ORR) according to RECIST 1.1 criteria. **Results:** A total of 21 patients (median age 57.6, 47.62% male) have been enrolled, 80.95% with G719X, 33.3% S768I, and 19.05% L861Q. Six (28.57%) patients had concurrent mutations of G719X and S768I, and one (4.76%) patient had co-mutations of G719X and L861Q. As of data cut-off (Jan, 6, 2022), median follow-up was 25.1 months. Among the 21 efficacy evaluable patients, ORR was 85.71% (95% CI, 63.66-96.95) with a duration of response (DOR) of 22.2 months (95% CI, 8.4-NA). Disease control rate (DCR) was 100% (95% CI, 83.89-100.00). Median progression-free survival (mPFS) was 20.6 months (95% CI, 8.3-NA). Median overall survival (OS) was not reached.. The most common treatment-related adverse events (TRAEs) were rash (20, 95.24%), diarrhea (19, 90.48%), stomatitis (15, 71.43%), and pandactilitis (9, 42.86%). Grade 3 TRAEs were reported in 47.63% patients. Common Grade 3 TRAEs (¡Ý5%) included diarrhea (8, 38.10%) and rash (5, 23.81%). No ¡ÝGrade 4 TRAE or treatment-related SAE reported. 33.33% (n=7) of patients experienced dose reduction due to AEs (mainly diarrhea and rash). All TRAEs were reversible and remained stable or recovered without sequelae after dose reduction. None of the patients discontinued treatment or died due to TRAE. **Conclusions:** Mefatinib has shown promising anti-tumor activity and a favorable safety profile in patients with advanced NSCLC harboring rare EGFR mutations. Clinical trial information: CTR20190110. Research Sponsor: HangZhou ZhongMei HuaDong Pharmaceutical Company.

Pts treated with Mefatinib	ORR, % 95%CI	DCR, % 95%CI	Median PFS, mos 95%CI	Median DOR,mos 95%CI
All (n=21)	85.71 (63.66,96.95)	100.00 (83.89,100.00)	20.6 (8.3,NA)	22.2 (8.4,NA)
G719X (n=17)	94.12 (71.31,99.85)	100.00 (80.49,100.00)	20.6 (8.3,NA)	18.7 (8.3,NA)
L861Q (n=4)	75.00 (19.41,99.37)	100.00 (39.76,100.00)	18.7 (7.0,NA)	24.9 (9.7,NA)
S768I (n=7)	71.43 (29.04,96.33)	100.00 (59.04,100.00)	20.6 (1.0,NA)	NA (6.9,NA)

9103 **Poster Session**

Co-occurring gene alterations associated with efficacy of osimertinib in EGFR-mutated lung cancer: Based on a large-scale genomic screening project (LC-SCRUM-Asia). *First Author: Yuji Shibata, Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan*

Background: Osimertinib is a standard drug for first-line treatment of patients with advanced non–small cell lung cancer (NSCLC) harboring EGFR mutations (mt). While tumor mutational burden (TMB)-high and co-occurring genetic alterations (alt) have been reported to be negatively associated with the efficacy of other EGFR-TKIs, the impact of co-occurring genetic alt with EGFR major mt on the efficacy of osimertinib remains unclear. **Methods:** In a multi-institutional genomic screening project (LC-SCRUM-Asia), we have analyzed lung cancer patients for genomic alt by a targeted next-generation sequencing (NGS) system, Oncomine Comprehensive Assay and Genexus/OPA. We retrospectively evaluated the association between the genomic profile and efficacy of first-line osimertinib for EGFR-mutated NSCLC based on the LC-SCRUM-Asia database. **Results:** Between March 2015 and January 2022, 12,705 NSCLC patients were enrolled in the LC-SCRUM-Asia database, and EGFR mt was detected in 2,232 patients. Of these, 324 patients, including 171 with ex19del (53%) and 153 with L858R (47%), received first-line treatment with osimertinib. The patient characteristics were as follows: median age, 69 years (range 31-97); females, 64%; never-smokers, 57%; adenocarcinoma, 97%; and performance status 0-1, 99%. The frequency of compound EGFR mt and TMB were higher in the L858R (LR) group than in the ex19del (Ex19) group (compound mt (%), 12 vs. 4; mean TMB (mt/Mb), 3.4 vs. 2.5). There were no differences in the frequencies of other co-occurring genetic alt between the two groups. Higher TMB, alt of genes encoding receptor tyrosine kinase (RTK), including FGFR1, RET, MET etc., and amp of cell-cycle related genes were significantly associated with shorter progression-free survival (PFS) in the entire group (median PFS: TMB > 3 vs. ≤3 mt/Mb = 11.4 vs. 17.1 months; p = 0.023; RTK gene alt+ vs. alt- = 9.7 vs. 15.2 months; p = 0.014; cell-cycle gene amp+ vs. amp- = 10.6 vs. 15.6 months, p = 0.001). EGFR subgroup analysis showed that a higher TMB was significantly associated with a shorter PFS in the LR group (> 3 vs. ≤3 mt/Mb = 10.0 vs. 17.1 months, p < 0.001), but not in the Ex19 group. On the other hand, alt of genes encoding RTK and amp of cell-cycle related genes were significantly associated with a shorter PFS in the Ex19 group (RTK gene alt+ vs. alt- = 8.4 vs. 17.8 months, p = 0.008; cell-cycle gene amp+ vs. amp- = 10.6 vs. 17.5 months, p = 0.003), but not in the LR group. Multivariate analysis identified RTK gene alt in the Ex19 group and higher TMB in the LR group as being independently associated with a shorter PFS. **Conclusions:** First-line osimertinib treatment was less effective in NSCLC patients harboring Ex19 with other RTK gene alt or LR with a higher TMB, indicating that co-occurring genetic alt affecting the efficacy of osimertinib differ between NSCLC patients harboring Ex19 and LR. Research Sponsor: Japan Agency for Medical Research and Development.

9105 **Poster Session**

Results of a phase 1b study of osimertinib plus sapanisertib or alisertib for osimertinib-resistant, EGFR-mutant non–small cell lung cancer (NSCLC). *First Author: Yasir Y Elamin, Department of Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The aurora kinase and mTOR pathways are implicated in resistance to EGFR inhibitor osimertinib. Here, we investigated the safety and efficacy of the aurora kinase inhibitor alisertib and the mTOR inhibitor sapanisertib in combination with osimertinib. **Methods:** This is a phase 1b study with dose finding and expansion portions (NCT04479306). The dose finding portion used a Bayesian optimal interval (BOIN) design to assess two arms: osimertinib 80 mg daily in combination with alisertib 20 mg, 30 mg, and 40 mg daily day 1-21 of 28-day cycle (osi-ali arm) and osimertinib 80 mg daily in combination with sapanisertib 2 mg and 3 mg daily (osi-sapa arm). Dose limiting toxicities (DLTs) were predefined in the protocol. Patients with EGFR (L858R/exon 19 deletion) mutant NSCLC whose disease have progressed on osi and up to one additional line of systemic therapy were assigned, at investigator discretion, to either study arm. Tumor biopsy was mandatory at study entry and optional upon progression. **Results:** As of February 1, 2022, 40 patients are enrolled (20 in each arm). One DLT was observed in each arm: grade 3 nausea in ali-osi arm and grade 3 AST elevation in osi-sapa arm. Grade 3 treatment emergent adverse events (TEAEs) occurred in 10% of each arm, and no grade 4 TEAEs were observed. The most common TEAEs in osi-ali arm was leucopenia (45%) and anemia (35%) while in osi-sapa arm, hyperglycemia (45%) and stomatitis (40%). In osi-ali arm (n = 20), median progression free survival (mPFS) was 1.9 months while objective response rate (ORR) and disease control rate (DCR) were 5% (95% CI: 0.1 ~ 24.9%) and 40% (95% CI: 19.1 ~ 63.9%), respectively. In osi-sapa arm (n = 16, evaluated for response to date), mPFS was 4.6 months while ORR and DCR were 12.5% (95% CI: 1.6 ~ 38.3%) and 68.7% (95% CI: 35.7 ~ 82.7%), respectively. **Conclusions:** Osimertinib with alisertib or sapanisertib is well tolerated in osimertinib-resistant, EGFR mutant NSCLC. The sapanisertib combination, but not the alisertib combination, demonstrates antitumor activity suggesting that mTOR inhibition warrants further exploration in this population. Biomarker analysis is ongoing to identify the molecular determinants of response and resistance to sapasertib. Clinical trial information: NCT04479306. Research Sponsor: Takeda.

9106 **Poster Session**

Efficacy and safety of ASK120067 (limertinib) in patients with locally advanced or metastatic EGFR T790M-mutated non–small cell lung cancer: A multicenter, single-arm, phase IIb study. *First Author: Baolan Li, Beijing Chest Hospital, Beijing, China*

Background: ASK120067 (Limertinib) is a newly developed third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) targeting both sensitizing *EGFR* and *EGFR* T790M mutations. This study aimed to evaluate the efficacy and safety of ASK120067 in patients with locally advanced or metastatic *EGFR* T790M mutated non-small cell lung cancer (NSCLC). **Methods:** This study was a single-arm, open-label, phase 2b study conducted at 62 hospitals across China. Patients with locally advanced or metastatic NSCLC with centrally confirmed *EGFR* T790M mutations in tumor tissue or blood plasma who progressed after first or second generation EGFR TKIs or with primary *EGFR* T790M mutations were enrolled. Patients received ASK120067 160mg orally twice daily, until disease progression, or unacceptable toxicity. The primary endpoint was objective response rate (ORR) assessed by Independent Review Committee (IRC) per RECIST1.1. Secondary endpoints included disease control rate (DCR), progression-free survival (PFS), duration of response (DOR), overall survival (OS), and safety. Safety was assessed according to CTCAE 4.03. **Results:** Between June 24th, 2019 and Feb 25th, 2021 301 patients were enrolled and received ASK120067 treatment. All patients entered the full analysis set (FAS) and safety set (SS). A total of 99 (32.9%) patients had central nervous system (CNS) metastases at baseline. By the data cutoff date on Sep 9th, 2021, 76 (25.2%) remained on treatment. The median follow-up time was10.4 (range 0.3-26.3) months. Based on FAS, the IRC-assessed ORR was 68.8% (95%CI 63.2%-74.0%) and DCR was 92.4% (95%CI 88.8%-95.1%). The median PFS was 11.0 (95%CI 9.7-12.4) months, median DOR was 11.1 (95%CI 9.6-13.8) months, and median OS was not reached (NR) (95%CI 19.7 months-NR). Objective responses were achieved across all pre-specified subgroups. For 99 patients with CNS metastases, the ORR was 64.6% (95%CI 54.4%-74.0%), median PFS was 9.7 (95%CI 5.9-11.6) months, and median DOR was 9.6 (95%CI 8.1-15.2) months. For 41 patients who had evaluable CNS lesion, the confirmed CNS-ORR was 56.1% (95%CI, 39.7%-71.5%) and median CNS-PFS was 10.6 (95%CI 5.6-NE) months. In SS, 289 (96.0%) patients experienced at least one adverse drug reaction (ADR), with the most common being diarrhea (81.7%), anemia (32.6%), rash (29.9%) and appetite decrease (28.2%). Grade ≥3 ADRs occurred in 104 (34.6%) patients, and the most common included diarrhea (13.0%), hypokalemia (4.3%), anemia (4.0%) and rash (3.3%). ADRs leading to dose interruption and dose discontinuation occurred 24.6% and 2% of patients, respectively. No ADR leading to death occurred. **Conclusions:** ASK120067 demonstrated promising efficacy and an acceptable safety profile for the treatment of patients with locally advanced or metastatic *EGFR* T790M mutated NSCLC. Clinical trial information: NCT03502850. Research Sponsor: Jiangsu Aosaikang Pharmaceutical Co. Ltd.

9107 **Poster Session**

A randomized phase II study comparing erlotinib with or without bevacizumab in patients with advanced non–small cell lung cancer (NSCLC) with *EGFR* mutation. *First Author: Youngjoo Lee, National Cancer Center, Goyang, South Korea*

Background: Synergistic anti-tumor effect of double blocking EGFR and VEGF pathways is proven by preclinical and clinical data. This study evaluated whether an addition of bevacizumab to erlotinib improves clinical outcomes in patients (pts) with untreated advanced *EGFR*-mutated NSCLC. **Methods:** This is an open-label, multi-center, randomized phase II study conducted in South Korea. Key eligibility was age ≥ 19 years old, untreated stage IIIB/IV NSCLC, *EGFR* exon 19 deletion or exon 21 L858R mutation, and ECOG performance status of 0 or 1. Asymptomatic brain metastasis (BM) was permitted without local treatment. Pts were randomly assigned to receive either oral erlotinib (E) 150 mg/day alone or erlotinib plus bevacizumab (E+B) at 15 mg/kg intravenously every 3 weeks. Primary endpoint was progression-free survival (PFS) with secondary endpoints including response rate (RR), overall survival (OS), and toxicity. **Results:** Between Dec 16, 2016, and Mar 8, 2019, a total of 127 pts were randomly assigned to receive E (n=63) or E+B (n=64). Median follow-up duration was 38.9 months. Fifty-nine (46.5%) pts had baseline BM. While the prevalence of baseline BM was similar between both arms (45.3% vs. 47.6%), more pts of the E arm received radiotherapy for BM before the study enrollment, compared to the E+B arm (40.0% vs. 10.3%). A trend toward improved PFS was observed with the E+B arm compared to the E arm (median PFS, 17.5 months vs 12.4 months; hazard ratio [HR] = 0.74 [95% confidence interval (CI), 0.51–1.08], *P*= 0.119). The RR was similar between both arms (85.9% vs. 83.9%; *P*= 0.746). The most significant PFS benefit from the E+B was found in the subgroup with baseline BM (median PFS, 18.6 months vs 10.3 months; HR = 0.54 [95% CI, 0.31–0.95], *P*= 0.032). The 12-month and 24-month cumulative central nervous system (CNS) progression rate was 4.4% and 6.8% in the E+B arm compared to 15.1% and 32.5% in the E arm. Thus, the E+B arm significantly reduced the risk for CNS progression than the E arm (HR = 0.33 [95% CI, 0.11–0.93], *P*= 0.035). Grade 3 or worse adverse events occurred in 56.6% of the E+B arm while 20.6% of the E arm. The E+B arm tended to increase the incidence or severity of some erlotinib-related adverse effects: grade 3 skin rash (17.2% vs. 4.8%) and any grade paronychia (60.9% vs. 46.0%), and oral mucositis (51.6% vs. 33.3). At the time of disease progression, more pts in the E arm showed *EGFR* T790M positivity (82% vs. 64%) and received 3rd generation EGFR tyrosine kinase inhibitor as the 2nd line therapy (58% vs. 22%) compared to the E+B arm. OS data are immature (events: 34%, HR = 1.24 [95% CI, 0.68–2.26]). **Conclusions:** A trend to improvement in PFS was observed with the combination of erlotinib and bevacizumab vs. erlotinib alone in advanced *EGFR*-mutated NSCLC. Especially, the PFS benefit from this combination was most significant in the pts with BM. Clinical trial information: NCT03126799. Research Sponsor: Roche Korea Inc.

9108 **Poster Session**

Molecular analysis of circulating tumor DNA (ctDNA) in patients (pts) with *EGFR* exon 20 insertion-positive (ex20ins+) advanced NSCLC treated with mobocertinib. *First Author: Sylvie Vincent, Takeda Development Center Americas, Inc., Lexington, MA*

Background: ctDNA is an important tool to diagnose and monitor mutations in pts with non–small cell lung cancer (NSCLC). We evaluated epidermal growth factor receptor gene (*EGFR)* ex20ins mutations in tumor vs plasma samples, assessed changes in *EGFR* ex20ins variant allele frequency (VAF) with mobocertinib treatment and correlation with response, and identified potential emerging variants of acquired resistance. **Methods:** Tumor tissue samples were collected at baseline (BL) from pts with *EGFR* ex20ins+ advanced NSCLC receiving mobocertinib 160 mg QD in a phase 1/2 study (NCT02716116); plasma samples were collected at BL, after 2 treatment cycles (Cycle 3, Day 1 [C3D1]) and at disease progression/end of treatment (DP/EOT). ctDNA samples were analyzed by next-generation sequencing for *EGFR* ex20ins to determine concordance rate detection between tissue and plasma ctDNA at BL. Changes in VAF for *EGFR* ex20ins from BL were analyzed at C3D1 and DP/EOT by confirmed response (RECIST v1.1) to mobocertinib per independent review committee. Emerging variants at DP/EOT were evaluated by elimination of germline variants seen in healthy populations (gnomAD databases and 1000 Genomes) and nonharmful variants predicted by PolyPhen and SIFT tools or annotated as benign in ClinVar database. **Results:** BL *EGFR* ex20ins mutations were detected by ctDNA sequencing in 29 of 38 pts (76%) with tissue-confirmed *EGFR* ex20ins+ NSCLC. VAFs for *EGFR* ex20ins significantly decreased at C3D1 in mobocertinib-treated pts with confirmed partial response (PR; *P*=0.0057) or stable disease (SD; *P*=0.0016), but not in pts with progressive disease (PD; *P*=0.14) (Table). ctDNA at EOT/DP analysis identified numerous genetic variants; *EGFR*, *TP53,* and *DNMT3A* were the most common genes with emerging variants. Twelve emerging missense mutations were identified in *EGFR* in 9 pts, including mutations located in the exon 20 loop following the C-helix (6), T790M (5), and D379E (1). **Conclusions:** Concordance between tissue and plasma ctDNA for *EGFR* ex20ins mutations at BL was 76%. *EGFR* ex20ins VAF decreased significantly after 2 treatment cycles in mobocertinib-treated patients with PR and SD. Plasma ctDNA longitudinal monitoring may be useful to assess mutation status and disease progression in pts with NSCLC treated with mobocertinib. Clinical trial information: NCT02716116. Research Sponsor: Takeda Development Center Americas, Inc., Lexington, MA, USA.

VAF by response to mobocertinib over time.

	Median VAF (%; IQR)		
Response	**BL**	**C3D1**	**DP/EOT**
PR (n=11)	2.75 (0.37–26.51)	0.01 (0.01–0.16)[a]	17.70 (12.73–30.61)
SD (n=35)	2.40 (1.08–17.33)	0.08 (0.01–2.17)[a]	3.47 (0.79–25.77)
PD (n=10)	3.86 (1.73–19.43)	0.30 (0.20–1.19)	1.32 (1.02–20.49)

IQR, interquartile range; PD, progressive disease. [a]*P*≤0.05 vs BL (Wilcoxon rank sum).

9109 **Poster Session**

Uncommon EGFR mutations on osimertinib, real-life data (UNICORN study): Updated results, brain efficacy, and resistance mechanisms. *First Author: Jair Bar, Institute of Oncology, Sheba Medical Center, Ramat Gan, Israel*

Background: About 10% of EGFR mutations (EGFRm) are 'uncommon mutations' (ucEGFRm). osimertinib is a 3rd generation EGFRi, active against common EGFRm. We aimed to collect real-world data about systemic and brain response and resistance mechanisms to osimertinib for ucEGFRm patients. **Methods:** This is a multi-center, retrospective study of ucEGFRm mNSCLC treated with osimertinib as first EGFRi. RECIST and RANO-BM response was evaluated by investigators. Progression free survival (PFS), overall survival (OS) and duration of response (DOR) were calculated from initiation of osimertinib. Mutations found at resistance were collected. **Results:** 62 patients (pts) were identified in 22 centers from 9 countries. Median age was 64 (35-91) years, 74% females, 84% Caucasian, never/former/current smokers were 48%/39%/11% respectively, ECOG PS was 0-1/2/3-4 in 84%/10%/5%. Histology was adenocarcinoma in 97%. The largest subgroups were G719X, de novo T790M and L861Q (Table). Compound EGFR mutations were found in 27 pts (44%), TP53 mutations in 21 pts (34%). In 17 cases (27%), compound mutations included the common L858R/deletion19 and/or de novo T790M. Most frequent metastatic sites were lung/bone/brain in 45%/44%/39%. Most frequent toxicities were gastrointestinal (32 pts, 52%) and skin (24 pts, 39%); 8 pts had grade 3-4 AEs. No grade 5 AE occurred. 3 pts had AEs leading to discontinuation. RECIST response (RR) was available for 53 pts, CR - 4 (8%), PR - 27 (51%), SD - 17 (32%), and PD - 5 (9%). Median DOR (mDOR) was 17.4 months (95% CI 9.1-NA). mPFS was 9.5 months (95% CI 8.5–17.4). mOS was 24.5 months (95% CI 17.4-35.1). See Table for efficacy in the major subgroups. 24 pts (39%) had brain metastasis at presentation, for 12 pts a brain response by RANO-BM was available with 25%/25%/33%/17% CR/PR/SD/PD. For 14 pts, rebiopsy mutation analysis at progression on osimertinib was available: 3 pts with an additional EGFR mutation (C797S,D585Y, E709K), 3 pts with a new TP53 mutation, 1 with c-Met amplification and 1 pt with transformation to neuroendocrine carcinoma. **Conclusions:** Osimertinib demonstrated activity in ucEGFRm with 91% disease control rate and encouraging PFS and DOR. Brain response was seen in 50% of cases. Several resistance mechanisms were identified. This report comprises, to the best of our knowledge, the largest dataset of osimertinib as the first EGFRi for ucEGFRm presented so far. Research Sponsor: AstraZeneca.

	N (% of 62)	**ORR -% of patients with evaluable disease (95% C.I.)**	**mPFS Months (95% C.I.)**	**mOS Months (95% C.I.)**	**mDOR Months (95% C.I.)**
G719X	18 (29)	47 (26-69)	8.8 (7.9-NA)	NA (17.4-NA)	9.1 (8.6-NA)
L861Q	12 (19)	80 (55-100)	16 (11-NA)	26.3 (22.1-NA)	16 (11-NA)
de novo T790M	10 (16)	40 (10-70)	12.7 (9.5-NA)	42.7(12-NA)	46.2 (3.8-NA)
Compound including L858R/del19* /de novo T790M	17 (27)	57 (31-83)	30 (12.7-NA)	34.5 (31.4-NA)	46.2 (30.7-NA)

*Common exon 19 deletion, without insertion. ORR: overall response rate.

9110 **Poster Session**

NEJ043: A phase 2 study of atezolizumab (atezo) plus bevacizumab (bev) plus carboplatin (carbo) plus paclitaxel (pac; ABCP) for previously treated patients with NSCLC harboring *EGFR* mutations (EGFRm). *First Author: Naoki Furuya, Division of Respiratory Medicine, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, OH, Japan*

Background: Previous studies have demonstrated poor clinical outcomes of patients (pts) with EGFRm NSCLC treated with PD-1/PD-L1 inhibitors. However, a recent subgroup analysis of the IMpower150 trial suggested the effectiveness of ABCP in NSCLC with EGFRm. The aim of this study is to further evaluate efficacy and safety of ABCP in patients with EGFRm NSCLC. **Methods:** This single-arm multicenter phase 2 study included pts with nonsquamous NSCLC harboring sensitizing EGFRm with prior EGFR-TKI therapy. Pts received the combination dose of atezo 1200 mg, bev 15 mg/kg, carbo AUC 6 mg/mL/min and pac 175 mg/m^2 every 3 weeks up to 4 cycles followed by atezo plus bev until loss of clinical benefit. The primary endpoint was PFS by extramural review (ER). The key secondary endpoints included OS, ORR, DoR, relative dose intensity of pac, and safety. **Results:** 60 pts were enrolled (median age 68 y [40–74 y], 67% were female, 55% were Ex19del and 40% were L858R). At data cutoff (November 30, 2021), median follow-up was 12.8 months in the ITT population. Median cycles of induction and maintenance therapy were 4 and 9, respectively. Median PFS was 7.4 month (95% CI, 5.7-8.2) and median OS was 18.9 month (95% CI, 13-not reached). Confirmed ORR by ER was 56% (95% CI, 43-69) and median DoR was 7.1 months (95% CI, 4.9-9.8). T790M was associated with a favorable PFS and response to the combination therapy (PFS 8.1 vs 6.8, ORR 71% vs 50%). Relative dose intensity of pac was 84%. Grade ≥3 adverse events (AEs) were reported in 92% of pts and the most common grade ≥3 AE was neutropenia (63%). Interstitial lung disease occurred in one patient (2%). AEs leading to treatment discontinuation occurred in 12% of pts. **Conclusions:** NEJ043 study showed that the median PFS of ABCP was 7.4 months with good tolerability. We will continue to investigate the tail plateau phenomenon of PFS and OS to conclude the clinical efficacy. Clinical trial information: 031190066. Research Sponsor: Chugai Pharmaceutical.

9111 **Poster Session**

Final progression-free survival analysis of phase II study with the combination therapy of DFP-14323, protease inhibitor, and low-dose afatinib as first-line therapy for common *EGFR* mutation–positive NSCLC. *First Author: Hiroshige Yoshioka, Department of Thoracic Oncology, Kansai Medical University Hospital, Osaka, Japan*

Background: DFP-14323(INN: ubenimex) was developed as a biological response modifier and has been approved for maintenance therapy of AML in Japan. Ubenimex is an inhibitor of aminopeptidase N (APN), originated from *Streptomyces olivoreticuli*. APN is well known as one of the prognostic factors for several cancer types, including non-small-cell lung cancer (NSCLC). Meanwhile, afatinib is one of the standard treatments in NSCLC with *EGFR* mutation, but the toxicities often require dose reduction. Recently, it is suggested that reducing afatinib doses can decrease treatment-related adverse events without affecting efficacy. We aimed to examine efficacy of DFP-14323 with low-dose afatinib by conducting phase II study in patients with metastatic NSCLC harboring *EGFR* mutation. **Methods:** The study was a multi-center, single-arm, open-label phase II trial. Stage III/IV and treatment-naïve patients with common *EGFR* mutation-positive (L858R/19del) NSCLC were treated with DFP-14323 at a fixed dose of 10mg/day and afatinib at a starting dose of 20 mg/day until disease progression or intolerable toxicity. The primary endpoint was disease control rate (DCR), defined by sum the CR, PR and SD. The secondary endpoints were progression-free survival(PFS), overall response rate(ORR), N/L ratio, and safety. A sample size of 26 patients was determined, assuming a threshold DCR 70% and an expected DCR 90% with a two sided α error of 0.05 and a β error of 0.20, based on the Simon's two stage design. **Results:** From July 2018 to March 2020, 26 patients were enrolled. A median age was 72 years (range, 53-82), 21(81%) were female, and 16 (62%) were never-smokers. Half of patients had Del-19 and other half had L858R. An efficacy analysis provided a DCR of 100% (previously reported) with 18 responders (ORR : 69%). Independent imaging evaluation at 72 weeks provided a median PFS was confirmed to be 16.6mts (95% CI 10.2, 22.9, median follow-up time for censored cases: 16.3mts). According to updated exploratory follow-up by physicians, as of the data cut-off of Dec 2021, median PFS was calculated 20.6 mts (95% CI, 12.6, 28.5, median follow-up time for censored case: 20.9mts). Seven Grade 3 adverse events were observed in 6patient(23%), and paronychias in 3 patients and diarrhea, stomatitis, dermatitis, and lymphocytopenia in 1 patient each. One paronychia was considered to be related to DFP-14323 and the other events to afatinib. No grade 4 or 5 adverse events were observed. One Grade 1 ILD was observed but recovered soon without treatment. **Conclusions:** Combination of DFP-14323 and low-dose afatinib has shown comparable potential as a first-line treatment for *EGFR* mutation positive NSCLC with feasible efficacy and good safety profile. We are planning a phase III study to evaluate this combination therapy as compared with other EGFR-TKIs. Clinical trial information: UMIN000033062. Research Sponsor: Delta-Fly Pharma Inc.

9112 **Poster Session**

Afatinib (Afa) + bevacizumab (Bev) versus afatinib alone as first-line treatment of patients with EGFR-mutated advanced non-squamous NSCLC: Primary analysis of the multicenter, randomized, phase II study—AfaBev-CS study. *First Author: Nobuhisa Ishikawa, Department of Respiratory Medicine, Hiroshima Prefectural Hospital, Hiroshima, Japan*

Background: Adding Bev to erlotinib prolonged PFS in NEJ026 and CTONG1509 trials, but limited data are available adding Bev to a second-generation EGFR-tyrosine kinase inhibitor. AfaBev-CS is a Japanese no-profit, randomized, open-label, multicenter phase II trial of Afa plus Bev vs Afa alone as first-line treatment for EGFR-mutated advanced NSCLC. **Methods:** This study enrolled untreated pts of advanced non-squamous NSCLC harboring EGFR sensitizing mutation (Del19 or L858R) and without symptomatic brain metastases. 100 eligible pts were randomized in a 1:1 ratio to receive either Afa (30 mg, daily) plus Bev (15 mg/kg, every 3 weeks) (AfaBev arm) or Afa (40 mg, daily) monotherapy (Afa arm), and stratified according to stage, EGFR mutation status and institution. The primary endpoint was PFS and the secondary endpoints were OS, tumor response and time to treatment failure. The sample size was set in terms of feasibility. The power is greater than 50% under the assumptions of a median PFS of 12 months for the Afa arm and HR of 0.6 for the AfaBev arm, with an accrual of 2.5 years and a minimum planned follow-up period of 2 years with the type 1 error of 0.05 (two-sided). **Results:** Between August 2017 and September 2019, 100 pts were enrolled (each arm, 50 pts). At a median follow-up of 31.3 months for all randomized pts, total 69 events occurred. Median PFS was 16.3 months for AfaBev arm and 16.1 months for Afa arm, with a hazard ratio (HR) of 0.865 (95%CI, 0.539 – 1.388; loglank p = 0.5476). In subgroup analysis, pts < 70 years old (HR 0.347) and pts with brain metastasis (HR 0.353) showed better trend of PFS in AfaBev arm. On the other hand, pts ≥ 70 years old (HR 1.738) and pts without brain metastasis (HR 1.196) did not show better trend in AfaBev arm. In terms of OS, result was immature because number of events was still small. Objective response rate was 77.6% in AfaBev arm and 72.0% in Afa arm. Severe adverse events were observed in 11 pts for each arm. Grade 3 or more diarrhea, hypertension, rash acneiform, paronychia and stomatitis were frequently observed in AfaBev arm. Pneumonitis was not observed for AfaBev arm and observed in 3 (6.0%) for Afa arm, and grade 3 in one patient. **Conclusions:** This study failed to show the efficacy of AfaBev arm for improving PFS in untreated pts with EGFR mutated non-squamous NSCLC. In pts < 70 years old, Afa plus Bev might be promising. Clinical trial information: jRCTs061180006. Research Sponsor: Boehringer Ingelheim.

9113 **Poster Session**

Acquired EGFR-resistant mutations in non–small cell lung cancer (NSCLC). *First Author: Luis E. Raez, Thoracic Oncology Program, Memorial Cancer Institute/Florida Atlantic University, Miami, FL*

Background: EGFR mutations are present in more than 10% of patients (pts) with NSCLC in the US. While EGFR with tyrosine kinase inhibitors (TKIs) are effective, acquired resistance is expected. Known mechanisms include acquired EGFR mutations (e.g. 718V, c797x, 724s, 721s or T790M); copy number amplifications in MET, ERBB2, and PIK3CA; gene fusion events; and histological transformation. We herein present the prevalence of resistance mutations in the largest reported cohort of EGFR mutant NSCLC. **Methods:** Non-small cell lung cancer (NSCLC) tumor samples were submitted to Caris Life Sciences (Phoenix, AZ) for NextGen Sequencing (NextSeq, 592 Genes) and whole exome sequencing (NovaSeq, WES). PD-L1 expression was tested by IHC using 22c3 (Dako) and TPS scores were reported (cutoff >1). TMB was measured by totaling somatic mutations (TMB-high cut-off > 10 mutations per MB), genomic loss of heterozygosity (gLOH) was determined by WES. Patient treatment information was obtained from insurance claims data. **Results:** A total of 27,848 NSCLC tumors were evaluated and 3,223 (12%) had a EGFR sensitizing mutations. We found 60 tumors with common missense resistance mutations: 790 (n = 30, 0.9%), 797 (n = 38, 1.2 %), 718 (n = 11, 0.3%), 724 (n = 7, 0.2%) and 721 (n = 4, 0.1). Table 1 describes the frequencies, PD-L1 expression and the most common co-mutations. TMB-H (> = 10) was found in 12.5% of the tumors and dMMR/MSI-H in 1.8%. The most prevalent co-alterations were TP53 54%), gLOH (28%), CTNNB1 (19%), NFKB1A (13%), APC (10%), PIK3CA (11%), SMAD4 (9%) and other 15 co-mutations in less than 7% were seen. In the 30 T790M mutants, in addition to TP53 mutations, other prevalent co-mutations were PIK3CA (14%) and CTNNB1 (17%). In 797-mutant tumors, in addition to T790M, the most prevalent co-mutations were TP53 (53%), CTNNB1 (22%), APC (16%) and PIK3CA (11%). L718 mutations co-occurred with either L858R (8/11), exon 19 (3/11) or T790M mutations (3/11). G724 mutations were found in 7 patients (0.02%) and G721 mutations in 4 patients (0.01%). **Conclusions:** Acquired resistance in EGFR mutant NSCLC is very heterogeneous and their frequency is still low most likely due to lack of enough sequencing of EGFR resistant tumors. While T790M and C797S mutations are well described, this report also notes a significant number of L718V mutations, primarily in osimertinib-treated pts with an original L858R. These data support the NGS evaluation of patients with resistant EGFR mutant lung cancers. Research Sponsor: None.

EGFR MT	N	%	T790M co-mt	PD-L1	TP53	LOH
797	38	1.2	26/38 (68%)	11/36 (30%)	20/38 (53%)	4/14 (28%)
718	11	0.3	3/11 (27%)	4/9 (44%)	7/10 (70%)	0/1 (0%)
724	7	0.2	1/7 (14%)	5/7 (71%)	3/7 (43%)	0/1 (0%)
721	4	0.1	0/4 (0%)	3/4 (75%)	2/4 (50%)	1/2 (50%)
Total	60			23/56 (41%)	32/59 (54%)	5/18 (28%)

9114 **Poster Session**

Improved survival from early combined radiotherapy: A phase II clinical study and underlying mechanisms of delaying EGFR-TKI acquired resistance in patients with advanced lung cancer. *First Author: Li Zhang, Tongji Hospital Tongji Medical College Huazhong University of Science and Technology, Wuhan, China*

Background: Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) have a significant therapeutic effect in the treatment of advanced non-small-cell lung cancer (NSCLC). However, patients treated with EGFR-TKIs had a median progression-free survival (PFS) of only 8 to 18 months. The occurrence of acquired resistance greatly limits the survival benefit of TKI for NSCLC patients. Extensive efforts have been paid to find a well-tolerated drug or treatment that works before acquired resistance to EGFR-TKI with low toxicity. Focusing on clinical trials of targeted combination radiotherapy, we observed some encouraging results. **Methods:** Stage IV NSCLC patients with EGFR sensitive mutation (19DEL or 21L858R) have received first-line EGFR TKIs treatment and achieved stable disease or partial response have been enrolled in this prospective, multicenter, randomized controlled, phaseIIstudy. Recruited from 4 hospitals in China, patients were divided into two groups: Stereotactic Body Radiation Therapy (SBRT) combined with TKIs group as the experimental and TKIs treatment group as an active comparator. The primary endpoint is PFS, and the secondary endpoint aims to overall survival (OS) and safety. To further confirmed these clinical observations in patients, xenograft experiments in nude mice were conducted. To examine the specific mechanism, transcriptome sequencing analysis was performed. **Results:** Between Mar 2015 and Mar 2018, A total of 61 patients who met the inclusion criteria were randomized to the TKI group and SBRT combined group. The median PFS of the TKI group and SBRT combined group were 9.0 vs 17.6 months (p = 0.016). Meanwhile, the median OS were 23.2 vs 33.6 months (p = 0.026). The total number of patients with T790m was 30(49.1%), and the incidence of T790M did not differ between the two groups. Toxicity data and subgroup analyses including different radiation sites will be presented at the conference. As for the xenograft experiments, data on tumor regression and time of drug resistance of early radiotherapy group was clearly superior to others. Transcriptome sequencing analysis found expression of c-Fos was the key point that led to the phenomena. **Conclusions:** The addition of SBRT significantly delayed the onset of EGFR TKIs acquired resistance and prolonged the PFS and OS of patients. Radiotherapy for the primary site alone might be superior to metastatic sites. Treatment-related adverse events were generally safe and controllable. The oncogenic role of c-Fos in the effect of radiotherapy on gefitinib resistance and promoting the proliferation of NSCLC cells is confirmed. Clinical trial information: NCT03595644. Research Sponsor: National Science Foundation of China (No. 82172825).

9115 **Poster Session**

Matching-adjusted indirect comparison (MAIC) of mobocertinib versus amivantamab in patients with non–small cell lung cancer (NSCLC) with *EGFR* exon 20 insertions (ex20ins). *First Author: Sai-Hong Ignatius Ou, Chao Family Comprehensive Cancer Center, University of California Irvine, Orange, CA*

Background: Mobocertinib (mobo) and amivantamab (ami) are FDA-approved treatments for patients (pts) with locally advanced or metastatic NSCLC with *EGFR* ex20ins whose disease progressed on or after platinum-based chemotherapy. An unanchored MAIC was used to compare confirmed overall response rate (cORR), duration of response (DoR), progression-free survival (PFS) and overall survival (OS) between mobo and ami. **Methods:** Clinical outcomes were compared in platinum-pretreated pts with *EGFR* ex20ins+ NSCLC treated with mobo 160 mg QD in a phase I/II single-arm study (NCT02716116, cut-off 1 Nov 2020, n=114) or with ami 1,050 mg (1,400 mg, ≥80 kg) in a phase I single-arm study (NCT02609776, cut-off 8 June 2020, n=81). Differences in baseline characteristics reported in both studies, including age, race, sex, smoking status, Eastern Cooperative Oncology Group, histology, sites of metastasis (brain, bone and liver), time from advanced diagnosis, number of prior lines of therapy, prior immunooncology therapy, prior EGFR tyrosine kinase inhibitor treatment and prior *EGFR* ex20ins targeted therapy, were adjusted with MAIC. **Results:** After MAIC weighting all reported baseline characteristics were balanced between mobo and ami. OS and cORR per investigator assessment (INV) were similar between mobo and ami (Table). cORR per independent review committee (IRC) was numerically higher for ami (odds ratio [OR]=0.64, p value=0.230). For PFS per IRC, the adjusted hazard ratio (HR) was numerically favorable for mobo (HR=0.82, p value=0.417). Among the responders, DoR was longer for mobo (DoR per INV: HR=0.44, p value=0.049; DoR per IRC: HR=0.56, p value=0.149). **Conclusions:** Mobo and ami appear to have overall similar efficacy. As each has a different mechanism of action and route of administration, they provide multiple options in the treatment of *EGFR* ex20ins+ NSCLC. Clinical trial information: NCT02716116. Research Sponsor: Takeda Development Center Americas, Inc.

Efficacy of Mobo vs. Ami (95% confidence interval).

Outcome	Unweighted mobo (n=114)	Weighted mobo (ESS=61)	Ami [1] (n=81)	Unweighted analysis[a]	Weighted analysis[a]
OS: median (mos)	24.0 (14.6, 28.8)	24.8 (14.6, NE)	22.8 (14.6, NE)	HR: 1.12 (0.71, 1.77)	HR: 0.95 (0.55, 1.67)
PFS (IRC): median (mos)	7.3 (5.5, 9.2)	7.4 (5.5, 14.6)	8.3 (6.5, 10.9)	HR: 1.00 (0.69, 1.44)	HR: 0.82 (0.52, 1.32)
DoR (IRC): median (mos)	17.5 (7.4, 20.3)	17.5 (8.3, 20.3)	11.1 (6.9, NE)	HR: 0.66 (0.33, 1.32)	HR: 0.56 (0.25, 1.23)
DoR (INV): median (mos)	11.2 (5.6, NE)	14.2 (7.0, NE)	11.1 (6.5, 13.1) [a]	HR: 0.71 (0.38, 1.30)	HR: 0.44 (0.19, 1.00)
cORR (IRC), %	28 (20, 37)	30 (19, 43)	40 (29, 51)	OR: 0.60 (0.32, 1.10)	OR: 0.64 (0.31, 1.33)
cORR (INV), %	35 (27, 45)	36 (24, 49)	36 (25, 47)	OR: 0.97 (0.53, 1.77)	OR: 0.99 (0.48, 2.02)

Abbreviations: ESS=effective sample size; mos=months; NE: not estimable. [1] Park K, et al. *JCO* 2021;39(30):3391-3402. [a] estimated using reconstructed patient-level data from swimmer and survival plots for ami.

9116 **Poster Session**

Updated study results of pelcitoclax (APG-1252) in combination with osimertinib in patients (pts) with *EGFR*-mutant non–small cell lung cancer (NSCLC). *First Author: Li Zhang, State Key Laboratory of Oncology in South China Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Investigational agent pelcitoclax is a dual BCL-2/BCL-xL inhibitor, which enhanced antitumor effects of osimertinib in preclinical models. A report presented at International Association for the Study of Lung Cancer 2021 World Conference on Lung Cancer demonstrated that the combination of pelcitoclax and osimertinib at the recommended phase 2 dose (RP2D) was safe, and preliminary efficacy was observed in some patients whose disease failed prior osimertinib or other third-generation EGFR-TKI treatments. Here, we further provide safety and efficacy results of this combination therapy. **Methods:** After RP2D was determined to be pelcitoclax 160 mg per week plus osimertinib 80 mg QD, pts were enrolled into 3 expansion cohorts of 20 pts each: Cohort 1 (EC-1) included those with disease resistant to third-generation EGFR-TKIs; Cohort 2 (EC-2) included those with osimertinib-naïve, *EGFR*-sensitive or *T790M*-positive mutations; and Cohort 3 (EC-3) included those with the *EGFR* exon 20 insertion mutation. **Results:** At the data cutoff date of January 6, 2022, 61 pts (median age, 56 years [69% female]) had been treated with pelcitoclax plus osimertinib. Among them, 13 were in dose escalation cohorts, 20 in EC-1, 20 in EC-2, and 8 in EC-3. Sixteen pts in EC-2 were EGFR-TKI naïve, and 4 were T790M positive with prior TKI treatment. All pts in EC-2 experienced treatment-related adverse events (TRAEs) but only 4 (20%) had grade ≥ 3. Common TRAEs included increased aspartate aminotransferase (90%) and alanine aminotransferase (85%) levels, reduced platelets (40%), diarrhea (40%), and increased lipase (35%). Among 20 evaluable pts, 17 PRs (85%) were observed and 16 (80%) confirmed. The median (range) time to response was 1.4 (1.2-7.0) months, and the median duration of response (DOR) was not reached. The DOR rate at 9 months after first response was 71.4% (95% CI 25.8-92.0). Seven pts had brain metastases at baseline in EC-2; 2 CRs and 3 PRs were observed intracranially. **Conclusions:** Osimertinib in combination with targeted therapies has been of clinical interest to improve the outcomes of patients with *EGFR*-mutant NSCLC. Pelcitoclax plus osimertinib was well tolerated and showed comparable efficacy in TKI-naïve pts. Further randomized control trials are warranted to elucidate the role of pelcitoclax when combined with osimertinib. Clinical trial information: NCT04001777. Research Sponsor: Ascentage Pharma Group Corp. Ltd (Hong Kong).

9117 **Poster Session**

Afatinib (AFA) plus bevacizumab (BEV) combination after osimertinib (OSI) resistance in advanced EGFR-mutant NSCLC: A phase II study (ABCD-study). *First Author: Akito Hata, Department of Thoracic Oncology, Kobe Minimally Invasive Cancer Center, Kobe, Japan*

Background: After OSI failure, various resistant mechanisms such as C797S and uncommon EGFR mutations, or MET amplification have been reported. AFA is an irreversible EGFR-TKI with a potency as pan-HER inhibitor, including high sensitivity to uncommon EGFR mutations. Many clinical studies have also shown a synergy of EGFR-TKIs and VEGF inhibitors. **Methods:** ECOG PS 0-1 patients (pt) with EGFR-mutant NSCLC were enrolled after OSI resistance. AFA was prescribed at 30-40 mg QD, and BEV was administered at 15 mg/kg tri-weekly until progression. Plasma/histologic rebiopsied samples taken after OSI failure but before enrollment were analyzed to examine resistant mechanisms including gene alterations/copy-number gain using cancer personalized profiling by deep sequencing. **Results:** Between January 2018 and October 2020, 28 pts were enrolled. Mutation subtypes were: 9 (32%) Del-19; 5 (18%) Del-19+T790M; 5 (18%) L858R; 7 (25%) L858R+T790M; 1 (4%) Del-19+L858R+T790M; and 1 (4%) G719S. Median line of prior OSI was 2 (range, 1-9). CR/PR was obtained by prior OSI in 24 (86%) pts. Regarding AFA+BEV efficacy, one (4%) CR, 4 (14%) PR, and 17 (61%) SD were confirmed, resulting in response rate of 17.9% and disease control rate of 78.6%. Median DoR was 9.0 (range, 4.2-22.3) months. Median PFS and OS were 2.7 (95% CI, 2.0-4.6) months and not reached, respectively. Twenty-eight (100%) plasma and/or 21 (75%) histologic rebiopsies identified: 17 (61%) TP53; 15 (54%) T790M; 9 (32%) uncommon EGFR; 9 (32%) MET; 6 (21%) C797S; 3 (11%) BRAF; 2 (7%) HER2; 2 (7%) KRAS; and 2 (7%) PI3K mutations; or 14 (50%) EGFR; 6 (21%) MET; and 2 (7%) HER2 amplifications. One (4%) small cell transformation was found. Among 6 C797S pts, 1 CR, 4 SD, and 1 PD were confirmed. Three (33%) of 9 uncommon EGFR and 1 (50%) of 2 HER2 mutation positive pts achieved radiographic response. All 15 T790M-positive pts showed no response, but 5 (38%) of 13 T790M-negative pts responded to AFA+BEV. None (0%) of six pts with EGFR downstream signaling mutations such as BRAF, KRAS, or PI3K responded. Five (50%) of 10 pts without T790M/BRAF/KRAS/PIK3 mutations exhibited confirmed response. FAT1 mutation was found in two (40%) of 5 responded pts. Dose reduction/interruption of AFA was performed in 15 (54%) pts. Median number of BEV administrations was 4 (range, 1-32). There were neither TRD nor ILD. Adverse events ≥grade 3: hypertension (29%); proteinuria (7%); diarrhea (7%); and rash (4%) were observed. One (4%) grade 4 duodenal perforation was reported. **Conclusions:** AFA+BEV after OSI resistance demonstrated moderate efficacy and favorable safety. A small portion of C797S pts exhibited the sensitivity. Higher potency was suggested in T790M/BRAF/KRAS/PIK3 mutation-negative and uncommon EGFR/HER2 mutation-positive pts. Selected population could obtain clinical benefit from AFA+BEV, based on rebiopsy results after OSI resistance. Clinical trial information: UMIN000030545. Research Sponsor: Boehringer Ingelheim.

9118 **Poster Session**

Efficacy and safety of capmatinib plus pembrolizumab in treatment (tx)-naïve patients with advanced non–small cell lung cancer (NSCLC) with high tumor PD-L1 expression: Results of a randomized, open-label, multicenter, phase 2 study. *First Author: Tony S. K. Mok, Chinese University of Hong Kong, Hong Kong, China*

Background: Capmatinib is a selective MET inhibitor approved for patients (pts) with metastatic NSCLC harboring *MET* exon 14 skipping mutation. Pembrolizumab (pembro) is a programmed death protein-1 (PD-1) inhibitor approved as monotherapy for pts with advanced NSCLC expressing PD-ligand 1 (PD-L1). Preclinical studies have shown that capmatinib enhances T cell mediated antitumor response in mice treated with PD-1 inhibitors. Combining capmatinib with pembro may be beneficial in pts with advanced NSCLC expressing high tumor PD-L1. **Methods:** Herein we evaluated the efficacy and safety of capmatinib plus pembro (combo) versus pembro alone in tx-naïve pts with advanced MET-unselected NSCLC expressing PD-L1 with tumor proportion score (TPS) ≥50%, and no *ALK* or *EGFR* tumor aberrations. Pts received pembro 200 mg IV q3w in the pembro alone arm or with capmatinib 400 mg orally BID in the combo arm. The primary endpoint was investigator-assessed progression-free survival (PFS) using RECIST v1.1. Secondary endpoints included overall response rate (ORR), disease control rate (DCR), pharmacokinetics and safety. **Results:** As of the data cut off (DCO) of 28 Feb 2021, 76 pts were randomized 2:1 to the combo arm (n = 51) or pembro alone arm (n = 25). Baseline demographics and disease status were mostly comparable across study arms. At this interim analysis, PFS data were not mature. Median PFS (95% CI) was 6.3 (3.2, not evaluable [NE]) months in the combo arm and 4.3 (2.3, NE) months in the pembro alone arm. The ORR (95% CI) was 15.7% (7.0%, 28.6%) and 28.0% (12.1%, 49.4%) in the combo and pembro alone arms, respectively. The DCR (95% CI) was comparable across study arms; combo: 56.9% (42.2%, 70.7%) and pembro alone: 56.0% (34.9%, 75.6%). In the combo arm, capmatinib exposure (C_{max}: 3580 ng/mL [n = 7] and AUC_{tau}: 19700 hr*ng/mL [n = 2]) was consistent with data from previous studies. Tx-related grade (GR) ≥3 adverse events (AEs) were more common in the combo (37.3%) vs pembro alone arm (16%). Tx-related AEs occurring in ≥10% of pts are shown in the Table. Tx discontinuation and dose adjustment/interruptions were more common in the combo (27.5% and 52.9%) vs pembro alone arm (16% and 16%). Capmatinib was stopped prematurely in the combo arm, and at DCO, 32 (62.7%) pts in the combo arm and 18 (72%) pts in the pembro alone arm were receiving pembro monotherapy. **Conclusions:** Combination tx with capmatinib and pembro was not well tolerated and did not improve antitumor activity in tx-naïve pts with advanced NSCLC with PD-L1 TPS ≥50%. Clinical trial information: NCT04139317. Research Sponsor: Novartis.

	Combo N = 51		Pembro alone N = 26	
	Any GR	GR ≥3	Any GR	GR ≥3
Elevated alanine aminotransferase	10 (19.6)	5 (9.8)	2 (8)	1 (4)
Elevated aspartate aminotransferase	10 (19.6)	4 (7.8)	2 (8)	1 (4)
Pruritus	5 (9.8)	0	7 (28)	0
Peripheral edema	11 (21.6)	0	0	0
Vomiting	10 (19.6)	1 (2)	1 (4)	0
Nausea	10 (19.6)	0	0	0

All data are n (%).

9119 **Poster Session**

Analysis of *MET* exon 14 skipping mutations in non–small cell lung cancer (NSCLC) by histology and specific mutation. *First Author: Jennifer Aline Marks, Emory University School of Medicine, Atlanta, GA*

Background: MET exon 14 skipping mutations (METex14) join a growing list of viable therapeutic targets in advanced NSCLC. Several unique features distinguish METex14 from other established targets. METex14 has been characterized as a tumor-agnostic genomic alteration, though most frequently reported in lung adenocarcinoma. However, METex14 represents a family of mutations (mt), not a single alteration, and there is notable heterogeneity in histology. The degree and significance of heterogeneity within METex14 have not been well characterized. **Methods:** NSCLC tissue samples were analyzed with DNA-based next-generation sequencing (NGS; 592 genes, NextSeq) or whole-exome sequencing (NovaSeq), RNA-based whole transcriptome sequencing (WTS, NovaSeq), and immunohistochemistry (IHC) at Caris Life Sciences (Phoenix, AZ). PD-L1 expression utilized the 22C3 clone (Dako); TMB-high was defined as ≥ 10 mt/Mb. Wilcoxon or Fisher's exact were used to determine statistical significance (p without and q with multi comparison correction). Immune cell fraction (QuanTiseq) and pathway analysis (ssGSEA) were informed by WTS analysis. **Results:** A total of 440 METex14 cases were identified: 49 (11.1%) with squamous histology, 381 (86.6%) with non-squamous histology, and 10 (0.2%) with adenosquamous histology. A total of 147 distinct METex14 mutations were detected. The most common METex14 mutations were D1028H (8.4%), D1028N (7.0%), c.3082+2T > C (5.7%), D1028Y (5.2%), and c.3082+1G > A (4.5%). Co-mutations in TP53 were common (43.9%) but varied by specific METex14 mutation; TP53 co-mutations were observed in 53.9% of c.3082+3A > T but only 21.1% of c.3082+1G > T. Among all METex14 cases, 8.6% were TMB-high, but this varied by specific mutation with a median TMB of 2 mt/Mb in MET c.3082+2T > A and a median of 7 mt/Mb in MET c.3082+1G > C ($q < 0.05$). PD-L1 expression ≥ 1% was present in 82.2% of METex14 samples but also varied by specific METex14 mutation with a median PD-L1 tumor proportion score (TPS) of 97.5% in MET c.3082+1G > C and a median TPS of 0% in MET c.3082+3A > G ($q < 0.05$). Co-mutations varied by histology: in squamous METex14, 90.4% had TP53 mt ($p < 0.001$), 17.9% had KMT2D mt ($p < 0.05$), and 10.7% had PIK3CA mt ($p < 0.05$), while in non-squamous METex14, 60.7% had TP53 mt, 2.7% had KMT2D mt, and 4.3% had PIK3CA mt. Survival was numerically shorter in squamous METex14 NSCLC compared to non-squamous (HR 1.22, p = 0.47, mOS 336 vs.1106 days). **Conclusions:** There is significant heterogeneity within METex14 NSCLC with differences in co-mutations, TMB, and PD-L1 expression noted among different METex14 mutations. While METex14 is detected in both squamous and non-squamous NSCLC, there are differences in enrichment of oncogenic pathways. The clinical impact of these differences warrants further investigation. Research Sponsor: None.

9120 **Poster Session**

Tepotinib in Asian patients with advanced NSCLC with *MET* exon 14 (*MET*ex14) skipping. *First Author: Terufumi Kato, Department of Thoracic Oncology, Kanagawa Cancer Center, Yokohama, Japan*

Background: Tepotinib is a highly selective, potent MET inhibitor approved in several Asian countries for the treatment of advanced *MET*ex14 skipping NSCLC. In VISION (n=275; data cut-off: Feb 1, 2021), tepotinib had an objective response rate (ORR) of 49.1% (95% CI: 43.0, 55.2) by independent review (IRC), with a median (m) DOR of 13.8 months (9.9, 19.4) across treatment lines. Here, we report outcomes in Asian pts. **Methods:** Pts with advanced *METex*14 skipping NSCLC, detected by liquid (L+) or tissue (T+) biopsy, received tepotinib 500 mg (450 mg active moiety) QD. Primary endpoint was objective response by IRC. Efficacy was assessed in 79 Asian pts with ≥3 months' follow-up, and safety was assessed in 88 Asian pts who received tepotinib by data cut-off (Feb 1, 2021). Only pts enrolled in Asia were assessed for HRQoL. **Results:** In 79 Asian pts assessed for efficacy (38% female, 42% smoking history, 34% treatment-naïve [1L] and 82% adenocarcinoma), ORR was 54.4% (42.8, 65.7), mDOR was 18.5 months (8.3, ne), mPFS was 12.1 months (6.9, ne) and mOS was 20.4 months (19.1, ne). ORR was 66.7% (46.0, 83.5) in 1L pts (n=27), and 48.1% (34.0, 62.4) in previously treated pts (n=52). Meaningful activity was observed irrespective of *MET*ex14 skipping detection method (Table). In pts analyzed for HRQoL (n=73), mean change from baseline for EORTC QLQ-C30 GHS (3.94), EQ-5D-5L VAS (0.83), and EORTC QLQ-LC13 for cough (-6.59), dyspnea (-1.26), and chest pain (-6.14) symptom scores, demonstrated stability in QoL. In 88 Asian pts analyzed for safety, the most common adverse events (AEs) were peripheral edema, increased blood creatinine, and diarrhea. 29.5% of pts had Grade ≥3 treatment-related (TR) AEs. TRAEs led to dose reductions in 29.5%, temporary interruption in 43.2%, and permanent discontinuation in 14.8% of pts. **Conclusions:** In VISION, tepotinib showed robust and durable clinical activity in Asian pts with *METex*14 skipping NSCLC. TRAEs were manageable, with few leading to treatment discontinuation. Currently, VISION has enrolled 106 Asian pts with *METex*14 skipping NSCLC; analysis in this population is ongoing. Clinical trial information: NCT02864992. Research Sponsor: the healthcare business of Merck KGaA, Darmstadt, Germany.

	Overall			Treatment-naïve			Previously treated		
Efficacy in Asian pts	L+ (n=37)	T+ (n=57)	Combined (n=79)	L+ (n=10)	T+ (n=20)	Combined (n=27)	L+ (n=27)	T+ (n=37)	Combined (n=52)
ORR, % (95% CI)	51.4 (34.4, 68.1)	57.9 (44.1, 70.9)	54.4 (42.8, 65.7)	70.0 (34.8, 93.3)	70.0 (45.7, 88.1)	66.7 (46.0, 83.5)	44.4 (25.5, 64.7)	51.4 (34.4, 68.1)	48.1 (34.0, 62.4)
DCR, % (95% CI)	70.3 (53.0, 84.1)	82.5 (70.1, 91.3)	77.2 (66.4, 85.9)	70.0 (34.8, 93.3)	85.0 (62.1, 96.8)	77.8 (57.7, 91.4)	70.4 (49.8, 86.2)	81.1 (64.8, 92.0)	76.9 (63.2, 87.5)
12-month rates, % (95% CI)									
DOR	41 (12, 69)	54 (26, 75)	53 (29, 72)	63 (14, 89)	83 (27, 97)	79 (38, 94)	25 (1, 65)	24 (1, 62)	29 (5, 60)
PFS	41 (22, 59)	53 (35, 68)	51 (37, 64)	53 (17, 79)	74 (43, 90)	66 (40, 83)	38 (16, 59)	42 (20, 63)	44 (26, 61)
OS	71 (53, 84)	85 (71, 93)	80 (69, 88)	80 (41, 95)	89 (64, 97)	84 (63, 94)	68 (46, 83)	83 (64, 93)	78 (63, 88)

9121 **Poster Session**

Clinical response to tepotinib according to circulating tumor (ct) DNA biomarkers in patients with advanced NSCLC with high-level *MET* amplification (*MET*amp) detected by liquid biopsy (LBx). *First Author: Xiuning Le, Department of Thoracic Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Tepotinib, a potent, highly selective, oral, MET inhibitor, showed meaningful activity in patients (pts) with NSCLC with high-level *MET*amp by LBx in VISION. Exploratory biomarker analyses are presented herein. **Methods:** Pts had 0–2 prior therapy lines, high-level *MET*amp by LBx (Guardant360; *MET* copy number ≥2.5), and no *MET* exon 14 skipping or *EGFR*/*ALK* alterations. Pts received tepotinib 500 mg once daily (450 mg active moiety). Primary endpoint was objective response by independent review; data cut-off: Aug 20, 2021. Exploratory biomarker analysis included LBx at baseline (BL), on treatment, and end of treatment (EOT). Early molecular response (eMR) was defined as undetectable *MET*amp 6–8 weeks on treatment. **Results:** 24 pts were enrolled (median age: 63.4 years [yrs]; smokers: 88%; ECOG PS 1: 88%; adenocarcinoma: 67%). Treatment duration was ≥1 yr in five pts and ≥2 yrs in two pts (both ongoing). Overall, objective response rate (ORR) was 41.7% (95% CI: 22.1, 63.4). Treatment-naïve pts (n=7) had an ORR of 71.4% (29.0, 96.3), median (m) DOR was 14.3 months (2.8, not estimable [ne]), and mPFS was 15.6 months (1.4, ne). BL biomarker analyses according to clinical benefit (CR/PR/SD [n=11] vs PD/NE [n=13]) showed association with better outcomes in pts with focal *MET*amp, or without *MYC*amp or *RB1* mutation (Table). *MYC*amp/*RB1* mutation was detected in 4/7 pts with neuroendocrine/not otherwise specified histology; *MYC*amp in 2/3 pts with neuroendocrine histology. Low BL ctDNA mutant allele frequency (MAF) was associated with better outcomes. 14 pts had eMRs (ORR 71.4%); persistent *MET*amp (n=4) was associated with lack of clinical response. 2/9 pts with EOT biomarker profiles had emerging resistance mechanisms (MET kinase domain mutations Y1230 and D1228); both had *MET*amp re-emergence. Treatment-related adverse events included edema (composite term; any grade: 46%; Grade 3: 13%) and constipation (any grade: 17%; Grade ≥3: 0%). **Conclusions:** Tepotinib showed meaningful activity, especially in first line, in the first trial of a MET inhibitor in *EGFR* WT NSCLC with high-level *MET*amp to enroll based on a convenient LBx assay. BL biomarker analyses indicated focal *MET*amp, *MYC/RB1* WT, and low ctDNA MAF were associated with improved outcomes. Serial LBx could monitor molecular response and evaluate resistance. Clinical trial information: NCT02864992. Research Sponsor: the healthcare business of Merck KGaA, Darmstadt, Germany.

Biomarker analyses		ORR, n (%) [95% CI]	mDOR, months (95% CI)	mPFS, months (95% CI)
Overall		10 (41.7) [22.1, 63.4]	14.3 (2.8, ne)	4.2 (1.4, 15.6)
BL *MYC*	WT (n=18)	10 (55.6) [30.8, 78.5]	14.3 (2.8, ne)	13.6 (1.4, ne)
	Amp (n=6)	0 [0, 45.9]	ne (ne, ne)	1.4 (0.8, ne)
BL *RB1*	WT (n=19)	10 (52.6) [28.9, 75.6]	14.3 (2.8, ne)	4.5 (1.4, ne)
	Mutation (n=5)	0 [0, 52.2]	ne (ne, ne)	1.4 (1.4, ne)
eMR	Responder (n=14)	10 (71.4) [41.9, 91.6]	14.3 (2.8, ne)	13.6 (4.1, ne)
	Non-responder (n=4)	0 [0, 60.2]	ne (ne, ne)	1.8 (1.4, ne)

9122 **Poster Session**

Characterization of *MET* exon 14 skipping alterations (*MET*ex14) in non–small cell lung cancer (NSCLC) using whole transcriptome sequencing (WTS). *First Author: So Yeon Kim, Montefiore Medical Center, Bronx, NY*

Background: Multiple DNA alterations in exon 14 splice sites have been identified in NSCLC and result in skipping of the juxtamembrane domain Cbl-E3 ubiquitin ligase binding region, leading to increased MET stability and oncogenesis. The effects of these alterations on transcriptome-level have not been fully characterized. We present the largest cohort study of *MET*ex14 using WTS and identify key cellular pathways associated with invasion and metastases in *MET*ex14. **Methods:** 17,666 NSCLC tumor samples underwent genomic profiling at Caris Life Sciences. Analyses included next generation sequencing of DNA (592 Gene Panel, NextSeq, whole exome sequencing, NovaSeq) and RNA (NovaSeq, WTS). *MET*ex14 was captured via WTS. ssGSEA analysis was used to evaluate pathway enrichment. Wilcoxon, Fisher's exact were used for statistical significance (p without and q values with multiple comparison correction). **Results:** 440 patients (2.5%) with *MET*ex14 were identified. *MET*ex14 patients were of older age, female gender, and enriched in sarcomatoid histology (Table 1). The most common alterations were point mutations (51.5%) and deletions (17.3%) at donor splice sites. Splice site alterations except point mutations at splice acceptor site translated to increased mRNA expression compared to wild-type *MET* (WT). *MET* amplification translated to higher mRNA expression compared to *MET*ex14 and WT with synergistic expression when co-altered with *MET*ex14 (q<0.05). The most common co-alterations were amplifications of *MDM2* (18.5% vs. 1.8% WT), *HMGA2* (13.7% vs 0.9% WT), and *CDK4* (10.4% vs 1.4% WT) (q < 0.05). *MET*ex14 were mutually exclusive to mutations in *KRAS* and *EGFR*. High PD-L1 (22c3) > 50% (53% vs. 27.6% WT, q<0.001) and lower TMB (4 mut/Mb vs. 7 mut/Mb WT, p<0.001) were observed with *MET*ex14 and pathways associated with skipping variants included IFNγ signaling, angiogenesis, and apical junction pathways on univariate analysis (q<0.05). **Conclusions:** We present the largest WTS analysis of *MET*ex14. Splicing alterations and *MET* co-amplification translated to higher and synergistic MET expression at transcriptome level, respectively. Association with upregulated angiogenic and apical junction pathways support preclinical observation of vascular and cytoskeletal remodeling as potential mechanisms of invasion and metastases in *MET* ex14 NSCLC. Research Sponsor: None.

Summary of clinico-genomic features.

	METex14 (N)	WT (N)	q-value	Alteration	%	mRNA expression relative to WT
Male	192	8673	<0.05			
Female	248	8553		Donor splice site point mutation	51.5	3.5
Age, median	77	69	<0.0001	Donor splice site deletion	17.3	4
Adenocarcinoma	273	10203	<0.001	Polypyrimidine site deletion	16.5	4
Squamous	49	3878		Acceptor splice site deletion	7.5	4
Adenosquamous	10	147		Acceptor splice site point mutation	2.1	1
Sarcomatoid	11	104		METex14 + MET Amp	0.07	24.4
Large cell	1	45		MET Amp	0.89	14.1
others	96	2831		METex14	2.45	3.3

9123 **Poster Session**

Real-world (rw) analysis of quantitative *MET* copy number (CN) as a biomarker in NSCLC. *First Author: David Chun Cheong Tsui, University of Colorado Cancer Center, Aurora, CO*

Background: *MET* amplification (amp) can be a de novo driver or mechanism of resistance to targeted therapy. We explored the genomic landscape of *MET* amp NSCLC, including co-driver alterations and amplicon size, and its association with outcomes to MET tyrosine kinase inhibitors (TKIs) using rw data. **Methods:** Comprehensive genomic profiling (CGP) results from 64,521 tissue and 5,177 liquid NSCLC samples were queried for *MET* amp (focal amplicons ≥4 copies above specimen ploidy). Sub analysis comparing focal (≤20Mbp) and non-focal (> 20Mbp) amp was performed. Using the nationwide (~280 US cancer clinics) de-identified EHR-derived Flatiron Health-Foundation Medicine aNSCLC clinicogenomic database (CGDB) linked to tissue CGP (8/2014-9/2021), we assessed co-driver presence (*EGFR*, *ALK*, *RET*, *ROS1*, *NTRK*, *BRAF*, *KRAS*) prior to therapy exposure and outcomes to MET TKIs. **Results:** *MET* amp was detected in 2,102 (3.3%) NSCLC tissue samples (median CN of 11, range 6-168). Evaluating full gene focal amplicons as well as non-focal *MET* amps (n = 398, median CN 7), smaller amplicon size significantly correlated with higher CN (p < 0.001). In 5,177 liquid samples, *MET* amp was detected in 40 (0.77%) cases; frequency increased to 3.2% (33/1,033) in those with a tumor fraction above 10%. In the CGDB, 261 (3.2%) pts had NSCLC with *MET* amp (median CN 11). Among 241 pts with *MET* amp detected prior to receipt of any targeted therapy, *MET* amp co-occurred with another driver in 32 (13%) cases (81% *KRAS*, 16% *EGFR*, 3.1% *BRAF*) and with a *MET* exon 14 skipping alteration (*MET*ex14) in 25 (10%). *MET* CN negatively correlated with the presence of a co-driver (median 11 with *MET* amp alone vs 9 with a non-*MET*ex14 co-driver, p < 0.001); however, *MET* CN was similar in *MET* amp cases with and without *MET*ex14 (median 11 for both, p = 0.60). Co-occurring non-*MET*ex14 drivers were detected in 26% of *MET* amp cases with CN < 8 and 19% with CN 8-9, but in only 9.1% with CN 10-20 and 2.6% with CN > 20. Tumor mutational burden was not significantly correlated with *MET* CN. In 14 cases with an *EGFR* or *ALK* co-driver and *MET* amp detected post-treatment with an EGFR or ALK TKI, median *MET* CN was 13. Of 241 targeted therapy naïve *MET* amp pts, 39 received a MET TKI after CGP (30 crizotinib, 9 capmatinib) and 26 had rw response assessment available. Excluding 5 pts with co-*MET*ex14, 12/21 (57%) pts had a partial response and median rwPFS was 3.6 months. This rw cohort analysis was underpowered to assess the relationship between CN and outcome. **Conclusions:** *MET* amp was detected in 3.3% of NSCLC tissue samples and 3.2% of high tumor fraction blood samples. In TKI-naïve pts, *MET* CN negatively correlated with the presence of a concurrent NSCLC driver. *MET* amp was associated with response to MET TKIs. Further studies evaluating *MET* CN, amplicon size and presence of other potential drivers in both blood and tissue, as predictive biomarkers for MET TKIs and potential combination strategies for targeting *MET* amp, are warranted. Research Sponsor: Foundation Medicine.

9124 **Poster Session**

Activating MET kinase domain mutations define a novel molecular subtype of non–small cell lung cancer that is clinically targetable with the MET inhibitor elzovantinib (TPX-0022). *First Author: Federica Pecci, Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, MA*

Background: In non-small cell lung cancer (NSCLC), *MET* exon 14 skipping (METex14) mutations and *MET* amplification can be targeted with MET inhibitors. Here, we describe a novel, actionable molecular subtype of NSCLC characterized by activating MET-tyrosine kinase domain (MET-TKD) mutations in the absence of METex14 mutations. **Methods:** Clinicopathologic and genomic data were abstracted from NSCLC cases included in a multi-institutional cohort of tumors that underwent genomic profiling in the GENIE v10, China PanCancer, and the International Cancer Genome Consortium/ The Cancer Genome Atlas (ICGC/TCGA) datasets. External validation of the prevalence of MET-TKD mutations was performed on an independent cohort of NSCLC tissue and liquid samples from the Foundation Medicine genomic database. **Results:** Among 14,099 NSCLC samples in the multi-institutional cohort, 71 (0.5%) harbored MET-TKD mutations without concurrent METex14 mutations: 55 of these had uncertain pathogenic significance and 16 had known oncogenic potential, including MET H1094Y/R, D1228H/N/V, N1100S, H1106D, V1188I, and M1250T, in order of decreasing prevalence. In a separate cohort of 91,515 NSCLC samples from the Foundation Medicine database, MET-TKD mutations lacking concurrent METex14 mutations were identified in 799 (0.9%) samples, including H1094Y, L1195V, D1228H/N, M1250T and others. Among 60 NSCLC samples harboring MET-TKD mutations without concurrent METex14 mutations with complete genomic data in the multi-institutional cohort, 36 (60%) had concurrent driver alterations in KRAS, EGFR, ROS1, BRAF, HER2, or RET, while 24 (40%) had no concurrent oncogenic drivers. Among patients with available demographic data in the multi-institutional cohort, those with MET-TKD-mutant NSCLC (N = 70) were significantly younger than patients with METex14-mutant NSCLC (N = 353) (median age 63 [range 30-86] vs 73 [range 44-88], p < 0.0001), and there was no significant difference in sex or self-reported race. Confirmed partial responses to the MET tyrosine kinase inhibitor elzovantinib (TPX-0022) were observed in two patients with MET-TKD-mutant NSCLC and no other detectable driver mutations: a 64-year-old man with MET H1094Y-mutant NSCLC, and an 80-year-old man with MET F1200I-mutant NSCLC. **Conclusions:** Potentially actionable MET-TKD mutations lacking concurrent METex14 mutations represent a novel genomic subtype in 0.5-0.9% of NSCLC, and occur in the absence of other known drivers in a subset of cases. Research Sponsor: None.

9125 **Poster Session**

Ancestry-based differences in gene alterations in non–small cell lung cancer: Real-world data using genetic ancestry analysis. *First Author: Keita Miura, Department of Respiratory Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan*

Background: Racial differences in morbidity and mortality of non-small cell lung cancer (NSCLC) have been demonstrated and some genomic alterations (e.g. *EGFR*) in NSCLC are known to differ according to race. However, studies have been limited in sample size and hence, limited in their capacity to detect discrepancies in less frequently altered genes. Here, we investigated alteration prevalence in a large real-world NSCLC cohort, stratified by genetic ancestry. **Methods:** 75,362 NSCLC patients from the United States, were profiled with comprehensive genomic profiling (CGP) of tissue biopsy, as part of routine clinical care (Foundation Medicine Inc., FMI; Frampton GM, et al. Nat Biotechnol 2013). 296 genes targeted across all assays were examined for known/likely pathogenic alterations of all classes. Predominant genetic ancestry was inferred using a SNP-based approach (Newberg J, et al. AACR 2019), and patients were categorized into European (EUR), African (AFR), East Asian (EAS), Admixed American (AMR), and South Asian (SAS) ancestry groups. Patients were additionally stratified by histological type, age (≥40/ < 40), and sex. The prevalence of high tumor mutational burden (TMB-High), defined as ≥ 10 mutations/mb (Chalmers ZR, et al. Genome Med 2017), and microsatellite instability status (Trabucco, et al. J Mol Diagn 2019) was also calculated. **Results:** In this NSCLC cohort, ancestry was split 82.2% for EUR, 10.0% for AFR, 4.4% for EAS, 2.7% for AMR, and 0.8% for SAS. 50.4% were female (n = 37,972) and 49.6% male (n = 37,360). The most prevalent alterations in the overall cohort included *TP53* (67.5%), *KRAS* (30.6%), *CDKN2A* (29.2%), *CDKN2B* (17.2%), *STK11* (16.1%), and *EGFR* (15.3%). The prevalence of TMB-High status in the overall cohort was 34.6%. Stratified by ancestry, the prevalence of *EGFR* alterations was significantly enriched in EAS vs. other ancestry groups ($p < 0.001$). *KRAS* and *STK11* were enriched in EUR and AFR vs. other groups ($p < 0.001$). TMB-High status was significantly enriched in AFR vs. all other groups ($p < 0.001$). In EAS and SAS, TMB-High was typically reduced vs. other ancestry groups (TMB-High AFR 41.6%, AMR 20.1%, EAS 14.1%, EUR 35.5%, SAS 11.7%). A similar analysis based on sex revealed differences in prevalence of 80 gene alterations and TMB-High with sex-specific enrichments (e.g., *EGFR* 19.0% female vs. 11.5% male; *KRAS* 34.6% vs. 26.6%). With respect to age, the prevalence of 41 gene alterations and TMB-High were significantly different between samples from patients age < 40 and age ≥ 40 (e.g., *ALK* 21.1% age < 40 vs. 2.7% age ≥ 40; *KRAS* 13.0% vs. 30.8%; TMB-High 14.4% vs. 34.8%). **Conclusions:** Comprehensive analysis of this real-world dataset, which includes the largest NSCLC patient cohort, revealed ancestry-associated differences in genomic alterations in NSCLC. Age and sex were also associated with differences in genomic alteration and TMB-High prevalence. Research Sponsor: None.

9126 **Poster Session**

Clinical and economic outcomes associated with upfront comprehensive genomic profiling in newly diagnosed advanced lung cancer in the United States from 2018-2020: Evidence from the SEQUENCE study. *First Author: Gboyega Adeboyeje, Merck & Co., Kenilworth, NJ*

Background: As the number of approved molecularly-targeted therapies for the treatment of lung cancer increases, the debate continues as to whether a clinical strategy leveraging next-generation sequencing (NGS) comprehensive genomic profiling (CGP) to match patients to targeted treatments is advantageous versus a narrow/single-gene (N/S) panel testing. We examined clinical and economic outcomes of patients with advanced lung cancer (aLC) in the United States (US). **Methods:** In this retrospective study, newly diagnosed aLC patients aged 65-89 years were identified from a US Medicare Advantage plan from 2018-2020. Patients receiving genomic testing within 90 days of diagnosis and an FDA-approved pharmacotherapy cancer treatment after diagnosis were categorized by initial sequencing with NGS CGP (51+ genes) vs N/S (≤50 genes) panel testing using administrative claims based on previously validated algorithms. We assessed the proportion of patients with an inpatient or emergency department (INP/ED) visit for select outcomes (e.g., neutropenia) within 6 months of start of treatment, all-cause mortality, and PPPM (per patient per month) total healthcare costs through all available follow-up. Genomic testing costs within 90 days of cancer diagnosis were estimated using the Medicare fee schedule. Among patients with treatment within 30 days of testing, we assessed the proportion who did not switch treatment and were alive within 6 months. Descriptive analyses were conducted, and average effects were estimated using inverse probability weighted regression models. **Results:** We identified 3,532 patients who received genomic testing and pharmacotherapy cancer treatment (NGS CGP, n = 968; N/S, n = 2,564). Characteristics were similar between testing groups. The proportion of patients with INP/ED for outcomes of interest was similar following NGS CGP vs. N/S panels (15.0% vs. 17.8%; IRR [95% CI]: 0.76 [0.57 – 1.02]; p = 0.066), as were mortality (56.2% vs. 59.2%; HR: 1.05 [0.95 - 1.16]; p = 0.323) and PPPM costs (PPPM median cost difference -$575; ratio from regression 0.99, 0.94-1.04; p = 0.228). Among a subgroup of patients treated within 30 days of testing, a higher proportion receiving NGS CGP did not switch treatment and were alive after 6 months (47.6%) vs those receiving N/S panels (39.8%) (OR [95% CI]: 1.33 [1.12 - 1.59]; p = 0.001). Median genomic testing costs were $3,049 for NGS CGP vs. $218 for N/S testing. **Conclusions:** Outcomes were similar between patients receiving NGS CGP and N/S panel testing. Among patients with treatment within 30 days of testing, upfront NGS CGP was associated with fewer patients switching treatment and 6-month survival. Upfront testing with NGS CGP may represent a beneficial genomic profiling strategy as part of the initial management of patients with aLC. Research Sponsor: Merck.

9127 **Poster Session**

Associations between biomarker testing and characteristics of patients with metastatic non–small cell lung cancer (mNSCLC): An analysis of CancerLinQ Discovery (CLQD) data. *First Author: Kathryn Finch Mileham, Levine Cancer Institute, Atrium Health, Charlotte, NC*

Background: Guidelines have evolved from 2011-2019; there are now 23 approved therapies targeting various predictive biomarkers in mNSCLC. 2021 NCCN Guidelines advocate for a minimum of ALK, EGFR, BRAF, METex14, NTRK1/2/3, RET, KRAS, and ROS1 testing before determining a treatment regimen. The study objective was to estimate the association between the presence of biomarker testing and smoking status, age, sex, race, ethnicity, histology, and diagnosis year in patients with mNSCLC. **Methods:** CLQD is a real-world data source that provides de-identified electronic health record (EHR) data from more than 60 U.S. oncology practices utilizing 10 different EHRs. This retrospective analysis included patients initially diagnosed with mNSCLC from January 1, 2011, to December 31, 2019. Standard logistic regression models were fit separately by practice to estimate practice-specific odds ratios to assess variability across practices in associations between covariates (smoking status, age, race, etc.) and the primary outcome of biomarker testing, defined as documented testing for EGFR, ALK, ROS1, BRAF, KRAS, MET, RET, ERBB2, and/or PD-L1 within -60 to +365 days of mNSCLC diagnosis. Random effects logistic regression was then used to estimate associations with random intercepts, accounting for clustering by practices. Results are reported as odds ratios (OR) with 95% confidence intervals (CI). **Results:** 8704 patients from 31 practices were eligible. Testing rates increased from 31.5% in 2011 to a peak of 62.3% in 2017. Patients with a smoking history were half as likely to receive testing than patients without a smoking history (OR = 0.50, 95% CI: 0.41, 0.60); patients with unknown smoking history were 0.66 times as likely (95% CI: 0.52, 0.84). Females were more likely to be tested than males (OR = 1.19, 95% CI: 1.07, 1.32). After adjusting for other covariates, Asian patients were 1.51 times more likely to be tested than patients of other races (95% CI: 1.05, 2.17); Hispanic patients were 1.33 times more likely to be tested than patients without Hispanic ethnicity (95% CI: 0.99, 1.78). The odds of receiving biomarker testing were 6x greater for patients with non-squamous mNSCLC versus squamous mNSCLC (95% CI: 5.45, 7.20). Patients > 70 years old were less likely to be tested (OR = 0.83, 95% CI: 0.75, 0.93) than younger patients. **Conclusions:** Our data demonstrate annual increases in testing rates, reflecting guideline changes. However, in this cohort of patients with mNSCLC, biomarker testing was more likely for non-squamous mNSCLC patients, females, Asians, Hispanics, or those who did not have a history of smoking. Patient characteristics should no longer factor into obtaining biomarker testing. Non-discriminant, broad panel-based reflex molecular testing in mNSCLC can reduce treatment choice ambiguity and enhance patient opportunities. Research Sponsor: None.

9128 **Poster Session**

Molecular testing and patterns of treatment in patients with NSCLC: An IASLC analysis of ASCO CancerLinQ Discovery Data. *First Author: Madhusmita Behera, Winship Cancer Institute of Emory University, Atlanta, GA*

Background: Precision medicine has resulted in improved outcomes for non-small cell lung cancer (NSCLC); while molecular testing is considered critical for guiding treatment decisions for advanced stage NSCLC, adoption of testing in routine practice is variable. We analyzed the factors contributing to molecular testing and treatment patterns in patients with lung cancer. **Methods:** The ASCO CancerLinQ Discovery dataset was queried to identify patients diagnosed with lung cancer between the years 2010-2018. Data on demographics, tumor stage, histology and treatments were extracted, and receipt of molecular testing was investigated as the primary outcome. Univariate association of each clinicopathological variable with molecular testing outcome was performed using chi-square test for categorical variables and ANOVA test for numerical variables. A multivariable logistic regression analysis with backward selection at an alpha of 0.05 was reported. All analyses were conducted using SAS 9.4. **Results:** A total of 37,925 NSCLC patients with stage IV disease were analyzed. Patient characteristics: median age 65 years, 51% male, 68% white, 33.5% adenocarcinoma. Approximately 22% of all NSCLC patients had molecular testing results. In adenocarcinoma patients, 49% had molecular testing results available. In the stage IV group, 47% were treated with chemotherapy, 16% with immunotherapy and 3% with targeted therapy. On multivariable analysis, females were more likely to have molecular testing compared to males [(OR: 1.29 (1.22-1.37); p < 0.001]. Compared to White patients, Black patients were less likely to have molecular testing [OR: 0.89 (0.81-0.97); p = 0.009] and Asians were more likely to undergo testing [OR: 2.22 (1.79-2.75); p < 0.001]. Hispanic patients were more likely to undergo molecular testing compared to non-Hispanics [OR:1.24 (1.02-1.52); p = 0.03]. Additionally, treatment with immunotherapy [OR: 1.86 (1.72-2.01); p < 0.001] and targeted therapy [OR: 2.29 (2.00-2.64); p < 0.001] were associated with significantly higher likelihood of having molecular testing. These results were also confirmed on a subgroup analysis of adenocarcinoma patients. **Conclusions:** In this analysis of a US-based real-world dataset of stage IV NSCLC patients, White race and female sex are associated with higher likelihood of having molecular test performed. The percentage of patients undergoing testing remains sub-optimal. Research Sponsor: IASLC.

9129 **Poster Session**

Increased adherence to molecular profiling recommendations in non–small cell lung cancer through use of prior authorization and peer review. *First Author: Stephen A. Hamilton, eviCore healthcare, Bluffton, SC*

Background: National oncology guidelines advocate for broad molecular profiling to detect potentially actionable driver mutations prior to initiation of first-line therapy for patients with advanced non-small cell lung cancer (NSCLC). Results of genomic tests can confirm the presence of specific cancer tumor mutations that are best treated with more targeted therapies. Recent studies have shown that up to 30% of lung cancer patients may not receive the most effective treatment due to a lack of guideline-concordant genomic testing. We analyzed data from our prior authorization medical oncology program to determine adherence to national guidelines recommendations, and then developed a program to improve adherence to broad molecular profiling utilizing our proprietary prior authorization algorithms and our proactive peer consultation model. **Methods:** eviCore healthcare uses the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) to support its proprietary program for medical oncology drug management, and requires attestation on the results of NCCN recommended genomic/molecular test results in advanced NSCLC during prior authorization of systemic therapy. In November 2019, we implemented a next-generation sequencing (NGS) testing results requirement for metastatic non-squamous NSCLC patients prior to first-line therapy approval. If testing had not been completed, a peer to peer consultation was performed to advocate for testing prior to initiation of chemoimmunotherapy regimens. The rate of appropriate tumor testing is defined by provider attestation of test results prior to initiation of therapy. We define the control period (pre- implementation) as October 2018 through September 2019 (*n = 667*). The measurement period (post-implementation) is January 2020 through December 2020 (*n = 390*). **Results:** From pre to post there was a 35% increase in testing adherence (p < 0.001). After the testing requirement was implemented, the appropriate tumor testing rate increased to 99% by the second half of 2020, compared to the control period (62%). Additionally, after the testing requirement began, pembrolizumab utilization for advanced stage NSCLC decreased by a net 4.2% per month. This decrease in pembrolizumab utilization likely reflected patients being matched to more appropriate targeted therapy based on genomic testing results. **Conclusions:** We demonstrate that by combining medical oncology prior authorization with focused peer consultation, adherence to national society recommendations for broad molecular profiling prior to initiating first line therapy in advanced NSCLC can be significantly improved. By improving testing adherence, the most effective and appropriate therapy can be matched to the patient. Research Sponsor: None.

9130 **Poster Session**

Predictors of biomarker testing among patients (pts) with metastatic non–small cell lung cancer (mNSCLC). *First Author: Nicholas J. Robert, Ontada, Irving, TX*

Background: The MYLUNG (Molecularly Informed Lung Cancer Treatment in a Community Cancer Network) Consortium pragmatic study assessed real-world biomarker testing rates for mNSCLC within The US Oncology Network of over 1,000 providers. We previously reported that 90% of pts had at least one test performed for ALK, BRAF, EGFR, ROS1, or PD-L1, but only 46% had testing for all 5. We examined patient factors associated with rates of biomarker testing. **Methods:** Retrospective observational chart review study of pts with mNSCLC initiating first-line systemic therapy between 04/01/2018 and 03/31/2020. Patient characteristics including age, sex, race, geographic location, BMI, laboratory values, histology, performance status, stage at diagnosis, and comorbidities were obtained from iKnowMed electronic health records. Predictors of biomarker testing were identified using multivariable logistic regression. **Results:** Of the 3474 adults included in the study, median age was 69 years (range 23-90), 51% female, 65% White, 8% Black or African American, and 46% treated in the South US census region. Histology was adenocarcinoma in 74% and squamous cell carcinoma in 19%. Modeling for any biomarker testing resulted in histology and geographic region as significantly associated with increased likelihood of testing: adenocarcinoma vs squamous cell, odds ratio (OR) 1.76 (CI 1.33-3.23, p<0.0001) and Midwest vs South, OR 2.04 (CI 1.24-3.34, p=0.005). For comprehensive testing of all 5 biomarkers, increased albumin, adenocarcinoma or not otherwise specified histology, Midwest, Northeast or West geographic regions, and larger practice size were all significantly associated with increased likelihood of testing, while Black or African American race was associated with significantly decreased likelihood of testing (Table). **Conclusions:** Black or African American race, smaller practice size, Southern practice, and squamous cell histology were significantly associated with lower comprehensive biomarker testing rates. Understanding clinical and social determinants of health will be important when evaluating interventions to improve testing rates in the prospective phases of the MYLUNG study. Research Sponsor: Amgen, AstraZeneca, Eli Lilly, Genentech, Mirati Therapeutics.

Multivariable model for predictors of comprehensive biomarker testing.

Covariate		OR	95% CI	Significance (p-value)
Race	White (ref)	–	–	
	Black or African American	0.71	0.54-0.93	0.01
	Other	1.08	0.78-1.50	0.66
	Not documented	1.35	1.12-1.63	0.00
Histology	Squamous cell carcinoma (ref)	–	–	
	Adenocarcinoma	1.87	1.54-2.26	<0.01
	Large cell carcinoma	1.01	0.51-1.98	0.97
	Not otherwise specified	1.85	1.30-2.65	0.00
Region	South (ref)	–		
	Midwest	2.18	1.69-2.82	<0.01
	Northeast	1.77	1.29-2.41	0.00
	West	1.35	1.14-1.60	0.00
Practice Size	<150 NSCLC pts/yr (ref)	–	–	
	150 - 300 NSCLC pts/yr	0.84	0.68-1.04	0.11
	>300 NSCLC pts/yr	1.29	1.07-1.57	0.01
Albumin	Per unit increase	1.16	1.00-1.34	0.04

9131 **Poster Session**

Impact of cancer susceptibility gene (CSG) mutations in advanced NSCLC (aNSCLC). *First Author: Danielle Klingberg, St. George Hospital, Kogarah, NSW, Australia*

Background: Next generation sequencing (NGS) is used widely to identify somatic oncogenic driver mutations in aNSCLC to guide treatment. Comprehensive profiling has led to identification of multiple gene mutations of unclear significance, including germline genes associated with cancer risk, termed CSG. Using data from two randomized trials comparing atezolizumab to docetaxel, we investigated the prognostic and predictive values of CSG in aNSCLC. **Methods:** We used publicly available data from the OAK (NCT02008227) and POPLAR (NCT01903993) trials. At baseline, plasma was analyzed for cfDNA using FoundationOne CDx NGS assay. We defined CSGs as pathogenic variants of APC, BAP1, BRCA1/2, BRIP1, CDH1, CDKN2A, CHEK2, FH, FLCN, MEN1, MET, MSH2/6, MLH1, PMS2, PALB2, PTCH1, PTEN, RAD51, RB1, SDHB, SMARCA4, STK11, TSC1/2 and VHL. Cox models with treatment covariate, CSG status (mutant [mt] vs wild-type [wt]) and their interaction was used to assess the predictive value by treatment of CSG mt for overall survival (OS) and progression free survival (PFS) using univariate and multivariate models. Similar analysis was performed for objective response rate (ORR). **Results:** Of 1137 patients, 853 with sufficient tumor content formed the analysis population. In total, 295 (35%) had a known/likely pathogenic CSG mt. The variant allele frequencies (vAF) of CSG mt ≥30%, 10-30%, and <10% were 8% (N=23), 25% (N=73), and 67% (N=199) respectively. Patients with CSG mt were more likely to be smokers (89% vs 81%, P=0.005), had squamous tumors (37% vs 26%, P=0.001) with higher blood-based tumor mutation burden (mean 13.8 vs 10.2 per megabase, P<0.001). CSG mt was not predictive of greater OS benefit with atezolizumab over docetaxel (Table). CSG mt was associated with 35% increase risk of death in univariable analysis (HR 1.35, 95% CI 1.15-1.59). CSG mt was associated with inferior OS in multivariable analysis adjusting for performance status, smoking status, tumor histology, age, sex and number of organ sites of metastasis (HR 1.26, 95% CI 1.07-1.48). **Conclusions:** Plasma CSG mt is an independent poor prognostic factor in two large aNSCLC clinical trial datasets. Majority of vAF of CSG were low, suggesting that very few were potentially germline in origin, but dedicated sequencing for confirmation will be required. If confirmed, CSG status could be used as a stratification factor in future aNSCLC trials. Research Sponsor: None.

	CSG mt (N=295)		CSG wt (N=558)		Treatment-biomarker Interaction P
	Atezolizumab (N=144)	Docetaxel (N=151)	Atezolizumab (N=285)	Docetaxel (N=273)	
Complete & partial response* (%)	19	15	14	16	
	Odds ratio=0.76		Odds ratio=1.13		0.34
	95% CI 0.40 – 1.46		95% CI 0.69 – 1.85		
PFS	4.1	3.9	4.0	4.7	
(median, months)	HR 0.71		HR 1.02		0.02
	95% CI 0.54-0.95		95% CI 0.84-1.24		
OS	10.6	7.3	13.5	9.7	
(median, months)	HR 0.60		HR 0.70		0.36
	95% CI 0.46-0.78		95% CI 0.58-0.86		

*89 patients were excluded (atezolizumab, N=34; docetaxel, N=55) from analysis for ORR because of non-measurable disease.

9132 **Poster Session**

Demographic and socioeconomic factors associated with stage at diagnosis in non–small cell lung cancer: An NCDB analysis. *First Author: Kiana Verplancke, Creighton University School of Medicine, Omaha, NE*

Background: There were 2.21 million new diagnoses of lung cancer worldwide in 2020, accounting for approximately 25% of all cancer related deaths. A factor that impacts the overall mortality of lung cancer is the stage at initial presentation for diagnosis. Current 5-year survival estimates of non-small cell (NSC) lung cancer range from 73% in early-stage disease to 13% in advanced disease. The stark differences in survival rate in early and late disease, highlight the importance of determining if socioeconomic and demographic factors impact the stage of cancer at diagnosis. This study sought to determine if certain socioeconomic and demographic factors are associated with receiving an early (Stage 0-I) or delayed (Stage IV) diagnosis of NSC lung cancer. **Methods:** Using the National Cancer Database, 1,149,539 patients were identified as having a NCDB Analytic Stage Group diagnosis of Stage 0-I (early) vs Stage IV (delayed/advanced) NSC lung cancer between 2004 and 2018. Using SPSS statistics 27, patients with early and delayed diagnoses were compared to each other based on certain characteristics including sex, race, ethnicity, and level of education. Results were analyzed using multivariate and chi square analyses, as well as one-way ANOVA. **Results:** We identified significant differences ($p < .005$) between stage at presentation and certain socioeconomic factors. Females were 70% less likely to be diagnosed with advanced disease in comparison to males ($p < .001$, 95% CI = .697-.708). African Americans and Native Americans were more likely to present with advanced disease in comparison to white patients ($p < .001$, 95% CI = 1.407-1.449 and 1.046 – 1.235, respectively). Hispanic patients were 49.3% more likely to present with advanced disease than non-Hispanic patients ($p < .001$, 95% CI = 1.389 – 1.605). Patients with at least one comorbidity (CCI score ≥ 1) were less likely to present with advanced disease ($p < .001$). Those who lived in a zip code where 21% or more of the residents lacked a high school degree were more likely to present with stage IV disease, in comparison to patients who lived in a zip code where less than 20.9% of its residents did not graduate from high school ($p < .001$). **Conclusions:** Demographic and socioeconomic factors associated with a delayed diagnosis of NSC lung cancer include male sex, non-white race, being Hispanic, having no comorbidities, and living in a zip code where 21% or more residents have no high school degree. Research Sponsor: None.

9133 **Poster Session**

The 10-year journey of non–small cell lung cancer: A real-world experience. *First Author: Hyun Ae Jung, Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea*

Background: Over the past 10 years, the treatment of non-small cell lung cancer (NSCLC) has been continuously revolutionized. This study evaluated how this revolution improved outcomes in the real-world. **Methods:** We collected clinical, pathological, and molecular data of patient with NSCLC using an in house real-time updated cohort (ROOT-HEALTH). The primary objective was the 3-year survival (OS3) rate by clinical stage, histology, and driver mutations including *EGFR*, *ALK*, *ROS1*, *RET*, *MET exon 14 skipping*, *BRAF V600E*, *KRAS G12C*, and *NTRK* between two time periods (Period I: 2010-2015 vs. Period II: 2016-2021). **Results:** We included data on 22,060 patients who received any anti-cancer treatment between January 2010 and December 2020. Adenocarcinoma (AD) was the predominant histology (70.2% in Period I vs. 74.2% in Period II) (Standardized mean difference [SMD] = 0.09, $P < 0.001$). In Period I, 36.8%, 10.4%, 15.9%, and 34.6% patients were in stage I, II, III, and IV respectively. In Period II, 44.8%, 9.6%, 15.1%, 29.9% were in each stage, respectively (SMD = 0.15, $P < 0.001$). Patients during Period II were more likely to perform molecular tests for *EGFR*, *ALK*, and/or others than those during Period I in both of AD (79.1% in Period I vs. 95.1% in Period II) and non-AD (53.5% in Period I and 85.0% in Period II). In patients with AD, 49.4% in Period I and 56.4% in Period II had any druggable mutations. Among non-AD patients, 4.9% and 6.2% of patients had any druggable mutations in Period I and II, respectively. In patients with AD, in Period I, the OS3 rates were 92.9 %, 72.6%, 56.6%, and 29.0% for each stage (I, II, III, and IV), respectively. In Period II, the OS3 rates of AD were 96.4 %, 86.8%, 70.2%, and 52.1% for each stage, respectively ($P < 0.001$). In stage IV AD with *EGFR* mutation, the OS3 rates were 42.5% and 65.4% in Period I and II, respectively ($P < 0.001$). In stage IV AD with *ALK* rearrangement, the OS3 rates were 53.2% and 73.6% in Period I and II, respectively ($P < 0.001$). In patients with non-AD, the OS3 rates were 71.6%, 60.2%, 38.8%, and 10.2% for each stage in Period I. In Period II, the OS3 rates of non-AD were 83.1%, 73.7%, 58.2%, and 29.6% for each stage ($P < 0.001$). In stage IV non-AD with any druggable mutations, the OS3 rates were 27.1% and 46.0% in Period I and II, respectively ($P = 0.05$). **Conclusions:** Our study is meaningful as a large-scale study that reflects changes of survival outcome in a timely manner.Through our real-world experience of over 10 years, the proportions of early stage and were found to be increased. The implementation of molecular testing has also been expanded. Of note, the survival outcomes were remarkably improved across all stages, especially in patients with stage III-IV. Further improvement of outcomes through effect of emerging driver mutations in the next five years is expected. Research Sponsor: This study was supported by a grant from the Korean Society of Medical Oncology (KSMO) 2021. This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Ministry of Science and ICT (No. NRF-2021R1F1A1054782).

9134 **Poster Session**

Effectiveness of nationwide insurance coverage for next-generation sequencing in advanced non–small cell lung cancer: A real-world data study. *First Author: Dong-Won Kang, Sungkyunkwan University, Suwon, South Korea*

Background: Next-generation sequencing (NGS) has been covered by Korean national health insurance since March 2017 for patients with advanced non-small cell lung cancer (NSCLC). We explored the clinical and socioeconomic impact of NGS compared with that of a single gene test (SGT) alone. **Methods:** From the nationwide database, we identified patients who 1) are diagnosed with advanced NSCLC classified as a distant disease using Summary Stage between March 1, 2017, and December 31, 2018; 2) had NGS or SGT within 2 months after diagnosis of advanced NSCLC. Patients with squamous cell carcinoma were excluded. We conducted multivariate logistic regression to identify factors (e.g., age, sex, Charlson comorbidity index, insurance type, year of diagnosis, and region and type of hospital with the initial diagnosis) affecting the performance of NGS. Further, we divided the cohort into subgroups based on whether patients received treatment targeting epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) mutations (group A) or not (group B). We conducted 1:5 propensity score matching for each group to minimize the impact of confounding factors. The median overall survival and the adjusted hazard ratio (aHR) for death were estimated using the Kaplan-Meier method and the Cox proportional hazard model, respectively. We calculated the total medical cost, and per patient per year (PPPY) cost adjusted for the survival period. **Results:** Among 10,247 patients with advanced NSCLC, 768 patients were identified as group A and 1,596 as group B after matching. Old age, low household income, and rural region were factors negatively impacting on having NGS tests. In Group A, we did not find a significant difference in survival outcome between the NGS cohort and the SGT cohort (median survival 31.6 vs. 27.5 months, $P = .331$; aHR 0.80, $P = .204$). In contrast, significantly favorable survival was observed for the NGS group in Group B (median survival 14.1 vs. 9.5 months, $P = .023$; aHR 0.80, $P = .009$). Although the total medical cost was higher in the NGS group ($39,145) than the SGT group ($36,207) for Group B, the PPPY cost was lower in the NGS group ($57,502 and $63,293, respectively). **Conclusions:** Socioeconomic factors hampering the implementation of NGS were identified. Lowering the barrier by covering the NGS cost publicly in a specific clinical setting may have survival and cost-benefit in patients with advanced NSCLC. Research Sponsor: Ministry of Health & Welfare (HI19C0481, HC19C0238).

9135 **Poster Session**

Multifocal bronchial neuroendocrine tumor (bNET): A new clinical entity. *First Author: Nirosha D. Perera, Department of Internal Medicine, Mayo Clinic, Rochester, MN*

Background: Bronchial carcinoid (BC) is often categorized into multifocal (MBC) or solitary (SBC). MBC, excluding tumorlet and diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, is considered a relatively uncommon subgroup of BC, with much of the MBC literature stemming from case reports/small series. Our study analyzes MBC among a large cohort of 569 patients with BC and argues for change to the current clinical understanding of MBC. We suggest using the term bronchial neuroendocrine tumor (bNET) to more accurately represent its cells of origin and move away from "carcinoid" (historically meaning "carcinoma-like") and the outdated associated connotation that carcinoids all have a similar, benign clinical and biological behavior. **Methods:** Using the Mayo Clinic Epidemiology and Genetics of Lung Cancer Database with Institutional Review Board approval, we retrospectively reviewed 569 patients with bNET (204 males, 365 females) presenting to Mayo Clinic Rochester between 1/1997-12/2012. We used univariate and multivariate Cox regression analyses to evaluate factors affecting overall survival. **Results:** 80 patients (of 569, 14.1%) were diagnosed with multifocal (MbNET) and 489 with solitary (SbNET). Two-sided Fisher's exact tests found that older age, female gender, never having smoked cigarettes, and tumorlets were associated with MbNET diagnosis. Family lung cancer history, histopathologic grading (pathology: typical vs. atypical), Ki67, and presence of syndromes (carcinoid, Cushing, and MEN1 syndromes) were similar between MbNET and SbNET groups. Most MbNET cases were stage III-IV at the time of diagnosis, while the majority of SbNET cases were stage I. 5-year OS (83%) and 5-year PFS (75%) of MbNET patients were higher than those of their SbNET counterparts (74% and 68%, respectively). Metastasis status was an independent prognostic factor of poor OS in SbNET (P<0.001) but not in MbNET (P=0.71)(Table). **Conclusions:** Clinical, radiologic, and histopathologic characteristics and prognostic factors differed between SbNET and MbNET. MbNET arose as a new entity often with advanced stage disease, but good prognosis, which does not follow the NSCLC TNM staging system as in the 2009 NCCN guidelines (used during this study) or the updated 2021 NCCN guidelines which continue to stage lung carcinoid similarly to NSCLC. It may be beneficial to consider multifocal lung carcinoid instead as multifocal bNET, a new clinical entity, warranting a novel staging approach that more accurately reflects prognosis. Research Sponsor: None.

Analysis of the correlation between various factors and overall survival in MbNET and SbNET.

	Univariate analysis				Multivariate analysis			
	HR	*P* value	95% CI		HR	*P* value	95% CI	
MbNET								
Pathology	3.46	0.41	0.18	67.61	13.51	**0.001**	3.00	60.91
Metastasis	2.28	0.24	0.58	8.92	-	0.71	-	-
SbNET								
Pathology	0.98	0.95	0.51	1.89	-	0.76	-	-
Metastasis	1.56	**0.02**	1.06	2.29	1.82	**<0.001**	1.38	2.38

HR: Hazard Ratio. 95% CI: 95% Confidence Interval.

9136 **Poster Session**

Patient-derived organoids to predict the drug response in locally advanced or metastatic lung cancer: A real-world study. *First Author: Chan-Yuan Zhang, Guangdong Lung Cancer Institute, Guangdong Provincial Key Laboratory of Translational Medicine in Lung Cancer, Guangdong Provincial People's Hospital & Guangdon, Guangzhou, China*

Background: Lung cancer organoids (LCOs) were expected to be the potential precision medicine approach for clinical response prediction. However, the clinical applications of both tissue and malignant serous effusions (MSE) derived LCOs were rarely reported. Our previous work demonstrated that MSE-derived LCOs maintain the genomic signature of the original tumor. In this study, we aimed to create LCOs using tissue or MSE, then validate the reliability of the model by comparing LCOs and their origin from the pathological and molecular levels. Furthermore, drug sensitivity tests of LCOs were also performed to evaluate the feasibility of LCO drug test as an approach for personalized medicine. **Methods:** Primary or metastatic tumor tissues were obtained from advanced lung cancer patients through core biopsy or surgically resected biopsy at the Guangdong Provincial People's Hospital. MSEs were also collected. LCOs were generated from the obtained tissue and MSE, and the pathological features and genomic profiles were verified by analyzing the consistency with their origin. Then, the drug sensitivity scheme was formulated to follow the principles of clinical medication. In addition, proteomics analysis by 4D LC-MS/MS was also performed to analysis the molecular details of combinational therapy. **Results:** In our study, we generated 213 LCOs from 106 patients, mainly from MSE. The success rate to generate LCOs derived from MSE was 81.4% (131/161). The concordance rate of pathological phenotypes of LCOs samples verified by immunohistochemistry with clinical samples was 75% (63/84). In our cohort, LCO based drug sensitivity tests (LCO-DST) of targeted therapies were performed to predict the tumor response, and the AUC value of ROC analysis of osimertinib in *EGFR*-mutant adenocarcinoma reached 0.94(LCOs samples = 15, $p = 0.0047$). There were 2 patients with advanced lung adenocarcinoma, one with *de novo EGFR* mutation*/MET* amplification and the other with *EGFR* mutation combined with acquired *RET* fusion. The results of LCO based drug tests of 2 patients showed that combined targeted therapy (osimertinib plus savolitinib/cabozantinib) showed high tumor inhibition rate validated in clinical treatment and made differences. Then, 4D label-free high through-put proteomic analysis was performed in the patient with *EGFR* mutation and acquired *RET* fusion, demonstrating caspase 3 increased dramatically in combination of osimertinib and BLU-667 and the downstream proteins of EGFR and RET were down-regulated. **Conclusions:** LCOs derived from MSE faithfully reflected the pathological and genomic features of their original patients. The LCOs based drug test results are remarkably consistent with the tumor response. These results suggested the important prospects of LCO as an in vitro model for lung cancer precision medicine. Research Sponsor: High-level Hospital Construction Project (Grant No. DFJH201809 to JJ Yang); the National Natural Science Foundation of China (Grant No. 81972164 to JJ Yang); the Natural Science Foundation of Guangdong Province (Grant No. 2019A1515010931 to JJ Yang) and K.

TPS9137 **Poster Session**

Open-label, randomized, multicenter, phase 3 study evaluating trastuzumab deruxtecan (T-DXd) as first-line treatment in patients with unresectable, locally advanced, or metastatic non–small cell lung cancer (NSCLC) harboring HER2 exon 19 or 20 mutations (DESTINY-Lung04). *First Author: Bob T. Li, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The standard of care (SOC) for patients with oncogene driver subsets of metastatic NSCLC is guided by specific molecular characterization and includes immunotherapy, chemoimmunotherapy, and matched targeted therapies. Although targeting HER2 has transformed the care of patients with breast and gastric cancers, there is currently no approved HER2-targeted therapy for NSCLC. T-DXd is an antibody-drug conjugate consisting of an anti-HER2 antibody, a cleavable tetrapeptide-based linker, and a topoisomerase I inhibitor payload. In a cohort of pretreated patients (median, 2 prior lines) with unresectable or metastatic HER2-mutant NSCLC, T-DXd demonstrated durable and robust anticancer activity, with a confirmed objective response rate (ORR) of 55% and median duration of response (DOR), progression-free survival (PFS), and overall survival (OS) of 9.3, 8.2, and 17.8 months, respectively (Li et al. *N Engl J Med.* 2022). Given the efficacy observed in later-line settings and the unmet need for targeted therapies in patients with HER2-mutant NSCLC, evaluating the efficacy of T-DXd in the first-line setting vs SOC is important to determine the optimal treatment. Here we describe the phase 3 DESTINY-Lung04 trial (NCT05048797) evaluating T-DXd as a first-line treatment in patients with NSCLC harboring HER2 mutations. **Methods:** DESTINY-Lung04 is an open-label, randomized, multicenter, phase 3 study evaluating the efficacy and safety of first-line T-DXd vs SOC in patients with unresectable, locally advanced (not amenable to curative therapy), or metastatic nonsquamous NSCLC with HER2 exon 19 or 20 mutations (detected in tissue or circulating tumor DNA). Patients must be naive to systemic therapy with palliative intent in the locally advanced or metastatic disease setting and must not have tumors with *EGFR* or other targetable oncogenic alterations. Patients with brain metastases must have previously completed local therapy. Patients will be randomized to receive T-DXd or SOC (platinum [investigator's choice of cisplatin or carboplatin], pemetrexed, and pembrolizumab). The primary endpoint is PFS defined by RECIST version 1.1 per blinded independent central review (BICR). Secondary endpoints include OS, ORR, and DOR (by RECIST 1.1 per BICR and investigator), investigator-assessed PFS (by RECIST 1.1) and time to second progression or death (per local standard clinical practice), central nervous system PFS (by RECIST 1.1 per BICR), landmark PFS at 12 months (by RECIST 1.1 per BICR and investigator), and landmark OS at 24 months. Safety and tolerability, pharmacokinetics, immunogenicity, and patient-reported outcomes, including pulmonary symptoms and tolerability, will be assessed. Clinical trial information: NCT05048797. Research Sponsor: This study is funded by AstraZeneca Pharmaceuticals. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201).

TPS9138 **Poster Session**

A phase I/II multisite study of rucaparib and pembrolizumab maintenance therapy in stage IV non-squamous non–small cell lung cancer after initial therapy with carboplatin, pemetrexed, and pembrolizumab. *First Author: Angel Qin, University of Michigan, Rogel Cancer Center, Ann Arbor, MI*

Background: Carboplatin, pemetrexed, and pembrolizumab (CPP) followed by pemetrexed and pembrolizumab maintenance is a standard of care (SOC) for non-squamous metastatic non-small cell lung cancer (NSCLC), based on results of the KEYNOTE-189 study. The progression free survival (PFS) on this study was 8.8 months. There is increasing data to support that certain sporadic tumors harbor somatic mutations in genes of the homologous recombinant repair (HRR) pathway resulting in a "BRCAness" phenotype rendering sensitivity to PARP inhibitors (PARPi). TCGA data suggest up to 38% of NSCLC have mutations in HRR pathway genes. Furthermore, treatment with PARPi is shown to upregulate PD-L1 expression, which is associated with pembrolizumab response in NSCLC. We therefore hypothesized that maintenance therapy with a PARPi and pembrolizumab will improve PFS compared to SOC pemetrexed and pembrolizumab. **Methods:** This is a single arm, multi-site, investigator-initiated phase I/II study that is enrolling treatment-naïve patients with stage IV nonsquamous metastatic NSCLC without any targetable driver mutations eligible for CPP. Patients without progression after 4 cycles of CPP then proceed to maintenance with rucaparib 600mg PO BID and pembrolizumab 200mg IV every 21 days. The primary objective is efficacy assessed by PFS and second objectives include overall survival, safety, tolerability, and objective response rate (ORR). Correlatives in this study include PD-L1 expression, tumor mutational burden (TMB), and measurements of HRR deficiency as assessed by homologous repair deficiency (HRD) and loss of heterozygosity (LOH) using established methods. Key exclusion criteria include untreated brain metastases and prior exposure to a PARPi or PD-1/PD-L1 inhibitor. The phase I cohort which consisted of 6 patients treated with the approved full doses of rucaparib and pembrolizumab was completed without dose limiting toxicity (DLT). Using a Bayesian decision-theoretic two-stage design, the first stage will enroll 38 patients. If predefined PFS parameters are met, an additional 17 patients, for a total of 55 patients, will be enrolled. To date, 21 patients have been enrolled. Clinical trial information: NCT03559049. Research Sponsor: Merck and Clovis.

TPS9139 **Poster Session**

A phase 1b/2 trial of dupilumab given in conjunction with PD-(L)1 blockade in the treatment of relapsed/refractory metastatic NSCLC. *First Author: Bailey Gleason Fitzgerald, The Tisch Cancer Institute at Mount Sinai Health System, New York, NY*

Background: Although tumor microenvironments may contain chronic inflammatory cells, this milieu can lead to immune evasion and may contribute to resistance to immunotherapy. Dendritic cells are one of the most potent cross presenters of tumor antigen, and their function is crucial to tumor-directed adaptive immune responses. In the KP mouse model of lung adenocarcinoma (KrasG12D; Tp53-/-), we recently identified interleukin-4 (IL-4)-driven suppression of tumor-antigen charged dendritic cells, which was similarly seen in human lung cancer lesions (Maier, B., et al., *A conserved dendritic-cell regulatory program limits antitumour immunity.* Nature, 2020.580(7802):257-262). In the mouse model IL-4 blockade resulted in an increase in IL-12, IFNg and TNF in CD8+ T cells and decreased tumor burden, and further antitumor activity was seen when combined with PD-L1 blockade. Dupilumab is a fully human monoclonal antibody that blocks the IL-4 receptor alpha subunit which disrupts signaling through receptors for both IL-4 and IL-13; it is FDA approved for patients with multiple atopic conditions, in whom series adverse effects are rare. Based on this pre-clinical data, we hypothesize that the addition of dupilumab to anti PD-(L)1 therapy will be well tolerated, and will rescue the anti-tumor effect of immune checkpoint blockade. **Methods:** This is a phase Ib/II trial. Patients with relapsed/refractory NSCLC who have received prior anti PD-(L)1 treatment are eligible for enrollment. In a phase Ib safety run-in, six patients will be enrolled in a modified set-dose 3+3 design. If no more than 1 DLT is observed during this phase, the trial will proceed to phase II. Phase II will enroll a further 15 patients in a minimax design with early stopping for futility to a maximum total of 21 patients. Patients will undergo pre-treatment biopsies and peripheral blood sampling prior to receiving 3 doses of dupilumab, administered every three weeks, in conjunction with continuing standard-of-care anti-PD-(L)1 therapy. Patients will undergo repeat biopsies 4 weeks after starting therapy. After completion of dupilumab (at 9 weeks) patients will undergo repeat staging. The primary endpoint of phase 1b is safety as measured by frequency and severity of adverse effects. The primary endpoint of phase II is overall response rate as assessed using RECIST 1.1 criteria at the time of post-dupilumab imaging. Exploratory endpoints include analysis of peripheral blood by CyTOF and O-link, and tissue biopsies will be analyzed by multiplex-IHC and bulk-RNA-sequencing. T cell receptor sequencing will be performed on tumor and matched peripheral blood samples, and circulating tumor DNA will be assessed at multiple time points. Phase 1b is currently enrolling as planned. Clinical trial information: NCT05013450. Research Sponsor: The Center of Excellence for Thoracic Oncology at Mount Sinai's The Tisch Cancer Institute.

TPS9140 **Poster Session**

Combi-TED: A multicenter, phase II, open-label, randomized trial evaluating efficacy of OSE2021 plus docetaxel or OSE2021 plus nivolumab as second-line therapy in metastatic NSCLC progressing after first-line chemo-immunotherapy. *First Author: Federico Cappuzzo, Istituto Nazionale Tumori Regina Elena, Roma, Italy*

Background: First line combination of chemotherapy and immune checkpoint inhibitors (ICIs) improves overall survival (OS) compared with chemotherapy alone in non-small cell lung cancer (NSCLC) patients. However, only few options are available at chemoimmunotherapy failure, with docetaxel representing the standard of care. Tedopi is a cancer vaccine which stimulates killer T cells, currently under development for the therapy of HLA-A2+ lung cancer. In the ATALANTE-1 Phase III trial (EudraCT no. 2015-003183-36), Tedopi provided clinical benefits in patients with advanced NSCLC who failed to respond to checkpoint inhibitors. Given the need for new therapeutic options in patients failing first-line chemo-immunotherapy and the encouraging preliminary data with Tedopi, there is a strong rationale for investigating the activity of Tedopi plus nivolumab or Tedopi plus docetaxel in patients with metastatic NSCLC failing standard first-line therapy. **Methods:** This is a phase II, non-comparative, randomized multicenter study assessing the combination of Tedopi with docetaxel or nivolumab in NSCLC patients failing after first-line chemoimmunotherapy (EudraCT no. 2020-005170-10). All NSCLC patient candidates for second-line therapy are considered eligible for the study if they are HLA-A2+, with no evidence of EGFR mutations or ALK/ROS1 rearrangement and if they progressed after at least 4 cycles of previous first-line chemo-immunotherapy. Patients are randomly assigned to Tedopi plus docetaxel, Tedopi plus nivolumab (treatment arms) or docetaxel monotherapy (standard arm). The primary endpoint is 1-year OS rate. Secondary endpoints include OS, 2-year OS rate, progression-free survival (PFS), objective response rate (ORR), and safety. An explorative analysis of the correlation of efficacy with several tumor or blood biomarkers (PD-L1 expression, tumor mutational burden, Tedopi neoantigen expression, T cell infiltration), is also performed. Sample size was calculated assuming a 1-year OS rate in the standard arm of 20%. According to the single-stage design, in both treatment arms a 1-year OS rate of 20% would imply that treatment does not warrant further investigation and a 1-year OS rate of 40%, would imply that treatment has a sufficient activity. With a one-sided significance level of 5% and a power of 80%, a total number of 105 patients (35 per treatment arm) need to be enrolled. At the drafting of this abstract, 7 patients have already been enrolled. Total follow-up will be 24 months from last enrolment, for an approximate duration of 48 months. Clinical trial information: NCT04884282. Research Sponsor: OSE Immunotherapeutics.

TPS9141 **Poster Session**

A randomized phase 3 study of entrectinib versus crizotinib in patients (pts) with locally advanced/metastatic *ROS1* fusion-positive (fp) NSCLC with or without baseline CNS metastases (mets). *First Author: Anne-Marie C. Dingemans, Department of Pulmonology, Erasmus University Medical Center, Rotterdam, Netherlands*

Background: ROS proto-oncogene 1 (*ROS1*) fusions are found in 1–2% of NSCLC cases. As CNS mets are common in pts with *ROS1*-fp NSCLC and associated with poor prognosis, CNS-active treatments are needed for these pts. Entrectinib and crizotinib are tyrosine kinase inhibitors (TKIs) of ROS1, recommended as first-line treatments for *ROS1*-fp NSCLC. Both drugs have shown robust systemic efficacy and good tolerability in pts with *ROS1*-fp NSCLC. While crizotinib may have suboptimal CNS activity, entrectinib has shown intracranial efficacy in pts with baseline CNS mets by blinded independent central review (BICR, PMIDs 30215676; 33646820). We hypothesized that entrectinib may have greater CNS activity than crizotinib, potentially addressing the unmet need for pts with *ROS1*-fp NSCLC with CNS mets. **Methods:** This randomized, open-label, multicenter, phase 3 trial (NCT04603807) aims to compare the efficacy and safety of entrectinib vs crizotinib in adult pts with TKI-naïve advanced/metastatic *ROS1*-fp NSCLC, with or without CNS mets. Key eligibility criteria: advanced/recurrent/metastatic NSCLC with *ROS1* fusion determined locally by certified clinical laboratory testing; measurable systemic disease (RECIST 1.1); age ≥18 years; ECOG PS ≤2; no prior ROS1 TKI or systemic treatment for advanced/metastatic disease; adequate hematologic, renal and hepatic functions; prior radiotherapy ≥14 days before randomization and neurologically stable CNS mets per RECIST 1.1 are permitted. Pts will be randomized 1:1 to receive 600 mg entrectinib once a day or 250 mg crizotinib twice a day. Stratification factors are baseline CNS mets (none/measurable/non-measurable) and prior brain radiotherapy ≤2 months (yes/no); to allow sufficient power, ≥30% of randomized pts will have baseline CNS mets. Study treatment will continue until progressive disease, unacceptable toxicity, death or withdrawal from the study. Pts with radiographic disease progression or isolated asymptomatic CNS progression may continue treatment at the investigator's discretion. Tumor assessments (brain MRI and chest, abdomen and pelvis CT/MRI) will occur at screening, Wk 4, Wk 8 and every 8 wks thereafter. Blood samples will be collected at every visit. Primary endpoint: progression-free survival (PFS) by BICR in pts with baseline CNS mets (CNS population, target HR = 0.57). Secondary endpoints: CNS-PFS by BICR and ORR, duration of response (DoR) and PFS (by BICR and investigator) in the intent-to-treat (ITT) population; overall survival in the CNS and ITT populations; CNS-ORR and CNS-DoR by BICR in the CNS population. Impact on quality of life, functioning and lung cancer-specific symptoms will be evaluated via questionnaires in the ITT population. Safety endpoints and biomarkers will also be evaluated. As of 12 Jan 2022, 8 pts are enrolled (first pt enrolled in Oct 2021). Clinical trial information: NCT04603807. Research Sponsor: F. Hoffmann-La Roche Ltd.

TPS9142 **Poster Session**

A phase 1/2 study of the highly selective EGFR inhibitor, BLU-701, in patients with *EGFR*-mutant non–small cell lung cancer (NSCLC). *First Author: Alexander I. Spira, NEXT Oncology Virginia and Virginia Cancer Specialists Research Institute, Fairfax, VA*

Background: Although 3rd-generation tyrosine kinase inhibitors (TKIs), such as osimertinib, are highly effective in front-line metastatic *EGFR*-mutated (*EGFR*m) NSCLC, treatment resistance ultimately occurs, including the emergence of the on-target C797X mutation for which there are no approved TKIs. BLU-701 is an investigational, reversible, brain-penetrant, wildtype-sparing oral TKI with nanomolar potency on common activating (exon 19 deletion and L858R) and C797X resistance mutations (Tavera L et al. AACR 2022). BLU-701 has shown promising preclinical data, including antitumor central nervous system (CNS) activity that may improve patient outcomes. Additionally, combining BLU-701 with standard of care therapies may provide enhanced disease control across multiple lines of treatment, including against heterogenous tumors, in patients with *EGFR*m NSCLC. **Methods:** HARMONY (NCT05153408) is an ongoing, global phase 1/2, open-label, first-in-human study designed to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and antitumor activity of BLU-701 as a monotherapy or in combination with osimertinib or platinum-based chemotherapy in patients with *EGFR*m NSCLC. Key inclusion criteria include patients ≥18 years of age with metastatic *EGFR*m NSCLC; Eastern Cooperative Oncology Group performance status 0–1; and previous treatment with ≥1 EGFR-targeted TKI. Patients in the phase 2 monotherapy part must harbor an *EGFR* C797X resistance mutation (locally assessed). Key exclusion criteria are tumors harboring *EGFR* T790M mutations, *EGFR* exon 20 insertions, or other known driver alterations, including *KRAS*, *BRAF* V600E, *NTRK1/2/3*, *HER2*, *ALK*, *ROS1*, *MET*, or *RET*. Phase 1 primary endpoints are maximum tolerated dose, recommended phase 2 dose (RP2D), and safety. The phase 2 primary endpoint is overall response rate (ORR) by RECIST 1.1. Secondary endpoints include ORR (phase 1), duration of response, and PK/PD (phase 1 and phase 2); disease control rate, progression-free survival, overall survival, antitumor CNS activity, and safety (phase 2). The phase 1 dose escalation will adopt a Bayesian optimal interval design. Patients will be enrolled into 3 treatment cohorts: part 1A (n≈40–80; BLU-701), part 1B (n≈35; BLU-701 + osimertinib), and part 1C (n≈18; BLU-701 + carboplatin and pemetrexed). Patients in the phase 2 dose expansion (n≈24) will be treated at the RP2D of BLU-701 as monotherapy. Patients may receive treatment until disease progression, unacceptable toxicity, or other discontinuation criteria are met. Enrollment in this study has started, and sites will be open across North America, Europe, and Asia. Clinical trial information: NCT05153408. Research Sponsor: Blueprint Medicines Corporation.

TPS9143 **Poster Session**

A phase I, open-label, dose escalation, confirmation, and expansion trial of BI 1810631 as monotherapy in patients with advanced/metastatic solid tumors with HER2 aberrations. *First Author: John Heymach, Department of Thoracic/Head and Neck Medical Oncology, Division of Cancer Medicine, MD Anderson Cancer Center, University of Texas, Houston, TX*

Background: *HER2* mutations are present in 2–4% of NSCLC tumors; of these ~50% are exon 20 insertion (ex20ins) mutations. There is an unmet need for effective targeted therapy against *HER2* mutations in solid tumors, particularly in NSCLC. Historically, ex20ins mutations have responded poorly to TKIs. Moreover, TKIs that inhibit both mutant EGFR and HER2 are typically limited by toxicities associated with inhibition of wild-type EGFR. Despite the promise of trastuzumab deruxtecan and other agents in this setting, the development of orally available selective TKIs is important given the heterogeneity of HER2 aberrations, potential for combination regimens, and the risk of ILD with ADCs. BI 1810631 is a HER2 selective TKI that covalently binds to both wild-type and mutated HER2 receptors, including ex20ins, whilst sparing EGFR signaling; preclinical data suggest good tolerability and efficacy. This Phase Ia/Ib, open-label, non-randomized study aims to determine the safety, MTD, PK, pharmacodynamics, and preliminary efficacy of BI 1810631 in pts with *HER2+* solid tumors (NCT04886804). **Methods:** ~96 pts from 5–7 sites in the US, Netherlands, Japan, and China will be recruited. Phase Ia: consecutive cohorts of pts will receive BI 1810631 QD or BID at escalating doses. Starting dose level: 15 mg BID (~36 pts); QD schedule will begin after one dose level above estimated therapeutic dose of BI 1810631 is determined safe by the Dose Escalation Committee (expected starting dose: 60 mg [~30 pts]). BI 1810631 dose escalation will continue until MTD/RP2D for each schedule is determined, as well as a preferred Phase Ib schedule. Phase Ib: an initial 30 pts with *HER2* ex20ins mutation-positive, pre-treated NSCLC will be enrolled, with possible inclusion of additional cohorts in the future. Overall pt inclusion criteria (Phase Ia): ≥18 years of age; histologically/cytologically confirmed *HER2+* (defined as overexpression, gene amplification, non-synonymous somatic mutation, or gene rearrangement involving *HER2* or *NRG1)* advanced/unresectable/metastatic solid tumor refractory/not suitable for standard therapy; exhausted treatment options; measurable/evaluable lesions (per RECIST v1.1); ECOG PS ≤1. Phase Ib criteria: *HER2* ex20ins mutation-positive NSCLC; received ≥1 line of platinum-based combination chemotherapy in the advanced/metastatic setting. Primary endpoints: MTD based on number of DLTs/number of pts with DLTs (Phase Ia); objective response (Phase Ib). Secondary endpoints: number of pts with DLTs throughout entire treatment period and PK parameters (Phase Ia/Ib); duration of response, disease control, duration of disease control, and PFS (Phase Ib). The trial is actively recruiting with 6 pts enrolled to date. More patients may be recruited depending on whether 2 dose levels have been completed and the MTD/RP2D determined. Clinical trial information: NCT04886804. Research Sponsor: Boehringer Ingelheim, Behbood Sadrolhefazi.

TPS9144 **Poster Session**

A phase II randomized, open-labelled, multicenter study of safety and efficacy of combination brigatinib and carboplatin-pemetrexed therapy or brigatinib monotherapy as first-line treatment in patients with advanced ALK-positive non–small cell lung cancer (IFCT-2101 MASTERPROTOCOL ALK). *First Author: Michael Duruisseaux, URCOT, Hôpital Louis Pradel, Hospices Civils de Lyon Cancer Institute, Bron, France*

Background: Second generation ALK tyrosine kinase inhibitors (ALK-TKI), including brigatinib, provide substantial therapeutic benefit in first-line treatment of ALK-positive NSCLC patients (pts) but relapse eventually occurs in all pts due to development of drug resistance, possibly caused by emergence of drug-tolerant cells (DTC). Combining chemotherapy to TKI may prevent DTC emergence in preclinical studies, and results in prolonged progression-free survival (PFS) and overall survival in *EGFR*-mutant NSCLC. We hypothesize that combination of second generation ALK-TKI with chemotherapy will improve clinical outcomes in advanced *ALK*-positive NSCLC patients. The IFCT-2101 MASTERPROTOCOL ALK trial will evaluate the efficacy and safety of brigatinib and carboplatin-pemetrexed combination in treatment-naïve metastatic *ALK*-positive NSCLC. **Methods:** The IFCT-2101 MASTERPROTOCOL ALK randomized, open-label phase II trial will enrol 110 pts in 30 French centers over 24 months. Eligible pts will have metastatic NSCLC with *ALK*-fusion according to local testing, be untreated for advanced disease, and have an ECOG Performance Status (PS) of 0-1 and at least one measurable lesion per RECIST 1.1. Pts with asymptomatic and stable brain metastases (BM) will be eligible. Exclusion criteria include leptomeningeal metastases. Patients will be randomized 1:1 to receive brigatinib monotherapy (Arm A) or combination brigatinib and carboplatin-pemetrexed therapy (Arm B), with PS (0 *vs* 1) and BM (presence *vs* absence) as stratification factors. Brigatinib will be administered at a dose of 90 mg QD for a 7-day lead-in period followed by 180 mg QD continuously, in 28-day cycles. In Arm B, 4 cycles of carboplatin (AUC 5) and pemetrexed (500 mg/m^2) therapy every 3 weeks will be added at Day 8 of brigatinib treatment. Treatment will continue until progression, intolerable toxicity or discontinuation. The first 26 pts enrolled in Arm B will represent the population of a safety phase, during which adverse events (AE) will be closely monitored by an independent data monitoring committee. The primary endpoint is investigator-assessed 12-month PFS rate. Secondary endpoints include independently-reviewed 12-month PFS rate, overall response rate (ORR), 12-month intracranial PFS and ORR, incidence, nature and severity of AEs, and impact of *ALK*-fusion detection, co-mutations and clearance of circulating tumor (ct) DNA (Guardant360) on outcome. Exploratory objectives include the evaluation of early blood ctDNA decrease on patient outcome. The study is enrolling and primary completion date is March 2025. Clinical trial information: NCT05200481. Research Sponsor: Takeda France, IFCT.

TPS9145 **Poster Session**

FoRT 05-BEAT: A phase II randomized trial comparing atezolizumab versus atezolizumab + bevacizumab as first-line treatment in patients with PD-L1 high advanced/metastatic NSCLC. *First Author: Rita Migliorino, Pulmonary Oncology Unit, San Camillo-Forlanini Hospital, Rome, Italy*

Background: Several ongoing phase III studies are evaluating the efficacy of first-line atezolizumab in combination with chemotherapy in patients with non small-cell lung cancer (NSCLC). Among angiogenesis inhibitors, bevacizumab is approved as first-line therapy in combination with chemotherapy or in combination with erlotinib in patients with NSCLC harboring activating EGFR mutations. Recent evidence (Wallin 2016) suggests that the combination of atezolizumab and bevacizumab increases intra-tumoral CD8+T cells, suggesting that dual VEGF and PD-L1 inhibition improves antigen-specific T-cell migration. In addition, preliminary clinical data suggested a strong synergistic effects of bevacizumab with immune checkpoint inhibitors. There is therefore a strong rationale for investigating the combination of atezolizumab and bevacizumab in patients with advanced/metastatic NSCLC. The FoRT 05-BEAT is a multicenter, Italian, phase II, randomized study comparing atezolizumab monotherapy versus the combination of atezolizumab and bevacizumab in patients with chemo-naive metastatic NSCLC and high levels of PD-L1 expression. **Methods:** The trial was conducted in 35 Italian centers: chemotherapy naive metastatic NSCLC patients, with high levels of PD-L1 expression (PD-L1 TPS ≥50% or TC/IC 3 scoring) were randomly assigned to atezolizumab monotherapy (1200 mg every 3 weeks) or to the combination of atezolizumab (1200 mg every 3 weeks) and bevacizumab (15 mg/kg every 3 weeks).The primary endpoint is overall survival (OS) rate at 18 months. Secondary endpoints include response rate (RR), PFS, OS according to presence of bone and/or hepatic metastases. Safety considerations will be considered. Exploratory analysis of predictive biomarker on tumor tissue and blood samples has been planned. Sample size has been calculated assuming a 18 months OS of 50% in the atezolizumab arm. Therefore, a total of 186 patients is needed to detect an absolute improvement of 20%, thus obtaining a 18mOS of 70% in the combination arm, with a power of 80% at a significance level of 5%. Taking into account the percentage of patients lost-to-follow-up, the sample size has been increased by 10% (N = 206 patients, 103 per arm). At the drafting of this abstract, 57 patients have already been enrolled (47 randomized). Clinical trial information: NCT03896074. Research Sponsor: Roche.

TPS9146 **Poster Session**

EVOKE-02: A phase 2 study of sacituzumab govitecan (SG) plus pembrolizumab (pembro) with or without platinum chemotherapy in first-line metastatic non–small cell lung cancer (NSCLC). *First Author: Edward B. Garon, Ronald Reagan UCLA Medical Center, Santa Monica, CA*

Background: Most patients (pts) with advanced NSCLC do not harbor genomic alterations associated with approved first-line targeted therapies. The standard of care for these pts is a programmed death (ligand)-1 (PD-[L]1) inhibitor alone, if the tumor highly expresses PD-L1, or in combination with platinum doublet chemotherapy, independent of PD-L1 expression. However, most pts do not respond to these therapies or achieve only a transient response, highlighting an unmet need. SG is an antibody-drug conjugate composed of an anti–Trop-2 antibody coupled to the cytotoxic SN-38 payload via a proprietary, hydrolyzable linker. In the phase 1/2 IMMU-132-01 basket study (NCT01631552), SG demonstrated an objective response rate (ORR) of 17% and median overall survival (OS) of 9.5 mo, with a manageable safety profile in 54 pts with metastatic NSCLC after multiple prior therapies (Heist RS, et al. *J Clin Oncol. 2017*). We hypothesize that combining SG with pembro or with pembro + platinum chemotherapy will improve outcomes for pts with advanced NSCLC. **Methods:** EVOKE-02 (NCT05186974) is an open-label, multicenter, multicohort, global phase 2 study evaluating SG plus pembro with or without carboplatin (carbo) or cisplatin (cis) in advanced NSCLC. Key eligibility criteria include age ≥18 y, stage IV NSCLC at enrollment, measurable disease by RECIST v1.1, ECOG performance status of 0 or 1, and adequate organ function. Pts must not have actionable genomic alterations and must not have received prior systemic therapy for metastatic NSCLC. Up to 164 pts will be enrolled. SG plus pembro will be assessed in squamous/nonsquamous NSCLC with Tumor Proportion Score (TPS) ≥50% (cohort A, ~30 pts) and TPS < 50% (cohort B, ~30 pts), and SG plus pembro with carbo/cis in nonsquamous (cohort C, ~40 pts) and squamous (cohort D, ~40 pts) NSCLC regardless of PD-L1 expression. Pts are randomly assigned if cohorts enrolling concurrently have overlapping eligibility. SG will be administered intravenously (IV) at 10 mg/kg on d 1 and 8 until disease progression or unacceptable toxicity, pembro 200 mg IV on d 1 for up to 35 cycles, carbo AUC 5 or cis 75 mg/m^2 on d 1 for up to 4 cycles in 21-d cycles. A safety run-in will be conducted for cohorts C and D (up to 24 pts each) to determine the optimal SG dose by dose de-escalation. Choice of platinum will be based on preliminary efficacy in safety run-in. The primary endpoints are ORR assessed by independent review per RECIST v1.1 and the incidence of dose-limiting toxicities per dose for the first 21 d of the safety run-in to determine the recommended phase 2 dose of SG in combination with pembro and a platinum. Key secondary endpoints include progression-free survival by independent review, OS, duration of response, disease control rate, and safety. This study is open for recruitment and is enrolling globally. Clinical trial information: NCT05186974. Research Sponsor: Gilead Sciences, Inc.

TPS9147 **Poster Session**

A phase 2 study of VS-6766 (RAF/MEK clamp) RAMP 202, as a single agent and in combination with defactinib (FAK inhibitor) in recurrent KRAS mutant (mt) and BRAF mt non–small cell lung cancer (NSCLC). *First Author: D. Ross Camidge, University of Colorado Cancer Center, Aurora, CO*

Background: KRAS is mutated (mt) in 25% of NSCLC adenocarcinoma, with KRAS G12V and G12C mt occurring in ~7% and ~13% of patients (pts), respectively. Whereas G12C inhibitors have demonstrated promising activity in pts with KRAS G12C NSCLC, KRAS G12V NSCLC remains an unmet need. BRAF mt occurs in ~4% of NSCLC with roughly equal split between BRAF V600E and non-V600E. VS-6766 is a small molecule RAF/MEK clamp that inhibits BRAF, CRAF and MEK, enabling VS-6766 to block MEK signaling without compensatory activation of MEK observed with MEK-only inhibitors. VS-6766 potently inhibits proliferation of KRAS and BRAF mt cell lines. Focal adhesion kinase (FAK) activation is a putative resistance mechanism to RAF and MEK inhibition, and defactinib, a small molecule FAKi, has shown synergistic anti-tumor activity with VS-6766 in KRAS mt NSCLC models. In a KRAS G12V mt NSCLC mouse model, which was shown to be especially dependent on CRAF, VS-6766 induced strong tumor regressions both as monotherapy and in combination with FAKi (Coma AACR 2021). Clinically, VS-6766 monotherapy has shown responses in KRAS mt NSCLC including pts with KRAS G12V and in pts with BRAF V600E solid tumors (Guo 2020; Martinez-Garcia 2012). The combination of VS-6766 + defactinib is currently being evaluated in the Investigator Sponsored FRAME study. In an updated analysis of response in 20 pts with KRAS mt NSCLC, there were 2 confirmed PRs, 1 unconfirmed PR and 10 SDs (ORR = 15%; DCR = 65%) with 7/20 pts remaining on treatment for ≥24 weeks. The 2 pts with KRAS G12V NSCLC both had confirmed PRs (ORR = 100%). This combination regimen exhibited a manageable safety profile with no NSCLC pts discontinuing for adverse events (Krebs AACR 2021). **Methods:** This is an international phase 2, adaptive, multicenter, randomized, open label study designed to evaluate the efficacy and safety of VS-6766 vs. VS-6766 + defactinib in pts with recurrent KRAS or BRAF mt NSCLC (NCT04620330). Part A will determine the optimal regimen, either VS-6766 monotherapy or VS-6766 + defactinib based on pts with KRAS G12V. Part A will consist of 5 NSCLC arms: Arm 1 VS-6766 monotherapy in KRAS G12V, Arm 2 VS-6766 + defactinib in KRAS G12V, Arm 3 the combination in KRAS non-G12V, Arm 4 the combination in BRAF V600E and Arm 5 the combination in BRAF non-V600E. Part B will determine the efficacy of the optimal regimen identified in Part A. Pts must have histologic or cytologic evidence of NSCLC, measurable disease according to RECIST V1.1, known KRAS or BRAF mt and at least 1 prior systemic therapy (appropriate therapy for activating mutation and/or platinum-based therapy). Part A will enroll 102 pts Arms 1 and 2 (KRAS G12V), and Arms 4 and 5 (BRAF V600E and non-V600E) are currently open. Arm 3 (KRAS non-G12V) enrollment is completed. The total number of pts in Part B will be determined by results from Part A. Clinical trial information: NCT04620330. Research Sponsor: Verastem.

TPS9148 **Poster Session**

A phase 1/2 study of VS-6766 (RAF/MEK clamp) in combination with sotorasib (G12C inhibitor) in patients with KRAS G12C mutant non–small cell lung cancer (NSCLC) (RAMP 203). *First Author: Ramaswamy Govindan, Washington University School of Medicine, St. Louis, MO*

Background: KRAS is mutated (mt) in 25% of non-small cell lung cancer (NSCLC) adenocarcinoma, with KRAS G12C mt occurring in ~13% of patients. The G12C inhibitor (G12Ci) sotorasib has recently received FDA approval for patients with KRAS G12C NSCLC. Several studies have shown that simultaneous targeting of multiple nodes in the RAS pathway may be optimal for durable pathway inhibition and response. Furthermore, acquired mutations and amplifications in the RAS pathway occur clinically upon progression on sotorasib or adagrasib. Accordingly, combination of G12Ci with a downstream blocker of the RAS pathway may be needed for more durable response. VS-6766 is a unique small molecule RAF/MEK clamp that inhibits BRAF, CRAF and MEK, enabling VS-6766 to block MEK signaling more consistently without the compensatory activation of MEK that reduces the efficacy of MEK-only inhibitors. In vitro 3D proliferation and in vivo tumor models were used to assess anti-tumor efficacy of VS-6766 ± G12Ci. In KRAS G12C mt NSCLC cell lines, VS-6766 was synergistic with both sotorasib and adagrasib in reducing tumor cell viability which correlated with deeper inhibition of RAS pathway signaling. In vivo, combination of VS-6766 with sotorasib induced strong tumor regressions in contrast to sotorasib monotherapy or sotorasib plus trametinib. Initial clinical activity of VS-6766 in KRAS G12C mt NSCLC is supported by the FRAME study [NCT03875820] results, in which 4/6 patients with KRAS G12C mt NSCLC showed tumor reduction including 1 PR. These results support the clinical evaluation of VS-6766 in combination with a G12Ci for treatment of KRAS G12C mt NSCLC. **Methods:** This is a Phase 1/2, multicenter, open label, dose evaluation/dose expansion study designed to evaluate the efficacy and safety of VS-6766 in combination with sotorasib in patients with KRAS G12C mt NSCLC who have not previously been treated with a KRAS G12Ci or have experienced disease progression while undergoing therapy with a KRAS G12Ci [NCT05074810]. The study will be conducted in two parts: Part A (dose evaluation) and Part B (dose expansion). Up to 3 dose levels will be evaluated in Part A to determine the Recommended Phase 2 Dose (RP2D) for Part B. Part B will assess the efficacy of the RP2D and will be conducted in 2 cohorts: patients who are G12Ci treatment naïve (cohort 1) and patients who have experienced disease progress during G12Ci therapy (Cohort 2). Patients enrolled must have histologic or cytologic evidence of NSCLC, measurable disease according to RECIST V1.1 and known KRAS G12C mutation. The study will enroll up to 121 patients with a minimum of 6 and a maximum of 12 patients in Part A and an additional 109 patients in Part B (minimum of 41 patients at RP2D stage 1 for cohort 1 and 2 or RP2D stages 1 and 2 in both cohorts). Clinical trial information: NCT05074810. Research Sponsor: Verastem.

TPS9149 **Poster Session**

EVOKE-01: A phase 3 study of sacituzumab govitecan (SG) versus docetaxel in patients with non–small cell lung cancer (NSCLC) progressing on or after platinum-based chemotherapy and checkpoint inhibitors. *First Author: Marina Chiara Garassino, University of Chicago, Department of Medicine, Chicago, IL*

Background: Single-agent chemotherapy, such as docetaxel, is the standard of care in patients with metastatic NSCLC who progressed on platinum-based therapy and checkpoint inhibitors. However, docetaxel is associated with poor survival (median overall survival [OS] of < 1 year); thus, novel agents are needed to further improve outcomes in this setting. SG is an antibody-drug conjugate composed of an anti–Trop-2 antibody coupled to the cytotoxic SN-38 payload via a proprietary, hydrolyzable linker. In a single-arm expansion of the phase 1/2 IMMU-132-01 basket study of advanced epithelial cancers (NCT01631552), SG demonstrated an objective response rate (ORR) of 17% and median OS of 9.5 months, with a manageable safety profile in 54 patients with metastatic NSCLC who had multiple prior therapies (Heist RS, et al. *J Clin Oncol.* 2017). EVOKE-01 randomized phase 3 study was designed to further evaluate SG in patients with metastatic NSCLC. **Methods:** EVOKE-01 (NCT05089734) is an open-label, global, multicenter, randomized, phase 3 study comparing the efficacy and safety of SG vs docetaxel in patients with metastatic NSCLC. Key eligibility criteria include age ≥18 years, pathologically documented stage IV NSCLC at time of study entry, and progression after platinum-based chemotherapy and anti-PD(L)1 therapy given either in combination or sequentially. Patients with EGFR, ALK, or other known actionable genomic alterations must have also received treatment with ≥1 approved appropriate TKI. Other inclusion criteria are ECOG performance status 0-1 and adequate hematologic, hepatic, and renal function. Patients with prior treatment with topoisomerase inhibitors are excluded. Patients are randomized 1:1 to receive intravenous SG (10 mg/kg on day 1 and 8) or docetaxel (75 mg/m^2 on day 1) in 21-day cycles until progressive disease or unacceptable toxicity. Stratification is based on predominant histology (squamous vs nonsquamous), best response to prior immune therapy (PD/SD vs CR/PR), and prior therapy for actionable genomic alteration (yes vs no). The primary endpoint is OS. Key secondary endpoints include progression-free survival, ORR, duration of response, and disease control rate, as assessed by investigator RECIST v1.1, mean change from baseline in NSCLC-SAQ total score and shortness of breath, and safety. This study plans to enroll ~520 patients globally and is open for recruitment. Clinical trial information: NCT05089734. Research Sponsor: Gilead Sciences, Inc.

TPS9150 **Poster Session**

Trial in progress: A phase 2 study of sotorasib as first-line treatment in patients with stage IV non–small cell lung cancer (NSCLC) whose tumors harbor a *KRAS p.G12C* mutation (CodeBreaK 201). *First Author: Kathryn Cecilia Arbour, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Chemo-immunotherapy regimens represent a standard of care for the first-line treatment of metastatic NSCLC, yet clinical outcomes in patients bearing tumors that lack PD-L1 expression [PD-L1 Tumor Proportion Score (TPS) < 1%)] or harbor a serine/threonine kinase 11 (*STK11*) mutation remain poor. Sotorasib is a selective, irreversible small molecule $KRAS^{G12C}$ inhibitor that is approved for the treatment of patients with locally advanced or metastatic *KRAS* p.G12C-mutated NSCLC following failure of at least one prior line of systemic therapy and has previously demonstrated robust antitumor activity in subgroups of *KRAS* p.G12C mutant NSCLC with PD-L1 TPS <1% and/or *STK11* co-mutations. We hypothesized that sotorasib may represent an effective first-line therapy for subgroups of NSCLC patients who may have suboptimal chemo-immunotherapy outcomes and a high unmet clinical need. **Methods:** This phase 2, open-label, global study is designed to evaluate the efficacy and safety of sotorasib (960 mg or 240 mg daily) as first-line treatment in approximately 170 patients with *KRAS* p.G12C-mutated, metastatic NSCLC with PD-L1 TPS <1% as determined by immunohistochemical assay and/or presence of *STK11* mutation as determined by next-generation sequencing (NGS). Key eligibility criteria include patients with untreated metastatic NSCLC without active brain metastases. Patients will be stratified by known presence of *STK11* mutation. The primary endpoint is objective response assessed by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Secondary endpoints include disease control, duration of response, time to response, progression-free survival per RECIST 1.1, overall survival, safety and tolerability, and pharmacokinetic profile. Enrollment began in January 2022 and is ongoing. Contact Amgen Medical Information for more information. Clinical trial information: NCT04933695. Research Sponsor: Amgen Inc.

TPS9151 **Poster Session**

Aumolertinib plus apatinib versus aumolertinib as first-line treatment in patients with EGFR mutation–positive locally advanced or metastatic non–small cell lung cancer (NSCLC). *First Author: Fan Zhang, Department of Oncology, Chinese PLA General Hospital, Beijing, China*

Background: Currently, EGFR-TKIs are widely accepted as the standard treatment for EGFR-mutant advanced NSCLC; however, acquired resistance is inevitable. Preclinical and clinical evidence has demonstrated that dual blockade of the EGFR and VEGF pathways is a viable strategy in the EGFR-mutant advanced NSCLC population to overcome the resistance to EGFR-TKIs. Aumolertinib (HS-10296) is a novel, third-generation EGFR-TKI approved in China to treat EGFR mutation positive non-small cell lung cancer. Apatinib is a small-molecule tyrosine kinase inhibitor that has promising anti-angiogenesis and antitumor activity for NSCLC. Here, we aimed to evaluate the safety and anticancer activity of aumolertinib alone/with apatinib for advanced/metastatic NSCLC patients with EGFR mutation. **Methods:** The phase III, multicenter, randomized, open-label, controlled study is evaluating the efficacy and safety of aumolertinib plus apatinib versus aumolertinib alone as first line therapy in adult patients with EGFR+ NSCLC. Adult patients with histologically confirmed stage IIIB/IV NSCLC harboring EGFR mutations without prior EGFR TKI treatment are eligible for this study. The performance status (Eastern Cooperative Oncology Group) is 0 or 1. This trial prepared to enroll approximately 300 patients, which will be randomized (1:1) to receive oral aumolertinib once daily 110 mg or adding apatinib 250 mg a day until assessed progressive disease(PD)，stratified by EGFR mutation (Ex19del /L858R/others) and distant metastases sites (brain/liver/others). The primary endpoint is progression free survival assessed by investigators using Response Evaluation Criteria in Solid Tumors 1.1. Secondary endpoints are disease control rate, duration of response, overall survival and safety. Adverse effects were graded per CTCAE v.4.03. This trial is registered as ChiCTR2100047453. Results: Recruiting. Conclusions: Recruiting. Clinical trial information: ChiCTR2100047453. Research Sponsor: Hansoh Pharma.

TPS9152 **Poster Session**

GALLANT-1: Galectin-3 (Gal-3) inhibitor GB1211 plus atezolizumab (atezo) in patients with non–small cell lung cancer (NSCLC)—A randomized, double-blind trial. *First Author: François Ghiringhelli, University of Burgundy, Genetic and Immunotherapy Medical Institute, Centre Georges Francois Leclerc, Dijon, France*

Background: Gal-3 is a protein that binds specifically to N-acetylglucosamine-expressing carbohydrates, which are upregulated on key tumorigenic cell surface proteins. Gal-3 is widely overexpressed in the tumor microenvironment and is generally linked to poor outcomes. Gal-3 regulates immune cell function of T cells and macrophages, and promotes neovascularization and fibrosis [Peng Cancer Res 2008; Markowska J Biol Chem 2011; Kouo Cancer Immunol Res 2015]. Gal-3 sequesters interferon gamma, reduces T-cell influx, and contributes to tumor cell evasion of the immune system via LAG-3 activation [Chen PNAS 2009; Gordon-Alonso Nat Commun 2017]. Gal-3 has been identified as a marker of resistance to checkpoint inhibitors (CPIs); patients with stage IV NSCLC with high Gal-3 levels (> 70% Gal-3 immunohistochemical staining) have been shown to be resistant to the CPI pembrolizumab [Capalbo Int J Mol Sci 2019]. Animal data indicate synergy between CPI therapy and Gal-3 inhibition [Vuong Cancer Res 2019; Zhang FEBS Open Bio 2021]. Thus, inhibiting Gal-3 together with CPI-based immunotherapy may enhance tumor-specific immune responses, and overcome CPI resistance. **Methods:** GALLANT-1 (NCT05240131) is a 3-part, placebo-controlled phase Ib/IIa trial that will investigate safety and efficacy of GB1211 (a Gal-3 inhibitor) + atezo vs placebo + atezo in patients with advanced NSCLC. Part A will include 8–12 patients and study safety and tolerability of 200 mg and 400 mg GB1211 twice-daily + atezo (open-label). Primary endpoint is number of adverse events (AEs) after 12 weeks' treatment and will determine the dosage for Part B. Part B will include 75–94 patients, and is a randomized, double-blind study of GB1211 + atezo or placebo + atezo. Primary endpoints are safety (number of AEs) and efficacy (percentage change from baseline in the sum of longest diameter of target lesions after 12 weeks' treatment). Part C is an expansion study including patients from Parts A and B, with safety and efficacy assessments. Eligibility criteria: advanced or metastatic stage IIIB or IV NSCLC adenocarcinoma; measurable disease per RECIST v1.1; expression of programmed death ligand-1 on ≥50% of tumor cells; eligible for 1200 mg atezo every 3 weeks. Exclusion criteria: symptomatic, untreated, or actively progressing central nervous system metastases; prior systemic chemotherapy for treatment of recurrent advanced or metastatic disease, except if part of neoadjuvant/adjuvant therapy; prior treatment with immune CPIs and/or GB1211; presence of *EGFR* mutation and *ALK*, *ROS1*, and *RET* alterations; treatment with antineoplastic or systemic immunotherapeutic agents prior to first GB1211 dose; severe infectious disease < 4 weeks prior to first GB1211 dose; active hepatitis B or C, HIV, or COVID-19. The study is being initiated; updated enrollment status will be presented at the meeting. Clinical trial information: NCT05240131. Research Sponsor: NCT05240131 (GALLANT-1) is sponsored by Galecto, Inc. Atezolizumab is manufactured by Roche Registration GmbH, Germany. Third-party medical writing assistance was provided by Lynda McEvoy, PhD, of Ashfield Health, funded by Galecto, Inc.

TPS9153 **Poster Session**

Capmatinib plus osimertinib versus platinum-pemetrexed doublet chemotherapy as second-line therapy in patients with stage IIIb/IIIc or IV *EGFR*-mutant, T790M-negative NSCLC harboring *MET* amplification. *First Author: Yi-Long Wu, Department of Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital and Guangdong Academy of Medical Sciences, Guangzhou, China*

Background: *MET* amplification can arise as a bypass resistance mechanism to EGFR tyrosine kinase inhibitors (TKIs) and occurs in ~5-26% of EGFR TKI resistant *EGFR*-mutant non-small cell lung cancer (NSCLC). These patients (pts) have limited treatment options, particularly in the *EGFR* T790M negative (T790M–) setting. Capmatinib, a MET inhibitor, is approved in about ten countries for the treatment of metastatic *MET* exon 14 skipping NSCLC. In preliminary studies, capmatinib plus EGFR TKIs showed antitumor activity in the post-EGFR TKI, *EGFR*-mutant NSCLC setting. GEOMETRY-E (NCT04816214) is a randomized, controlled, open-label, multicenter, phase 3 study evaluating the efficacy and safety of capmatinib + osimertinib vs platinum-pemetrexed doublet chemotherapy as second line treatment for advanced NSCLC. **Methods:** This ongoing study began enrollment in September 2021 and is recruiting adult pts with stage IIIB/IIIC or IV *EGFR*-mutant, T790M–, *MET*-amplified NSCLC who had progressed on either $1^{st}/2^{nd}$ generation EGFR TKIs, osimertinib or other 3^{rd} generation EGFR TKIs. Pts with neurologically unstable, symptomatic CNS metastases or those requiring increasing doses of steroids ≤2 weeks prior to study entry to manage CNS symptoms are ineligible. This is a 2-part study where Part 1 (initial run-in,~10 pts) will confirm the recommended dose for the randomized Part 2 and evaluate the safety and tolerability of capmatinib + osimertinib. In Part 1, pts will receive oral capmatinib 400 mg twice daily + osimertinib 80 mg once daily in 21-day cycles. Part 2 will evaluate the efficacy and safety of capmatinib + osimertinib vs platinum (cisplatin/carboplatin)-pemetrexed. Part 2 will enroll ~225 pts, in 2:1 randomization, stratified by the presence of brain metastases (yes/no) and prior treatment with 3^{rd} generation EGFR TKIs (yes/no). In Part 1, the primary endpoint is the incidence of dose limiting toxicities during the first 21 days of treatment. Secondary endpoints include safety; tolerability; pharmacokinetics (PK); investigator-assessed overall response rate (ORR), duration of response (DOR), time to response (TTR), disease control rate (DCR) and progression-free survival (PFS) per the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). In Part 2, the primary endpoint is blinded independent review committee (BIRC)-assessed PFS per RECIST 1.1. The key secondary endpoints are ORR by BIRC per RECIST 1.1 and overall intracranial response rate (OiRR) by BIRC per Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM). Other secondary endpoints include DOR, TTR and DCR by BIRC; investigator-assessed PFS after next line of treatment; PK; safety; overall survival; patient-reported outcomes; intracranial DCR, duration of and time to intracranial response by BIRC per RANO-BM. Clinical trial information: NCT04816214. Research Sponsor: Novartis Pharmaceuticals.

TPS9154 **Poster Session**

Phase I trial of in situ vaccination with autologous CCL21-modified dendritic cells (CCL21-DC) combined with pembrolizumab for advanced NSCLC. *First Author: Aaron E. Lisberg, University of California-Los Angeles, Los Angeles, CA*

Background: Effective immunotherapy options are lacking for patients with advanced non-small cell lung cancer (NSCLC) who progress on a programmed cell death-(ligand)1 [PD-(L)1] inhibitor and for those that are epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) rearrangement positive after progression on tyrosine kinase inhibitor (TKI) therapy. One potential approach to improve immune checkpoint efficacy in these patient populations is to promote cytolytic T cell infiltration into tumors. This can be accomplished via *in situ* vaccination with functional antigen presenting cells (APCs) which can take advantage of the full repertoire of tumor antigens and convert the tumor into a lymph node-like environment promoting both local and systemic T cell activation. The chemokine CCL21 promotes co-localization of naive T cells and antigen-experienced dendritic cells (DCs) to facilitate T cell activation. Our preclinical studies and phase I trial of intratumoral (IT) administration of DC genetically modified to overexpress CCL21 (CCL21-DC) revealed augmentation of tumor antigen presentation *in situ*, resulting in systemic antitumor immunity. However, increased PD-L1 expression was observed in some patient tumors, suggesting that tumor-mediated impairment of T cell function may be forestalling a more robust CCL21-DC mediated antitumor response. Similarly, improved PD-(L)1 inhibitor efficacy may be possible with enhanced T cell infiltration and augmented APC function following IT CCL21-DC. Therefore, we are conducting a phase I trial, combining IT CCL21-DC with pembrolizumab in patients with advanced NSCLC that are either (1) EGFR/ALK wild-type after progression on a PD-(L)1 inhibitor or (2) EGFR/ALK mutant after progression on TKI therapy. **Methods:** Phase I, dose-escalating, multi-cohort trial followed by dose expansion. Maximum of 24 patients (9-12 escalation + 12 expansion) with stage IV NSCLC will be evaluated who have tumors accessible for IT injection and are either (1) EGFR/ALK wild-type after progression on a PD-(L)1 inhibitor or (2) EGFR/ALK mutant after progression on TKI therapy. Three IT injections of autologous CCL21-DC (days 0, 21, 42) will be concurrently administered with pembrolizumab, followed by q3wk pembrolizumab up to 1 year. Primary objective of dose escalation is safety and determination of maximum tolerated dose (MTD) of IT CCL21-DC ($5x10^6$, $1x10^7$, or $3x10^7$) when combined with pembrolizumab. Primary objective of dose expansion is objective response rate at MTD. Secondary objectives include adverse event profiling and determination of drug target activity by immune monitoring studies. This trial is currently open for enrollment. Clinical trial information: NCT03546361. Research Sponsor: CIRM, NIH.

TPS9155 **Poster Session**

Phase 1/2 study of BLU-451, a central nervous system (CNS) penetrant, small molecule inhibitor of EGFR, in incurable advanced cancers with *EGFR* exon 20 insertion (ex20ins) mutations. *First Author: Alexander I. Spira, Next Oncology Virginia and Virginia Cancer Specialists Research Institute, Fairfax, VA*

Background: Oncogenic *EGFR* ex20ins mutations, found in ~2% of non-small cell lung cancers (NSCLC) and a small percentage of other cancers, are generally not responsive to EGFR-targeted agents that have been approved for treatment of NSCLC with a common *EGFR* mutation, including L858R and exon 19 deletion. Similar to these more common types of *EGFR*-mutated NSCLC, CNS metastases are a challenge with *EGFR* ex20ins NSCLC and are associated with poor outcomes. While two EGFR ex20ins-targeting drugs were recently approved by the FDA (amivantamab and mobocertinib), neither have established CNS activity. BLU-451 is a CNS penetrant, wild type-sparing, covalent small molecule inhibitor of EGFR ex20ins as well as atypical (G719C, G719S, L861Q) and common EGFR mutants. Preclinical data have shown BLU-451 to have potent antitumor activity, including in an intracranial xenograft model, which has led to its clinical development in *EGFR*-mutant NSCLC. **Methods:** BLU-451-1101 (NCT05241873) is a phase 1/2, global, open-label study designed to evaluate single-agent BLU-451 in patients with NSCLC harboring *EGFR* ex20ins that has progressed following prior treatment for incurable recurrent or metastatic disease. Patients with Eastern Cooperative Oncology Group performance status 0–1 and EGFR ex20ins, exon 18 G719X or exon 21 L861Q mutant NSCLC (phases 1 and 2) or other cancers except primary CNS tumors (phase 1 only) are eligible. Patients with known ROS, RAF, ALK, or *EGFR* C797S mutations will be excluded. Stable, asymptomatic brain metastases are permitted, and active asymptomatic brain metastases are permitted in specific cohorts. Primary endpoints are determination of maximum tolerated dose (MTD), recommended phase 2 dose (RP2D), safety and tolerability (phase 1), in addition to evaluation of antitumor activity at the RP2D by RECIST v1.1 (phase 2). Secondary endpoints are evaluation of pharmacokinetics (PK) and antitumor activity by RECIST v1.1.(phase 1) and PK, safety, tolerability, and CNS antitumor activity (phase 2). Dose escalation will utilize a 3+3 design with up to 6 patients per cohort in phase 1 dose escalation and up to 12 per cohort in phase 1 dose expansion. Phase 2 will enroll patients in 3 cohorts (n = 18 each): patients with prior platinum-based chemotherapy and an EGFR ex20ins-targeted agent; patients with prior platinum but no EGFR ex20ins-targeted agent; and patients with active asymptomatic brain metastases with prior platinum with or without an EGFR ex20ins-targeted agent. The study is planned for approximately 40 centers in North America, the Asia-Pacific region, and/or Europe. Clinical trial information: NCT05241873. Research Sponsor: Blueprint Medicines Corporation.

TPS9156 **Poster Session**

A phase 1/2 study of BLU-945 in patients with common activating *EGFR*-mutant non–small cell lung cancer (NSCLC): SYMPHONY trial in progress. *First Author: Elaine Shum, Perlmutter Cancer Center, New York University Langone Health, New York, NY*

Background: Although EGFR-targeted therapies have improved outcomes in patients with *EGFR*-mutant (*EGFR*m) NSCLC, such as *EGFR* ex19del and L858R, resistance to these drugs is inevitable. BLU-945 is an investigational next-generation EGFR tyrosine kinase inhibitor (TKI) designed to suppress common activating and on-target resistance EGFR mutations, such as C797S and T790M. Preclinically it has shown activity as monotherapy in osimertinib-resistant patient-derived xenograft (PDX) models. In addition, BLU-945 has > 450-fold selectivity for C797S and T790M mutants over wildtype, advantageous for combinations with complementary EGFR-targeting agents, such as osimertinib. These combinations have shown enhanced activity in PDX models. The SYMPHONY trial (BLU-945-1101; NCT04862780) is an international, open-label, first-in-human, phase 1/2 study designed to evaluate safety, tolerability, and antitumor activity of BLU-945 as monotherapy and in combination with osimertinib in patients with *EGFR*m NSCLC. **Methods:** Key eligibility criteria include adults with pathologically confirmed metastatic NSCLC with an activating *EGFR* mutation, Eastern Cooperative Oncology Group performance status 0–1, and previous treatment with ≥1 EGFR-targeted TKI. Patients with asymptomatic brain metastases who are on stable doses of corticosteroids are eligible. Tumors with additional known driver alterations, including *EGFR* exon 20 insertions and other kinase drivers, are excluded. Primary endpoints are maximum tolerated dose, recommended phase 2 dose (RP2D) and safety (phase 1); and overall response rate (ORR) by RECIST 1.1 (phase 2). Key secondary endpoints include ORR, duration of response (DOR), pharmacokinetics (PK), and pharmacodynamics (PD; phase 1); and DOR, progression-free survival, overall survival, CNS efficacy, PK, and safety (phase 2). Phase 1 dose escalation will be done using Bayesian optimal interval design; ~85 patients will receive BLU-945 monotherapy and ~18 will receive combination BLU-945 and osimertinib. In the phase 2 dose expansion, patients will receive BLU-945 at the RP2D of the monotherapy in 3 groups based on *EGFR* mutational profile: T790M and C797S (n≈37), T790M, but not C797S (n≈12), and C797S, but not T790M (n≈12). In a combination group, BLU-945 plus osimertinib will be administered at RP2D of the combination to n≈24 patients, ≥12 with both T790M and C797S mutations. Patients may receive treatment until disease progression or unacceptable toxicity. Recruitment has started and approximately 30 sites will be open for enrollment across North America, Europe, and Asia. Clinical trial information: NCT04862780. Research Sponsor: Blueprint Medicines Corporation.

TPS9157 **Poster Session**

Additional chemotherapy for EGFRm patients with the continued presence of plasma ctDNA EGFRm at week 3 after start of osimertinib first-line treatment (PACE). *First Author: Jan Alexander Stratmann, University Hospital Frankfurt, Frankfurt, Germany*

Background: *Epidermal growth factor receptor* (EGFR) – mutated non-small cell lung cancer (NSCLC) is susceptible to *EGFR* targeting tyrosine kinase inhibitors (TKI), such as the third generation TKI osimertinib. However, response rate and duration vary between patients. Among others, the specific subtype of EGFR-mutation, its co-occurrence with other genetic alterations, and the detection of phosphorylated EGFR (pEGFR) in the plasma, and its clearance upon treatment were previously identified as markers that predict therapy response. A high proportion of patients with early (3-6 weeks after start) pEGFR clearance from plasma show impressive survival upon single-agent TKI. However, failure to achieve early clearance upon Osimertinib is associated with unfavorable outcome. For these patients, treatment concepts are lacking. Here, we report about the initiation of a clinical trial that evaluates the combination of EGFR-directed TKI and platinum-based chemotherapy as an early treatment escalation strategy for this high-risk patient population. **Methods:** PACE is a prospective multicenter single-arm investigator-initiated phase II trial. Patients with NSCLC harboring *L858R or del19 EGFR* mutation, who are treated with first-line Osimertinib are subjected to liquid biopsy-based early response assessment three weeks after start of therapy. Failure to clear pEGFR from plasma at this time point triggers treatment escalation with the addition of platinum-based doublet chemotherapy to the Osimertinib treatment. The primary outcome measure of the trial is progression-free survival (PFS), with the objective to assess the efficacy of biomarker-driven escalation of osimertinib therapy with a combination platinum-based regimen. Secondary outcome measures are the overall response rate (ORR), overall survival (OS), and the Quality of life (QLQ-C30, CTCAE-PROs) of the treated patients. In exploratory analyses, we will assess whether specific patterns of co-mutations are associated with early treatment failure (upon TKI) and pEGFR persistence. Fig. 1 illustrates the trial concept. A sample of 46 subjects achieves 80% power at a 0.05 significance level to detect a PFS of 14.4 months in the experimental treatment group when the PFS of the historic control group is 9.1 months; a total of 400 patients need to be screened within the national Network Genomic Medicine. Enrollment started in 12/2021. The clinical trial is supported by AstraZeneca and Guardant. EudraCT registration number: 2019-004757-88.

TPS9158 **Poster Session**

Randomized phase 2 study evaluating efficacy and safety of inupadenant in combination with chemotherapy in adults with metastatic non–small cell lung cancer (mNSCLC) who progressed on immunotherapy. *First Author: Mary E.R. O'Brien, The Institute of Cancer Research and the Royal Marsden NHS Foundation Trust, Surrey, United Kingdom*

Background: In cancer, the accumulation of adenosine in the tumor microenvironment (TME) mediates immune suppression mainly via the high affinity A2A receptor (A2AR), causing dysregulation of innate and adaptative immune cell subsets and dampening the antitumor immune response. This results in increased tumor cell survival and immune escape (Blay 1997; Merighi 2003; Muller-Haegele 2014). Therefore, inhibiting A2AR could reverse immunosuppression and re-establish immune surveillance in the tumor microenvironment. Inupadenant is an antagonist of the A2AR with potent inhibition of A2AR even at the high concentrations of adenosine present in the tumor microenvironment. Ongoing clinical studies have established inupadenant as a molecule with a favorable safety profile with preliminary evidence of clinical activity in multiple tumor types, including durable PRs in patients who have exhausted standard treatment options (Buisseret 2021). The standard treatment for patients without a driving mutation who progress on first-line IO is a platinum-based doublet chemotherapy regimen. Carboplatin plus Pemetrexed (C+P) is the preferred chemotherapy in nonsquamous mNSCLC. Study A2A-005 will evaluate the efficacy of inupadenant in combination with C+P as a second-line therapy in adult patients with nonsquamous mNSCLC (post-IO). A successful outcome from study A2A-005 will help address a high unmet need for this patient population and could lead to new therapeutic options. **Methods:** This is a 2-part study. The first part is an open label dose-finding part to determine the safety and recommended Phase 2 dose (RP2D) of inupadenant in combination with C+P (N = 40). In Part 2, 150 patients will be randomized 1:1 to inupadenant or placebo, both in combination with C+P. Tumor response will be determined according to RECIST 1.1 criteria and safety findings will be reviewed by the Safety Review Committee (for Part 1) and the Data Monitoring Committee (for Part 2). Key eligibility criteria include 1) mNSCLC of nonsquamous pathology, 2) have received only 1 line of anti-PD-(L)1 therapy in the metastatic setting, without concomitant chemotherapy, and have progressed (IO/IO combination therapy is allowed), 3) have measurable disease as defined by RECIST v1.1 criteria and 4) Eastern Cooperative Oncology Group status ≤1. Primary endpoints are RP2D (for Part 1) and PFS (for Part 2). Secondary endpoints include change in tumor size, ORR, OS, and adverse events. Correlative aims include assessing blood and tissue biomarkers for association with clinical benefit. The study will be conducted in approximately 11 countries in North America and Europe. Clinical trial information: EudraCT 2021-005487-22. Research Sponsor: Iteos Therapeutics, Gosselies, Belgium.

TPS9159 **Poster Session**

AcceleRET Lung: A phase 3 study of first-line pralsetinib in patients with *RET* fusion–positive advanced/metastatic NSCLC. *First Author: Sanjay Popat, Lung Cancer Unit, Department of Medicine, The Royal Marsden Hospital, London, United Kingdom*

Background: *RET* gene fusions have been identified as oncogenic drivers in multiple tumor types, including 1–2% of non-small cell lung cancer (NSCLC). Pralsetinib is a potent, selective RET inhibitor, approved in the US and EU for the treatment of metastatic *RET* fusion–positive NSCLC based on the phase 1/2 ARROW study (NCT03037385). In the ARROW study (data cutoff: Nov 6, 2020), patients who initiated 400 mg once daily (QD) of pralsetinib after platinum-based chemotherapy achieved an overall response rate (ORR) of 62%, per independent central review. In the treatment-naïve group, the ORR was 79%. Most treatment-related adverse events were grade 1–2 across the entire safety population treated at 400 mg QD (n=471). AcceleRET Lung, an international, open-label, randomized, phase 3 study (NCT04222972), will evaluate the efficacy and safety of pralsetinib versus standard of care (SOC) for first-line treatment of advanced/metastatic *RET* fusion–positive NSCLC. Abstracts for this study were previously submitted to the European Lung Cancer Congress 2020, the American Society of Clinical Oncology 2020 annual meeting, and 2020 World Conference on Lung Cancer. **Methods:** Approximately 226 patients with metastatic *RET* fusion–positive NSCLC will be randomized 1:1 to oral pralsetinib (400 mg QD) or SOC (non-squamous histology: platinum/pemetrexed ± pembrolizumab followed by maintenance pemetrexed ± pembrolizumab [at investigator's discretion]; squamous histology: platinum/gemcitabine or platinum + pembrolizumab + paclitaxel/nab-paclitaxel followed by maintenance pembrolizumab). Stratification factors include intended use of pembrolizumab, history of brain metastases, and Eastern Cooperative Oncology Group Performance Status. Key eligibility criteria include no prior systemic treatment for advanced/metastatic NSCLC; *RET* fusion–positive tumor by local or central assessment; no additional actionable oncogenic drivers; no prior selective RET inhibitor; measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Patients with central nervous system metastases were permitted if asymptomatic and on a stable dose of corticosteroids. Cross-over to receive pralsetinib upon disease progression will be permitted for patients randomized to SOC. The primary endpoint is progression-free survival (blinded independent central review; RECIST v1.1). Secondary endpoints include ORR, overall survival, duration of response, disease control rate, clinical benefit rate, time to intracranial progression, intracranial ORR, safety/tolerability and quality of life evaluations. Identification of potential biomarkers of antineoplastic activity and resistance was an exploratory endpoint. Recruitment has begun with sites (active or planned) in North America, Central America, Europe and Asia. Clinical trial information: NCT04222972. Research Sponsor: F. Hoffmann-La Roche, Ltd.

TPS9160 **Poster Session**

A randomized, double-blind, phase 3 trial of MK-7684A plus chemotherapy versus pembrolizumab plus chemotherapy as first-line therapy for metastatic non–small cell lung cancer (NSCLC): KeyVibe-007. *First Author: Marina Chiara Garassino, University of Chicago Medicine & Biological Sciences, Knapp Center for Biomedical Discovery (KCBD), Chicago, IL*

Background: Pembrolizumab (pembro) plus chemotherapy is a standard first-line treatment for patients with metastatic NSCLC without *EGFR* or *ALK* genomic alterations regardless of PD-L1 expression. The combination of pembro and vibostolimab, a humanized monoclonal antibody that blocks the interaction between the T-cell immunoreceptor with immunoglobulin and ITIM domains (TIGIT) and its ligands CD112 and CD155, showed antitumor activity and manageable safety in patients with advanced or metastatic NSCLC in the phase 1 MK-7684-001 study. The phase 3 KeyVibe-007 (NCT05226598) study is evaluating the efficacy and safety of pembro and vibostolimab, coformulated as MK-7684A, in combination with chemotherapy versus pembro plus chemotherapy as first-line therapy for metastatic NSCLC. **Methods:** his randomized, double-blind study is enrolling adults with histologically or cytologically confirmed, previously untreated, stage IV squamous or nonsquamous NSCLC without *EGFR* mutations or *ALK/ROS1* gene rearrangements. Patients must have measurable disease per RECIST v1.1, ECOG PS of 0 or 1, and a tumor tissue sample for PD-L1 assessment. Patients are randomized 1:1 to receive MK-7684A (MK-7684 200 mg + pembro 200 mg) IV or pembro 200 mg IV plus chemotherapy (squamous: carboplatin area under the curve [AUC] 6 mg/mL/min plus paclitaxel 200 mg/m^2 or nab-paclitaxel 100 mg/m^2 [days 1, 8, 15]; nonsquamous: pemetrexed 500 mg/m^2 plus cisplatin 75 mg/m^2 or carboplatin AUC 5 mg/mL/min) Q3W for 4 cycles followed by MK-7684A or pembro Q3W, per randomized therapy, for up to 31 additional cycles (plus continued pemetrexed maintenance, nonsquamous only) or until PD, unacceptable AEs, investigator decision, or patient withdrawal. Patients with PD after completing first-course treatment may be eligible for up to 17 additional cycles of their randomized therapy (MK-7684A or pembro). Randomization is stratified by ECOG PS (0 vs 1), tumor histology (squamous vs nonsquamous), PD-L1 expression (TPS < 50% vs ≥50%), and region (East Asia vs North America/Western Europe vs rest of world). Dual primary endpoints are PFS per RECIST v1.1 by blinded independent central review (BICR) and OS. Secondary endpoints are ORR and duration of response per RECIST v1.1 by BICR, change from baseline and time to true deterioration in patient-reported outcomes (PROs), and safety. Imaging assessments occur at weeks 6, 12, and 18, then Q9W through week 63 and Q12W thereafter until disease progression, start of new anticancer treatment, withdrawal of consent, or death. PROs are assessed using validated instruments including the EORTC Quality of Life Questionnaire Lung Cancer13 and NSCLC Symptom Assessment Questionnaire. AEs are graded according to National Cancer Institute Common Terminology Criteria for Adverse Events v5.0. Enrollment is ongoing. Clinical trial information: NCT05226598. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

LBA9500 **Oral Abstract Session**

Distant metastasis-free survival with pembrolizumab versus placebo as adjuvant therapy in stage IIB or IIC melanoma: The phase 3 KEYNOTE-716 study. *First Author: Georgina V. Long, Melanoma Institute Australia, The University of Sydney, Royal North Shore and Mater Hospitals, Sydney, Australia*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

9501 **Oral Abstract Session**

Survival data of PRADO: A phase 2 study of personalized response-driven surgery and adjuvant therapy after neoadjuvant ipilimumab (IPI) and nivolumab (NIVO) in resectable stage III melanoma. *First Author: Christian U. Blank, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: In the OpACIN-neo study, 2 cycles neoadjuvant (neoadj) IPI 1mg/kg + NIVO 3mg/kg (I1N3) have been identified as most favorable dosing scheme with a pathologic response rate (pRR) of 77% and 20% grade 3-4 irAEs. After 24.6 months median follow-up (FU), the 2-year (2y) RFS was 96.9% for patients (pts) with pathologic response versus 35.5% for non-responders (>50% viable tumor; pNR). These data raised the question whether therapeutic lymph node dissection (TLND) could be safely omitted in pts achieving a major pathologic response (MPR; ≤10% viable tumor) in their index node (ILN; largest LN metastasis at baseline), and if additional adjuvant (adj) therapy could improve the outcome of pNR pts. **Methods:** PRADO is an extension cohort of the phase 2 OpACIN-neo study aiming to confirm the pRR and safety of neoadj I1N3 and to test response-driven subsequent therapy. Pts with stage III melanoma were included to receive 2 cycles neoadj I1N3 after marker placement in the ILN. ILN resection was planned at week 6. Pts that achieved MPR in the ILN did not undergo TLND; pts with partial response (pPR; >10 – ≤50% viable tumor) underwent TLND; and pts with pNR underwent TLND and received adj NIVO or dabrafenib plus trametinib (D+T) for 52 weeks ±radiotherapy (RT). Primary endpoints were pRR in the ILN and RFS at 2y. The 2y RFS rates were calculated using a Kaplan Meier based method. **Results:** Between Nov 2018 and Jan 2020, 99 patients were enrolled and treated with at least 1 cycle of neoadj I1N3. We previously showed a pRR of 72% (95% CI 62 - 80), including 60 (61%) pts with MPR and 11 (11%) pts with pPR. TLND omission in MPR pts resulted in significant reduced surgical morbidity and improved quality of life. There were 27 non-responders of whom 6 developed distant metastasis before ILN resection. Of the other 21 pNR pts, 7 received adj NIVO, 10 adj D+T, 3 no adj therapy, and 1 was lost to FU. After a median FU of 27.9 months (data cutoff Jan 31, 2022), the estimated 2y RFS rate for MPR pts was 93.3% (95% CI 87.2 – 99.9), with 4/60 pts developing a regional relapse. Distant metastasis-free survival (DMFS) was 100%. Of the 11 pPR pts, 4 developed a relapse (all distant), resulting in a 2y RFS and DMFS rate of 63.6% (95% CI 40.7 – 99.5). The 2y RFS rate of the pNR pts was 71.4% (95% CI 54.5 – 93.6), and DMFS 76.2%. At data cutoff, relapse occurred in 2/7 pNR pts with adj NIVO and 3/10 with adj D+T. Final data cutoff is planned mid Feb, 2022. **Conclusions:** MPR pts in whom TLND was omitted showed a 2y RFS rate of 93.3% and DMFS of 100%, indicating that the ILN procedure and omitting adj therapy could become a safe approach in these pts. Adj systemic therapy in pNR pts seems to improve RFS as compared to historic control (OpACIN-neo), thus should be considered in this unfavorable pNR group. The DMFS rate of 63.6% observed in the pPR group advocates the consideration of adj therapy also for this subgroup in the future. Clinical trial information: NCT02977052. Research Sponsor: BMS.

9502 **Oral Abstract Session**

Neoadjuvant PD-1 blockade in patients with resectable desmoplastic melanoma (SWOG 1512). *First Author: Kari Lynn Kendra, The Ohio State University Comprehensive Cancer Center, Department of Internal Medicine, Columbus, OH*

Background: Desmoplastic melanoma (DM) is a rare cancer defined by a dense fibrous collagen matrix. It is associated with high UV exposure leading to a high mutational load. When locally advanced, the standard of care is wide excision and radiation therapy due to its propensity for local relapses. Metastatic DM has a high response rate (RR) to PD-1 blockade therapy (Eroglu et al. Nature 2018). We hypothesized that neoadjuvant treatment with anti-PD-1 monotherapy may induce pathologically confirmed regressions in a high percentage of cases, potentially allowing for less extensive local treatment. **Methods:** Patients > 18 years old with histologically confirmed resectable (primary, recurrent, or regional lymph node metastasis) DM with clinical evidence of residual disease received pembrolizumab 200 mg q3 weeks (wk) 3 followed by excision. No adjuvant therapy was administered. Primary endpoint: pathological complete response (pCR), with the assumption that pCR of 25% would be considered a positive result worthy of future study. To test this hypothesis, a single arm trial with 25 eligible patients would have a 3.4% probability of a positive result with a true pCR of 5%, and a power of 90% of a positive result if the true pCR is 25%. Secondary endpoints: clinical RR by imaging and clinical exam, median overall survival (OS), and evaluation of safety/tolerability of neoadjuvant pembrolizumab. Adverse events were assessed q3 wk. Disease assessments occurred at baseline and q9 wk. NCT02775851. **Results:** We enrolled-29 eligible patients with resectable DM. One patient refused treatment and was omitted from further analysis. Median age was 75, 79% were male, primary sites of disease were 72% H&N, 10% torso, 14% extremities, 3% unknown. No patients received prior systemic therapy. Mean time from C1D1 treatment to surgery was 84.2 (range: 52-135) days, mean number of cycles received 3.3 (range: 2-4). 26/27 (93%) of patients underwent wide excision of the resectable disease, of which 14 (54%) underwent sentinel lymph node biopsy. One patient underwent resection of a nodal recurrence thus did not require wide excision. pCR was noted in 15/27 (56%) of patients (95% CI: 35%-75%). One patient without a pCR had a major pathologic response with 0.2 mm residual melanoma. In addition, one patient with a clinical CR did not undergo resection by choice. None became inoperable. Clinical RR was 52% (95% CI: 32%-71%). Median OS has not been reached, with two nontreatment related deaths (acute hypoxic respiratory failure; unknown). No > grade 2 related adverse events were observed. **Conclusions:** Neoadjuvant pembrolizumab in resectable DM results in a high pCR rate with excellent tolerance, which supports consideration of PD-1 blockade therapy prior to surgery. Funding: U10CA180888 and U10CA180819; and in part by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. Clinical trial information: NCT02775851. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

9503 **Oral Abstract Session**

NeoTrio: Randomized trial of neoadjuvant (NAT) pembrolizumab (Pembro) alone, in sequence (SEQ) with, or concurrent (CON) with dabrafenib plus trametinib (D+T) in resectable BRAF-mutant stage III melanoma to determine optimal combination of therapy. *First Author: Georgina V. Long, Melanoma Institute Australia, The University of Sydney, Royal North Shore and Mater Hospitals, Sydney, NSW, Australia*

Background: Combination anti-PD(L)1 and BRAF/MEK-targeted therapy (TT) improves PFS in stage IV melanoma vs TT. In stage IV melanoma recent data suggest immunotherapy 1st until progression, rather than BRAF-TT, improves OS, and induction TT upfront adds little benefit. NeoTrio explored the optimal combination of BRAF-TT and anti-PD1 using the NAT platform in pts with stage III melanoma (NCT02858921). **Methods:** 60 pts with resectable, RECIST measurable stage III (no in-transit) $BRAF^{V600}$-mutant melanoma were randomized 1:1:1 to 3 arms of 6 wks of NAT followed by complete lymph node dissection (CLND): A) Pembro ALONE (200mg Q3W x 2); B) SEQ - D+T (150mg bd + 2mg od) for 1 wk followed by pembro (200mg x 2); C) CON – D+T+pembro (doses as SEQ). Pts had 46 wks pembro post-CLND. Primary endpoint was the pathological response rate (pRR) and pathological complete response (pCR) at wk 6. Secondary endpoints; RECIST RR at wk 6, event-free survival (EFS), RFS, OS, adverse events (AE) and translational endpoints. **Results:** At data cutoff 2 Jan 2022, 20 pts per arm had similar baseline characteristics; overall 42% female, med age 53 yrs, 82% BRAF V600E, 62% clinical N1b. Med f/u was 20 months (95% CI 17-31). The pCR rate and pRR were highest in CON arm, and similar in ALONE and SEQ arms (Table). Events (progression before surgery, recurrence after surgery or death) were highest in ALONE arm at this 1st analysis (Table). Assessment of the durability of path response subtypes in each arm is ongoing. Most common Rx related AE were fatigue (65%, 70%, 70%, ALONE, SEQ and CON respectively), pyrexia (0%, 25%, 85%) and rash (50%, 35%, 35%). Gd 3/4 AE occurred in 30%, 25% and 55%, respectively; pyrexia and hepatitis were common in CON during NAT. Rx interruptions during NAT occurred in 0, 3 and 19 pts, respectively; 1, 0 and 8 pts permanently discontinued. Post NAT surgical operability was the same or improved in 81%. Longitudinal analysis of melanoma tissue, microenvironment and microbiome is ongoing. **Conclusions:** CON D+T+pembro achieved the highest pRR, pCR rate, but with greater toxicity. Recurrences were seen in those with pCR/near pCR in BRAF-TT containing arms, but not in pembro ALONE, in keeping with previous data of NAT with checkpoint inhibitors vs BRAF-TT. Short course of D+T prior to PD1 did not improve path response, despite previous translational data showing increased tumour infiltrating T-cells early-during treatment with D+T. Follow up is ongoing. Clinical trial information: NCT02858921. Research Sponsor: Melanoma Institute Australia and MSD.

	ALONE (n=20)	SEQ (n=20)	CON (n=20)
pRR	11 (55%)	10 (50%)	16 (80%)
pCR	6	4	10
Near-pCR	2	2	1
pPR	3	4	5
pNR	7	10	3
RECIST ORR/CR	60% / 10%	45% / 0%	70% / 30%
No. Events	7*	6	4†
No. Recurred by pCR/near-pCR/pPR/pNR	0/0/2/3	0/1/0/5	1/0/2/0
No. Death	3	1	2
1-yr EFS (95% CI)	80% (64-100)	80% (64-100)	79% (62-100)

*2 pts and †1 pt progressed prior to surgery; no CLND was performed.

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9505 **Oral Abstract Session**

Nivolumab (NIVO) + relatlimab (RELA) versus NIVO in previously untreated metastatic or unresectable melanoma: OS and ORR by key subgroups from RELATIVITY-047. *First Author: Hussein A. Tawbi, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: In the phase 2/3 RELATIVITY-047 trial, NIVO + RELA as a fixed-dose combination (FDC) significantly improved the primary endpoint of progression-free survival (PFS) versus NIVO in patients (pts) with previously untreated metastatic or unresectable melanoma. Secondary endpoints showed a clinically meaningful improvement in overall survival (OS), although not statistically significant, and a higher objective response rate (ORR). As previously reported, PFS and OS favored NIVO + RELA over NIVO across prespecified stratification factors (LAG-3 expression, PD-L1 expression, *BRAF* V600 mutation status, and metastasis stage). Here we report the first disclosure of ORR analyzed by prespecified stratification factors and OS and ORR in additional subgroups. **Methods:** Pts were randomized 1:1 to receive NIVO 480 mg + RELA 160 mg FDC or NIVO 480 mg intravenously Q4W. The primary endpoint was PFS per RECIST v1.1 assessed by blinded independent central review (BICR). Secondary endpoints were OS and ORR by BICR, tested in hierarchy. Exploratory analyses were performed for PFS, OS, and ORR by prespecified subgroups. **Results:** PFS continued to favor NIVO + RELA over NIVO across key subgroups. OS and ORR also favored NIVO + RELA over NIVO across key subgroups including those associated with poor prognosis (Table). ORR favored NIVO + RELA over NIVO for pts with LAG-3 expression ≥ 1% (47% vs 35%) and < 1% (31% vs 24%), PD-L1 expression ≥ 1% (53% vs 45%) and < 1% (36% vs 24%), and *BRAF* wild-type (43% vs 34%) and mutant (43% vs 31%) melanoma, respectively. Additional key prespecified subgroups will be presented. In all treated pts, NIVO + RELA maintained a manageable safety profile with no new or unexpected safety signals. **Conclusions:** NIVO + RELA was favored over NIVO across key subgroups for PFS, OS, and ORR, and findings appeared consistent with outcomes in the overall population. NIVO + RELA had a favorable benefit-risk profile. Clinical trial information: NCT03470922. Research Sponsor: Bristol Myers Squibb.

	Patients, n		mOS, months (95% CI)			ORR, % (95% exact CI)	
Subgroup	N+R	N	N+R	N	Unstratified HR (95% CI)	N+R	N
Overall	355	359	NR	34 (25.2–NR)	0.81^ (0.64–1.01)	43 (37.9–48.4)	33 (27.8–37.7)
Metastasis stage M1c*	151	127	34 (17.9–NR)	22 (13.8–33.2)	0.78 (0.56–1.08)	37 (29.4–45.3)	29 (21.4–37.9)
High tumor burden (≥ Q3)†	84	75	17 (10.8–34.0)	9 (6.2–19.1)	0.75 (0.51–1.11)	32 (22.4–43.2)	23 (13.8–33.8)
LDH ≤ ULN	225	231	NR	NR	0.76 (0.55–1.06)	50 (43.1–56.5)	35 (28.5–41.2)
LDH > ULN	129	128	17 (10.8–31.5)	14 (9.7–21.0)	0.81 (0.59–1.11)	32 (23.9–40.6)	29 (21.2–37.6)

CI, confidence interval; HR, hazard ratio; LDH, lactate dehydrogenase; mOS, median overall survival; NR, not reached; N, nivolumab; N+R, nivolumab plus relatlimab; n, number of patients; Q3, quartile 3; R, relatlimab; ULN, upper limit of normal. *AJCC v8; †Tumor burden quartile as determined by BICR at baseline; ^Unstratified HR was 0.81 and stratified HR was 0.80.

9506 **Oral Abstract Session**

Navtemadlin (KRT-232) activity after failure of anti-PD-1/L1 therapy in patients (pts) with *TP53^{WT}* Merkel cell carcinoma (MCC). *First Author: Michael K.K. Wong, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: MCC is a rare, aggressive, neuroendocrine skin cancer with a high risk of recurrence and metastases. A median survival of about 4 mo for pts with metastatic MCC who failed anti-PD-1/L1 therapy highlights an urgent need for novel therapies. In *TP53^{WT}* MCC, oncoproteins from the Merkel cell polyomavirus (MCPyV) inhibit p53 tumor suppressor functions by activating murine double minute 2 (MDM2). Navtemadlin is a potent, selective, orally available MDM2 inhibitor that overcomes MDM2 dysregulation by restoring p53 activity and inducing apoptosis of *TP53^{WT}* tumors. **Methods:** The dose-finding, phase 1b/2 KRT-232-103 study (NCT03787602) evaluated navtemadlin in adult *TP53^{WT}* MCC pts who failed anti-PD-1/L1 therapy. Pts were randomly assigned to oral navtemadlin once daily in 21- or 28-day cycles: 240 mg 7 days (D) on/14D off or 5D on/23D off, 180 mg 5D on/23 D off or 7D on/21D off, or 120 mg 7D on/14D off, until disease progression or unacceptable toxicity. The primary endpoint was Recommended Phase 2 Dose (RP2D); objective response rate (ORR) was assessed per RECIST v1.1. **Results:** As of Nov 30, 2021, 31 pts were enrolled with median age 66 y (range, 25-82); 52% had visceral disease and 71% had received ≥2 lines of prior therapy. Baseline tumor profiling of available samples showed low tumor mutation burden, MCPyV-positivity, and nonamplified *MDM2* gene in 100%, 92%, and 100% of pts, respectively. Treatment-emergent adverse events (TEAEs) were observed in 100% (68% grade 3/4) of pts. The most common Grade 3/4 TEAEs were hematologic: 32% anemia, 32% lymphopenia, and 19% thrombocytopenia. Navtemadlin doses ≤180 mg were well tolerated with fewer dose reductions and longer treatment durations; subsequently the 240 mg arms were closed to further enrollment. Evaluable pts receiving 180 mg 5D on/23D off showed a 25% confirmed ORR, a 38% unconfirmed + confirmed ORR, and a 63% disease control rate (Table); median duration of response was not reached (range, 6-16.2+ mo) and median time to treatment response was 4.1 mo (range, 1.2-7). Notably, one responder, following a prolonged partial response, achieved complete metabolic remission by PET/CT after 2 y on treatment. The 120 mg arm was closed due to a low response rate. The 180 mg dose has been selected for further evaluation. **Conclusions:** Navtemadlin is the first targeted agent to show promising single-agent activity in heavily pretreated MCC pts who failed anti-PD-1/L1 therapy. This study demonstrates that upregulation of the p53 pathway is a viable therapeutic strategy in MCC. Clinical trial information: NCT03787602. Research Sponsor: Kartos Therapeutics, Inc.

Navtemadlin activity in evaluable* MCC Pts (n=29).

n (%)	240 mg 7D on/ 14D off (n=6)	240 mg 5D on/ 23D off (n=7)	180 mg 5D on/ 23D off (n=8)	180 mg 7D on/ 23D off (n=1)	120 mg 7D on/ 14D off (n=7)
Confirmed ORR	1 (17)	1 (14)	2 (25)	0	1 (14)
Unconfirmed + confirmed ORR	2 (33)	1 (14)	3 (38)	0	1 (14)
Disease control rate	2 (33)	2 (29)	5 (63)	0	1 (14)

*Pts who have ended treatment or been on treatment for >10 wk.

9507 **Oral Abstract Session**

Nivolumab (NIVO) + tacrolimus (TACRO) + prednisone (PRED) +/- ipilimumab (IPI) for kidney transplant recipients (KTR) with advanced cutaneous cancers. *First Author: Kara M. Schenk, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD*

Background: Cancer is a leading cause of death among KTR, but these patients (pts) have been excluded from trials of immune checkpoint inhibitors due to immunosuppression and risk of allograft loss. We report findings from the first prospective clinical trial of NIVO + TACRO + PRED +/- IPI in KTR with selected advanced cutaneous cancers. **Methods:** The primary composite endpoint was lack of tumor progression per RECIST v1.1 without allograft loss at 16 weeks (W) on NIVO. Adult KTR with advanced melanoma, basal, cutaneous squamous, or Merkel cell carcinoma (MEL, BCC, CSCC, MCC), for whom non-immune therapies were insufficient were eligible. Immunosuppression was standardized to low-dose TACRO (goal trough 2-5 ng/mL) + PRED 5mg daily; pts then received NIVO 480mg IV q4W. Pts with progressive disease (PD) could receive NIVO 3mg/kg + IPI 1mg/kg IV q3W x 4 followed by NIVO 480mg IV q4W. Donor-derived cell-free DNA (dd-cfDNA) levels were measured q2W as a potential predictor of allograft rejection. **Results:** From 11/2019 - 4/2021, of 12 pts enrolled, 8 pts with CSCC, MCC or MEL were evaluable for response (Table). All pts experienced PD on NIVO; treatment-related allograft loss (TRAL) occurred in 1 pt. 6 pts then received IPI + NIVO. Responses: 2 (33%) with marked tumor regression at 6W and eventual complete response (CR; 1 with TRAL), and 4 (67%) with PD (1 with TRAL). 7/8 pre-NIVO tumor biopsies contained a paucity of infiltrating immune cells. Only 2/5 on-NIVO biopsies demonstrated moderate immune infiltrates; both of these pts later developed a CR to IPI + NIVO. Rejecting allografts contained dense immune responses (plasma cells, CD4+ & CD8+ lymphocytes, PD-1+ lymphocytes, macrophages, PD-L1+ glomerular endothelium, and focal PD-1 & PD-L1 positivity in renal tubules). In 2/3 pts with TRAL, elevations in dd-cfDNA levels occurred 10 and 15 days earlier than increases in weekly serum creatinine levels. TRAL #3 occurred after discontinuation of study therapy (including TACRO) and dd-cfDNA monitoring. **Conclusions:** In KTR receiving low-dose TACRO + PRED, NIVO augments tumor immune cell infiltration in some pts but is insufficient to mediate tumor regression. Adding IPI can enhance anti-tumor immunity and mediate tumor regression. TACRO + PRED was insufficient to prevent allograft rejection after PD-1 +/- CTLA-4 blockade in 2/8 pts. In pts with TRAL, increased dd-cfDNA levels preceded increased serum creatinine. Based on these findings, we are modifying the trial therapy regimen to augment anti-tumor immunity and preserve allograft function. Clinical trial information: NCT03816332. Research Sponsor: U.S. National Institutes of Health, The Marilyn and Michael Glosserman Fund for Basal Cell Carcinoma and Melanoma Research, and The Bloomberg~Kimmel Institute for Cancer Immunotherapy.

		CD8+ Immunohistochemistry (0-3= none, mild, moderate & severe; *no specimen available)			NIVO		IPI+NIVO	
Pt ID	Diagnosis	Pre-NIVO	On-NIVO	On-IPI/NIVO	Tumor response	Allograft loss	Tumor response	Allograft loss
1	MCC	1	1	*	PD	N	PD	N
2	CSCC	1	2	3	PD	N	CR	N
3	MCC	1	0	0	PD	N	PD	Y
4	CSCC	1	*	*	PD	N	PD	N
5	CSCC	1	*	N/A	PD	N	N/A	N/A
6	CSCC	3	2	*	PD	N	CR	Y
7	MEL	1	1	*	PD	Y	PD	N
8	CSCC	1	*	N/A	PD	N	N/A	N/A

9508 **Oral Abstract Session**

A phase II clinical trial of camrelizumab (CAM, an IgG4 antibody against PD-1) combined with apatinib (APA, a VEGFR-2 tyrosine kinase inhibitor) and temozolomide (TMZ) as the first-line treatment for patients (pts) with advanced acral melanoma (AM). *First Author: Lu Si, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/ Beijing), Department of Melanoma and Sarcoma, Peking University Cancer Hospital and Institute, Beijing, China*

Background: PD-1 monotherapy as the first line stand treatment for advanced melanoma yields an objective response rate (ORR) of < 20% in AM. Although multiple clinical trials are ongoing testing TMZ/APA, TMZ/PD-1 and APA/PD-1 combo therapies in AM, the reported ORR (range 17-23.8%) are far from satisfactory. We therefore conducted a phase II study of CAM/APA/TMZ combo in this subtype aiming for improved efficacy. **Methods:** We performed a single center, single arm phase II study (NCT04397770) testing the efficacy and safety of CAM/APA/TMZ combo as first-line therapy in pts with advanced AM. The primary endpoint was ORR per RECIST1.1, secondary endpoints included progression free survival (PFS), disease control rate (DCR), overall survival (OS), and safety. All pts received iv CAM (200mg q2w), iv TMZ (200mg/m2 d1-5, q4w) and po APA (250mg qd) until disease progression or intolerable toxicity. **Results:** By Jan 2022, fifty pts were enrolled (48 evaluable), the median follow-up was 12.1 mo (IQR 8.4-14.5). Thirty-one pts achieved CR/PR as the best response (including 1 CR and 30 PR), the ORR was 64.6% (95% CI 49.4-77.4%). The DCR was 95.8% (95%CI, 84.6-99.3%). Both the median PFS and OS was not reached (NR); 6-mo and 12-mo PFS rate was 81.7% (95%CI 71.6-93.3%) and 62.9% (95%CI 48.4-81.7%), respectively; 12-mo OS rate was 82.3% (95%CI 68.2-99.2%). The incidence of treatment-related adverse events (TRAEs) was 94% (47/50). Of 50 patients, the most common grade ≥3 TRAEs included γ-glutamyl transferase elevation (24.0%), direct bilirubin elevation (22.0%), aspartase transaminase elevation (20.0%), alanine transaminase elevation (16.0%), and hypertriglyceridemia (14.0%). No treatment-related deaths occurred. **Conclusions:** The CAM/APA/TMZ combination demonstrated promising efficacy as the first-line treatment for pts with advanced AM, and was generally well tolerated. Phase III randomized control trial is warranted. Clinical trial information: NCT04397770. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

LBA9509 **Poster Discussion Session**

Isolated hepatic perfusion as a treatment for uveal melanoma liver metastases, first results from a phase III randomized controlled multicenter trial (the SCANDIUM trial). *First Author: Roger Olofsson Bagge, Wallenberg Centre for Molecular and Translational Medicine, University of Gothenburg, Gothenburg, Sweden*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

9510 **Poster Discussion Session**

FOCUS phase 3 trial results: Percutaneous hepatic perfusion (PHP) with melphalan for patients with ocular melanoma liver metastases (PHP-OCM-301/301A). *First Author: Jonathan S. Zager, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: Ocular melanoma, the most common intraocular malignancy, frequently metastasizes to the liver but to date there is no established standard of care for hepatic-dominant ocular melanoma patients. The FOCUS trial began as a randomized, Ph 3 trial (301) comparing PHP with best alternative care (BAC). The trial was subsequently amended (301A) to halt the BAC arm due to enrollment concerns. **Methods:** Eligible patients with hepatic-dominant ocular melanoma were randomized 1:1 to receive PHP or BAC (investigator's choice of TACE, pembrolizumab, ipilimumab, or dacarbazine) on the 301 trial. All eligible patients received PHP on the 301A trial. PHP patients could receive up to 6 PHP treatments, repeated every 6-8 weeks with melphalan dosed at 3.0mg/kg ideal body weight (IBW). Patients with progressive disease (PD) were discontinued from study treatment and all patients are followed until death. Patientswere imaged every 12 (±2) weeks until PD. The primary endpoint, ORR (per RECIST 1.1) as assessed by Independent Review Committee, was characterized by the point estimate and 95% CI for each group (PHP and BAC). **Results:** 144 patients were enrolled overall; 102 were assigned to PHP (301: n = 43; 301A: n = 59) and 42 were assigned to BAC. 91 PHP patients received treatment (301: n = 40; 301A: n = 51) and 32 BAC patients received treatment. ORR among PHP patients was 35.2% (32/91; 95% CI: 25.44-45.88%). ORR among BAC patients was 12.5% (4/32; 95% CI: 3.51-28.99%; p= 0.0154). The median DOR was 14 months for PHP patients and not calculable for BAC patients. The DCR among PHP patients was 73.6% (67/91; 95% CI: 63.35-82.31%) and among BAC patients was 37.5% (12/32; 95% CI: 21.10-56.31%; p= 0.0002). The median PFS was 9.03 months (95% CI: 6.34-11.56) among PHP patients and was 3.12 months (95% CI: 2.89-5.65) among BAC patients (p= 0.0007). The median OS was 20.53 months (95% CI: 16.59-24.35) among PHP patients and was 14.06 months (95% CI: 9.99-19.78) among BAC patients. With the last treatment occurring in May 2021, the OS, DOR, and PFS data continues to mature as patients are still being followed for survival. Among the 94 patients assessed for safety after treatment with PHP, 42.6% of patients experienced a serious treatment-emergent adverse event, the majority of which were hematological, transient in nature, and resolved without sequelae. There were no treatment related deaths in the trial. **Conclusions:** In this analysis of data from the FOCUS trial, PHP demonstrates superior ORR, DOR, DCR, PFS, and OS in comparison with BAC in the treatment of hepatic metastases from ocular melanoma. This therapy offers a potential option for patients with this rare indication that is associated with a poor prognosis and few treatment options. Clinical trial information: NCT02678572. Research Sponsor: Delcath Systems, Inc.

9511 **Poster Discussion Session**

First interim analysis of the SirTac trial: A randomized phase II study of SIRT and DSM-TACE in patients with liver metastases from uveal melanoma. *First Author: Caroline-Anna Anna Peuker, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Hematology, Oncology and Cancer Immunology, Berlin, Germany*

Background: The liver is the most common site of metastases in patients (pts) with uveal melanoma (UM). Here, we present results from the prespecified first interim analysis of the SirTac trial, a prospective, single-center, randomized, investigator-initiated, open-label phase 2 study of Selective Internal Radiation Therapy with Yttrium-90-bearing resin microspheres; SIR-Spheres (SIRT) vs Transarterial Chemoembolization with Cisplatin and degradable starch microspheres; EmboCept S (DSM-TACE) in pts with liver-dominant metastatic UM. **Methods:** Pts with histologically confirmed, liver-dominant metastatic UM and ECOG PS 0-2 were enrolled and randomized 1:1 to SIRT or DSM-TACE. Randomization was stratified by lactate dehydrogenase (<2x vs ≥2x upper limit of normal) and pre-treatment with antiangiogenic agents. Extrahepatic metastases were allowed, if asymptomatic. Primary endpoint was progression-free survival (PFS). A total of 108 pts (54 per arm) were planned to be enrolled. Pts received TACE every 4-6 weeks until tumor devascularization or disease progression or intolerable toxicity was observed, and SIRT either as one whole-liver application or in two sequential sessions for each liver lobe. The primary objective of this prespecified analysis was to assess response by RECIST criteria v1.1 in the per-protocol (PP) population of the first 40 pts (20 pts in each arm). **Results:** Two patients had been treated with previous liver surgery, whereas all other patients had not received previous treatment for metastatic disease. There were no clinicopathological differences between the groups, except for a difference in age (median age SIRT arm 64 y vs 75 y in the TACE arm, p=0.018). All but 1 pt received treatment as randomized. This pt was excluded and replaced by the next TACE pt for this PP interim analysis. There were no differences in best overall response rates between the groups (no complete response, 1 partial response in both arms, stable disease in 19 (95%) and 17 (85%) pts in the SIRT and TACE arm, respectively, and 2 pts with progressive disease in the TACE arm). At a median follow-up of 13.9 mo from treatment start, median PFS in the PP population was 4.9 mo in the SIRT arm vs 2.2 mo in the TACE arm (p=0.037), with a higher median liver-PFS in the SIRT vs TACE arm (8.3 vs 2.2, p=0.026). **Conclusions:** In this planned interim analysis treatment in both arms was feasible with no differences in response. The explorativePFS analysis allows no conclusions on the final outcome after completion of the trial. The study continues recruitment. Clinical trial information: NCT02936388. Research Sponsor: Sirtex Medical, PharmaCept GmbH, Other Foundation.

9512 **Poster Discussion Session**

Toripalimab plus axitinib versus toripalimab or axitinib alone in patients with treatment-naive unresectable or metastatic mucosal melanoma: Interim results from a randomized, controlled, phase II trial. *First Author: Chuanliang Cui, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China*

Background: A phase IB trial had showen promising antitumor activity with toripalimab (T, a PD-1 antibody) plus axitinib (A, a VEGF receptor inhibitor) in treatment-naive unresectable or metastatic mucosal melanoma. Now we conducted a phase II trial to compare the combined treatment with monotherapy. **Methods:** In this randomized, controlled, phase II trial, patients with pathologically confirmed treatment-naive unresectable or metastatic mucosal melanoma were stratified by PD-L1 expression and randomized 1:1:1 into three groups to receive treatment of T+A (toripalimab 240 mg i.v. every 3 weeks, axitinib 5 mg orally twice a day) , T (toripalimab 240 mg i.v. every 3 weeks) or A (axitinib 5 mg orally twice a day). Subjects in T or A who meet the criteria after disease progression may cross over to receive T+A. The primary endpoint was progression-free survival (PFS). Secondary endpoints included Objective response rate (ORR), Duration of response (DOR), overall survival (OS), and safety. The protocol was registered at ClinicalTrials.gov (NCT03941795). This is the interim analysis for efficacy and safety. **Results:** Between Nov 2019 and Jan 2022, 51 patients were randomized (18 to T+A, 20 to T, and 13 to A due to preliminary efficacy analysis). Anatomic site of head and neck, gastrointestinal, gynecological were 49.0%, 29.4%, 21.6%, respectively. Stage II or III unresectable, M1a, M1b, M1c were 3.9%, 23.5%, 17.6%, 51.0%, respectively. PD-L1 positivity was defined as ≥1% of tumor cells and/or infiltrating immune cells and were identified in 55.6%, 45.0%, 53.8% patients in T+A, T, A group, respectively. 17, 17 and 12 patients could be evaluated in T+A, T and A group, respectively. 24 patients from T or A crossover to T+A group. At a median follow-up of 6.60 months, patients receiving T+A had a higher median PFS (5.83 vs 2.80 vs 1.40 months; HR = 0.538; 95% CI, 0.237 to 1.221; HR = 0.444; 95% CI, 0.182 to 1.081; P = 0.170), ORR (35.3% (29.7% if including crossover patients) vs 17.6% vs 8.3%), DOR (82.4% (70.3% if including crossover patients) vs 52.9% vs 58.3%) versus T or A group. The median OS was not reached. 80.4% patients experienced treatment-related adverse events (TRAEs). The most common TRAEs were mild (grade 1 or 2) and included diarrhea, proteinuria, hand and foot syndrome, fatigue, elevated transaminase, elevated bilirubin, hypertension, hypo- or hyperthyroidism, and rash. Grade 3 or greater TRAEs occurred in 33.3%, 30.0%, 30.8% of patients in T+A, T, A groups. **Conclusions:** Toripalimab plus axitinib showed promising antitumor activity versus toripalimab or axitinib alone in patients with treatment-naive unresectable or metastatic mucosal melanoma. Clinical trial information: NCT03941795. Research Sponsor: None.

9513 **Poster Discussion Session**

AMBER parts 1c and 1e: A phase 1 study of cobolimab plus dostarlimab in patients (pts) with advanced/metastatic melanoma. *First Author: Antoni Ribas, University of California Los Angeles, Los Angeles, CA*

Background: TIM-3 and PD-1 are markers of T-cell suppression that are upregulated in melanoma. AMBER (NCT02817633) is evaluating cobolimab (TSR-022/GSK4069889), an anti-TIM-3 therapy, monotherapy or with PD-1 inhibitors, including dostarlimab, in pts with solid tumors. **Methods:** This multicenter, open-label study was conducted in 2 parts: dose escalation (Parts 1 A–D and F–H) and cohort expansion (Parts 2 A–D). Part 1C and exploratory cohort 1E (reported here) included pts with advanced/metastatic melanoma; prior therapies, except for immunotherapies, were permitted. Pts received cobolimab (100 [1C only], 300, or 900 mg IV) with dostarlimab (500 mg IV) Q3W. Part 1C primary endpoints were safety, tolerability, and recommended Phase 2 dose. Objective response rate (ORR; complete [CR] or partial [PR] response per RECIST v1.1) was a secondary endpoint in 1C and the primary endpoint in 1E (ad hoc efficacy analysis reported). An integrated safety analysis for all pts (Parts 1 and 2) receiving cobolimab with dostarlimab, regardless of tumor type or cobolimab dose, is reported here. **Results:** 28 pts were enrolled in 1C (n=10) and 1E (n=18). Most pts (n=23; 82.1%) had cutaneous disease of the skin. One pt had anorectal mucosal disease and 3 pts in the 900-mg cohort had uveal melanoma. Most pts (67.9%) had an ECOG PS=0. At data cut-off (May 19, 2021), treatment was ongoing in 5 pts. In the integrated safety analysis of pts who received cobolimab 100 mg (n=41), 300 mg (n=167), or 900 mg (n=69) with dostarlimab, treatment-related treatment-emergent AEs (TR-TEAEs) occurred in 53.7%, 57.5%, and 59.4%, respectively. The most common TR-TEAEs (any grade, ≥10% in 100 mg, 300 mg, or 900 mg groups, respectively) were fatigue (22.0%, 13.2%, 24.6%), rash (9.8%, 5.4%, 11.6%), diarrhea (4.9%, 6.0%, 10.1%), and dyspnea (2.4%, 0%, 10.1%). Grade ≥3 TR-TEAEs occurred in 12.2% (100 mg), 10.8% (300 mg), and 20.3% (900 mg); serious TR-TEAEs occurred in 7.3%, 7.8%, and 11.6%, respectively. No pts died due to TR-TEAEs; 2.4% (100 mg), 4.2% (300 mg), and 7.2% (900 mg) discontinued due to TR-TEAEs. ORR and disease control rate (DCR: stable disease [SD] ≥16 weeks, PR, or CR) are shown in the Table. Twelve pts achieved a PR and an immune-related (ir)PR (1 in 100 mg; 8 in 300 mg; 3 in 900 mg groups). Three pts achieved SD (2 in 300 mg; 1 in 900 mg groups); 8 pts had irSD (1 in 100 mg; 4 in 300 mg; 3 in 900 mg groups). **Conclusions:** Cobolimab with dostarlimab showed preliminary clinical responses in pts with advanced/metastatic melanoma and an acceptable safety profile across advanced cancers. Funding: GSK (213348). Clinical trial information: NCT02817633. Research Sponsor: GlaxoSmithKline.

Efficacy by cobolimab dose with dostarlimab.

n (%)	100 mg N=3	300 mg N=14	900 mg N=11	Total N=28
ORR	1 (33.3)*†	8 (57.1)	3 (27.3)	12 (42.9)
irORR	1 (33.3)*	8 (57.1)	3 (27.3)	12 (42.9)
DCR	1 (33.3)*†	10 (71.4)	4 (36.4)	15 (53.6)
irDCR	1 (33.3)*	11 (78.6)	4 (36.4)	16 (57.1)

*n=1 had no post-baseline tumor assessments; †n=1 was not evaluable.

9514 **Poster Discussion Session**

Phase II study of nivolumab (nivo) with relatlimab (rela) in patients (pts) with first-line advanced melanoma: Early on-treatment major pathologic response on biopsy. *First Author: Lilit Karapetyan, UPMC Hillman Cancer Center, Pittsburgh, PA*

Background: A phase II study of nivo and rela was designed to evaluate the antitumor activity and mechanism of this combination and components for first-line treatment of pts with advanced melanoma. Pts received lead-in treatment with 1 cycle of nivo (480mg IV q4wk), rela (160mg IV q4wk), or nivo-rela followed by combination therapy. We assessed the effect of each lead-in treatment on immune-related pathological response (irPR) at 4-wk biopsy to develop early biomarkers of antitumor response. **Methods:** Core biopsy of an index lesion was performed at baseline and after 4 wk on-treatment. Immune characteristics of pathological response were assessed on H&E sections, including presence of tumor-infiltrating lymphocytes (TIL), neovascularization, proliferative fibrosis, plasma cells, and lymphoid aggregates. irPR score was calculated as described by Stein JE et al Ann Oncol 2019, from 0 (no irPR features) to 3 (major pathologic response on biopsy [MPRbx], ≤10% residual viable tumor). We assessed the association between irPR and radiological response (RECIST v1.1) at 4-wk evaluations. **Results:** The current cohort includes 22 pts, median age = 67, male = 13. Pts were randomized to nivo = 7, rela = 7, and nivo-rela = 8 lead-in groups. Two pts had no irPR evaluation due to early progression and unscorable tumor. Among 20 evaluable pts, proliferative fibrosis, neovascularization, plasma cells, brisk TIL, and lymphoid aggregates were identified in 50%, 35%, 26.3%, 25%, and 5% of cases, respectively. Lead-in nivo (n = 2/6), rela (n = 0/6), and nivo-rela (n = 3/8) resulted in irPR = 3 in 25% of pts. Radiological response was identified as partial response (PR) = 1/22 (4.5%), stable disease (SD) = 12/22 (54.5%), and progressive disease (PD) = 9/22 (41%). Among pts with PD, 44% received rela-, 33% nivo-, and 22% nivo-rela- lead-in. Pts with irPR score = 3 had radiological PR = 1, SD = 3, and PD = 1 at 4wks. No association was found between MPRbx and radiological response at 4 wks. **Conclusions:** Four-wk MPRbx may serve as an early biomarker of treatment response in advanced melanoma. Lead-in treatment resulted in MPRbx of 25% and was greatest with nivo-rela lead-in. Correlations between 4 wk MPRbx and later radiological responses, survival and other endpoints will be made at completion of trial accrual. Clinical trial information: NCT03743766. Research Sponsor: Bristol Myers Squibb, Melanoma and Skin Cancer SPORE Program.

	All (N = 20)	Nivo (N = 6)	Rela (N = 6)	Nivo-Rela (N = 8)
irPR = 0	20%	33.3%	33.3%	0%
irPR = 1	50%	33.3%	50%	62.5%
irPR = 2	5%	0%	16.7%	0%
irPR = 3	25%	33.3%	0%	37.5%

9515 **Oral Abstract Session**

Atezolizumab (A), cobimetinib (C), and vemurafenib (V) in patients (pts) with *BRAF*^{V600} mutation–positive melanoma with central nervous system (CNS) metastases (mets): Primary results from phase 2 Tricotel study. *First Author: Reinhard Dummer, Skin Cancer Center, University Hospital of Zurich, Zurich, Switzerland*

Background: Despite recent advances in the treatment of melanoma, there remains an urgent need to improve outcomes in pts with CNS mets. To date, studies evaluating intracranial activity of immunotherapies and targeted therapies have included limited numbers of pts with symptomatic CNS mets. Cohort 2 of the phase 2 Tricotel study evaluated the safety and efficacy of A + C + V in *BRAF*^{V600}-mutated melanoma with CNS mets, including symptomatic pts receiving corticosteroids. **Methods:** Eligible pts were aged ≥18 y and had melanoma, MRI-confirmed CNS mets ≥5 mm in ≥1 dimension, and no prior systemic treatment for metastatic disease. Pts received A (840 mg on days 1 and 15 of each 28-d cycle) + C (60 mg once daily for 21 d on, 7 d off) + V (720 mg twice daily) except in cycle 1, during which A was withheld. Primary outcome was intracranial objective response rate (ORR; confirmed by assessments ≥4 wk apart per independent review committee [IRC]). Secondary end points were investigator-assessed intracranial ORR, extracranial ORR, overall ORR, duration of response (DOR), disease control rate, progression-free survival (PFS), overall survival (OS), and safety. Prespecified subgroup analyses were performed in pts receiving corticosteroids (>2 mg/d dexamethasone) and/or with CNS-related symptoms at baseline vs asymptomatic pts. **Results:** This study enrolled 65 pts (median age, 55 y; 63% male). At baseline, 37% were on corticosteroids and/or were symptomatic; 49% had elevated lactate dehydrogenase. Median follow-up was 9.7 mo for all pts, 10.0 mo for pts on corticosteroids and/or symptomatic at baseline (n = 24), and 9.7 mo for asymptomatic pts (n = 41). Intracranial ORR was 42% by IRC and 51% by investigator (BOR concordance: 68%). Intracranial DOR and PFS are listed in the Table. In pts on corticosteroids and/or symptomatic at baseline, ORR was 58%, DOR was 10.2 mo, and PFS was 7.2 mo by investigator; in asymptomatic pts, ORR was 46%, DOR was 5.7 mo, and PFS was 5.5 mo. Additional secondary efficacy end points will be presented. In 60 pts who received A + C + V, grade 3/4 adverse events (AEs) occurred in 70% of pts; most commonly lipase increased (27%) and blood CPK increased (17%). Serious AEs occurred in 30% of pts. AEs led to discontinuation of any study treatment in 27% of pts. **Conclusions:** Addition of A to C + V provides promising intracranial activity in pts with *BRAF*^{V600}-mutated melanoma with CNS mets, particularly in those receiving corticosteroids and/or in symptomatic pts. The safety profile of A + C + V is consistent with that observed in the IMspire150 study. Clinical trial information: NCT03625141. Research Sponsor: Roche.

Intracranial outcomes (N = 65).

	IRC	Investigator
ORR, % (95% CI)	42 (29–54)	51 (38–63)
Median DOR, mo (95% CI)	7.4 (5.7–11.0)	7.4 (5.6–10.2)
Median PFS, mo (95% CI)	5.3 (3.8–7.2)	5.8 (5.4–7.4)
6-mo PFS rate, % (95% CI)	41 (28–53)	48 (36–61)

9516 **Poster Discussion Session**

Pembrolizumab (pembro) plus dabrafenib (dab) and trametinib (tram) in *BRAF*$^{V600E/K}$-mutant melanoma: Long-term follow-up of KEYNOTE-022 parts 1, 2, and 3. *First Author: Antoni Ribas, UCLA, Los Angeles, CA*

Background: KEYNOTE-022 (NCT02130466) was a phase 1/2 study of pembro + dab + tram or pembro + tram in patients (pts) with unresectable stage III/IV melanoma (parts 1-3) or solid tumors (parts 4 and 5). In previous analyses of pts with *BRAF*$^{V600E/K}$-mutant melanoma, pembro + dab + tram was shown to have manageable safety in parts 1-3, albeit with a higher incidence of TRAEs in part 3, and substantially improved PFS, DOR, and OS vs placebo + dab + tram in part 3, although the primary end point of a statistically significant improvement in PFS was not met. Long-term follow-up of pts with *BRAF*$^{V600E/K}$-mutant melanoma in parts 1-3 are presented. **Methods:** Eligible pts were ≥18 y with unresectable stage III/IV *BRAF*$^{V600E/K}$-mutant melanoma, ≥1 measurable lesion per RECIST v1.1, ECOG PS 0/1, and no prior systemic therapy for advanced disease. In parts 1 and 2, which involved dose finding and confirmation, pts received pembro 2 mg/kg IV Q3W + dab 150 mg PO BID + tram 2 mg PO QD (MTD). In part 3, pts were randomized 1:1 to pembro + dab + tram at MTD or placebo + dab + tram. Primary end points were safety, tolerability, and MTD (parts 1 and 2); ORR per RECIST v1.1 by investigator review (part 2); and PFS per RECIST v1.1 by investigator review (part 3). Data cutoff was July 14, 2021. **Results:** Median (range) study follow-up was 72.9 mo (68.4-84.5) in parts 1 and 2 (n = 15) and 61.2 mo (50.7-67.5) for all pts (n = 120; 60 each arm) in part 3. Safety of pembro + dab + tram in parts 1 and 2 was consistent with prior reports; grade 3/4 TRAEs occurred in 11 pts (73%), and no additional DLTs occurred. ORR in parts 1 and 2 was 67% (95% CI, 38-88), which was similar to that reported at an earlier data cut (73% [95% CI, 45-92]); median DOR was 19.4 mo (95% CI, 2.8-NR), median OS was NR (95% CI, 10.3-NR), 48-mo OS rate was 60%, median PFS was 15.2 mo (95% CI, 4.2-NR), and 48-mo PFS rate was 28% (Ribas A et al. *Nat Med.* 2019;25:936-940). In part 3, median PFS was 17.0 mo (95% CI, 11.3-NR) for pembro + dab + tram vs 9.9 mo (95% CI, 6.7-15.6) for placebo + dab + tram (HR, 0.46; 95% CI, 0.29-0.74) and 24-mo PFS rate was 47% vs 16%, and median OS was 46.3 mo (95% CI, 23.9-NR) vs 26.3 mo (95% CI, 18.2-38.6); and 24-mo OS rate was 63% vs 52%, respectively. ORR was 65% (95% CI, 52-77) for pembro + dab + tram vs 72% (95% CI, 59-83) for placebo + dab + tram; median DOR was 30.2 mo (95% CI, 14.1-NR) vs 12.1 mo (95% CI, 6.0-15.7). Safety in part 3 was similar to prior reports; grade 3-5 TRAEs occurred in 42 pts (70%) in the pembro + dab + tram arm vs 27 pts (45%) in the placebo + dab + tram arm (Ferrucci PF et al. *J Immunother Cancer.* 2020;8:e001806). No additional grade 5 TRAEs occurred (1 grade 5 pneumonitis had occurred at prior analysis). **Conclusions:** At long-term follow-up, first-line pembro + dab + tram continued to show improved PFS, DOR, and OS compared with placebo + dab + tram in pts with *BRAF*$^{V600E/K}$-mutant melanoma. TRAEs were more common with pembro + dab + tram but no new safety signals were identified. Clinical trial information: NCT02130466. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

9517 **Poster Discussion Session**

Newly updated activity results of alrizomadlin (APG-115), a novel MDM2/p53 inhibitor, plus pembrolizumab: Phase 2 study in adults and children with various solid tumors. *First Author: Meredith McKean, Sarah Cannon Research Institute, Tennessee Oncology, PLLC, Nashville, TN*

Background: Alrizomadlin restores *TP53* function, activating p53-mediated apoptosis in tumor cells with wild-type *TP53* and/or *MDM2* amplification. Alrizomadlin also functions as a host immunomodulator and may restore antitumor activity in pts with cancers that progressed on PD-1/PD-L1 inhibitors. **Methods:** This US/Australian multicenter trial evaluated alrizomadlin, an investigational MDM2-selective, small-molecule inhibitor, combined with pembrolizumab, in pts with unresectable/metastatic melanoma that progressed on I-O drugs; pts with malignant peripheral nerve sheath tumor (MPNST), well-differentiated/dedifferentiated liposarcoma, non-small cell lung cancer (NSCLC), or solid tumors with *ATM* mutations that progressed on available standard therapy; or pts for whom therapy was unavailable. Eligible pts had ECOG performance status of 0-2 and, if present, stable brain metastases. Alrizomadlin 150 mg PO was administered QOD for 2 consecutive weeks, with 1 week off, and pembrolizumab 200 mg IV over 30 minutes on Day 1 of a 21-day cycle. **Results:** As of November 3, 2021, preliminary and interim results are reported for 130 pts in 6 cohorts: melanoma (n = 44), NSCLC (n = 26), *ATM* mutation (n = 18), liposarcoma (n = 17), urothelial (n = 13), and MPNST (n = 12). In the melanoma cohort, confirmed ORR by RECIST, (PR + CR) was 13% (2 CRs + 3 PRs/38 efficacy evaluable [EE] pts). In cutaneous and uveal melanoma subcohorts, confirmed ORR was 24% (2 CRs + 2 PRs/17 EE pts) and 9% (1 PR/11 EE pts), respectively. In the MPNST cohort, the clinical benefit rate, defined by confirmed ORR + SD of > 4 cycles, was 40% (4 SDs/10 EE pts). Additional confirmed PRs were reported in NSCLC, urothelial, and liposarcoma cohorts (1 each). Common treatment (alrizomadlin or pembrolizumab)-related adverse events (TRAEs; ≥ 10%) were nausea (62%), thrombocytopenia (39%), vomiting (38%), fatigue (38%), decreased appetite (29%), diarrhea (25%), neutropenia (15%), and anemia (12%). Grade 3^{+} TRAEs (≥ 5%) included thrombocytopenia (23%), neutropenia (10%), and anemia (7%). A total of 16 pts discontinued treatment due to AEs; 6 were treatment related, including grade 4 thrombocytopenia (n = 3), grade 2 vomiting (n = 1), grade 2 fatigue (n = 1), and grade 2 posterior reversible encephalopathy syndrome (PRES; n = 1). A total of 10 pts reported treatment-related SAEs: 1 each of abdominal pain, asthenia, colitis, febrile neutropenia, hypophysitis, peripheral edema, overdose, PRES, pulmonary embolism, pyrexia, and thrombocytopenia**. Conclusions:** Alrizomadlin, combined with pembrolizumab, is well tolerated and demonstrates preliminary antitumor activity in multiple tumor types and may restore antitumor effects in pts with cancer resistant or intolerant to I-O drugs. Internal study identifiers: APG-115-US-002; Keynote MK-3475-B66. Clinical trial information: NCT03611868. Research Sponsor: Ascentage Pharma Group Corp. Ltd (Hong Kong).

9518 **Poster Discussion Session**

Primary analysis of a phase 2, open-label, multicenter trial of talimogene laherparepvec (T-VEC) plus pembrolizumab (pembro) for the treatment (Tx) of patients (pts) with advanced melanoma (MEL) who progressed on prior anti–PD-1 therapy: MASTERKEY-115. *First Author: Brian Gastman, Cleveland Clinic Lerner College of Medicine, Cleveland, OH*

Background: Despite advances in anti–PD-1–based Tx for MEL, an unmet need remains for immunotherapy failure in advanced metastatic or unresectable MEL. Also, there is a growing population of pts who received adjuvant anti–PD-1 and recurred; yet trials to address this population are lacking. Combination Tx with T-VEC, an oncolytic viral intratumoral Tx designed to produce GM-CSF, and pembro, an anti–PD-1 agent, may overcome immunotherapy failure. We report the MASTERKEY-115 primary analysis on the efficacy and safety of T-VEC + pembro in pts with advanced MEL who had progressive disease (PD) on prior anti–PD-1. **Methods:** This open-label, single-arm, multicenter, phase 2 study (NCT04068181) enrolled pts at 26 international sites (Jan 2020–Feb 2021). Cohorts 1 and 2, primary and acquired resistance, respectively, received anti–PD-1 in a locally recurrent or metastatic setting and had PD within 12 wks of the last anti–PD-1 dose. Cohorts 3 and 4 included only pts who received adjuvant anti–PD-1 and were disease-free for < 6 mos (Cohort 3) or ≥ 6 mos (Cohort 4) before confirmed PD. Eligible pts had histologically confirmed unresectable or metastatic stage IIIB–IVM1d MEL, measurable and injectable disease, ECOG PS 0/1, and progressed on anti–PD-1 directly before enrollment. T-VEC at standard dosage and pembro 200 mg were given Q3W. The primary endpoint was objective response rate (ORR). Key secondary endpoints were complete response (CR) rate, progression-free survival (PFS), and safety. Tx decisions were per modified immune-related response criteria (irRECIST). **Results:** 72 pts (median age, 65 y) were enrolled. Of the 71 evaluable pts, 37 (52.1%) had stage IVM1b–d disease, 30 (42.3%) had confirmed PD-L1–positive tumor (CPS ≥ 1%), 20 (28.2%) had a $BRAF^{V600}$ mutation, and 21 (29.6%) had LDH > 1ULN. At data cutoff (Aug 2021), 47 (65.3%) pts remained on study. ORR was 0%, 6.7%, 40%, and 46.7% in cohorts 1–4, respectively (table). Any-grade Tx-related adverse events (TRAEs) were reported in 54 (76.1%) pts; the most common were pyrexia (29.6%), fatigue, and influenza-like illness (15.5% each). Grade ≥ 3 TRAEs occurred in 9 (12.7%) pts. **Conclusions:** T-VEC + pembro showed manageable safety in pts with advanced MEL after anti–PD-1 failure; the promising ORR observed in pts who progressed on prior adjuvant anti–PD-1 warrants further analysis. Clinical trial information: NCT04068181. Research Sponsor: Amgen Inc; Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

	Cohort 1 (N = 26)	Cohort 2 (N = 15)	Cohort 3 (N = 15)	Cohort 4 (N = 15)
ORR[a], n (%)	0	1 (6.7)	6 (40.0)	7 (46.7)
95% CI		0.2–32.0	16.3–67.7	21.3–73.4
PFS[b], Median (mos), 95% CI	5.5	8.2	NE	NE
	2.8–NE	2.7–15.0		
CR[b], n (%)	0	0	2 (13.3)	2 (13.3)
PR[b], n (%)	1 (3.8)	1 (6.7)	6 (40.0)	5 (33.3)
SD[b], n (%)	12 (46.2)	5 (33.3)	3 (20.0)	6 (40.0)
PD[b], n (%)	5 (19.2)	4 (26.7)	1 (6.7)	0

[a]Per modified RECIST1.1; [b]Per modified irRECIST; NE, not estimable; PR, partial response; SD, stable disease

9519 **Poster Discussion Session**

Long-term outcomes of a phase II trial of neoadjuvant immunotherapy for advanced, resectable cutaneous squamous cell carcinoma of the head and neck (CSCC-HN). *First Author: Neil D. Gross, The University of Texas MD Anderson Cancer Center, Department of Head and Neck Surgery, Houston, TX*

Background: In a pilot phase II trial, we investigated the use of neoadjuvant immunotherapy to induce a pathologic response in patients with stage III/IV (M0) cutaneous squamous cell carcinoma of the head and neck (CSCC-HN). Here, we report the long-term outcomes according to pathologic response. **Methods:** Patients with newly diagnosed or recurrent stage III/IV (M0) (AJCC 8th Ed) CSCC-HN were treated with 2 doses of cemiplimab 350 mg intravenously every 3 weeks prior to surgery. The primary endpoint was overall response rate (ORR) per RECIST v1.1. Secondary endpoints included safety, pathologic response, disease-free and overall survival. **Results:** Of 20 patients enrolled, 7 (35%) had recurrent disease and 12 (60%) were stage IV on presentation. Neoadjuvant immunotherapy was generally well-tolerated and there were no surgical delays. Adverse events (AEs) were observed in 7 (35%) patients; 1 (5%) grade 3 diarrhea, 6 (30%) ≤ grade 2 AEs. ORR by RECIST was 30%. However, 85% (17/20) achieved a pathologic response (≤50% viable tumor), with pathologic complete response (pCR) in 11 (55%), major pathologic response (MPR, ≤10% viable tumor) in 4 (20%) and pathologic partial response (pPR, >10% and ≤50% viable tumor) in 2 (10%). Patients with a pCR did not receive planned radiotherapy after surgery. Patients who did not have a pathologic response (> 50% viable tumor) either progressed and died (1, 5%) or developed recurrence (2, 10%) despite surgery and adjuvant radiation or chemoradiation. At a median follow up of 34.5 months (range: 7.7-42.7), none of the patients who achieved a pathologic response have recurred. **Conclusions:** Consistent with other cancer types, pathologic response to neoadjuvant immunotherapy is durable in patients with advanced, resectable CSCC-HN. Adjuvant radiation therapy may be spared in patients who achieve a pCR and warrants further investigation. Clinical trial information: NCT03565783. Research Sponsor: Regeneron.

9520 **Poster Discussion Session**

Immunotherapy followed by cetuximab in locally advanced/metastatic (LA/M) cutaneous squamous cell carcinomas (cSCC): The I-TACKLE trial. *First Author: Paolo Bossi, Medical Oncology Unit, Department of Medical & Surgical Specialties, Radiological Sciences & Public Health, University of Brescia, ASST Spedali Civili, Brescia, Italy*

Background: In LA/M cSCC patients (pts), immunotherapy with pembrolizumab (P) and cemiplimab showed an overall response rate (ORR) of 34-49%, with durable antitumor activity. However, primary and acquired resistance represents a therapeutic challenge. In cSCC, monotherapy with cetuximab (C) showed promising signs of activity (ORR 28%), but with limited duration of response. This study aims at reverting P resistance by adding C, leveraging on its mechanism of action in reducing immune escape process. **Methods:** I-TACKLE is an open-label, nonrandomized, phase II trial in pts with LA/M cSCC conducted in 3 Italian centers. Eligible pts had LA/M cSCC not manageable with surgery or radiation and with ECOG PS= 0 or 1. They received intravenous P 200 mg every 3 weeks. In case of partial (PR) or complete response (CR), pts continued to receive P alone. In case of stable disease (SD) or progression (PD), pts received C (400 mg/sm loading dose, then weekly 250 mg/sm) in addition to P until progression. The primary endpoint was cumulative ORR by single agent or by combination strategy; safety, PFS (since start of P and P+C), OS and duration of response (DOR) were secondary endpoints. **Results:** Between May 2019 and April 2021, 43 pts were enrolled and treated with P. Table 1 depicts population baseline features. The median follow up was 24 (range 7-30) months. Twenty-three pts underwent the combination treatment (17/23 due to PD and 6/23 due to SD); 21 of them due to primary resistance and 2 because of acquired resistance. Median treatment exposure was 3 and 4 months to P and combination therapy, respectively. Cumulative ORR was 63% [95% confidence interval 48-77], including 19/43 (44%) pts with response to P and 8/21 (38%) with response to combination strategy after primary resistance to P. Both pts experiencing an acquired resistance to P obtained PR when C was introduced. Overall, 10/23 pts (44%) obtained a response to combination therapy. Median DOR and OS were not reached both with P alone and with P+ C. One-year PFS was 51% with P alone and 42% with P+C. Overall, grade 3-4 treatment-related adverse events occurred in 7/43 (16%) pts during treatment with P and 8/23 (35%) pts during P+C, mostly dermatitis 7/23 (30%). Three out of 43 (7%) pts discontinued treatment because of toxicity, one pancreatitis, one impaired renal function and one for worsening of clinical condition, all during treatment with P. Four patients died during treatment, due to PD. **Conclusions:** In LA/M cSCC, the addition of C to P reverts primary and acquired resistance, with manageable toxicities. The sequential approach deserves to be studied in future clinical trials. Clinical trial information: NCT03666325. Research Sponsor: Merck Sharp & Dohme MISP (Merck Investigator Studies Program).

Baseline characteristics of pts.

Characteristics	N° (%)
Median Age (range), years	79 (48-96)
Male	34 (79)
ECOG PS 0	11 (26)
Previous treatments	
Chemotherapy	7 (16)
Radiation therapy	21 (49)
T3-T4	35 (81)
N2-N3	17 (40)
M1	13 (30)
Head and Neck primary T	30 (70)

9521 **Poster Session**

A retrospective study of ipilimumab plus nivolumab in anti–PD-L1/PD-1-refractory merkel cell carcinoma. *First Author: Sophia Z. Shalhout, Division of Hematology/Oncology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA*

Background: Merkel cell carcinoma (MCC) is a rare cutaneous neuroendocrine carcinoma with a high recurrence and mortality rate. Immune checkpoint inhibitors (ICIs) targeting the PD-L1/PD-1 axis have shown significant clinical benefit with durable responses in patients with advanced MCC leading to regulatory approvals by the U.S. Food and Drug Administration for two agents: avelumab (anti-PD-L1) and pembrolizumab (anti-PD-1). However, many patients (~50%) with advanced MCC treated with ICI do not experience tumor regression. Studies regarding systemic therapy options following progression due to primary or acquired resistance to immunotherapy are limited and management remains a clinical challenge. In this retrospective study, we evaluated objective clinical response to combination ipilimumab and nivolumab (ipi-nivo) salvage therapy in advanced MCC refractory to anti-PD-L1/PD-1 treatment. **Methods:** We reviewed the electronic medical record at Mass General Brigham associated institutions to identify patients with advanced MCC that progressed on upfront immunotherapy (e.g., pembrolizumab, avelumab or nivolumab) and were re-challenged with combination ipi-nivo between 2016 to 2021. Patients treated with prior surgery, radiation, or cytotoxic chemotherapy after progressing on immunotherapy were not excluded. Responses to ipi-nivo were evaluated for every patient at each re-staging/interval assessment following baseline analysis utilizing Response Evaluation Criteria in Solid Tumors (RECISTv1.1) as well as immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) to ensure conventional RECIST did not underestimate the benefit of ipi-nivo. **Results:** Four patients (31%) experienced grade III/IV immune-related adverse events. No patients (0/13) in this case series achieved an objective response via RECISTv1.1/irRECIST. Stable disease was seen in 23% (3/13) and the median progression-free survival was 1.3 months (90% CI, 1.1-1.5). The median overall survival from the initiation of ipi-nivo was 4.7 months (95% CI, 3-17). **Conclusions:** This study suggests limited, if any, clinical benefit of ipi-nivo in patients with advanced anti-PD-L1/anti-PD-1-refractory MCC. New strategies for second-line treatment of MCC are needed and referral to innovative clinical trials should be a priority for patients with refractory metastatic MCC. Research Sponsor: Project Data Sphere; ECOG-ACRIN , Fund for Medical Discovery Clinical Research Fellowship Award (MGH-ECOR), American Skin Association.

9522 **Poster Session**

Long-term survival in advanced melanoma for patients treated with nivolumab plus ipilimumab in CheckMate 067. *First Author: F. Stephen Hodi, Dana-Farber Cancer Institute, Boston, MA*

Background: Durable clinical benefit has been achieved with nivolumab (NIVO) + ipilimumab (IPI), including an overall survival (OS) of 49% and a melanoma-specific survival (MSS) of 56%, with median MSS not reached (NR) at 6.5-y minimum follow-up. Here we report sustained efficacy outcomes at 7.5 y. **Methods:** Patients (pts) with previously untreated, unresectable stage III/IV melanoma were randomly assigned 1:1:1 and stratified by PD-L1 status, *BRAF* mutation status, and metastasis stage to receive NIVO 1 mg/kg + IPI 3 mg/kg for 4 doses Q3W, followed by NIVO 3 mg/kg Q2W (n = 314); NIVO 3 mg/kg Q2W + placebo (n = 316); or IPI 3 mg/kg Q3W for 4 doses + placebo (n = 315) until progression or unacceptable toxicity. Co-primary endpoints were progression-free survival (PFS) and OS with NIVO + IPI or NIVO alone versus IPI. **Results:** With a minimum follow-up of 7.5 y, median OS remained stable at 72.1 mo (NIVO + IPI), 36.9 mo (NIVO), and 19.9 mo (IPI); median MSS was NR, 49.4 mo, and 21.9 mo, respectively (Table). While the objective response rate remained stable at 58% (NIVO + IPI), 45% (NIVO), and 19% (IPI), median duration of response had now been reached for NIVO at 90.8 mo and remains NR and 19.2 mo for NIVO + IPI and IPI, respectively. Subsequent systemic therapy was received by 36%, 49%, and 66% of NIVO + IPI-, NIVO-, and IPI-treated patients, respectively, and median time to that therapy was NR (95% CI, 45.9–NR), 24.7 mo (16.0–38.7), and 8.0 mo (6.5–8.7). Of patients alive at 7.5 y, 106/138 (77%, NIVO + IPI), 80/115 (70%, NIVO), and 27/60 (45%, IPI) were off treatment and had never received subsequent systemic therapy. No change to the safety summary was observed with additional follow-up; updated health-related quality of life data will be reported. Of the 10 new deaths since the 6.5-y follow-up (ie, 5 NIVO + IPI; 3 NIVO; 2 IPI), none were treatment-related; 4 were due to melanoma progression; 1 was due to an unknown cause; and 5 were due to other causes, but not associated with a COVID diagnosis. **Conclusions:** The 7.5-y follow-up continues to demonstrate the durability of responses with NIVO + IPI and an ongoing survival plateau. A substantial difference in median OS and MSS between patients treated with NIVO + IPI or NIVO was observed in descriptive analyses. Clinical trial information: NCT04540705. Research Sponsor: Bristol Myers Squibb, Pharmaceutical/Biotech Company, Grant P30CA008748 to J. D. W. from the National Cancer Institute, and a grant to J. L. from the National Institute for Health Research Royal Marsden–Institute of Cancer Research Biomedical Research Centre.

	NIVO + IPI(n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS: all pts, mo (95% CI)	72.1 (38.2–NR)	36.9 (28.2–58.7)	19.9 (16.8–24.6)
7.5-y OS rate: all pts, % (95% CI)	48 (42–53)	42 (36–47)	22 (18–27)
***BRAF* mutant subgroup**	57 (47–66)	42 (32–52)	25 (17–34)
Median MSS: all pts, mo (95% CI)	NR (71.9–NR)	49.4 (35.1–NR)	21.9 (18.1–27.4)
7.5-y MSS rate: all pts, % (95% CI)	55 (50–61)	47 (41–52)	26 (21–32)
Median PFS: all pts, mo (95% CI)	11.5 (8.9–20.0)	6.9 (5.1–10.2)	2.9 (2.8–3.1)
7.5-y PFS rate: all pts, % (95% CI)	33 (27–39)	27 (22–33)	7 (4–11)

9523 **Poster Session**

Androgen receptor blockade promotes response to BRAF/MEK-targeted therapy. *First Author: Michael White, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Treatment with BRAF+/-MEK inhibition (BRAF+/-MEKi) has revolutionized treatment in melanoma and other cancers, but resistance is common and innovative treatment strategies are needed. Sexual dimorphism in response to BRAF+/-MEKi have been noted, but mechanisms behind this are poorly understood and hormonal modulation has not been well-studied in this setting. **Methods:** We examined outcomes by sex in five clinical cohorts of patients (pts) (total n = 792, 362 female, 430 male) with *BRAF*-mutated melanoma who were treated with BRAF/MEKi in either the neoadjuvant or metastatic setting. Rates of major pathologic response (MPR), clinical benefit (CB), progression free survival (PFS) relapse-free survival (RFS) and overall survival (OS) were assessed. Translational research studies were performed on available pre- and on-treatment tumor samples (n = 27 pts) including RNA sequencing and profiling androgen receptor (AR) expression. Parallel studies were performed in preclinical models to assess the effect of sex and AR modulation on response to BRAF+/-MEKi. **Results:** In this study, improved rates of MPR, CB, PFS and OS were observed in female vs male pts. Specifically, female patients treated with neoadjuvant BRAF+MEKi showed significantly higher rates of MPR (66% v. 14%, p = 0.001), and improved RFS (64% versus 32% at 2 years, p = 0.021) vs male pts in the neoadjuvant setting (n = 51). These findings were not observed in a 2nd smaller trial of pts (n = 35), but were validated in a cohort of pts with unresectable metastatic melanoma treated with BRAF+MEKi (n = 69), with significantly higher rates of CB (80% v. 68%, p = 0.022) and PFS (12 v. 7 months, p = 0.003) in female vs male pts. Data from several published trials was analyzed (COMBI-D and METRIC trials), demonstrating improved PFS/OS at 2 years in female vs male pts treated with combined BRAF/MEKi (n = 211; p = 0.03 and, p = 0.04) and in female vs male pts treated with MEKi monotherapy (n = 206; p = 0.04 and p = 0.002), but not in female vs male pts treated with BRAFi monotherapy (n = 211; p = 0.21 and 0.095). Significantly higher expression AR expression was observed in available on- vs pre-treatment samples from male pts (p = 0.01), suggesting that treatment with BRAF/MEKi may induce AR expression in tumors. Findings were recapitulated in several preclinical models, and treatment with pharmacologic inhibitors of AR signaling (enzalutamide) in combination with BRAF/MEKi was associated with significantly enhanced anti-tumor activity in both male and female mice (p = 0.003 and p < 0.0001). Conversely, systemic treatment with testosterone was associated with significantly impaired tumor control in male and female mice (p = 0.021 and < 0.001). **Conclusions:** These data suggest that AR blockade may promote BRAF/MEKi response in melanoma, warranting further investigation in clinical trials. The impact of AR signaling, and modulation should be studied in MAPK-targeted therapy across other cancer types. Research Sponsor: U.S. National Institutes of Health.

9524 **Poster Session**

Tumor mutational burden (TMB) in immune checkpoint inhibitor (ICI)-naïve and -experienced patients with metastatic melanoma treated with lifileucel, a tumor-infiltrating lymphocyte (TIL) cell therapy. *First Author: Harriet M. Kluger, Yale University School of Medicine, Smilow Cancer Center, New Haven Hospital, New Haven, CT*

Background: Cutaneous melanoma is characterized by high TMB, which is associated with increased tumor-specific neoantigen expression (Schumacher Science 2015) and an increased response rate to ICI (Yarchoan NEJM 2019). The TMB in tumors that recur/progress after ICI is not well defined. Lifileucel is a one-time, autologous TIL cell therapy under investigation for treatment of patients (pts) with advanced melanoma. We conducted a matched case-control study of prospectively enrolled pts with advanced melanoma treated with lifileucel in the ICI-naïve (IOV-COM-202 trial, Cohort 1A [C1A]) and post-ICI (C-144-01 trial, Cohort 2 [C2]) setting to investigate the potential association between prior ICI therapy, TMB, and response to lifileucel. **Methods:** All pts had unresectable or metastatic melanoma. Available cases from C1A (ICI-naïve pts receiving lifileucel + pembrolizumab [pembro]) were matched to controls from C2 (pts receiving lifileucel alone after progression on antiPD-1/PD-L1 therapy); 3 controls per case were matched at least for BRAF status and disease stage at study entry, and if possible, for anatomic site of tumor harvest. Lifileucel regimen was similar in C1A and C2. In C1A, 1 dose of pembro was given after tumor harvest and before nonmyeloablative lymphodepletion and resumed after lifileucel per standard treatment, for up to 2 y. Objective response rate (ORR) was assessed by investigators per RECIST v1.1. TMB of the resected tumor was measured using the ImmunoID NeXT (C1A) or PGDx elio (C2) platform; a validated conversion factor was used to compare TMB between platforms (Vega Ann Oncol 2021). High TMB was defined as ≥10 mut/MB. **Results:** Seven pts in C1A and 21 in C2 were included in the case-control study and had ORR of 71.4% and 38.1%, respectively. The percentage of pts with high TMB was 57.1% in C1A and 19.0% in C2 (P = 0.1). ORR in the low and high TMB groups was 66.7% and 75.0%, respectively, in C1A and 41.1% and 25.0% in C2; 60% of responders in C1A and 12.5% in C2 had high TMB. In logistic regression analysis adjusted for cohort, TMB was not associated with response to lifileucel (odds ratio, 1.0; 95% CI, 0.91.1; P = 0.8). Data on tumor mutations and neoantigens, T-cell receptor repertoire, and tumor microenvironment profile will be presented. **Conclusions:** Our preliminary data indicate that the efficacy (ORR) of lifileucel may be independent of TMB, regardless of treatment setting, consistent with its proposed immune checkpoint pathway-independent mechanism of action. The percentage of patients with high TMB tended to be lower in tumors with prior ICI exposure than in those that were ICI-naïve. Clinical trial information: NCT03645928; NCT02360579. Research Sponsor: Iovance Biotherapeutics.

9525 **Poster Session**

Atezolizumab plus bevacizumab in patients with unresectable or metastatic mucosal melanoma: A multicenter, open-label, single-arm phase 2 study. *First Author: Lili Mao, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Melanoma and Sarcoma, Peking University Cancer Hospital and Institute, Beijing, China*

Background: Anti-programed cell death-1 (PD-1) monotherapy is a part of the standard therapy for cutaneous melanoma but has demonstrated low efficacy in mucosal melanoma. This study evaluated the efficacy and safety of atezolizumab plus bevacizumab as a first-line therapy in patients with advanced mucosal melanoma. **Methods:** This multicenter, open-label, single-arm, phase 2 study utilized a Simon's two-stage design. Atezolizumab (fixed-dose, 1200 mg) and bevacizumab (7.5 mg/kg) were administered by intravenous infusion every 3 weeks. The primary endpoint was objective response rate (ORR), determined by the investigator per RECIST v1.1. Secondary endpoints included progression-free survival (PFS), overall survival (OS), duration of response (DOR), disease control rate (DCR), and safety with adverse events summarized using NCI-CTCAE v5.0. **Results:** In total, 43 patients were enrolled, including 20 (46.5%) with unresectable and 23 (53.5%) with metastatic mucosal melanoma. Median follow-up was 13.4 months at data cut-off (July 30, 2021). Forty patients were evaluable for response: In stage I analysis set (n=22), the best confirmed ORR according to RECIST v1.1 was 40.9% (9/22; 95% CI 20.7-63.7), including one CR and eight PRs. The ORR in the FAS population was 45.0% (95% CI, 29.3-61.5) (1 CR, 17 PRs) and the DCR was 65.0% (95% CI, 48.3-79.4). The median PFS was 8.2 months (95% CI, 2.7-9.6), the 6- and 12-month PFS rates were 53.4% (95% CI, 36.6-67.6) and 28.1% (95% CI, 14.2-43.9), respectively. The median OS was not reached (NR) (95% CI, 14.4-NR). The 6- and 12-month OS rates were 92.5% (95% CI, 78.5-97.5) and 76.0% (95% CI, 57.1-87.5), respectively. The median DOR was 12.5 months (95% CI, 5.5-NR). Overall, 90.7% (39/43) of patients experienced treatment-related adverse events, and 25.6% (11/43) experienced grade ≥ 3 events. **Conclusions:** Atezolizumab in combination with bevacizumab showed promising efficacy and a manageable safety profile in patients with advanced mucosal melanoma. Research Sponsor: Shanghai Roche Pharmaceuticals Ltd., China. Clinical trial information: NCT04091217. Research Sponsor: Shanghai Roche Pharmaceuticals Ltd., Shanghai, China.

9526 **Poster Session**

Encorafenib plus binimetinib in patients with locally advanced, unresectable, or metastatic BRAF^{V600}-mutant melanoma: Updated data from the multicenter, multinational, prospective, non-interventional longitudinal study BERING^{MELANOMA}. *First Author: Erika Richtig, Department of Dermatology, Medical University of Graz, Graz, Austria*

Background: For the treatment of advanced BRAF^{V600}-mutated melanoma, targeted BRAF/MEK-inhibition is a standard of care. Encorafenib + binimetinib (EB) were approved 2018 in the EU and 2019 in Switzerland, based on positive results from COLUMBUS (NCT01909453), median progression-free survival (PFS) 14.9 mo (5-yr PFS: 23%), overall survival (OS) 33.6 mo (5-yr OS: 35%). As data from controlled trials are based on selected populations, BERING^{MELANOMA} investigates EB-use under real-world conditions in a broader population. **Methods:** BERING^{MELANOMA} (NCT04045691) is an ongoing, multi-national, prospective, longitudinal, non-interventional study. It analyzes the effectiveness (prim. endpoint: 1-yr PFS-rate), QoL and safety of EB-therapy in the unresectable advanced or metastatic setting under real-world conditions, focusing on the first- (1L) and second-line setting including an evaluation of the impact of prognostic factors. The project aims to enroll up to 750 patients (pts) in a total of 80 German, Austrian and Swiss sites (study duration: 8 yrs). So far (10/2019-01/2022), 280 pts have been included. Pts with prior BRAF-/MEK-inhibition (except adjuvant use completed > 6 mo) and > 1 prior therapy line with CPI in the palliative setting were excluded (adjuvant CPI allowed). **Results:** Here we present the 2nd planned interim snapshot based on the initial 200 enrolled pts (186 treated / 182 evaluable; median FU: 14.2 mo). This analysis set shows a median age of 60.5 yrs (range 20.0-89.0), 45% of pts were female. 87% presented with distant metastases (brain: 30%), with an involvement of ≥3 organ systems in 51% and elevated LDH in 43%. 54% of pts underwent any prior systemic therapy (adjuvant: 30%; 1L CPI palliative: 24%, mainly with ipilimumab + nivolumab). EB was mainly administered in the 1L-setting (60%). Main reasons for EB-selection were: efficacy (44%), physician's preference (34%), QoL (17%). Median estimated EB treatment duration was 11.6 mo (95%CI 8.8-18.6), median relative dose intensity for both drugs: 100%, main reasons EB-discontinuation: PD (55%), toxicity (16%). Treatment adaptations were required in 40% of pts (interruption E 26%, B 29%), toxicity as main reason (E 26%, B 29%). Adverse events were reported in 86% of pts (grade 3/4: 34%), mainly (≥10%, all grades): diarrhea, nausea, fatigue (each 17%), CK increase (16%), GGT increase (11%). No fatal toxicities were observed. **Conclusions:** This 2nd interim snapshot shows an investigation of EB in a real-world population with advanced disease. Despite the poorer prognosis configuration as compared to the pivotal study, the observed tolerability profile is largely consistent with data derived from COLUMBUS without any new safety signals. The 3rd interim snapshot will be performed after enrollment of 300 pts. Research Sponsor: Pierre Fabre Pharma.

9527 **Poster Session**

Dabrafenib (D) and trametinib (T) plus spartalizumab (S) in patients (pts) with previously untreated *BRAF* V600–mutant unresectable or metastatic melanoma: Three-year overall survival (OS) data from the randomized part 3 of the phase III COMBI-i trial. *First Author: Reinhard Dummer, Universitäts Spital Zürich, Zurich, Switzerland*

Background: Combination of immune checkpoint inhibitors and targeted therapy may produce durable and deep response in a higher proportion of pts with *BRAF* V600–mutant unresectable or metastatic melanoma. A recent report from the randomized, double-blind, placebo (PBO)-controlled Part 3 of the Phase 3 COMBI-i trial (NCT02967692) failed to show a statistically significant progression-free survival (PFS) benefit (hazard ratio (HR) of 0.82 (95% CI, 0.66–1.03, *p*= .042)). Here, we report 3-year OS data from COMBI-i part 3. **Methods:** Eligible pts were randomized 1:1 to receive either S+D+T (n = 267; S 400 mg IV Q4W + D 150 mg orally BID + T 2 mg orally QD) or PBO+D+T (n = 265), until progression or unacceptable toxicity. Although the primary endpoint of PFS was not met, exploratory OS and safety analyses were performed. OS was summarized descriptively using Kaplan–Meier methods and HR was estimated using a stratified cox regression model. **Results:** As of October 19, 2021 (median follow-up, 42.8 months), the median OS was not reached in S+D+T arm and was 40.4 months with PBO+D+T (HR 0.796; 95% CI, 0.615–1.029). There were 113 (42.3%) deaths in the S+D+T and 126 (47.5%) in the PBO+D+T. Estimated 2-year and 3-year OS rates were 67.7% (95% CI 61.6–73.1) and 60.1% (95% CI 53.8–65.8) with S+D+T vs 61.9% (95% CI 55.6–67.5) and 52.9% (95% CI 46.6–58.9) with PBO+D+T, respectively. An OS benefit was observed with S+D+T in these prespecified subgroups – Eastern Cooperative Oncology Group Performance Status (ECOG PS) 1 (HR 0.50; 95% CI, 0.32–0.8), age ≥65 years (HR 0.58; 95% CI, 0.36–0.94), PD-L1 negative (< 1%) (HR 0.62; 95% CI, 0.42–0.91), sum of lesion diameters ≥ 66 mm at baseline (HR 0.63; 95% CI, 0.43–0.91) and metastatic sites ≥ 3 (HR 0.66; 95% CI, 0.47–0.94). Adverse events (AEs) irrespective of study treatment relationship were observed in 99.3% of pts in S+D+T vs 97.3% in PBO+D+T. The most common AEs (in > 30%; all grades) were pyrexia, diarrhea, and nausea. Grade ≥3 treatment-related AEs (TRAEs) occurred in 56.9% vs 35.2% of pts treated with S+D+T vs PBO+D+T, respectively. Dose reductions of D and T due to AEs were more frequent in the S+D+T arm than PBO+D+T arm (47.2% vs 25.4% and 45.7% vs 25.4%, respectively), contributing to a lower relative dose intensity; the TRAEs leading to discontinuation of all 3 study drugs occurred in 13.5% vs 8% of pts, respectively. **Conclusions:** Results from this landmark 3-year OS analysis from COMBI-i- part 3 was consistent with the primary analysis, while the PBO+D+T showed a higher OS rate than previously observed for D+T alone in COMBI D/V studies, with a longer median follow-up. Subgroup analyses showed that ECOG PS 1, age ≥65 years, negative PD-L1 status and high tumor burden were associated with better OS in S+D+T in terms of HR. Clinical trial information: NCT02967692. Research Sponsor: Novartis.

9528 **Poster Session**

Efficacy and safety of nivolumab for locally advanced or metastatic cutaneous cell carcinoma (NIVOSQUACS trial). *First Author: Roland Lang, Department of Dermatology and Allergology, Paracelsus Medical University Salzburg, Salzburg, Austria*

Background: Cutaneous squamous cell carcinoma (cSCC) is the second most frequent skin cancer and considered as a tumor with strong immunogenicity. Consistently, immune checkpoint-inhibition with programmed death (PD)-1 antibodies has become the novel standard of care in the treatment of advanced cSCC. In this study, we evaluated efficacy and safety of the PD-1 antibody nivolumab in patients with locally advanced or metastatic cSCC, including individuals with concomitant hematological malignancies (CHM) – a highly vulnerable subgroup of cSCC patients typically excluded from clinical trials. **Methods:** This phase II, open-label, single-arm multicentre study included patients aged ≥ 18 years with histologically confirmed locally advanced and/or metastatic cSCC and at least one measurable lesion according to RECIST v1.1. Enrolled patients received nivolumab 240 mg intravenously over 30 min every 2 weeks for up to 2 years. A sample size of 31 patients was needed to provide 90% power to detect an objective response rate (ORR) of at least 12.6% after 24 weeks with a type I error of 5% assuming a dropout-rate of 15%. The primary endpoint was investigator assessed ORR as per RECIST v1.1. Secondary endpoints included disease control rate (DCR), progression-free survival (PFS) and overall survival (OS). **Results:** Between July 2017 and October 2020, 31 patients with advanced cSCC, including 11 patients with CHM, were enrolled and received at least one dose of nivolumab. The median age was 80 years (range 66-92) and the majority of patients was male (71%). Upon enrollment, 19.4% of patients had locally advanced, 51.6% loco-regional metastatic and 25.8% distant metastasic disease. Seven patients (22.6%) had received one prior systemic therapy for cSCC. At data-cut-off (March 2021; week-24 RECIST assessment completed in all available patients), five patients (16.1%) were still on treatment, one patient completed treatment per protocol, whereas 25 patients had discontinued therapy. Of 29 patients who were evaluable for response assessment, 12 patients achieved a partial and 7 a complete response, resulting in a best ORR of 65.2% (95% CI: 45.7% - 82.1%), a DCR of 68.9% (95% CI: 50.8%-82.7%) and a median PFS of 11.1 months (95% CI: 3.7 - 12.9). Treatment related adverse events occurred in 18 patients (58.1%) and led to nivolumab discontinuation in two patients (6.5%). Subgroup analysis of patients with CHM revealed a best ORR of 55.6% (95% CI: 21.2% - 86.3%), a DCR of 66.7% (95% CI: 35.4% -87.9%) and a median PFS of 10.9 months (95% CI: 0.6 - 21.4). Median OS in this subgroup was 20.7 months (95% CI: 6.5 - 35.0), whereas overall median OS was not reached. **Conclusions:** Nivolumab showed a robust antitumor-activity similar to other anti-PD-1 agents in advanced cSCC. Although ORR and OS were slightly reduced in patients with CHM, nivolumab proved effectiveness also in this subgroup while no new safety signals occurred. Clinical trial information: NCT04204837. Research Sponsor: Bristol-Myers Squibb.

9529 **Poster Session**

Efficacy of immune checkpoint inhibitor (ICI) rechallenge in advanced melanoma patients responders to a first course of ICI: A multicenter, national, retrospective study of the French group of skin cancers (GCC). *First Author: Charlee Nardin, Université de Franche-Comté, Inserm 1098 RIGHT, Besançon, France*

Background: The efficacy of ICI rechallenge for progressive/recurrent disease of advanced melanoma patients (pts) after a first course of ICI interrupted for disease control has not been systematically described. **Methods:** A retrospective observational multicenter national real-life study evaluated the efficacy and tolerance of ICI rechallenge (anti-PD1, anti-CTLA-4, or combination therapy) in melanoma pts who progressed after disease control with an ICI subsequently interrupted. Primary objective was to evaluate tumor response using RECIST version 1.1. Secondary objectives were the factors associated with tumor response, progression-free survival (PFS), overall survival (OS) and the tolerance of the rechallenge. **Results:** 85 pts from 12 French different centers rechallenged with an ICI between July 2014 and June 2021 were included. Median (IQR) age of pts was 72.00 (30–89) years. Most pts were male (n = 47, 55%) with an AJCC stage IV melanoma (n = 75, 88%). BRAFV600-mutant melanoma and elevated LDH were reported in 19 pts (22%). Pts were rechallenged with anti-PD1 (Pembrolizumab (n = 44, 52%), Nivolumab (n = 35, 41%)), anti-CTLA-4 (Ipilimumab (n = 2, 2%)) or the combination therapy (Ipilimumab + Nivolumab (n = 4, 5%)). Median follow-up after rechallenge was 13 months (1.1-76.2). All pts included had had disease control with the first course of ICI including complete response (CR) in 47 pts (55%), partial response (PR) in 28 pts (33%) and stable disease (SD) in 10 pts (12%). Adverse events (AEs) of the first course of ICI had occurred in 51% pts including grade 3-4 AEs (22%). Median time between ICI interruption and ICI rechallenge was 9,3 months (1.2-63,9). The response rates of ICI rechallenge (2nd course of ICI) were CR in 30 pts (35%), PR in 17 pts (20%) and SD in 17 pts (20%). Progression occurred in 21 pts (25%). The use of steroids for brain metastases was the only factor associated with a higher recurrence rate in multivariate analysis (p = 0,002) and tends to be associated with lower outcomes. There was no correlation between best overall response to the first course of ICI and response to ICI rechallenge. Median duration of response, PFS and OS after ICI rechallenge were not reached. At last follow-up, 23 pts have died. 28 AEs of ICI rechallenge occurred in 23 pts (27%) with a median time of 3 (0.4-36.2) months, including grade 1-2 and grade 3-4 AEs in 13 (15%) and 9 (11%) pts respectively. **Conclusions:** ICI rechallenge for progressive/recurrent disease was associated with high objective response rate (CR+PR = 55%) and disease control rate (CR+PR+SD = 75%) in melanoma pts with a previous disease control induced by ICI. Thus, ICI rechallenge should be considered as an attractive therapeutic option for melanoma pts with progressive/recurrent disease after ICI interruption. Research Sponsor: None.

9530 **Poster Session**

Characterization of patients with metastatic melanoma that relapses following complete metabolic response from anti–PD-1 therapy. *First Author: Vincent T Ma, University of Wisconsin, Madison, WI*

Background: Treatment with PD-1 inhibitor-based therapy has significantly improved survival in patients with metastatic melanoma over the past decade. Many of these patients achieve complete metabolic response (CMR) by FDG-PET/CT and electively stop treatment. However, the outcomes of patients who relapse after CMR remain uncertain. In this study, we attempt to further characterize metastatic melanoma patients who relapsed following elective discontinuation of anti-PD-1 based therapy due to CMR. **Methods:** We performed a single-center, retrospective analysis on a cohort of patients with metastatic or unresectable melanoma from 2012 to 2021 who were treated with anti-PD-1 monotherapy (pembrolizumab or nivolumab) or combination ipilimumab/nivolumab (I/N), with or without local therapies (surgery or radiation therapy). Patients who achieved a CMR from treatment were identified. CMR was defined as no evidence of metabolically active disease on full-body ^{18}F-FDG-PET/CT and no evidence of new intracranial metastasis on MRI brain. Multiple clinical variables and survival outcomes were assessed. **Results:** Among 386 advanced stage melanoma patients analyzed, 87 achieved a CMR followed by elective treatment cessation with a median anti-PD-1 therapy duration of 10.4 months. 19/87 patients had brain metastasis at baseline. 17/87 patients had disease relapse with a median time to relapse from CMR of 12.1 months. Of those 17 patients, 8 received I/N, 9 received anti-PD-1 monotherapy, and 2 required local therapies to obtain CMR. 7/17 patients were able to achieve CMR again following resumption of anti-PD-1 monotherapy (n = 6) and BRAF/MEK targeted therapy (n = 1). 10/17 patients relapsed in the brain with 7 of those patients having no history of brain metastasis at baseline. Median overall survival after relapse from CMR was 34.1 months. The most common cause of death following relapse from CMR was brain metastasis progression (n = 5). **Conclusions:** A small proportion of metastatic melanoma patients who achieve complete metabolic (CMR) following treatment with anti-PD-1 therapy develop disease relapse. We found that relapse in the brain is common, regardless of baseline involvement at time of therapy, and is a common cause of mortality suggesting the importance of intracranial surveillance following treatment cessation. Ongoing studies are warranted to identify clinicopathologic factors that predict relapse to better inform patients and providers who elect to stop anti-PD-1 therapy. Research Sponsor: None.

9531 **Poster Session**

Progression and mortality post-immunotherapy discontinuation among patients with BRAFV600-mutant (BRAF+) metastatic melanoma. *First Author: Sunandana Chandra, Northwestern University Feinberg School of Medicine, Chicago, IL*

Background: Immunotherapy (IO) is commonly used to treat BRAF+ metastatic melanoma (MM) patients in the first line (1L) setting and has demonstrated durable outcomes in clinical trials. However, most patients discontinue IO therapy for toxicity, disease progression, or other reasons. To date, no multi-center or nationwide US-based study has examined treatment patterns and outcomes for patients with BRAF+ MM post discontinuation of 1L IO. The aim of this study is to describe real-world treatment patterns and outcomes among patients who discontinued 1L IO. **Methods:** This retrospective cohort study used the Novartis BRAF+ meLanoma patients ObsErvational (NOBLE) database, the harmonized customized data from Flatiron and ConcertAI. Patients were ≥18 years old, had a diagnosis of BRAF+ MM, were treated with pembrolizumab, nivolumab, or ipilimumab + nivolumab on or after 9/1/2014, and then discontinued 1L therapy. Reason for discontinuation was extracted from medical records. Descriptive statistics were used to describe baseline characteristics and treatment patterns. Kaplan–Meier curves were used to analyze time to progression or death (TTPD) and time to death (TTD). **Results:** Of the 898 included patients (mean age: 61 years; male: 65%); 46% initiated ipilimumab + nivolumab, 24% nivolumab, and 30% pembrolizumab. The most common reasons for 1L discontinuation were toxicity (26%) and progression (25%). Medical records noted 5.3% completed therapy on discontinuation and 34.5% provided no reason of discontinuation with median duration of therapy (MDOT) of 379 and 138 days respectively. At 6 months, 34 % (n = 303) remain on IL IO. MDOT for patients who discontinued IO due to toxicity and those who discontinued due to progression were 54 and 63.5 days respectively. Patients who discontinued due to toxicity had a median time of 142 days to next treatment. TTPD was best for patients who discontinued therapy due to completion or toxicity (6-month progression rate: 13% and 20%). Patients who discontinued due to progression did especially poorly (6-month progression rate: 59%). About 33% of patients (n = 296) needed second line (2L) therapy, and the majority (80.7%) received combination BRAF+ targeted therapy. Overall, 38% and 50% of patients died post IO discontinuation for any reason at 1 and 2 years, respectively. 31% of patients had brain metastases and a greater proportion (56%) died within a 2-year period compared with those without brain metastases (56% vs 49%, p = 0.0036). **Conclusions:** IO, although effective, is not curative for all patients. A significant number of patients discontinue therapy due to progression. Patients with BRAF+ MM who progress early on 1L IO therapy have a high risk of death and should be considered for other therapy options, including targeted therapy. Research Sponsor: Novartis Pharmaceuticals Corporation.

9532 **Poster Session**

Real-world evaluation of the association between baseline metastatic patterns and clinical outcomes among patients with BRAF-positive metastatic melanoma. *First Author: Zeynep Eroglu, Moffitt Cancer Center, Tampa, FL*

Background: While immunotherapy (IO) and BRAF-targeted therapy (TT) have benefit in BRAFV600 mutant (BRAF+) metastatic melanoma (MM), there is a paucity of real-world data on the impact of systemic therapy choice on outcomes based on key characteristics such as site and number of baseline metastases. Patients with >1 baseline site and certain sites of metastases are also underrepresented or excluded in clinical trials. The aim of this study was to evaluate the association between these characteristics and survival among BRAF+ MM patients. **Methods:** This was a retrospective cohort study using the Novartis BRAF+ meLanoma patients ObsErvational (NOBLE) dataset – harmonized customized data from Flatiron and ConcertAI. It included patients ≥18 years, who received treatment with a first-line (1L) IO (anti-PD-1 mono or combination therapy ipilimumab + nivolumab) or TT (any BRAF/MEK-inhibitors) after 1/1/2014. Progression free survival (PFS) and overall survival (OS) for IO and TT were analyzed according to number (1, 2, 3+ sites) and location (brain, lung, liver, bone) of baseline metastasis. Treatment sequence from 1L to 2L (i.e. IO/TT vs TT/IO) were also compared for PFS and OS outcomes. **Results:** A total of 1,961 patients were included, with 620 patients (32%) on IO monotherapy, 501 patients (26%) on IO combo therapy, and 840 patients (43%) on TT in the 1L. When adjusted for sex, age, ECOG, and Charlson Comorbidity Index, there was no difference in PFS or OS between 1L IO mono, IO combo and TT therapies in patients who had 1, 2, or 3+ baseline metastases. For patients who had either baseline brain, liver, lung, or bone metastasis, there was no difference in PFS and OS between IO mono, IO combo, and TT combo therapies. Of the 521 patients included in the sequencing analysis (only patients who received 2L therapy), 239 patients (46%) had 1L IO/2L TT. There was no difference in PFS or OS between treatment sequences for patients with any number or location of baseline metastasis. **Conclusions:** In this real-world retrospective cohort study, there is no difference in survival between 1L TT and IO for BRAF+ MM patients. Outcomes are comparable regardless of number and location of metastases, including brain metastasis. Whether switching from 1L TT to IO before progression may account for differences compared to trial data will be explored further. Research Sponsor: Novartis Pharmaceuticals Corporation.

Outcomes stratified by number of metastases and metastatic site among patients who received sequencing therapy 1L TT/2L IO.

Reference group: 1L IO/2L TT		PFS		OS	
Number of metastases	N	HR	95% CI	HR	95% CI
1	165	0.96	0.57 - 1.61	1.51	0.53 – 4.34
2	132	0.56	0.29 - 1.07	0.95	0.22 – 4.03
3+	218	0.75	0.54 – 1.04	1.43	0.60 – 3.38
Metastatic site					
Brain	177	0.82	0.49 – 1.38	1.45	0.41 – 5.14
Liver	150	1.00	0.59 – 1.70	0.57	0.22 – 1.53
Lung	272	0.89	0.61 – 1.29	1.22	0.58 – 2.53
Bone	160	1.24	0.76 – 2.02	1.57	0.59 – 4.17

HR = Hazard ratio; CI = confidence interval.

9533 **Poster Session**

Fecal microbiota transplantation followed by anti–PD-1 treatment in patients with advanced melanoma. *First Author: Wilson H. Miller, Segal Cancer Centre at the Jewish General Hospital, McGill University, Montreal, QC, Canada*

Background: The gut microbiome has been shown to be a biomarker of response in patients (pts) with melanoma. Strategies to modify the microbiome are currently being investigated. We report the effects of Fecal Microbiota Transplantation (FMT) on safety and anti-PD-1 response in pts with melanoma from a phase I trial (NCT03772899). **Methods:** 20 pts with advanced melanoma with RECIST-evaluable disease, without prior anti-PD-1 treatment for advanced disease, were recruited from 3 Canadian academic centers. Pts with ECOG > 2, autoimmune diseases, immunosuppression or unstable brain metastases were excluded. Pts received 80-100 g of healthy donor stool via oral capsules and were treated with anti-PD-1 one week later. The primary objective was safety of combining FMT with anti-PD-1 therapy. Objective response rate (ORR) by RECIST 1.1 and correlative studies were secondary objectives. Flow cytometry and multiplex ELISA were performed on pts blood samples. Avatar mice were transplanted with stool samples obtained from participants on the trial before and after FMT. Mice were subsequently implanted with B-16 or MCA-205 tumors and received anti-PD-1 antibodies. **Results:** Median age was 75.5 years, 12 (60%) were male, 18 (90%) had stage 4 disease, and 5 (25%) pts harbored a BRAF mutation. Median follow-up was 11.2 months. FMT-related adverse events included grade 2 diarrhea (2 pts) and hypophosphatemia (1 pt), and 13 pts (65%) experienced grade 1 gastrointestinal toxicities. Grade 3 immune-related adverse events (irAE) were one each of myocarditis, nephritis, and fatigue. Anti-PD-1 therapy was discontinued for toxicity in 2 (10%) pts. No unexpected irAE or death on treatment occurred. ORR was 65% (13/20), of which 3 were CR. Clinical benefit rate (includes SD lasting > 6 months) was 75% (15/20). Median PFS was not reached, and one pt died from their disease. Translational analyses demonstrated upregulation of IL-17 post-FMT in responders, which correlated with upregulation of the frequency of Th17 cells in peripheral blood. In parallel, murine experiments showed that feces from pts pre-FMT did not sensitize tumors to anti-PD-1. In both tumor models, only feces obtained post-FMT from responders restored anti-PD-1 efficacy in mice, providing strong support that FMT contributed to the anti-tumor response observed in pts. **Conclusions:** FMT followed by anti-PD-1 treatment in melanoma pts undergoing therapy is safe and may lead to improved anti-tumor responses that can be reproduced in tumor mouse models. The gut microbiome plays an important role in responses to anti-PD-1 in patients with advanced melanoma, paving the way for future microbiome-based interventions. Clinical trial information: NCT03772899. Research Sponsor: Canadian Cancer Society, Lotte & John Hecht Memorial Foundation and the Division of Medical Oncology at London Regional Cancer Program.

9534 **Poster Session**

Outcomes of combined ipilimumab/nivolumab in metastatic uveal melanoma: A prevalence meta-analysis. *First Author: Ceren Durer, SUNY Upstate Medical University, Syracuse, NY*

Background: Uveal melanoma is the most common primary intraocular malignant tumor in adults and, approximately 40-50% of the patients eventually develop metastatic disease. Metastatic uveal melanoma has a dismal prognosis with an overall survival of < 50% at 1-year. Single-agent check point inhibitors revealed minimal benefit and novel approaches are underway to improve the outcomes with the recent approval of Tebentafusp in uveal melanoma. The purpose of this metanalysis was to assess the safety and efficacy of combined immunotherapy with ipilimumab (3 mg/kg x q3w for 4 cycles) and nivolumab (1 mg/kg x q3w for 4 cycles) in metastatic uveal melanoma. **Methods:** A comprehensive literature search on PubMed, Embase, Cochrane and Web of Science was conducted. Two independent reviewers screened the literature and extracted data. Our search strategy included MeSH terms and key words for metastatic uveal melanoma; ipilimumab and nivolumab. OpenMeta[Analyst] software was used for the analysis. The endpoints included the prevalence of overall response rate (ORR), complete response (CR), ≥grade-III diarrhea/colitis, and ≥grade-III hepatic toxicity. Additional endpoint included the median overall survival (OS) was reported as a range. Random-effects model (DerSimonian-Laird method) was applied. **Results:** Overall, eight studies (n = 379) were included for the analysis. Five studies were phase II, three studies were retrospective. 52% of the patients were male with good performance status. Median follow-up ranged from 9.2 mo-28 mo. 40% of the patients (n = 142) had elevated LDH at the time of treatment . GNAQ and GNA11 mutations were reported in three studies, BRAF mutation was reported in two studies. The pooled prevalence for ORR was 13.7% (95% CI: 9.2–18.2%, N = 6 studies, n = 33/226) with CR of 2.1% (95% CI: 0.3–3.9%, N = 6 studies, n = 8/226). The median OS ranged from 12.7 to 19.1 months (N = 7 studies). Majority of the patients experienced treatment-related adverse events. Most common side effects included diarrhea, colitis, hepatic toxicities, skin disorders, hypothyroidism. The pooled prevalence for ≥grade III hepatic toxicity was 26.2% (95% CI: 13.9–0.385%, N = 5 studies, n = 60/219). **Conclusions:** Combined checkpoint blockade with ipilimumab and nivolumab showed an ORR of 13.7% which appears to show better clinical activity than single-agent checkpoint inhibitor. Most common treatment side effect was hepatic toxicity. Research Sponsor: None.

9535 **Poster Session**

Phase II study SECOMBIT (sequential combo immuno and target therapy study): A subgroup analysis with a longer follow-up. *First Author: Paolo Antonio Ascierto, Melanoma, Cancer Immunotherapy and Development Therapeutics Unit, Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale", Naples, Italy*

Background: To investigate the best sequential strategy, we started the SECOMBIT study, a randomized three parallel arms phase 2 study (NCT02631447). We used the combination of encorafenib/binimetinib (E+B) as targeted therapy (T-T) and the combination of ipilimumab/nivolumab (I+N) as immunotherapy (I-O). We explored the two different sequences and the "sandwich" strategy with a short course of target therapy, switched by combo immunotherapy at the best response, and not at progression of disease. In our previous report we have observed a trend in favor of the arms where I-O was given as first, confirmed by the first report of the DreamSeq study, a phase III study which compared the two different sequences with T-T and I-O. Here we updated the study data with a subgroup analysis. **Methods:** From Nov 2016 to May 2019, 37 centers in 9 countries enrolled 251 patients with untreated, metastatic *BRAFV600* melanoma. Patients were randomized to Arm A [E+B until PD, followed by I+N], or Arm B (I+N until PD, followed by E+B) or Arm C (E+B for 8 weeks, followed by I+N until PD, followed by E+B). The overall survival (OS) is the primary endpoint of the study. Secondary endpoints included total progression-free survival (tPFS), 2- and 3-years survival rate, best overall response rate, duration of response, biomarkers evaluation. **Results:** The study primary endpoint was met in each arm with at least 30 patients alive at 24 months. The median follow-up estimated with the reverse Kaplan-Meier method was 37.1 months (IQR: 32.8-46.4). The OS at 2 and 3 years was calculated in the three arms for all patients, and in the subgroups normal or elevate LDH level and < 3 or ≥ 3 metastatic sites. OS and tPFS rates at 2 and 3 years are shown in the table. **Conclusions:** With a 37.1 months median follow-up, 2 and 3-years OS as well as tPFS rates are higher in Arm B and C. In line with recent findings, the SECOMBIT results confirm a better trend in favor of Arm B and C treatment sequence. The analysis of the secondary endpoints is ongoing. Clinical trial information: NCT02631447. Research Sponsor: BMS and Array Biopharma/Pfizer.

	2-year tPFS	3-year tPFS	2-year OS	3-year OS	2-year OS < 3ms	3-year OS < 3ms	2-year OS ≥ 3ms	3-year OS ≥ 3ms	2-year OS nLDH	3-year OS nLDH	2-year OS eLDH	3-year OS eLDH
Arm A	44%	34%	62%	53%	70%	62%	50%	36%	73%	67%	50%	42%
Arm B	65%	56%	73%	63%	74%	63%	72%	61%	76%	69%	67%	50%
Arm C	57%	54%	69%	60%	79%	64%	54%	54%	70%	56%	65%	65%

tPFS = time from randomization to second progression; OS = overall survival; ms = no. of metastatic sites; nLDH = normal LDH levels; eLDH = elevated LDH levels.

9536 **Poster Session**

Autoantibodies as potential biomarkers of immune-related adverse events in patients with advanced cutaneous melanoma treated with immune checkpoint inhibitors. *First Author: Aesha Gandhi, Edith Cowan University, Perth, Australia*

Background: The majority of patients treated with immune checkpoint inhibitors (ICIs) develop immune-related adverse events (irAE). It is currently not possible to predict the development of irAEs using biomarkers. Here we evaluated the IgG autoantibodies (AAbs) profile in pre-treatment sera of cutaneous metastatic melanoma patients treated with ICIs to identify AAbs that are associated with irAEs. **Methods:** Clinical data of patients with metastatic melanoma treated with pembrolizumab or nivolumab monotherapy (n = 48) or combination ipilimumab and nivolumab (n = 37) was retrospectively evaluated. irAEs were graded using CTCAE v5.0. Sera from the 85 patients were evaluated for IgG AAbs using the HuProt™ microarray v4.0 covering 23,059 proteins (> 81% of the human proteome). AAb profiles were compared between groups (any irAEs vs no irAEs), using the no irAEs group as control group. Results were inputted into the Advaita Bio's iPathwayGuide software to find significantly differentially expressed AAbs using $p < 0.05$ and Log2FC > 0.6, and identify relevant biological pathways. **Results:** Out of 85 patients, 60 experienced any grade irAEs, 29 of 48 (60.4%) in the PD-1 group and 31 of 37 (83.8%) in the combination group. We found 758 proteins were differentially elevated, 102 in the in the PD-1 group and 666 in the combination treatment group. A comparison of these groups identified 10 AAbs that were elevated in patients experiencing irAEs independent of ICI regimen. These targeted proteins are highly expressed in tissues that are commonly affected by irAEs. Previous studies have shown their links to autoimmune and inflammatory conditions such as dermatitis and thyroiditis. Pathway analysis shows the RIG like receptor signalling pathway, which has been associated with autoinflammatory conditions, was significantly affected in the PD-1 group ($p = 0.011$), but not in the combination group ($p = 0.442$). Other pathways involved included the NOD-like receptor, purine and D-amino acid metabolism which play a role in innate immune system and assembly of inflammasomes and maturation, pro-inflammatory cytokines and mediators that contribute to inflammatory response. **Conclusions:** Further analyses are being conducted to identify the correlation of irAE type and severity to specific autoantibodies which will be presented. Prospective studies are required for validation of these AAbs specificities. This approach could be used to identify patients at high risk of irAEs, for treatment monitoring to maintain an effective stimulation of the patient's anti-cancer immune response, to determine if treatment cessation is required and prevent hospitalisation or lengthy immunosuppression to treat irAEs. Research Sponsor: Western Australia Cancer and Palliative Care Network.

9537 **Poster Session**

Efficacy and safety of cosibelimab, an anti–PD-L1 antibody, in patients with metastatic cutaneous squamous cell carcinoma. *First Author: Philip R. Clingan, Southern Medical Day Care Centre, Wollongong, Australia*

Background: Programmed death receptor-1 (PD-1)–blocking antibodies are approved as monotherapy treatment for patients (pts) with metastatic or locally advanced cutaneous squamous cell carcinoma (CSCC) who are not candidates for curative surgery or radiation. Cosibelimab is a high-affinity, fully human programmed death ligand-1 (PD-L1)–blocking antibody with a functional Fc domain capable of inducing antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) against tumor cells. Study CK-301-101 (NCT03212404) is a global, multicenter, multicohort, pivotal trial that enrolled pts with select advanced cancers for treatment with cosibelimab. Here we present the primary analysis of the registration-enabling expansion cohort in pts with metastatic CSCC. **Methods:** Adult pts with Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 who had metastatic (nodal and/or distant) CSCC not amenable to local therapy were eligible to participate. Cosibelimab was administered as a fixed dose of 800 mg every 2 weeks (Q2W) intravenously. The primary endpoint was confirmed objective response rate (ORR; complete response [CR] + partial response [PR]) assessed by independent central review according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and the key secondary endpoint was duration of response. **Results:** Seventy-eight pts with metastatic CSCC were treated with cosibelimab and comprise the efficacy and safety populations (59M/19F; median age: 71 years). The confirmed ORR was 47.4% (95% CI: 36.0, 59.1; 6 CRs and 31 PRs) and the median duration of response was not reached at the time of data cutoff (median duration of follow-up: 15.2 months), with 76% of responses ongoing (range: 1.4-31.8+ months). The Kaplan–Meier estimated probability of maintaining a response at 6 and 24 months was 88.1% and 72.5%, respectively. Treatment-related adverse events (TRAEs) were reported in 54 pts (69.2%); 7 pts (9.0%) experienced at least 1 grade 3 TRAE (no grade 4 or grade 5 TRAEs were reported) with the most common being increased serum lipase in 2 pts. **Conclusions:** Treatment with cosibelimab monotherapy resulted in a robust ORR with durable responses and demonstrated a predictable and manageable safety profile in pts with metastatic CSCC, supporting its use in the treatment of this cancer. Clinical trial information: NCT03212404. Research Sponsor: Checkpoint Therapeutics.

9538 **Poster Session**

Anti-LAG-3 antibody LBL-007 in combination with toripalimab in patients with unresectable or metastatic melanoma: A phase I, open-label, multicenter, dose escalation/expansion study. *First Author: Xue Bai, Key laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Melanoma and Sarcoma, Peking University Cancer Hospital and Institute, Beijing, China*

Background: LBL007 is a novel, fully human IgG4 monoclonal antibody targeting human Lymphocyte-activation gene3 (LAG-3). Dual inhibition of anti-programmed cell death protein 1 (PD-1) and LAG-3 is anticipated to synergistically increase immune response against tumor growth. Here we report the preliminary safety and efficacy of LBL-007 in combination with Toripalimab (an anti-PD-1 antibody has approved for treatment of melanoma in China) in patients (pts) with unresectable or metastatic melanoma. **Methods:** Pts with unresectable or metastatic melanoma with or without prior anti-PD-(L)1 therapy were enrolled. This trial comprised 2 parts, namely part 1 (dose escalation), pts received LBL-007 (0.25/1/3/6 mg/kg) /Toripalimab (3 mg/kg) both i.v., Q2W; and part 2 (expansion), pts received LBL-007 (3/6 mg/kg)/Toripalimab (3 mg/kg) both i.v., Q2W. The primary objective was safety, the second objectives included pharmacokinetics, pharmacodynamics and efficacy (per RECIST 1.1). **Results:** By Jan 2022, 37 pts (15 [40.5%] male, median age 59 [range 31-74] years, 9 pts [24.3%] with baseline LDH elevation, 18 [48.6%] with acral, 12 [32.4%] mucosal, 5 [13.5%] nonacral cutaneous, 2 [5.4%] primary site unknown) were enrolled, with 17 in part 1 and 20 in part 2. No dose-limiting toxicity was observed in part 1, and the MTD was not reached. Of all 37 pts, the most common treatment-emergent adverse events (TEAEs) included anemia (24.3%), creatine phosphokinase elevation (24.3%), hypothyroidism (21.6%), and aspartate aminotransferase elevation (21.6%). For 32 radiologically evaluable pts, ORR was 12.5%, DCR was 53.1%. In a preplanned subtype-specific analysis in anti-PD-(L)1 treatment-naïve pts, ORR was 27.3 % vs. 0%, and DCR was 81.8% vs. 50.0% in acral and mucosal melanoma subtypes, respectively. For anti-PD-(L)1-resistant pts (n = 11), DCR was 18.2%. **Conclusions:** LBL007/Toripalimab combination is well tolerated and promising efficacy in pts with unresectable or metastatic melanoma, especially in the acral type without prior anti-PD-(L)1 therapy. Clinical trial information: NCT04640545. Research Sponsor: Nanjing Leads Biolabs Co.,Ltd.

9539 **Poster Session**

The interferon-gamma (IFN-γ) signature from baseline tumor material predicts pathologic response after neoadjuvant ipilimumab (IPI) + nivolumab (NIVO) in stage III melanoma. *First Author: Irene L.M. Reijers, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: Neoadjuvant IPI + NIVO induces high pathologic response rates (pRR) of 74-78% in macroscopic stage III melanoma. Pathologic response (< 50% viable tumor) is strongly associated with improved relapse-free survival (RFS); the previous OpACIN-neo study demonstrated a 2-year RFS of 96.9% in patients (pts) with pathologic response, whereas the 2-year RFS in non-responders was 35.5%. These data highlight the need for baseline biomarkers predictive for response and survival. Here, we present the predictive value of the 10-gene IFN-γ expression signature algorithm (based on Ayers et al.) for pathologic response and relapse in a cohort of melanoma pts treated with neoadjuvant IPI + NIVO. **Methods:** Baseline tumor biopsies from lymph node metastases of stage III melanoma pts were used for IFN-γ signature assessment. Pts were treated with a maximum of two cycles of neoadjuvant IPI 1mg/kg + NIVO 3mg/kg in the OpACIN-neo (arm B) and PRADO studies. RNA expression analysis was conducted using the nCounter® PanCancer Immune Profiling panel on the NanoString Flex machine (NanoString Technologies), which is clinically applicable due to its fast turn-around-time (two days). An IFN-γ signature gene expression score (IFN-γ score) was calculated using a NKI-developed algorithm. Association between IFN-γ score and pathologic response or event-free survival (EFS) was examined by logistic regression and Cox analyses. The optimal cutoff between a high and low IFN-γ score was defined based on a summary receiver operating characteristic (sROC) curve. **Results:** In total, 103 pts treated in the OpACIN-neo and PRADO studies had baseline tumor material available. Median age was 56 years, 62% was male, and 52% had a high baseline IFN-γ score. The pRR of the total cohort was 70% (72/103 pts), including 56% (58/103) major pathologic response (MPR, 0-≤10% viable tumor) and 14% (14/103) partial responses (pPR, 10-≤50% viable tumor). 30% (31/103 pts) had no pathologic response. After a median follow-up of 25.2 months, 26 pts (25.2%) developed a melanoma relapse. The IFN-γ score was significantly associated with response (OR 1.061, p < 0.001) and relapse (OR 0. 974, p = 0.029). The pRR was 89% (48/54) in pts with a high IFN-γ score versus 49% (24/49) in those with a low IFN-γ score (p < 0.001). Pts with a high IFN-γ score were also less likely to develop a relapse (11% [6/54] versus 41% [20/49], p = 0.001). **Conclusions:** Pts with a high IFN-γ score in pre-treatment biopsies are more likely to respond to neoadjuvant IPI + NIVO with favorable EFS. A rapid gene expression analysis enables the IFN-γ score to be used in daily clinical practice to identify pts who might qualify for treatment escalation or de-escalation. The DONIMI study [NCT04133948] currently investigates different neoadjuvant treatment combinations in stage III melanoma pts based on their intratumoral IFN-γ score. Research Sponsor: None.

9540 **Poster Session**

EMRseq: Registry-based outcome analysis on 1,000 patients with BRAF V600–mutated metastatic melanoma in Europe treated with either immune checkpoint or BRAF-/MEK inhibition. *First Author: Michael Weichenthal, University Department of Dermatology, Kiel, Germany*

Background: In BRAF mutated metastatic melanoma, potential outcome differences for different choices of 1st line treatments including immunotherapy or BRAF-/MEK inhibition are not completely understood. We therefore analyzed the treatment patterns and outcome of systemic therapies for patients BRAF mutated metastatic melanoma. **Methods:** From the EUMelaReg treatment registry, patients fulfilling the following inclusion criteria were consecutively included until a number of 1,000 evaluable cases was reached. 1) Patients with metastatic melanoma and BRAF V600 mutation 2) First line treatment with either combined BRAF-/MEK or immune checkpoint inhibition (ICI) with PD-1 single agent or combined PD-1/CTLA-4 antibodies. Multivariable cox regression analysis as well as propensity score based weighting were used to control for bias from baseline imbalances. Primary outcomes of interest were overall survival (OS) and 2nd line PFS (PFS-2), stratified for upfront treatment decision of ICI versus targeted therapy. PFS-2 was defined as the interval from start of first line treatment to a progression after a 2nd line treatment or death of any cause. Further endpoints were evaluated including time on treatment (ToT), time to next treatment and 2nd line treatments. **Results:** In total 529 (52.9 %) patients received BRAF/MEK-i, and 471 (47.1%) ICI. For various co-variates there were significant imbalances between strata, including number of metastatic sites, AJCC substage, serum LDH, and ECOG performance status, with more favorable prognostic variables for patients receiving immunotherapy. The ORR for BRAF/MEK-i was significantly higher than for ICI (53.3% vs. 42.0%; p=0.0004), but for OS and PFS2 the adjusted hazard ratios were significantly in favor for ICI (HR 0.62 and 0.66, respectively; p <0.0001). In 2nd line, patients switching from ICI to BRAF/MEK-i had again markedly higher ORR than patients switching vice versa (57.7% vs. 19.9%; P<0.0001), and also significantly longer unadjusted PFS (8.1 vs. 3.1 months; p <0.0001) and OS (15.7 vs. 10.6 mths; p=0.01) after start of 2nd line treatment. **Conclusions:** The two cohorts had imbalances on key prognosis variables. After adjustment for these imbalances, upfront ICI still resulted in significantly longer OS as compared to BRAF/MEK-i. Due to the nature of real-world observational data causing inherent imbalances in the treatments cohorts and being unable to account for potential unknown confounders, outcome may still be biased despite adjustment efforts. Research Sponsor: None.

	1st line Therapy		
	BRAFi+MEKi (N = 529)	ICI (N = 471)	P value
Objective Remissions	282 (53.3%)	198 (42.0%)	0.0004
Median PFS2 [m] (95% CI)*	12.3 (11.3-14.8)	21.9 (17.6-33.0)	< 0.0001
Median OS [m] (95% CI)*	16.9 (15.2-22.3)	45.0 (30.2-NA)	< 0.0001

*Adjusted by inverse propensity score weighting for confounding factors.

9541 **Poster Session**

Meta-analysis of randomized phase II-III trials evaluating triplet combinations of immunotherapy and targeted therapy for BRAF V600-mutant unresectable or metastatic melanoma. *First Author: Pier Francesco Ferrucci, European Institute of Oncology, Milan, Italy*

Background: Immune-checkpoint inhibitors (ICI) and targeted-therapies (TT) have become standard options for BRAF -V600 metastatic melanoma (B-mut MM) patients. However, still more than 50% of those patients do not respond or relapse to these current strategies. Preclinical and translational data suggest that ICI plus TT may improve treatment outcomes in patients with B-mut MM, but with conflicting results in the clinical setting. **Methods:** We performed a systematic review and meta-analysis of randomized phase II-III studies published until January 2022 comparing first-line ICI+TT vs TT alone in B-mut MM. We obtained summary estimates through random-effects models. Overall survival (OS) and progression-free survival (PFS) were the main outcomes retrieved but we look also at difference in responses and adverse events. **Results:** We summarized data from 3 independent trials and we showed a significant advantage in terms of PFS and OS for the experimental arms in B-mut MM patients treated with ICI+TT rather than TT alone. The summary estimate indicates a significant 23% decrease in risk of progression (SHR = 0.77, 95%CI: 0.66-0.89, with no between-study heterogeneity I^2= 0%) and a significant 21% reduction in risk of death (SHR = 0.79, 95%CI: 0.66-0.96, with no heterogeneity I^2= 0%). However, no difference was shown (p-value = 0.56) between arms in terms of summary Objective Response Rate (ORR) estimates (Summary ORR doublet = 65.4% [61.5%; 69.2%] and Summary ORR triplet = 67% [63%; 70.9%], respectively). From the subgroup analysis on PFS risk estimates, no significant differences were observed in summary HRs by age (< 65 vs ≥65 years, p-value = 0.11), sex (female vs male, p-value = 0.58), ECOG PS (0 vs 1, p-value = 0.36), LDH levels (lower vs upper, p-value = 0.59) and PDL1 status (positive vs negative, p-value = 0.89). Significant differences were found in frequencies of grade 3 or more adverse events with higher number of events occurring in B-mut MM vs TT alone (Summary Odd Ratio = 2.01, 95%CI: 1.16-3.47, I^2= 74%), whereas no significant differences were found in terms of any adverse event between arms (SOR = 1.83, 95%CI: 0.70-4.78, I^2= 0%). **Conclusions:** This study supports and extend the discussion on first-line available combinations to be offered to B-mut MM patients. Combining ICI with TT demonstrated an effective advantage on both PFS and OS, although augmenting toxicities. Further biomarker-driven investigation may identify patient subpopulations who could benefit from ICI+TT combinations in order to expand their window of therapeutic opportunities. Research Sponsor: None.

9542 **Poster Session**

The prognostic impact of immune-related adverse events in real-world patients with metastatic melanoma treated with single-agent and combination immune checkpoint blockade. *First Author: Alexander Watson, Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada*

Background: Immune checkpoint blockade (ICB) has revolutionized the treatment of metastatic melanoma (MM). Immune-related Adverse Events (irAEs) associated with ICB have been shown to correlate positively with survival outcomes across solid tumours. In MM, conclusions on the impact of irAE severity have been conflicting, and combination ICB therapy experience is limited to smaller cohorts. We sought to clarify these relationships using the Alberta Immunotherapy Database (AID). **Methods:** The AID provides a multi-centre, province-wide observational cohort comprising consecutive patients treated with ICB. We included adult patients with MM, treated with ICB (single agent nivolumab or pembrolizumab, or combination ipilimumab and nivolumab) at any line of therapy, agnostic to site of origin, from August 2013 to May 2020, with analysis in December 2021. The primary endpoint of interest was the identification of a relationship between development of irAEs and subsequent overall survival (OS, defined from time of ICB initiation). To minimize immortal time bias from poor prognosis patients who may have died prior to the development of irAEs, patients who died before 12 weeks were excluded from OS and time-to-next-treatment (TTNT) analysis. Adjusted Cox regression analyses were performed to determine the association of variables with OS. **Results:** Of 492 MM patients receiving ICB, 124 received combination ICB, 198 developed an irAE and 67 required hospitalization for an irAE. irAEs were more common in patients < 50 years old (p = 0.02), with ECOG 0 (p < 0.001) and normal albumin (p = 0.002). Median time to irAE development (2.6 months) and frequency of individual irAEs were consistent with the published literature. In the overall population, patients who experienced an irAE had longer median OS (56.3 vs 18.5mo, p < 0.0001), and TTNT (49.6 vs 12.9mo, p < 0.0001). This remained consistent in combination ICB-treated patients (median OS 56.3 vs 19mo, p < 0.0001). Patients hospitalized for an irAE had improved OS and TTNT over patients requiring only outpatient treatment (median OS NR vs 27.9mo, p = 0.0039), while ICB re-challenge after an irAE also improved OS (56.3 vs 31.5mo, p = 0.0093). Development of an irAE retained independent association with OS after adjusted multivariable regression (HR 0.376, p < 0.001). **Conclusions:** These data support the association of irAEs and improved survival outcomes in MM, including those patients treated with combination ICB. Among patients with irAE, hospitalization for irAE, and ICB re-challenge post-irAE, were further associated with improved outcomes. Research Sponsor: None.

9543 **Poster Session**

Metabolic complete responses (mCR) in patients with metastatic uveal melanoma (mUM) treated with image-guided injection (IGI) of PV-10. *First Author: Krysta McVay, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Traditional CT imaging can underestimate the degree of anti-cancer treatment effect due to reliance on morphological changes of visualized tumors. In contrast, PET imaging offers information on metabolic activity using a positron emitting radiolabeled agent (e.g. FDG) but is less sensitive to changes in tumor size. FDG-PET images acquired, co-registered, and superimposed on CT images (PET-CT) allow spatial detection of anti-cancer activity. Moreoever, FDG-PET-CT can provide information regarding anti-tumor immune responses in patients receiving immunotherapy. Rose bengal (PV-10) is a small molecule autolytic immunotherapy in development for metastatic disease. When administered by intralesional injection, PV-10 can produce immunogenic cell death and a T-cell mediated immune response against treatment-refractory and immunologically-cold tumors. Herein, we report the FDG-PET-CT imaging responses of 7 metastatic uveal melanoma (mUM) patients who received percutaneous image-guided injection (IGI) of PV-10 into hepatic tumors. **Methods:** The Phase 1 study is evaluating safety, tolerability, and efficacy of intralesional PV-10 in hepatic tumors. PV-10 is administered percutaneously via IGI into designated tumors ≤4.9 cm in diameter. Response is assessed at Day 28, then every 3 months, using CT/MRI or PET-CT. Patients with multiple tumors may receive further IGI of PV-10 after Day 28. **Results:** To date, 25 mUM patients with liver metastases have been treated; 16 patients received standard of care immune checkpoint inhibitor (ICI) during or post PV-10 treatment. Seven subjects had FDG-PET-CT imaging during the study (baseline 1, follow-up 6). Two follow-up FDG-PET-CTs were performed 1 and 3 years after PV-10 injection with intervening ICI, and another was 1.5 years after PV-10, without any follow-on treatment. Four patients experienced mCR in all metastatic sites, including extrahepatic metastasis. **Conclusions:** FDG-PET-CT shows that PV-10 is capable of inducing mCR in injected (adscopal) and non-injected (abscopal) lesions. This pattern of response is suggestive of immunogenic cell death in mUM patients with liver metastases. Clinical trial information: NCT00986661. Research Sponsor: Provectus Biopharmaceuticals.

9544 **Poster Session**

Better (a little) late than never: The impact of steroidal treatment initiation timing on the outcome of patients with melanoma treated with immunotherapy. *First Author: Nethanel Asher, The Ella Lemelbaum Institute for Immuno-Oncology at Sheba Medical Center, Ramat Gan, Israel*

Background: The immune-system manipulation by immune-checkpoint inhibitors (ICI) has led to unprecedented clinical advances in melanoma. The management of the consequent immune-related adverse events (irAEs) is based mostly on steroids and other immune-modulators. **Methods:** A real world single-site cohort of metastatic melanoma patients who were treated with immunotherapy as first line between 2014 and 2020. This study explores the effect of dose, timing, and duration of steroid exposure on treatment efficacy. **Results:** Four hundred and forty patients were treated with either anti PD-1 (n = 285, 65%) or combination of anti PD-1 and ipilimumab ICI (n = 112, 25%), or ipilimumab alone (n = 43, 10%). The median age was 68 years [12-99y], and 57% were male. Any-grade irAEs were seen in 71% of the patients, and 49% were exposed to steroids. The median steroid dose was 0.75mg/kg prednisolone equivalent [0.03- 80mg/kg], the median duration of steroidal treatment was 11.2 weeks [0.1-316w] and the median time to onset of steroids was 7.6 weeks [0-193w]. Both experiencing irAEs, and the associated steroid exposure were associated with a significant progression free survival (PFS) benefit [HR 0.47, p < 0.001; 95%CI 0.39-0.6 and HR 0.77, p = 0.026; 95%CI 0.60-0.97, respectively], regardless of dose and duration. Notably, within those who were exposed to steroids, an earlier onset of < 4 weeks from immunotherapy initiation was significantly associated with a shorter PFS [HR = 3.5, p < 0.001 (95%CI 2.32-5.45)]. This observation resulted significant also on multivariable analysis including other prognostic variables – ECOG PS, M-stage, LDH and protocol. **Conclusions:** Steroidal treatment during the immunotherapy priming phase (first 4 weeks) might have a deleterious effect on its' efficacy and should be explored in larger prospective cohorts. Research Sponsor: None.

9545 **Poster Session**

Glycoproteomics as a powerful liquid biopsy-based predictor of checkpoint inhibitor treatment benefit in metastatic malignant melanoma. *First Author: Klaus Lindpaintner, InterVenn, South San Francisco, CA*

Background: Protein glycosylation is the most abundant and complex form of post-translational protein modification. Glycosylation profoundly affects protein structure, conformation, and function. The elucidation of the potential role of differential protein glycosylation as biomarkers has so far been limited by the technical complexity of generating and interpreting this information. We have recently established a novel, powerful platform that combines liquid chromatography/mass spectrometry with a proprietary artificial-intelligence-based data processing engine that allows, for the first time highly scalable interrogation of the glycoproteome. **Methods:** Using this platform, we interrogated 526 glycopeptide (GP) signatures derived from 75 serum proteins in pretreatment blood samples from a cohort of 205 individuals (66 females, 139 males, age range 24 to 97 years) with metastatic malignant melanoma treated either with nivolumab plus ipilimumab (95 patients) or pembrolizumab (110 patients) immune-checkpoint inhibitor (ICI) therapy. **Results:** In an optimized assay containing 27 glycopeptides and 20 non-glycosylated peptides, we identified 14 GPs with abundance differences at FDR q≤0.05 with regard to PFS. Using 40% of the cohort as a training set and selecting 12 glycopeptide and non-glycosylated peptide biomarker features of the 47 total by LASSO shrinkage, we created a multivariable-model-based classifier for PFS that yielded a hazard ratio (HR) for prediction of likely ICI benefit of 7.5 at $p < 0.0001$. This classifier was validated in the test set comprised of the held-out 60% of patients, yielding a HR of 4.7 at a similar p-value for separating patients likely benefiting from ICI therapy and those likely not benefiting from ICI therapy (50% PFS of 18 months vs. 3 months based on classifier score above/below cutoff). This classifier has a sensitivity of > 99% to predict likely ICI benefit, while still performing at a specificity of 26%, thus helping to safely reduce ultimately unnecessary and non-beneficial exposure to these agents of one in four who otherwise would unnecessarily be exposed to them. **Conclusions:** Our results indicate that glycoproteomics holds a strong promise as a predictor for checkpoint inhibitor treatment benefit that appears to significantly outperform other currently pursued biomarker approaches in this context. Research Sponsor: None.

9546 **Poster Session**

Management of checkpoint inhibitor toxicity and survival in patients with advanced melanoma. *First Author: Olivier Jules van Not, University Medical Center Utrecht, Leiden, Netherlands*

Background: Management of checkpoint-inhibitor-induced immune-related adverse events (irAEs) is primarily based on expert opinion. Recent studies have suggested detrimental effects of immunosuppressive treatment with anti-TNF on checkpoint-inhibitor efficacy. **Methods:** Advanced melanoma patients experiencing grade ≥3 irAEs after treatment with first-line ipilimumab-nivolumab between 2015 and 2021 were included from the Dutch Melanoma Treatment Registry. Progression-free survival (PFS), overall survival (OS) and melanoma-specific survival (MSS) were analyzed according to toxicity management regimen. A cox proportional hazards model was used to account for the confounders age, sex, performance status, lactate dehydrogenase, site of metastases and type of irAE. **Results:** Out of 771 ipilimumab-nivolumab treated patients, 350 were treated with immunosuppression for severe irAEs. Of these patients, 235 received steroids only and 115 received steroids with second-line immunosuppressants consisting of anti-TNF, mycophenolic acid, tacrolimus and other immunosuppressants. Median PFS was significantly longer for patients treated with steroids (11.3 months) than for patients treated with steroids and second-line immunosuppressants (5.4 months; HR 1.43; 95%CI 1.07-1.90; p = 0.01). Median OS was also significantly longer for the steroids group (46.1 months) than for the steroids and second-line immunosuppressants group (22.5 months; HR 1.64; 95%CI 1.16-2.32; p = 0.005). Results for MSS were similar (not reached versus 28.8 months; HR 1.70; 95%CI 1.16-2.49; p = 0.006). Median PFS, OS and MSS are shown in Table 1. After adjustment for potential confounders, patients treated with steroids + second-line immunosuppressants showed a non-significant trend towards a higher risk of progression (HR_{adj} 1.40; 95%CI 1.00-1.97; p = 0.05), a higher risk of death (HR_{adj} 1.54; 95%CI 1.03-2.30; p = 0.04) and of melanoma-specific death (HR_{adj} 1.62; 95%CI 1.04-2.51; p = 0.032) compared to the steroids group. **Conclusions:** Second-line immunosuppression for irAEs is associated with impaired PFS, OS, and MSS in advanced melanoma patients treated with first-line ipilimumab-nivolumab, irrespective of being anti-TNF or other second-line immunosuppressants. These findings stress the importance of assessing the effects of differential irAE management strategies, not only in melanoma but also in other tumor types. Research Sponsor: The Netherlands Organization for Health Research and Development (ZonMW, project number 836002002).

	Median PFS mo (95% CI)	P-value*	Median OS mo (95% CI)	P-value*	Median MSS mo (95% CI)	P-value*
Steroids (n = 235)	11.3 (9.6 – 19.5)		46.1 (39.0 – NR)		NR(46.1 – NR)	
Steroids + all second-line immunosuppressants (n = 115)	5.4 (4.5 – 12.4)	0.014	22.5 (36.5 – NR)	0.005	28.8 (20.5 – NR) 0.0	0.006
Steroids + anti-TNF (n = 67)	5.4 (4.7 – 13.1)	0.034	28.7 (12.2 – NR)	0.019	31.7 (15.7 – NR)	0.033
Steroids + other second-line immunosuppressants (n = 35)	4.3 (2.5 – 13.2)	0.025	22.4 (13.2 – NR)	0.084	22.4 (13.2 – NR)	0.024

*Compared to steroids group.

9547 **Poster Session**

Overall survival (OS) with first-line atezolizumab (A) or placebo (P) in combination with vemurafenib (V) and cobimetinib (C) in *BRAF*^{V600} mutation-positive advanced melanoma: Second interim OS analysis of the phase 3 IMspire150 study. *First Author: Grant A. McArthur, Melanoma and Skin Service and Cancer Biology and Therapeutics Program, Peter MacCallum Cancer Centre, Melbourne, Australia*

Background: Primary analysis of the phase 3 IMspire150 study (NCT02908672) demonstrated improved investigator-assessed progression-free survival (PFS) with first-line A + V + C vs P + V + C in patients (pts) with *BRAF*^{V600} mutation–positive advanced melanoma (hazard ratio [HR] 0.78; 95% CI, 0.63-0.97; *P*= 0.025). With median follow-up of 18.9 months at primary analysis, OS data were immature; interim analysis of OS at the time of the primary analysis demonstrated a trend in favor of A + V + C over P + V + C (estimated 2-year OS rate, 60.4% vs 53.1%) (Gutzmer et al. *Lancet* 2020;395:1835-1844). Herein, we present results from the second interim OS analysis of the IMspire150 study. **Methods:** IMspire150 enrolled previously untreated pts with stage IV or unresectable stage IIIc *BRAF*^{V600} mutation-positive melanoma (n = 514). Pts were randomized 1:1 to receive 28-day cycles of A + V + C (n = 256) or P + V + C (n = 258). Pts received V + C in cycle 1; A or P was added on days 1 and 15 from cycle 2 onwards. The second interim OS analysis was planned after ~270 OS events were recorded, and was projected to have a minimally detectable difference of HR of 0.74 with a *P* value boundary of 0.0140. OS was estimated using the Kaplan-Meier method. **Results:** At data cutoff (Sept 8, 2021), 273 OS events had occurred. Median follow-up was 29.1 months (range, 1-54) for A + V + C and 22.8 months (range, 0-54) for P + V + C. A continued trend toward OS benefit in favor of A + V + C over P + V + C was observed with median OS of 39.0 vs 25.8 months, but the difference did not reach statistical significance (HR, 0.84; 95% CI, 0.66-1.06; *P*= 0.1432). A delayed treatment effect was observed, with landmark OS rates for A + V + C vs P + V + C of 76.1% vs 76.5% at 12 months and 61.5% vs 53.3% at 24 months. With additional follow-up, A + V + C continued to show PFS benefit over P + V + C (HR, 0.79; 95% CI, 0.64-0.97; *P*= 0.0224); overall response rates (66.7% vs 65.0%) and median duration of response (21.0 vs 12.6 months) remained consistent with those reported at primary analysis. No new safety signals were observed with additional follow-up. **Conclusions:** With further follow-up, A + V + C demonstrated a consistent, but not statistically significant, improvement in OS and continued benefit in duration of response versus P + V + C in previously untreated pts with *BRAF*^{V600} mutation–positive advanced melanoma. Clinical trial information: NCT02908672. Research Sponsor: This study and medical writing and editorial support for this abstract was funded by F. Hoffmann-La Roche Ltd.

9548 **Poster Session**

Efficacy and safety of sequencing with vemurafenib (V) plus cobimetinib (C) followed by atezolizumab (Atezo) in patients (pts) with advanced *BRAF*^{V600}-positive melanoma: Interim analysis of the ImmunoCobiVem study. *First Author: Dirk Schadendorf, Department of Dermatology, University Hospital Essen, Essen, Germany*

Background: Immunotherapies (ICI) and targeted therapies (TT) have improved PFS and OS in *BRAF*^{V600}-mutated advanced melanoma pts, but evidence regarding their optimal sequence is limited. The randomized phase 2 ImmunoCobiVem study evaluated efficacy and safety of an early switch to Atezo after initial treatment with V + C. Interim results are reported. **Methods:** Pts with previously untreated *BRAF*^{V600}-mutated advanced melanoma received a 3-mo run-in with V (960 mg twice daily) + C (60 mg once daily for 21/28 days). Pts without PD/treatment interruption due to AEs during run-in were then randomized 1:1 to continue V + C (Arm A) or switch to Atezo (1200 mg every 3 wks; Arm B) until first documented PD (PD1), followed by crossover to the alternate treatment until second documented PD (PD2). End points were PFS1 (time from start of run-in until PD1 or death from any cause), PFS2 (time from start of run-in until PD2 or death from any cause), PFS3 (time from PD1 until PD2 or death from any cause), DCR, ORR, OS, and safety. **Results:** 185 pts were enrolled between Nov 2016 and Dec 2019 (63% male; median age 58 y); 135 pts completed run-in and were randomized to Arm A (n=69) or Arm B (n=66). At data cutoff, median follow-up for all pts was 19.0 mo. In Arm A, 36/69 pts (52%) discontinued V + C due to PD and 21/36 (58%) crossed over to Atezo; in Arm B, 49/66 pts (74%) discontinued Atezo due to PD and 35/49 (71%) crossed over to V + C. Median PFS1 was significantly longer in Arm A vs Arm B (HR 0.55; 95% CI 0.37–0.84; *P*=0.001), while median PFS3 was significantly shorter in Arm A vs Arm B (HR 2.24; 95% CI 1.17–4.30; *P*=0.013); median PFS2 was not significantly different between arms (HR 1.57; 95% CI 0.83–2.96; *P*=0.163) (Table). During the randomized phase, ORR and DCR were higher in Arm A before crossover and in Arm B after crossover (Table). OS was similar between arms (HR 1.22; 95% CI 0.69–2.16; *P*=0.389). Median (range) treatment duration across treatment phases was 11.2 mo (2.3–56.1) for Arm A and 10.7 mo (2.8–56.7) for Arm B. Grade 3/4 AEs occurred in 55% of pts in Arm A and 64% in Arm B; AEs led to discontinuation in 10% and 12%, respectively. **Conclusions:** Early switch from V + C to Atezo is feasible and safe, but tumor control achieved in run-in is maintained in only a subset of pts on subsequent ICI monotherapy. Crossover to ICI monotherapy at PD results in low response, while response to TT re-exposure is frequent. Clinical trial information: NCT02902029. Research Sponsor: This study and medical writing and editorial support for this abstract was funded by F. Hoffmann-La Roche Ltd.

	Arm A		Arm B	
PFS	Events/pts	Median, mo(95% CI)	Events/pts	Median, mo(95% CI)
PFS1	42/67	13.9 (9.9–16.6)	51/65	5.9 (5.4–8.3)
PFS2	18/21	12.6 (8.3–17.0)	21/35	14.9 (8.6–25.6)
PFS3	18/21	2.8 (2.0–3.1)	21/35	6.0 (2.4–12.6)
Response, % (95% CI)	ORR	DCR	ORR	DCR
Run-in phase	74 (62–83)	99 (92–100)	74 (63–83)	98 (92–100)
Randomized phase				
Before crossover	67 (55–77)	72 (61–82)	36 (26–48)	42 (31–54)
After crossover	5 (1–23)	10 (3–29)	40 (26–56)	54 (38–70)

9549 **Poster Session**

Merkel polyoma virus specific T-cell receptor transgenic T-cell therapy in PD-1 inhibitor refractory Merkel cell carcinoma. *First Author: Joshua Veatch, Hutchinson Cancer Rsrch Ctr, Seattle, WA*

Background: Merkel cell carcinoma is an aggressive neuroendocrine tumor of skin origin with most cases caused by the Merkel polyoma virus (MCPyV). While many patients benefit from PD-1/PD-L1 axis blockade, most patients do not respond or develop resistance. We sought to ask whether adoptive transfer of autologous T cells transduced with MCPyV specific T cells could lead to clinical responses in PD-1 inhibitor refractory patients. **Methods:** Five MCPyV positive, HLA-A02 patients with PD-1 inhibitor refractory metastatic Merkel cell carcinoma were treated with adoptive transfer of CD62L+ CD8+ and CD4+ autologous T cells transduced with a T cell receptor (TCR) targeting an HLA-A0201 restricted MCPyV epitope. Two different strategies were used to facilitate T cell expansion: In 3 patients, single fraction radiation was administered to a subset of lesions prior to T cell transfer. In 2 patients, lymphodepleting chemotherapy with cyclophosphamide and fludarabine was administered prior to T cell transfer. Anti PD-1/PD-L1 therapy was given 14 days after T cell infusion. Transgenic T cells were visualized in tumor biopsies by multiplex immunohistochemistry. **Results:** 5 patients were treated, with 4 patients receiving 100 million tetramer positive CD8+ T cells and one patient receiving 500 million cells. 3 patients received second infusions with between 300 million and 900 million tetramer positive cells. No dose limiting toxicities or cytokine release syndrome were observed. T cell persistence was lower in the 2 patients treated with lymphodepleting chemotherapy relative to the 3 patients treated with single fraction radiation. Transgenic T cells persisted at tumor sites greater than 1 month following transfer. 4 patients experienced progressive disease, and a single patient had a mixed response and greater than 1 year disease free interval following local therapy of an isolated site of progression. The responding patient was the only patient with class I MHC staining on tumor cells prior to treatment, and the site of local progression in that patient showed the presence of TCR transgenic T cells but loss of class I MHC expression. **Conclusions:** MCPyV specific transgenic T cells are safe, traffic to tumor sites, and can result in a clinical response, but their clinical activity may be limited by down-regulation of class I MHC expression on tumors. A future trial will address strategies to increase class I MHC expression on Merkel tumors. Clinical trial information: NCT03747484. Research Sponsor: Bluebird, Other Government Agency.

9550 **Poster Session**

Camrelizumab plus apatinib for patients with advanced mucosal melanoma: A prospective single-arm study. *First Author: Zhengyun Zou, Nanjing Drum Tower Hospital, Nanjing, China*

Background: Mucosal melanoma is a rare subtype in white populations, but the second most common subtype in Asian populations. This subtype is a more aggressive malignancy, with high risk of metastasis and death. Immune checkpoint inhibitor combined with anti-angiogenic agent has been investigated in many solid tumors, including some preliminary evidence (NCT03086174 and NCT04091217) in Chinese patients with advanced mucosal melanoma. This study investigated the efficacy and safety of camrelizumab plus apatinib in patients with advanced mucosal melanoma. **Methods:** In this prospective, single-arm study (ChiCTR1900023277), patients with inoperable stage III-IV or recurrent/metastatic mucosal melanoma and Eastern Cooperative Oncology Group performance status of 0-1 were enrolled. Patients received camrelizumab 200 mg once every 2 weeks and apatinib 500 mg once daily until disease progression or intolerable toxicity. The primary endpoint was objective response rate (ORR) according to the Response Evaluation Criteria In Solid Tumors, version 1.1. **Results:** Between April 2019 and January 2022, a total of 30 patients were enrolled (Table). As of January 2022, 21 patients had at least one efficacy assessment, and the median follow-up duration was 8.1 months. The ORR was 42.9%, including one (4.8%) patient with confirmed complete response, six (28.6%) with confirmed partial response (PR), and two (9.5%) with unconfirmed PR. The disease control rate (DCR) was 81.0%. The median progression-free survival was 7.2 months (95%CI, 5.8-not reached [NR]) in 21 patients, 7.7 months (95%CI, 5.8-NR) in 19 patients with first-line camrelizumab plus apatinib treatment, and 9.8 months (95%CI, 4.2-NR) in 11 patients without prior chemotherapy. The most common treatment-related adverse events in 27 patients with available safety data were fatigue (17 [63.0%]), hypertension (15 [55.6%]), and elevated transaminase (14 [51.9%]). No treatment-related deaths occurred. Exploratory analysis found a tendency that patients with high T cell receptor diversity had better prognosis. Higher frequencies of Vβ-Jβ (including Vβ5-8Jβ2-7, Vβ28J2-4 and Vβ12-5Jβ1-1) indicate better survival, and Vβ12-5Jβ1-1 is an independent factor after multivariate adjustment. **Conclusions:** Camrelizumab plus apatinib showed favorable ORR and DCR in patients with advanced mucosal melanoma, with an acceptable safety profile. Follow-up for survival outcomes is ongoing. Clinical trial information: ChiCTR1900023277. Research Sponsor: National Natural Science Foundation of China (No. 81872484 and 82073365), Other Foundation.

Characteristics	Patients (n = 30)
Age (years), median (range)	62 (35-77)
Sex (male/female)	13/17
Current therapy line (1/≥2)	27/3
Prior chemotherapy (perioperative therapy/for advanced disease/no)	12/3/15
Primary site (head and neck/esophagus/vagina and cervix/rectum)	16/2/7/5
Metastatic site (liver/lung/lymph node)	7/11/12
Lactate dehydrogenase level (≤upper limit of normal/ > upper limit of normal)	20/10
Gene mutation (BRAF/C-KIT/NRAS/unknown)	3/3/8/2

9551 **Poster Session**

Analysis of overall survival (OS) and relapse-free-survival (RFS) in the phase 1b clinical trial of anti–PD-1 ab (toripalimab) plus intralesional injection of OrienX010 in stage IV **melanoma with liver metastases.** *First Author: Chuanliang Cui, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China*

Background: Advanced melanoma with liver metastasis has reduced response to anti-PD-1 monotherapy with ORR of 4.3% in a pooled analysis, and initial results of the phase 1b trial, systemic toripalimab combined with intrahepatic OrienX010 injection - a HSV-1-derived oncolytic virotherapy with expression of GM-CSF had shown its efficacy. Here we report the RFS and OS outcomes. **Methods:** Eligible pts included those over 18 with injectable liver metastasis confirmed by biopsy with or without extra-hepatic metastasis; the ocular melanoma and brain metastasis were excluded. Pts received intravenous toripalimab Q2W combined with ultrasound guided intratumoral injection of OrienX010 Q2W (8×10^7 pfu/ml, 10ml per injection) until intolerance or disease progression per iRECIST criteria. Liver biopsy would be performed at baseline and first tumor evaluation (8-12weeks). The primary endpoint was toxicity; secondary endpoints included ORR, DCR and PFS. **Results:** From Jul 2019 to Jan 2022, 23 pts were eligible and enrolled. Baseline characteristics: median age 69 yrs; primary: mucosal 60.9%, cutaneous 13.0%, unknown primary 13.0%, acral 13.0%; gene mutation status: Braf 17.4%, Nras 4.3%; 69.6% got extra-hepatic metastasis: regional or distant lymph node 56.3%, lung 37.5%, bone 31.3%; LDH > ULN 26.1%; median size of injected lesions: 35mm(10-94mm); median number of liver metastasis: 7(1-10); median number of injection: 10 (3-36). Among these pts, 20 pts could be evaluated for efficacy. The median PFS was 7.0 months (95%CI: 4.3-9.7 months) and the median OS was 18.6 months (95%CI: 13.4-23.7 months) with a median follow-up time of 19.8 months (range, 0.9-29.7). The global ORR by investigator was 15% (3/20), DCR 50% (10/20); the response rate was 35%(7/20) for injected lesions, 27.8%(5/18) for non-injected lesions in liver, and 26.7% (4/15) for extra-hepatic metastases. Biopsies of 15 pts for injected lesions at 8 to 12 weeks after first injection were examined to determine the situation of TIL infiltration. Among them, the median PFS of the pts (7/15) with impressive TIL infiltration (Brisk n = 4 and Nonbrisk n = 3 according to the definition of AJCC 8th edition) was 7.8 months (95%CI: 2.8-12.8 months) versus 4.1 months (95%CI: 0-9.1 months) of the pts without impressive TIL infiltration. For pts (21.7%(2 PR and 3 SD)) with no melanoma cells residual by immunohistochemistry in biopsies the median PFS was 13.8 months (95%CI: 4.0-23.6 months), and it was much longer than that of other pts which was 5.6 months (95%CI: 2.4-8.8 months). The median OS of the pts with no melanoma cells was 19.7 months (95%CI: 7.5-31.9 months). **Conclusions:** Systemic toripalimab combined with intrahepatic OrienX010 injection has shown remarkable long PFS and OS in melanoma pts with liver metastases. Clinical trial information: NCT04206358. Research Sponsor: None.

9552 **Poster Session**

IMPemBra, a phase 2 study comparing pembrolizumab with intermittent/short-term dual MAPK pathway inhibition plus pembrolizumab in patients with melanoma harboring the BRAFV600 mutation: Three-year survival data and translational analyses. *First Author: Elisa A. Rozeman, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: Continuous combination of MAPK pathway inhibition (MAPKi) and anti-PD-(L)1 showed high response rates, but also high frequency of treatment-related adverse events (TRAE) in BRAFV600-mutated melanoma patients (pts). Short-time MAPKi already induces T cell infiltration in pts and was synergistic with anti-PD-1 in a pre-clinical model. This phase 2b trial aimed to identify the optimal duration of MAPKi with dabrafenib + trametinib (D+T) in combination with pembrolizumab (PEM). We have previously shown that no SUSARs were observed, toxicity was related to duration of D+T, and response rates increased after addition of D+T. Here we present 3-year PFS and OS data and results of translational analyses. **Methods:** In IMPemBra, pts with treatment-naïve BRAFV600E/K mutant advanced melanoma started with PEM 200mg Q3W. After 2 cycles, pts were randomized to continue PEM only (cohort 1) or to receive in addition intermittent dabrafenib 150 mg BID + trametinib 2mg QD for 2 x 1 week (cohort 2), 2 x 2 weeks (cohort 3) or continuous for 6 weeks (cohort 4). All cohorts continued PEM for up to 2 years. Primary endpoints were safety, treatment adherence and immune-activating capacity of the different regimens. Secondary endpoints were objective response rate (ORR) and PFS, OS was an exploratory endpoint. For survival analyses, pts that received D+T (cohort 2-4) were pooled. **Results:** Thirty-two pts were randomized, 56% were male, 53% had M1c disease and 88% had a LDH level < ULN. No new grade 3-4 TRAE were observed; frequencies were 12%, 12%, 50% and 62% for pts in cohort 1, 2, 3 and 4, respectively. ORRs were 75% in cohort 1 and 2, and 88% in cohort 3 and 4. The frequency of $PD1^+CD8^+$ T cells in peripheral blood decreased slightly during treatment and there were no differences between cohorts. In cohort 1 and 2, an increase in IFNγ signature in tumor biopsies was already observed after 6 weeks of PEM, in cohort 3-4 an increase in IFNγ signature was observed in week 9, after addition of D+T. The same pattern was observed for $CD8^+$ T cell infiltration and PD-L1 expression. After a median follow-up of 43.5 months, the median PFS of pts treated with PEM monotherapy was 10.6 months versus 32.3 months for pts treated with PEM plus D+T ($p = 0.19$). The 3-year PFS rates were 25.0% and 50.0% respectively. Median OS was 40.5 months in the PEM pts and not reached for pts treated with PEM plus D+T ($p = 0.32$); 3-year OS rates were 62.5% and 70.8% respectively. **Conclusions:** IMPemBra demonstrated that short-term addition of intermittent D+T to PEM seems a more feasible, tolerable and an effective alternative for the continuous triple combination. In addition, it gives the opportunity to treat with second line targeted therapy after disease progression. Therefore, this regimen should be considered for further investigation in a larger cohort. Clinical trial information: NCT02625337. Research Sponsor: MSD.

9553 **Poster Session**

Updated results from the skin cancer cohorts from an ongoing phase 1/2 multicohort study of RP1, an enhanced potency oncolytic HSV, combined with nivolumab (IGNYTE). *First Author: Mohammed M. Milhem, University of Iowa, Iowa City, IA*

Background: RP1 is an enhanced potency oncolytic version of HSV1 that expresses human GM-CSF and the fusogenic protein GALV-GP R-. IGNYTE is a multicohort phase 1/2 study that evaluates the safety and efficacy of RP1 in combination with nivo (NCT03767348) in a range of tumor types. Preliminary data demonstrated a durable anti-tumor activity and tolerability for RP1+nivo. Here, we present updated results from the initial and melanoma (mel) and anti-PD1 naïve non-melanoma skin cancer (NMSC) cohorts with RP1+nivo. **Methods:** RP1 is administered via intratumoral injection Q2W, up to 10 mL/visit, first alone at a dose of 10^6 PFU/mL and then starting with the 2nd dose at 10^7 PFU/mL in combination with nivo (240 mg IV Q2W for 4 months (mos) then 480 mg IV Q4W up to 2 yrs) for up to 8 doses, with the option to re-initiate RP-1. Eligible patients (pts) must have at least one measurable & injectable tumor of ≥ 1 cm, ECOG 0-1, and no prior oncolytic therapy. For mel, both anti-PD1 naïve and failed pts were eligible, for NMSC pts who were anti-PD1 naïve. **Results:** As of data extraction on January 31, 2022, 13/36 pts with mel (36.1%) and 19/31 pts with NMSC (61.3%) had a best response of PR or CR. For mel this was 5/8 (62.5%), 6/16 (37.5%), 0/6 and 2/6 (33.3%) for pts with anti-PD1 naïve cutaneous, anti-PD1/anti-PD1+anti-CTLA-4 failed cutaneous, uveal and mucosal mel respectively. For the anti-PD1 naïve NMSC this included 11/17 (64.7%), 1/4 (25%), 3/4 (75%) and 4/6 (66.6%) patients with CSCC, BCC, MCC and angiosarcoma respectively, including 8/17 (47.1%) being CR for CSCC. Current immature median DOR was 13.27 mos (current range 3.67-16.93 mos) for mel, and 7.32 mos (current range 1.88-23.11mos) for anti-PD1 naïve NMSC. Any grade TEAE (> 25%) in all cohorts combined were fatigue, nausea, pyrexia, chills, diarrhoea, pruritus, and influenza-like illness. TEAE ≥grade 3 (> 5%) were disease progression and fatigue. No deaths related to RP1 was observed, with one death related to nivo (myocarditis). Biomarker data from paired biopsies indicated robust T cell infiltration and an increase in tumor inflammation gene signature post-treatment. Clinical responses observed were independent of baseline tumor PD-L1 expression status. **Conclusions:** RP1 in combination with nivo provides a durable anti-tumor activity in pts with skin cancers, including anti-PD1 failed and anti-PD1/anti-CTLA-4 failed mel. The combination continued to be generally well tolerated with no new safety signals identified. Based on this data, enrollment into both a registration-directed cohort of pts who have anti-PD1 failed cutaneous mel (n = 125) and a cohort of pts with anti-PD1 failed NMSC (n = 30) is ongoing. Up-to-date data from this ongoing trial will be reported at the conference. A randomized Ph2 trial of RP1+cemiplimab vs. cemiplimab alone in anti-PD1 naïve NMSC is also underway (NCT04050436). Clinical trial information: NCT03767348. Research Sponsor: Replimune Group Inc.

9554 **Poster Session**

A phase II study to evaluate the safety and efficacy of IMM-101 in combination with checkpoint inhibitors in patients with advanced melanoma: Final results of the IMM-101-015 trial. *First Author: Alberto Fusi, St. George's University Hospitals NHS Foundation Trust, St. George's University of London, London, United Kingdom*

Background: IMM-101 is a suspension of heat-killed whole cell *Mycobacterium obuense* (NCTC 13365), which enhances the innate immune response and dendritic cell maturation. In animal models, it increases antigen specific responses and number of CD8+ CTL and CD4 + Th1 cells. The clinical studies with IMM-101 have shown promising efficacy signals in pancreatic cancer when combined with gemcitabine and in melanoma as adjunctive or single agent. **Methods:** IMM-101-015 is an open-label Phase 2a study to investigate the safety and efficacy of IMM-101 in combination with checkpoint inhibitors (CPIs) in patients (pts) with advanced melanoma who were either treatment-naive (cohort A), or whose disease had progressed during PD-1 blockade (cohort B). Pts with evaluable lesions, adequate performance status and organ function were eligible. Pts received 1.0 mg of IMM-101 every 2 weeks for the first 3 doses followed by a rest period of 4 weeks, then every 2 weeks for the next 3 doses, and thereafter every 4 weeks. Nivolumab was given every 2 or 4 weeks (dependent on Investigator choice). Pts in cohort B had the option to change to ipilimumab and IMM-101 if their disease continued to progress. Biopsies and blood samples were obtained at baseline and during treatment for assessment of tumor biomarkers and immune correlatives. The primary objectives of the study were to evaluate the overall response rate (ORR) after a maximum of 18 months of treatment by RECIST 1.1 and to assess the safety and tolerability of the combination of IMM-101 + CPIs. **Results:** Sixteen pts (11 Cohort A and 5 Cohort B) were treated between October 2018 and May 2021. The median age was 68.5 yrs (range 36-92) and 11 (69%) were male. The ECOG ps was 0 in 9 (56%) and 1 in 7 (44%) pts. Four (25%) had unresectable stage III melanoma and 12 (75%) stage IV. In Cohort A (3 stage III, 5 stage IV M1b and 3 M1c) 3 pts (27%) had an elevated baseline LDH, 6 (55%) a positive PD-L1 status and 3 (27%) a BRAF mutation. Pts in cohort A were on study for a median time of 8.5 months (range 1.5 - 19.1) and those in cohort B for 3.0 months (range 1.5 - 7.4). All pts were evaluated for response. The ORR was 73% (95% CI 39.03, 93.98) in cohort A whereas all pts in cohort B reported progressive disease. With respect to cohort A, 2 (18%) pts had CR, 6 (55%) PR and 1 (9%) SD. The median progression-free survival time was 10.2 months (95% CI 2.50, NE) with 41% of the pts progression-free at 18 months. The most frequent treatment emergent adverse events (TEAEs) were injection site reaction (63%), pruritus (44%), fatigue (38%), skin rash (25%), hypothyroidism (25%) and diarrhoea (19%). There were no grade 4 TEAEs. Grade 3 TEAEs occured in 10 patients (63%), mostly skin toxicity (19%) and lab abnormalities (13%). **Conclusions:** IMM-101 in combination with nivolumab is safe and shows encouraging antitumor activity in treatment-naive patients with advanced melanoma. Clinical trial information: NCT03711188. Research Sponsor: Immodulon Therapeutics Ltd.

9555 **Poster Session**

Clinical predictors of longer survival in patients with BRAF^{V600}-mutated metastatic melanoma receiving immunotherapy prior to BRAF/MEK inhibition in the metastatic setting. *First Author: Adriana Matutino Kahn, Yale School of Medicine, New Haven, CT*

Background: Patients with advanced BRAF^{V600}-mutated melanoma are typically treated with immunotherapy in the first-line setting, followed by BRAF/MEKi upon disease progression based on an absolute 20% improvement in 2-year overall survival over initial treatment with BRAF/MEKi in the DREAMseq trial. Our goal was to identify clinical predictors of longer survival for patients treated in our institution with this approach. **Methods:** We identified 40 patients with BRAF^{V600}-mutated metastatic melanoma treated at our institution from 2011 to 2020 with immunotherapy followed by BRAF/MEKi upon progression. Clinical data were collected and analyzed by Cox regression and Kaplan-Meier methods. Favorable outcome was defined as survival > 2 years (y) after starting BRAF/MEKis. **Results:** Median follow up was 33 months (m, 3 – 172 m). Median age was 54 y (20 - 83). Most patients were female (n = 24, %). Most patients were initially treated with ipilimumab plus nivolumab (n = 34, 85%), with 13 of these patients (38%) tolerating all 4 cycles of initial ipilimumab. Adverse events of any grade were seen in 28 (70%) patients after first-line immunotherapy, with the most common being hepatitis, colitis, hypothyroidism, rash, and fatigue. Median duration of first-line immunotherapy was 3.5 m (.75 - 42.5 m). Most common sites of progression on immunotherapy were lymph nodes (n = 14, 35%), liver (n = 12, 30%), bone (n = 10, 25%) and brain (n = 10, 25%). Prior to BRAF/MEKis, median ECOG-PS was 1 (0-4) and median LDH was 268 mg/dL (151 - 11,300). Most common BRAF/MEKi regimen was dabrafenib plus trametinib (n = 34, 85%). Adverse events of any grade were seen in 30 (75%) patients, with the most common being fever, fatigue, nausea, and vomiting. Best response to BRAF/MEKi was CR (n = 4, 10%), PR (n = 26, 65%), SD (n = 4, 10%) and PD (n = 6, 15%), and at the data cutoff, 35 (87.5%) patients progressed on BRAF/MEKi. Median duration of BRAF/MEK inhibition was 7 m (0.5 – 106 m). Median survival since starting BRAF/MEKi was 19.2 m (1.7 – 106 m). On multivariable analyses assessing predictors of survival, presence of bone metastases after disease progression on first-line immunotherapy was associated with worse 2-year survival after initiation of BRAF/MEKi (OR 2.5, 95% CI, 0.51-5.6, p = 0.0121). Other factors, such as ECOG-PS 0-2, normal LDH prior to BRAF/MEKi, and age at metastatic diagnosis < 60 years were not significantly associated with longer survival after initiation of BRAF/MEKi. **Conclusions:** We showed that the presence of bone metastases upon progression on first-line immunotherapy was associated with worse 2-y survival on salvage BRAF/MEKi for patients with BRAF^{V600}-mutated metastatic melanoma. Predictive and prognostic biomarkers for long-term response to both immunotherapy and BRAF/MEKi are needed to optimize treatment strategies and patient outcomes. Research Sponsor: None.

9556 **Poster Session**

Efficacy and tolerance of systemic therapies in metastatic melanoma of unknown primary versus known cutaneous: A multicenter retrospective study from the MelBase French Cohort. *First Author: Perrine Rousset, CHU de Nice, Nice, France*

Background: Melanoma of unknown primary (MUP) account for 3% of all melanomas. Clinical outcome of advanced MUP in the era of novel therapies including immunotherapies (ICI) and targeted therapies (TT) have been only scarcely studied, whereas a possibly different biologic background might introduce changes in its management. Recent retrospective studies suggested that patients with advanced MUP could benefit at least as much from novel therapies as patients with known primary cutaneous melanoma (cMKP). **Methods:** Based on the nationwide MelBase prospective database (NCT02828202) this retrospective study included patients with advanced melanoma treated with first-line ICI, TT or CT. MUP was defined by upfront occurrence of (sub)cutaneous, nodal and/or visceral metastasis without any known prior or concomitant primary tumor. Patients with primary mucosal or ocular melanoma were excluded. Both progression-free survival (PFS) and overall survival (OS) were analyzed as co-primary variables in MUP vs cMKP, stratified by treatment subset (ICI vs TT vs CT vs whole cohort). Secondary variable was treatment-related toxicity. Multivariate analyses and propensity score analysis were performed. Objective: To investigate the efficacy and safety of systemic treatments (ICI, TT and chemotherapy (CT)) in patients with advanced MUP comparatively to stage-matched cMKP. **Results:** A total of 1882 patients were analyzed, including 265 (14.1%) MUP. Most patients were treated with first-line ICI. Median follow-up was 16 months. Patients in the MUP cohort more often displayed unfavorable initial prognostic factors (Table). PFS and OS did not significantly differ in MUP compared to MKP patients (p=0.73 and p=0.93 respectively). Stratification of cohorts by treatment type and application of propensity score did not lead to data modification. Treatment-related toxicity rate and severity did not differ between MUP and MKP, regardless of treatment type. **Conclusions:** Our results suggest that advanced MUP should be managed with similar strategies as advanced MKP. In our cohort, MUP patients benefited from novel therapies as much as MKP patients despite less favorable baseline prognostic factors. Exploratory studies investigating mutational burden and host immunity are needed to identify the underlying mechanisms. Research Sponsor: None.

Baseline characteristics	MKPN=1617	MUP N=265	p-value
Age, years (median (range))			
Sex, N (%)	66 (21-97)	64 (18-92)	1.0
Men	965 (60)	164 (62)	0.54
AJCC 7th edition, N (%)			
III	247 (15)	8 (3)	**<0.001**
IV	1370 (85)	257 (97)	
Brain metastases, N (%)			
Yes	289 (18)	100 (38)	**<0.001**
ECOG PS, N (%)			
0	1189 (74)	178 (67)	0.27
1	309 (19)	61 (23)	
≥2	119 (7)	26 (10)	
Mutation Status, N (%)			
BRAF V600	653 (40)	97 (37)	0.24
LDH, N (%) > ULN			
N > ULN	467 (29)	85 (32)	0.32
N > 2 x ULN	125 (8)	33 (12)	**0.01**
First line treatment			
ICI	1059 (66)	165 (62)	0.44
TT	488 (30)	86 (33)	
CT	70 (4)	14 (5)	

9557 **Poster Session**

Prophylactic lymphaticovenous bypass performed during complete lymphadenectomy is oncologically safe. *First Author: Cagri Cakmakoglu, Cleveland Clinic Lerner College of Medicine, Cleveland, OH*

Background: Lymphaticovenous anastomosis (LVA) is a physiologic surgery indicated for secondary lymphedema of the extremities, particularly for disease refractory to conservative management. Immediate lymphatic reconstruction (ILR) is prophylactic LVA concurrently performed with CLND. After the transected lymphatics are mapped through a dye injection, they are anastomosed to a nearby venous outflow tract. Though prophylactic LVA is increasingly being performed, its risk on cancer recurrence and distant metastasis is currently unknown. The purpose of this study was to compare the distant-metastasis free survival (DMFS) and relapse-free survival (RFS) times in melanoma patients who underwent prophylactic LVA during CLND versus those who underwent conventional CLND for grossly metastatic disease. Our study is the first prospective evaluation of the impact of prophylactic LVA on DMFS in patients undergoing CLND. **Methods:** This was a prospective study of patients with cutaneous melanoma who underwent CLND with concurrent LVA (LVA group) or CLND alone (comparison group) between 2012 and 2021. Patients were excluded if they had non-melanoma skin cancers, stage IV cancers before CLND, microscopic lymphatic disease only or follow-up time of less than 12 months who did not die from melanoma-related causes. The comparison group consisted of all consecutive patients that underwent CLND alone and met inclusion criteria. To reduce surgical technique variability, all cases were performed by a single, high-volume surgeon at a tertiary care center. **Results:** A total of 46 melanoma patients underwent prophylactic LVA during this time period. Twenty-three of these patients met all inclusion criteria and were included in the LVA group. Twenty-two consecutive patients that underwent CLND alone were included in the comparison group. All patients underwent either axillary or inguinal CLND. Average number of lymph nodes removed during CLND were 18.20 ± 9.61 and 17.04 ± 9.97 for the LVA and comparison groups, respectively (p = 0.69). Size of largest metastatic tumor in lymph nodes was 45.91 ± 35.03 mm and 44.54 ± 23.32 mm, respectively (p = 0.99). Average time to first recurrence diagnoses was 6.75 ± 3.54 months vs 8.28 ± 5.66 months. For distant metastases only, the average time to first recurrence diagnoses was 6.16 ± 3.79 months and 9.39 ± 6.19 months, respectively (p = 0.25). There was no significant difference in recurrence type between the two groups (p = 0.66). There were no differences in DMFS and RFS times between the LVA and comparison groups. **Conclusions:** Prophylactic LVA performed for grossly metastatic melanoma does not negatively impact DMFS nor RFS. Considering the extremely aggressive nature of melanoma, our finding is potentially applicable to other cancers that are amenable to CLND and LVA. Research Sponsor: None.

9558 **Poster Session**

Preferences for adjuvant immunotherapy in patients with resected stage III melanoma: A discrete choice experiment. *First Author: Ann Livingstone, University of Sydney, Sydney, Australia*

Background: Adjuvant immunotherapy has revolutionized the management of resectable melanoma, substantially reducing the risk of recurrence but at the risk of immune-related adverse events (AE). This study aimed to quantify patients' preferences for adjuvant immunotherapy, the influence of varying levels of key attributes, and baseline characteristics associated with preferences. **Methods:** We performed a discrete choice experiment (DCE), including patients with resected stage III melanoma considering or having received adjuvant immunotherapy. Patients chose between twelve randomly presented choice tasks of two alternative options (adjuvant immunotherapy versus observation without adjuvant immunotherapy). The two options varied across two-three levels of six attributes: chance of 3-year melanoma recurrence, mild, permanent, or fatal AE, drug regimen, and out-of-pocket costs. We calculated the marginal rate of substitution (MRS, how much an individual was willing to trade one attribute for preferred levels of another) and willingness-to-pay (WTP, maximum price to trade their preferred attributes) per year. **Results:** One hundred and sixteen patients completed the DCE. Patients chose adjuvant immunotherapy over observation without adjuvant immunotherapy in 70% of choice tasks. Patients preferred adjuvant immunotherapy with reduced probabilities of recurrence (OR 0.76, 95% CI 0.70-0.83, p<0.001), fatal AE (OR 0.60, 95% CI 0.44-0.80, p=0.006), permanent AE (OR 0.94, 95% CI 0.89-0.99, p=0.046), and lowered out-of-pocket costs, for those with lower incomes (OR 0.63, 95% CI 0.47-0.85, p=0.003) and higher incomes (OR 0.84, 95% CI 0.15-4.86, p=0.064). Patients accepted an increase in their chance of mild AE from 1% to 37% (OR 2.06, 95% CI 1.13-3.78, p=0.019) in return for adjuvant immunotherapy. Willingness-to-pay was lower for patients with incomes that were lower rather than higher: US$595 (95% CI US-$555 to 1,305) and US$1,638 (95% CI US$ -1,235 to 3,419) per year for adjuvant immunotherapy with an absolute reduction of 1% in the 3-year risk of recurrence. **Conclusions:** Almost three-quarters of patients preferred adjuvant immunotherapy over observation without adjuvant immunotherapy. Patients were more likely to select immunotherapy if the risk of melanoma recurrence and the chance of fatal AE were reduced. Understanding patient preferences and acceptable trade-offs for adjuvant immunotherapy may allow better-informed decisions for individuals and assist policymakers in decisions about access and subsidization of effective and expensive treatments. Research Sponsor: Australian National Health and Medical Research Council (NHMRC), Cancer Institute New South Wales, Melanoma Institute Australia, Sydney Catalyst, Nicholas and Helen Moore, and the University of Sydney.

9559 **Poster Session**

Early quality of life (QOL) and symptom analysis from the DREAMseq phase III randomized control trial of combination immunotherapy versus targeted therapy in patients (pts) with *BRAF*-mutant metastatic melanoma (MM) (ECOG-ACRIN EA6134). *First Author: Roxanne E. Jensen, National Cancer Institute, Bethesda, MD*

Background: Combinations of either immune checkpoint inhibitors (anti-PD-1/anti-CTLA-4) or BRAF/MEK-targeted therapies have shown significant clinical benefit in pts with BRAFV600 mutant MM. Until recently, little prospective data existed to guide the choice of initial therapy or sequence. Results of the DREAMseq Trial showed that the treatment sequence beginning with nivolumab/ipilimumab (Nivo/Ipi) immunotherapy produced a clinically meaningful 20% improvement in 2-year overall survival (OS) compared to the sequence beginning with dabrafenib/trametinib (Dab/Tram) targeted therapy. The OS and progression-free survival (PFS) curves were biphasic crossing at 10 and 6 months, respectively. Our aim is to characterize QOL trends within and between the initial therapies through 24 weeks (wks). **Methods:** 265 pts were randomly assigned to Nivo/Ipi for up to 12 wks then Nivo alone (Arm A) or Dab/Tram continuously (Arm B) and at disease progression (PD) received the alternate therapy. QOL was assessed by the PROMIS Profile 29 at baseline, wk 12 (end of cycle (C) 2), and wk 24 (end of C4). Wilcoxon Signed Rank test was used to examine changes over time within treatment arms. OS was estimated by Kaplan-Meier method to compare between pts who stopped treatment for toxicity on Arm A by C2 and who continued on Arm A therapy to C4. A complete case analysis compared QOL domain means for (C2) vs. (C4). Pt-reported adverse events were also collected. **Results:** Baseline completion rates for the PROMIS-29 for Arm A (n = 108, 81.2%) and Arm B (n = 117, 88.6%) and decreased to 28.6% and 53.8%, respectively at C4. Through C4, the principal reasons for drop-out were toxicity (35.2% for Arm A and 11.9% for Arm B) and PD (26.1% for Arm A and 18.6% for Arm B). From Baseline to C2: Arm B reported statistically significant improvements in Pain Interference (-3.45, P = 0.007), Sleep (-2.11, P = 0.014), and Anxiety (-3.74, P < 0.001). By C4, these early differences had dissipated (mean diff. = 0.73 – 1.73, all p = NS). For pts remaining on treatment to C4 (n = 157), a complete case analysis indicates no significant QOL differences between C2 vs C4. Pts stopping for toxicity on Arm A after C2 had similar 2-yr OS to pts who continued on Arm A to C4. QOL at C2 (Arm A: stopping for toxicity vs. on treatment) were meaningful, but underpowered (Physical Health (PH) mean difference = -3.5, p = 0.18). **Conclusions:** Over the first 12 wks, Dab/Tram is associated with significant improvement in overall function and less disturbance in in sleep, pain, physical function, and PH than Nivo/Ipi as expected by PFS curves and toxicity profiles. These differences dissipate by 24 wks when Arm A therapy has switched to Nivo alone and PFS curves cross. Early QOL and treatment cessation due to Nivo/Ipi toxicity was not associated with differences in 2-yr OS. Clinical trial information: NCT02224781. Research Sponsor: U.S. National Institutes of Health.

9560 **Poster Session**

Safety and efficacy of combined melphalan percutaneous hepatic perfusion (M-PHP) and ipilimumab plus nivolumab (IPI+NIVO) in metastasized uveal melanoma (mUM): First results of the phase Ib part of the CHOPIN trial. *First Author: Thaï s M.L. Tong, Leiden University Medical Center, Department of Medical Oncology/Radiology, Leiden, Netherlands*

Background: Uveal melanoma (UM) is the most frequent intraocular malignant tumor in adults. Approximately 50% of all patients (pts) will develop metastatic disease in the liver. Until now, there is no systemic therapy that has been shown to improve overall survival (OS), apart from tebentafusp. M-PHP is frequently applied for liver-only UM. However, the majority of pts eventually develops extrahepatic disease after M-PHP. IPI+NIVO has been shown to induce up to 20% response rates in mUM. Our observations that checkpoint inhibition was most effective on extrahepatic UM disease has led to the CHOPIN trial testing the combination of M-PHP and IPI+NIVO. Here we present the safety and efficacy data of the phase 1b part of CHOPIN. **Methods:** Adult pts with confirmed measurable hepatic mUM and WHO PS 0-1 were included. Two courses of 6 weekly M-PHPs (melphalan 3mg/kg, max 220mg) were combined with four courses IPI+NIVO three-weekly escalating the dosing from 1mg/kg each IPI+NIVO (cohort 1) to IPI 1mg/kg + NIVO 3mg/kg (cohort 2). Primary endpoint was safety of IPI+NIVO plus M-PHP. Secondary endpoints were best overall response (BOR) according to RECIST 1.1, progression-free survival (PFS), and OS. **Results:** 7 pts were included (4 male, median age 63.6 years (range 50-74)). Both cohorts were tolerated with no dose-limiting toxicities or deaths. Grade III/IV adverse events (AE) were observed in 2/3 pts in cohort 1 and in 3/4 pts in cohort 2 consisting of SIRS, febrile neutropenia, cholecystitis, neutropenia, thrombopenia, leukopenia, increased transaminases and fever. Grade I/II immune-related AEs occurred in all pts (myositis, hypothyroidism, hepatitis and dermatitis). BOR was 1 complete response, 5 partial responses and 1 stable disease accounting for an objective response rate (ORR) of 85.7%. At a median FU time of 20.2 months, 4 pts have an ongoing response. Currently the median PFS is 22.4 months, and all pts are still alive. **Conclusions:** Combining M-PHP with IPI+NIVO is safe at a dosing of IPI 1 mg/kg and NIVO 3 mg/kg and very promising ORR, PFS and OS have been observed. The randomized phase II part comparing M-PHP versus M-PHP+IPI+NIVO is currently recruiting. Clinical trial information: NCT04283890. Research Sponsor: Bristol Myers Squibb and Delcath Systems Inc.

9561 **Poster Session**

A phase 1b/2a study of safety and efficacy of NT-I7 in combination with anti-PD-L1 (atezolizumab) in patients with anti-PD-1/PD-L1 naïve or relapsed/refractory (R/R) high-risk skin cancers: The phase 1b report. *First Author: Brian Gastman, Cleveland Clinic Lerner College of Medicine, Cleveland, OH*

Background: Novel immunotherapy approaches have changed the treatment landscape of patients (pts) with high-risk cancers like melanoma, Merkel cell carcinoma (MCC) and cutaneous squamous cell carcinoma (cSCC). However, despite the widespread use of checkpoint inhibitors (CPI) in these indications, most pts either fail to respond or eventually have progressed. NT-I7 (efineptakin alfa) is a long-acting human IL-7 that can increase the number and functionality of T-cells in peripheral blood and within the tumors. NT-I7 in combination with atezolizumab (atezo), may augment the efficacy in high-risk skin cancers. **Methods:** This is a phase 1b/2a study to evaluate the safety and efficacy of NT-I7 in combination with atezo in pts with CPI- naïve or relapsed/refractory (R/R) high-risk skin cancers. Phase 1b dose escalation followed a 3+3 design, in which pts who received NT-I7 IM every 3 weeks (Q3W) at 3 dose levels (DL1-3): 120, 360, and 840 μg/kg or Q6W at DL4 1200 μg/kg, and atezo IV 1200 mg Q3W. The objectives of the phase 1b were to evaluate dose-limiting toxicity (DLT), determine the MTD and the recommended phase 2 dose (RP2D), pharmacokinetics (PK), pharmacodynamics and preliminary antitumor activity. **Results:** As of January 14, 2022, 16 pts were enrolled in phase 1b: DL1 (n = 3), DL2 (n = 3), DL3 (n = 7), and DL4 (n = 3). The median age was 66 years [46-86], with ECOG PS 0 in 6 (37%), 1 in 7 (44%) and 2 in 3 (19%), and median number of prior therapies 1 [1-2]. One pt had a DLT at DL3 [Grade (G)3 confusion and G3 increased AST] but no DLTs were reported at DL4 and MTD was not reached. The RP2D was 1200 μg/kg Q6W of NT-I7 plus atezo 1200 mg Q3W. All pts had drug related AEs. Most AEs were G 1- 2 in 11(69%) pts; 5 (31%) in G3. There were no related G4/G5 AEs. Eleven pts had stable disease and the disease control rate was 69% (11/16). Preliminary PK analysis of DL1- 3 showed dose dependent C_{max}, with T_{max} at ~24hr and $T^1/_2$ ranging ~75hr to 125hr. NT-I7 dose-dependent expansion of the absolute lymphocyte count, $CD3^+$, $CD4^+$ and $CD8^+$ T-cells peaked after one dose and the increase was maintained by repeat dosing until the end of treatment. Immunophenotyping of memory T-cell subsets showed a 5-fold expansion in most T-cell subsets and a 30-fold expansion of the stem cell memory CD8+ T-cell subset (Tscm) at DL4. **Conclusions:** This trial is the first time an IL-7 cytokine-based therapy and CPI has been assessed in UV induced high-risk skin cancers including in IO refractory pts. The combination of NT-I7 and atezo showed favorable safety and anticancer activity. NT-I7 significantly increased total lymphocyte and the T-cell compartment, with a greatest expansion of the CD8+ Tscm, a vital population for eliciting antitumor activity. Additional safety and efficacy updates will be provided by the ongoing phase 2a trial in CPI-naïve cSCC and MCC and CPI R/R MCC, cSCC and melanoma. Clinical trial information: NCT03901573. Research Sponsor: Neoimmunetech, Inc.

9562 **Poster Session**

Distinct mutational landscapes characterize melanomas metastatic to different anatomical sites. *First Author: Mahesh Y. Iddawela, Alfred Health, Central Clinical School,Monash University, Melbourne, VIC, Australia*

Background: Despite revolutionary advances in systemic therapies for melanoma, many patients with metastatic disease have limited treatment options and some sites of disease remain particularly challenging to control, such as brain and liver metastases. We sought to define anatomical site-specific mutational profiles of melanoma metastases from which potentially novel personalized therapeutic opportunities may be developed. **Methods:** Targeted exome genomic profiling was performed via the FoundationOneCDx platform and known or likely pathogenic variants retained for analysis. PD-L1 immunohistochemistry was performed with the Dako 22C3 assay with PD-L1+ defined as tumor proportion score ≥1. Tumor mutational burden (TMB)-high was defined as TMB ≥10mut/Mb. UV signature was calculated using established algorithms. Aberrations in 23 genes potentially actionable in melanoma (*BARD1*, *BRAF*, *BRCA1/2*, *CDKN2A*, *DDX3X*, *FANCC*, *HRAS*, *IDH1*, *KIT*, *KRAS*, *MAP2K1*, *NF1*, *NRAS*, *PALB2*, *PIK3CA*, *PPP6C*, *PTEN*, *RAC1*, *RAD51C/D*, *RB1*, *TP53*) were compared across metastatic sites including skin, lymph node, lung, liver, and brain. **Results:** A total of 4918 cutaneous-type melanoma tumors was evaluated, including 2854 skin lesions (primary/metastasis) and metastases from lymph nodes (n = 858), liver (n = 194), lung (n = 342), and brain (n = 200). The commonly mutated genes were *CDKN2A* (2220/4918, 45.1%), *BRAF* (2148/4918, 43.7%), *NRAS*(1347/4918, 27.4%), *NF1* (1038/4918, 21.1%), *TP53* (1234/4918, 25.1%) and *PTEN* (1038/4918, 13.5%). Compared with skin lesions, metastases to the lung were enriched for variants affecting *NF1* (OR 2.57, p = 8.99e-13), *TP53* (OR 1.65, p = 3.04e-04) and depleted in *NRAS* (OR 0.49, p = 9.00e-06) and *BRAF* (OR 0.70, p = 1.13e-02). Lung metastases were associated with higher prevalence of UV signatures, PD-L1 positivity and high TMB. *PTEN* variants were enriched in both brain (OR 3.00, p = 2.38e-08) and small intestine (OR3.46, p = 6.63e-3) metastases. Brain metastases were also enriched for *CDKN2A* variants (OR 1.56, p = 4.50e-02). Lymph node metastases had lower rates of UV signatures, *NF1* variants, or high TMB, but were associated with PD-L1 positivity. Positional analysis of variants revealed that several, including *NRAS*, *MAP2K1*, *KRAS*,*HRAS*, *IDH1*, *RAC1*, *GNA11* and *GNAQ* were highly restricted to hotspot loci, without definite variation by metastatic site. Conversely, variants affecting *CDKN2A*, *PTEN*, *TP53* and *NF1* were distributed widely across the gene, with high levels of non-hotspot mutations observed in skin lesions, suggesting that such non-hotspot subclones contribute less to distant metastatic potential and are lost during disease evolution. **Conclusions:** We observed distinct and organ site-specific mutational patterns in patients with metastatic melanoma. These data raise the possibility of metastatic phenotype-directed therapy to improve the personalization and outcomes of treatment for this disease. Research Sponsor: None.

9563 **Poster Session**

Adjuvant dabrafenib plus trametinib (D + T) versus placebo in patients with resected stage III *BRAF*^{V600}-mutant melanoma: Updated 5-year distant metastases-free survival (DMFS) analysis of COMBI-AD. *First Author: Dirk Schadendorf, University Hospital Essen, Essen and German Cancer Consortium, Heidelberg, Germany*

Background: DMFS is an important endpoint for patients with stage III cutaneous melanoma, as delaying or preventing systemic disease is associated with improved clinical and patient-reported outcomes. Prior results from the phase 3 COMBI-AD trial (NCT01682083) showed 5-year DMFS rates of 65% with adjuvant D + T vs 54% with placebo (PBO; hazard ratio [HR] = 0.55; 95% CI: 0.44-0.70). An analysis of DMFS by AJCC-7 stages IIIA-C suggested a similar benefit of D + T vs PBO regardless of stage (Dummer R et al. *N Engl J Med*. 2020). Here, we report 5-year DMFS rates by AJCC-8 stages IIIA-D, other prognostic subgroups, and results of a regression tree analysis with DMFS. **Methods:** Patients with resected AJCC-7 stage III *BRAF*$^{V600E/K}$-mutant melanoma were randomized to either D (150 mg twice daily) + T (2 mg once daily) or 2 matched PBOs for 12 months. Primary endpoint was relapse-free survival (RFS); DMFS was a secondary endpoint. Kaplan-Meier survival analyses were performed to assess the long-term benefits for DMFS rates with D + T vs PBO. The regression tree analysis (data cutoff: 5 years) for all patients (N = 870) evaluated potential prognostic/predictive factors of long-term DMFS including baseline age, sex, region, *BRAF* mutation type, body mass index, lactate dehydrogenase levels, ECOG, T and N categories, histology, primary tumor ulceration, treatment type, number of lymph nodes with metastases, tumor mutational burden, and interferon-gamma gene expression signature (IFN-γ GES). **Results:** At 5 years, DMFS rates were higher for patients with AJCC-8 stages IIIB-D disease receiving adjuvant D + T vs PBO (table). Five-year DMFS rates also favored D + T vs PBO in subgroups of patients with microscopic or macroscopic lymph node involvement (table) and those with or without primary tumor ulceration and/or in-transit metastases. A regression tree revealed T and N stage, treatment type, and IFN-γ GES as important variables defining 5-year DMFS subgroups. **Conclusions:** In this retrospective analysis, adjuvant D + T provided long-term DMFS benefit vs PBO in stage IIIB-D patients with resected *BRAF*$^{V600E/K}$-mutant melanoma. Key clinical and patient factors impacting DMFS were similar to prior RFS findings (ESMO 2021; Robert C et al. *Ann Oncol*. 2021) and included T and N stage, treatment type, and IFN-γ GES. These results further validate the robust long-term clinical benefit of adjuvant D + T for patients with melanoma. Clinical trial information: NCT01682083. Research Sponsor: Novartis Pharmaceuticals Corporation.

	Stage								Lymph node involvement			
	IIIA		IIIB		IIIC		IIID		Macroscopic		Microscopic	
Statistic	D + T n = 50	PBO n = 39	D + T n = 145	PBO n = 154	D + T n = 217	PBO n = 214	D + T n = 22	PBO n = 17	D + T n = 158	PBO n = 161	D + T n = 152	PBO n = 157
5-year DMFS rate, %	75.3	84.5	66.5	52.8	63.0	50.8	64.6	25.6	63.3	47.1	75.3	62.5
HR (95% CI)	1.24 (0.42-3.63)		0.56 (0.38-0.83)		0.54 (0.39-0.75)		0.20 (0.07-0.55)		0.52 (0.37-0.75)		0.49 (0.31-0.79)	
Log-rank *P*	0.695		0.004		< 0.001		0.001		< 0.001		0.002	

9564 **Poster Session**

Prognostic significance of the CP-GEP assay combining clinicopathologic factors and gene expression profiling in patients (pts) with AJCC v8 stage I/II cutaneous melanoma (CM). *First Author: Teresa Maria Santos Amaral, Center for Dermatooncology, Department of Dermatology, Eberhard Karls University of Tuebingen, Tuebingen, Germany*

Background: AJCC v8 includes Breslow thickness and ulceration to subdivide stage I and II CM pts into risk groups. In light of the results from adjuvant therapy in stage II CM, it has been discussed that pts' follow-up and eventually treatment should consider additional markers, namely CP-GEP, to further refine the risk classification provided by the AJCC v8. The aim of this single center study was to clinically validate a prognostic CP-GEP-based risk score for stage I/II CMs combining Breslow, age and the expression of 8 genes *SERPINE2*, *GDF15*, *ITGB3*, *CXCL8*, *LOXL4*, *TGFBR1*, *PLAT* and *MLANA*. **Methods:** All obtainable formalin-fixed paraffin-embedded primaries of stage I/II CMs with negative sentinel lymph node (SLN) from the Central Malignant Melanoma Registry of Germany diagnosed between 2000-2017 and archived in Tuebingen were included. Study hypothesis and protocol were prospectively formulated. Tumors were analyzed blinded to clinical outcome. Quantitative reverse transcription polymerase chain reaction of the 8 genes was performed and combined with age and tumor thickness to define CP-GEP low- vs. high-score groups. Relapse-free survival (RFS), distant metastasis free survival (DMFS) and overall survival (OS) were evaluated using Kaplan-Meier curves. CP-GEP score performance was tested using multivariate Cox regression adjusted for tumor thickness, ulceration and age. **Results:** We included 543 pts with Stage IA (n=78); IB (n=223); IIA (n= 123); IIB (n=73); IIC (n=46). 43% were females, median Breslow was 1.7mm and 25% of tumors had ulceration. The median follow-up was 78 months (IQR 47-116). 311 (57%) patients had a high-risk CP-GEP score. The 5-y RFS rate was 71% and 92% (HR 4.2; p<0.001), the 5-y DMFS rate was 86% and 96% (HR 4.35; p<0.001) and the 5-y OS was 85% and 95% (HR 3.2; p=0.001), respectively for high and low-risk CP-GEP score. In multivariate Cox regression analysis for RFS including Breslow thickness, ulceration and age, contribution of CP-GEP score remained independently significant (HR 2.75; p=0.0008) compared to age (HR 1.03; p<0.0007), Breslow (HR 1.21; p<0.0001) and ulceration (HR 1.37; p=0.1694). **Conclusions:** CP-GEP risk score is a non-invasive and independent prognostic model for risk of relapse in stage I/II melanoma validated in this study. It identifies SLN negative pts at high risk of relapse and should be considered for complementing AJCC classification and for inclusion in future clinical trials. Research Sponsor: SkylineDX.

5y-RFS, DMFS and OS rates.

	CP-GEP high N=311	CP-GEP low N=232	IA N=78	IB N=223	IIA N=123	IIB N=73	IIC N=46	All N=543
5y RFS % (95% CI)	71 (65-76)	92 (87-95)	96 (85-99)	89 (83-92)	75 (65-82)	69 (57-79)	41 (25-55)	80 (76-83)
5y DMFS % (95% CI)	86 (81-90)	96 (92-98)	96 (84-99)	96 (92-98)	91 (84-96)	82 (69-90)	60 (42-74)	90 (87-93)
5y OS% (95% CI)	85 (80-89)	95 (91-97)	97 (90-99)	97 (93-98)	86 (77-91)	80 (68-88)	65 (48-78)	89 (86-92)

9565 **Poster Session**

Immune profiling of metastatic uveal melanoma and response to immune checkpoint inhibitors. *First Author: Yusra F. Shao, Barbara Ann Karmanos Cancer Institute, Wayne State University, Detroit, MI*

Background: Response to immune checkpoint inhibitors (ICI) in uveal melanoma (UM) is low. We aimed to elucidate tumor markers correlated with improved survival in ICI treated UM patients. **Methods:** Tumor samples of UM patients were tested at Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing on DNA (592 genes assay or whole exome sequencing) and RNA (whole transcriptome sequencing). Somatic mutations were totaled to calculate tumor mutational burden (TMB) and cutoff for high vs low was 10 mt/MB. PDL1 was tested with immunohistochemistry for tumor staining and cutoff was ≥2+, 5% for high vs low. *NCOA2* gene amplification was considered a surrogate for gain of chromosome 8q (cutoff ≥6). Median RNA expression level for LAG3 was calculated for each cohort and used as cutoff for high vs low. All ICI treated patients were considered to have metastatic disease. Real-world overall survival (rwOS) was obtained from insurance claims data and calculated from tissue collection to last contact. Time on treatment (TOT) was calculated from start to finish of ICI treatment and was considered as surrogate for progression-free survival (PFS). Comparison of survival was performed by Kaplan-Meier analysis. **Results:** A total of 450 UM samples were analyzed. Of these, 108 were from ICI treated patients and were obtained from primary (10/108) or metastatic (98/108) sites. Most tumors were PDL1 low in the entire UM (86%, 240/279) and ICI treated (62%, 55/89) cohorts. There was no difference in TOT between PDL1 high vs low in ICI treated cohort (HR 1.46, 95% CI 0.82-2.6, median TOT 3.1 months vs 2.3 months). Similarly, 98% (257/263) of all UM samples had low TMB. ICI treated patients with high LAG3 expression had similar TOT compared to low (HR 1.3, 95% CI 0.59-2.9, median TOT 6 months vs 2 months). In the entire UM cohort, most tumors were *NF1*-wildtype (95%, 56/59). *NF1*-wildtype status was associated with a longer rwOS compared to *NF1*-mutated (HR 0.18, 95% CI 0.051-0.64, median rwOS of 20.8 months vs 7 months). *NCOA2* amplification was associated with a worse rwOS as compared to patients without *NCOA2* amplification in the entire UM (HR 0.68, 95% CI 0.50-0.91) but not in ICI treated cohort (HR 0.84, 95% CI 0.52-1.4). There was no difference in TOT in ICI treated patients by *BAP1* and *SF3B1* mutational status. **Conclusions:** UM lacks traditional markers of response to ICI. Short TOT seen in our study is consistent with PFS of 3 to 5.5 months seen in clinical trials. High LAG3 expression was associated with a clinically significant improvement in TOT. Traditional markers of poor prognosis were not implicated in survival differences in ICI treated patients. This likely represents a poor prognosis in all mUM patients regardless of traditional prognostic markers. *NF1* mutation is uncommon in UM and its significance as a prognostic marker should be validated in a larger cohort. Ongoing research is needed to understand the biology of UM and approach to treatment. Research Sponsor: None.

9566 **Poster Session**

The relationship between circulating tumor DNA with Merkel cell carcinoma tumor burden and detection of recurrence. *First Author: Tomoko Akaike, University of Washington, Seattle, WA*

Background: Merkel cell carcinoma (MCC) is an aggressive skin cancer with a recurrence rate of 40%. Early detection of recurrence can improve outcomes, and effective surveillance is crucial for management of patients with MCC. While Merkel cell polyomavirus (MCPyV) oncoprotein serology is useful in surveillance for MCPyV-positive MCC tumors, patients with MCPyV-negative tumors have no available blood biomarkers and require frequent imaging. This prospective, multicenter study assessed whether circulating tumor DNA (ctDNA) can assess disease burden and detect recurrence regardless of virus status. **Methods:** A total of 328 blood samples were collected from 125 patients at various time points with a median follow-up of 6 months (range: 0-21 months) between April 2020 to January 2022. Whole-exome sequencing was performed on tumor tissue and matched normal blood to identify a set of somatic, clonal single nucleotide variants, which were tracked in subsequent blood (plasma) samples using a personalized and multiplex PCR-NGS based ctDNA assay (Signatera). Clinically evident disease was defined as MCC noted either by physical exam or by imaging, and molecular evidence of disease was defined as a positive ctDNA test. Surveillance phase began once there was no clinically evident or molecular evidence of disease. **Results:** Among 125 patients, 47 (38%) had clinically evident MCC and all were found to be ctDNA-positive at the first time point (sensitivity: 100%; 95% CI: 91-100%). Of the 47, 24 were newly diagnosed with MCC and had a median primary tumor size of 2.2 cm (range 0.5-8.5 cm) and a median ctDNA value of 26 mean tumor molecules (MTM)/mL (range: 0.08-1470 MTM/mL). Primary tumor diameter and ctDNA value were strongly correlated (Spearman's $r = 0.81$, $p < 0.001$). Of the 125 patients, 73 (58%) patients were assessed in the surveillance setting and had a total of 152 plasma samples available for longitudinal ctDNA testing. Over this period, 7 ctDNA tests were positive while 145 were negative. After a positive test, 5/7 developed a clinically evident recurrence (4 within 60 days). Of the remaining 2 without clinical recurrence, one had < 60 days of follow-up at time of data analysis. The estimated risk of recurrence, accounting for incomplete follow-up, was 57% within 60 days of a positive ctDNA test (n = 7 tests). In contrast, after a negative ctDNA test (n = 145 tests), the risk of recurrence was 0% within 60 days and 3% between 60-90 days. **Conclusions:** To our knowledge, this is the largest study to explore ctDNA testing in MCC patients. This study demonstrates that ctDNA testing can detect MCC recurrence early and is a promising clinical surveillance tool regardless of tumor viral status. Research Sponsor: U.S. National Institutes of Health, MCC Patient Gift Fund.

9567 **Poster Session**

Plasma methylated DNA markers of cutaneous melanoma: Association with PET/CT-positive disease. *First Author: Alexander Meves, Mayo Clinic, Rochester, MN*

Background: Cutaneous melanoma surveillance is important to identify low-volume systemic disease, but imaging is costly and poorly accessible to patients; frequent skin checks lack sensitivity and specificity. We aimed to establish clinical feasibility of a liquid biopsy blood test, which quantifies validated, melanoma-specific, methylated DNA markers (MDMs), previously discovered, and reported by our team, using tissue extracted DNA. **Methods:** We prospectively collected blood from adult patients with histologically confirmed melanoma metastases and no other internal malignancies (within 5-years) who underwent surveillance by FDG-PET/CT (N = 88). Blood from age- and sex balanced cancer-free controls (N = 100) were compared. From PET/CT, we extracted the number of organs involved, SUV-max, and largest tumor diameter. Unequivocal metastasis was defined as SUV ≥ 4 and largest diameter > 5 mm. Because PET/CT is inadequate for the screening of brain metastases, we excluded the brain from the analysis. MDMs (*chr11.149, HOXA9, chr20.210, FLJ22536, CLIC5, SIX4, chr7.155, chr17.730, chr1.110*) were assayed using target enrichment long-probe quantitative-amplified signal assays, normalized to *B3GALT6*, in blinded fashion. Using a logistic regression approach and nine candidate MDMs, we calculated the sensitivity for detecting patients with metastasis on PET/CT at 100% specificity. **Results:** 52/88 (59%) of melanoma patients showed evidence of metastasis on PET/CT at the time of blood draw. At 100% specificity, a panel of 4 MDMs (*HOXA9, chr20.210, chr17.730, chr1.110*) yielded a sensitivity of 86.5% (45/52 cases) vs. 100 cancer-free controls. When applying this model to the 36 PET/CT-negative patients, specificity was as high as 97.2% (35/36 cases) while maintaining a sensitivity of 86.5% (one patient with a positive test result had a complete metabolic response to binimetinib / encorafenib prior to negative PET/CT). For patients with ≥ 2 organs involved by metastasis, sensitivity was 100% (29/29 cases). False-negative cases had metastasis in single organs and were characterized by minimal tumor burden and oral corticosteroid use. One false-negative patient had localized stage III disease without known primary melanoma. **Conclusions:** Plasma MDM levels appear highly concordant with FDG-PET/CT in patients with metastatic cutaneous melanoma. A liquid biopsy approach has potential to lower cost and improve patient access to surveillance. Additional prospective studies in larger intended use cohorts are needed to validate our results. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

9568 **Poster Session**

The effect of the microbiome on immune checkpoint inhibitor toxicity in patients with melanoma. *First Author: Nyelia Williams, The Ohio State University, Columbus, OH*

Background: Immune-checkpoint inhibitor (ICI) immunotherapy has increased survival in patients with melanoma. However, only half of the patients respond, and many experience immune-related adverse events (irAEs). Recent evidence suggests that modification of the gut microbiome may increase response to ICIs and decrease toxicity. Here we describe the first results of a clinical trial to determine if the microbiome can predict the response or toxicity during the first 16 weeks of ICI treatment. **Methods:** We enrolled patients aged 18 or older in a prospective observational cohort study at The Ohio State University Comprehensive Cancer Center Skin Cancer Clinic (OSUCCC-SCC) who were to receive treatment with pembrolizumab or nivolumab alone or in combination with other treatments (e.g. nivolumab and ipilimumab) for melanoma. Patients receiving systemic or oral corticosteroids at the start of ICI cycle 1 were excluded but were eligible if receiving adrenal physiologic replacement. Patients collected stool samples at baseline, within 2 days of an adverse event (if applicable), and at 12 weeks. The response to ICIs was evaluated by Response Evaluation Criteria in Solid Tumors (RECIST v1.1) at a 12-week computed tomography scan. Metagenomic whole-genome shotgun sequencing was performed on an Illumina NovaSeq 6000 and then classified using HUMAnN3. The effect of microbe relative abundances on potential irAEs was modeled by logistic regression with the R package glmm. **Results:** In total, 88 patients consented to the trial. Pre-treatment microbiome samples were collected from 49 patients. Potential irAEs were observed in 16 out of the 49 patients for whom pre-treatment microbiome samples were collected. There was no significant difference in the ages ($p = 0.150$, genders ($p = 0.2$), stages ($p = 0.2$) or treatments ($p = 0.07$) of those who developed potential irAEs . Pretreatment abundance of the family *Ruminococcaceae* was most strongly associated with the development of a potential irAE ($p = 0.03$), followed by a taxon in an unclassified order within the phylum *Firmicutes* ($p = 0.05$). The family *Bacteroidaceae* was most strongly associated with no potential irAE ($p = 0.05$). **Conclusions:** Longitudinal and event-driven biospecimen collection in the context of treatment with immunotherapies was feasible in the OSUCCC-SCC. The abundance of the two high-taxonomic rank microbe groups was significantly associated with potential irAEs. The association with *Ruminococcaceae* is consistent with previous studies where it was associated with response to ICIs and, in separate studies, development of an irAE was associated with a better response. The unclassified taxon is potentially a new biomarker for the prediction of toxicity and a therapeutic target to reduce treatment side effects. Future analyses will associate microbes with treatment response and test for consistent microbiome changes at the time of irAE development. Clinical trial information: NCT05102773. Research Sponsor: Pelotonia Junior Investigator Award.

9569 **Poster Session**

The efficacy of immune checkpoint blockade for melanoma in-transit with or without nodal metastases: A multicenter cohort study. *First Author: Roger Olofsson Bagge, Sahlgrenska Center for Cancer Research, Department of Surgery, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden*

Background: Guidelines addressing melanoma in-transit metastasis (ITM) recommend immune checkpoint inhibitors (ICI) as a first-line treatment option, despite the fact that there are no efficacy data available from prospective trials for exclusively ITM disease. The aim of this study was to analyze the outcome of patients with ITM treated with ICI based on data from a large cohort of patients treated at international high-volume melanoma centers. **Methods:** A multicenter retrospective cohort study of patients treated between January 2015 and December 2020 from Australia, Europe, and USA, evaluating treatment with ICI for ITM with or without nodal involvement (AJCC8 N1c, N2c and N3c) and without distant disease (M0). Patients were treated with PD-1 inhibitor (nivolumab or pembrolizumab) and/or CTLA-4 inhibitor (ipilimumab). We assessed response rates, progression-free survival (PFS), melanoma-specific survival (MSS) and overall survival (OS). **Results:** A total of 287 patients from 21 institutions in 8 countries were included. Immunotherapy was first-line treatment in 64 (22%) patients. Monotherapy with a PD-1 or CTLA-4 inhibitor was given in 233 (81%) and 23 (8%) patients respectively, while 31 (11%) received both in combination. Overall response rate was 56%, complete response (CR) rate 36% and progressive disease (PD) rate 32%. Median PFS was 10 months (95% CI 7.4-12.6 months) with a 1-, 2- and 5-year PFS rate of 48%, 33% and 18% respectively. Median MSS was not reached, and the 1-, 2- and 5-year MSS rates were 95%, 83% and 71% respectively. **Conclusions:** Systemic immunotherapy is an effective treatment for melanoma ITM. Future studies should evaluate the optimal role for systemic immunotherapy in the context of multimodality therapy including locoregional treatments such as surgery, intralesional therapy, and regional therapies. Research Sponsor: Institutional support from Knut and Alice Wallenberg Foundation.

9570 **Poster Session**

Multicenter real-world data of adjuvant treatment and disease outcome of patients with melanoma with high-risk of recurrence. *First Author: Elisabeth Livingstone, Department of Dermatology, University Hospital Essen, Essen, Germany*

Background: Clinical trials demonstrated a significantly improved recurrence-free survival (RFS) of melanoma patients treated adjuvantly with immune checkpoint inhibition (ICI) and targeted therapy (TT). As data from controlled trials are based on selected populations, we investigated melanoma patients with high risk of recurrence who opted for ICI, TT, or no adjuvant treatment (NoTx) under real-world conditions. **Methods:** In a prior analysis of this multicenter, retrospective cohort study, patients with resected melanoma stage III-IV between 06/2018 and 09/2019 were analyzed for adjuvant therapy choice (Lodde et al., Cancers 2021). In this follow-up study, the treatment course of ICI- and TT-treated patients as well as recurrence characteristics, subsequent management and outcomes also including NoTx patients were examined. **Results:** 814 patients were included (72 stage IIIA, 266 IIIB, 383 IIIC, 24 IIID, 69 IV; 309 BRAF mut); 533 patients received ICI (66%), 114 TT (14%, 36.9% of all BRAF mutated patients), 167 patients had opted for NoTx (21%). Median treatment duration was 10.2 and 11.7 months for ICI and TT, respectively. ICI was discontinued prematurely in 51% (273/533) and TT in 44% (50/114) of patients. The main reason for discontinuation was progressive disease (PD) in ICI patients (58%, 158/273) and adverse events in TT patients (60%, 33/50). At a median follow-up (FU) of 24.6 months for ICI, 25.3 months for TT, and 21.8 months for NoTx, 48% of ICI (255/533), 35% of TT (40/114), and 45% of NoTx (75/167) patients had developed a recurrence mostly at distant sites (ICI 62%, TT 63%, NoTx 64%). In patients with recurrence, median time from start of adjuvant treatment to 1st recurrence was 6.1 months in ICI and 17.6 months in TT. Median RFS was 32.0 months for ICI (95% CI 25.7-38.3), not reached for TT, and 22.3 months for NoTx (95% CI 15.2-29.4). Among BRAF mut patients with stage III, risk of recurrence was higher for ICI than TT (hazard ratio adjusted for age, sex and tumor stage, 2.31; 95% CI 1.56-3.43). Subsequent systemic treatment for the 1st recurrence was given in 76% (192/253) of ICI, 83% (33/40) of TT, and 53% (40/75) of NoTx patients. Among patients who received the 1st subsequent systemic treatment for metastatic disease, PD was the best response in 67% (82/123) for ICI, 55% (11/20) for TT, and 50% (16/32) for NoTX. **Conclusions:** After 2 years of FU, recurrences were mostly at distant sites in all groups. ICI had higher discontinuation rates and more and earlier recurrences than TT. BRAF mut melanoma patients treated with ICI had a significantly higher risk of relapse than TT-treated patients. Response to subsequent systemic treatment was low for both ICI and TT. Research Sponsor: None.

9571 **Poster Session**

Use of Merlin Assay to identify patients with a low-risk for SN metastasis in a prospective multicenter Dutch study of a primary melanoma gene-signature (CP-GEP model) to predict sentinel node status during COVID-19. *First Author: Robert Stassen, Erasmus MC Kankerinstituut, Rotterdam, Netherlands*

Background: Approximately 70%-85% of patients who undergo sentinel lymph node biopsy (SLNb) show no nodal metastasis in the sentinel node (SN). The clinicopathological and gene expression profile (CP-GEP) model (*Merlin Assay*) was developed and validated to identify patients that may forgo the SLNb surgery due to their low risk for for nodal metastasis This study was initiated during the first wave of Covid-19 pandemic to allow for surgical triage on SLNb and evaluate the implementation of the Merlin assay in clinical practice. **Methods:** This study was conducted in four designated melanoma centers in the Netherlands. Patients (age > 18y) with newly diagnosed melanoma of the skin, eligible to undergo SLNb were screened for study inclusion. Main exclusion criteria was prior history of primary melanoma (> T1b) in the past 5 years. After enrollment, tissue sections of the primary melanoma were centrally reviewed at the Erasmus MC Cancer Institute to determine Breslow thickness at primary diagnosis. FFPE tumor tissue was dispatched for molecular analysis of eight target genes known to play a role in cancer development. In combination with age, Breslow thickness, and GEP outcome, risk of having nodal metastasis was calculated. Results were binary presented as 'CP-GEP low risk' and 'CP-GEP high risk'. SLNb status was used as gold standard for comparison. **Results:** A total of 177 patients were analyzed using the CP-GEP model. Median age was 64 years (IQR 52-73) Median Breslow thickness was 1.4mm (IQR 1.0-2.4). Of all patients 28.2% was diagnosed with T1, 40.7% with T2 and 20.9% with T3 melanoma. Corresponding positivity rate was 7%, 14% and 29% respectively. A total of 24 out of 177 patients had a positive SLNb. Median turn-around time from inclusion to CP-GEP result was 15 days. Overall 37.1.% of patients had a CP-GEP low risk profile. The CP-GEP model had a NPV of 94.6%. **Conclusions:** This is the first prospective multicenter implementation study for the Merlin assay. Results are in line with previous validation studies. The CP-GEP model could accurately identify patients at low risk for SN metastasis. Implementation in clinical practice is feasible based on current turn-around time. In the future, using the Merlin assay to deselect patients for SLNB may allow for a reduction of surgery in patients with melanoma. Research Sponsor: None.

9572 **Poster Session**

Survival update of neoadjuvant ipilimumab + nivolumab in macroscopic stage III melanoma: The OpACIN and OpACIN-neo trials. *First Author: Judith M. Versluis, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: OpACIN was the first trial testing neoadjuvant ipilimumab (IPI) + nivolumab (NIVO) versus the same combination given adjuvant. An unexpected high pathologic responses of 78% was observed in the neoadjuvant arm with a 2-year relapse-free survival (RFS) rate of 80%. The subsequent OpACIN-neo trial tested 3 different dosing schedules of neoadjuvant IPI + NIVO and identified 2 cycles IPI 1 mg/kg + NIVO 3 mg/kg q3w as most favorable schedule with a pathologic response rate of 77% and 20% grade 3-4 immune-related adverse events. Long-term data on the durability of the pathologic (path) responses upon neoadjuvant checkpoint inhibition are lacking so far. Therefore, we present here the updated RFS and overall survival (OS) data of both trials. **Methods:** In OpACIN 20 macroscopic stage III melanoma pts were randomized to receive either IPI 3 mg/kg + NIVO 1 mg/kg q3w 4 cycles adjuvant after lymph node dissection or split 2 cycles neoadjuvant and 2 adjuvant. In OpACIN-neo 86 macroscopic stage III melanoma pts were randomized to arm A (2x IPI 3 mg/kg + NIVO 1 mg/kg q3w, n=30), arm B (2x IPI 1 mg/kg + NIVO 3 mg/kg q3w, n=30), or arm C (2x IPI 3 mg/kg q3w followed by 2x NIVO 3 mg/kg q2w, n=26) followed by lymph node dissection in week 6. RFS and OS were estimated using Kaplan Meier method. All comparative efficacy endpoints are descriptive for OpACIN, since the trial was not powered for comparison of the arms. **Results:** After a median follow-up (FU) of 68.6 months for OpACIN (minimum FU of 59.8 months), median RFS and OS were not reached. Only 1/7 patients (pts) with a pathologic response on neoadjuvant therapy has relapsed. Estimated 5-year RFS and OS rates for the neoadjuvant arm were 70.0% (95%CI: 46.7-100.0) and 90.0% (95%CI: 73.2-100.0) versus 60.0% (95%CI 36.2-99.5) and 70.0% (95%CI: 46.7-100.0) for the adjuvant arm. After a median FU of 46.8 months for OpACIN-neo (minimum FU of 38.2 months), median RFS and OS were not reached. Of pts with path response on neoadjuvant therapy, 3/64 (4.7%) had an event (2 pts relapsed, 1 pt died due to toxicity), versus 14/21 (66.7%) without path response. This resulted in a 3-year RFS rate of 95.3% (95%CI: 90.3-100.0) for responding versus 36.8% (95%CI: 20.4-66.4) for non-responding pts (p<0.001). Of the pts who relapsed after response, 1 had major path response (<10% vital tumor) and 1 a partial response (10-15% vital tumor). Estimated 3-year RFS and OS rates are presented in the Table. **Conclusions:** Updated data from OpACIN and OpACIN-neo trials confirm the durability of responses upon neoadjuvant combination checkpoint inhibition in high risk stage III melanoma. Pathologic response remains a reliable surrogate marker for RFS and OS. Clinical trial information: NCT02437279, NCT02977052. Research Sponsor: BMS, with NKI as sponsor.

	3-year RFS (95%CI)	3-year OS (95%CI)
OpACIN	80.0% (58.7-100.0)	90.0% (73.2-100.0)
OpACIN-neo	81.9% (74.1-90.6)	91.9% (86.3-97.8)
Arm A	86.7% (75.3-99.7)	90.0% (79.9-100.0)
Arm B	79.3% (65.9-95.5)	93.3% (84.8-100.0)
Arm C	79.2% (64.5-97.2)	92.3% (82.6-100.0)

9573 **Poster Session**

SALVO: Single-arm trial of ipilimumab and nivolumab as adjuvant therapy for resected mucosal melanoma. *First Author: Lisa A. Kottschade, Mayo Clinic, Rochester, MN*

Background: Mucosal melanoma is a rare, highly aggressive form of melanoma with extremely high recurrence rates, despite definitive surgical resection. Median RFS has been reported to be 5.4m, with RFS rates at 1 and 2 years of 10%, and 0%, respectively (Lian B, Si L, Cui C, et al. Phase II Randomized Trial Comparing High-Dose IFN-α2b with Temozolomide Plus Cisplatin as Systemic Adjuvant Therapy for Resected Mucosal Melanoma. *Clinical Cancer Research* 2013, **19**(16):4488-4498). Currently there is no consensus on recommendations for adjuvant therapy. Data on the use of immune checkpoint inhibitors (ICI) adjuvantly is lacking. **Methods:** We performed a single arm, multicenter clinical trial using "flip dose" ipilimumab (1mg/kg q3w x4 cycles),and nivolumab (3 mg.kg q3w x4 cycles), then Nivolumab 480 mg q4w x 11 cycles to complete a year of adjuvant therapy. The primary endpoint was recurrence-free survival (RFS), and the study had 85% power to detect an improvement in RFS between 5.5 and 9.5 months using a one-sided log rank test. Participants must have had R0/R1 resection <90 days prior to registration, and no prior systemic therapy (adjuvant radiation allowed), ECOG 0/1, no uncontrolled significant autoimmune disease or other invasive cancer. Patients were recruited through the Midwest Melanoma Partnership/Hoosier Oncology Network. **Results:** From 9/17 to 8/21, 44 patients were approached at 6 centers. Of these 9 were ineligible, and 35 were enrolled. Of these, 29 (83%) had R0 resections, and 7 (20%) had adjuvant radiation prior to enrollment. As of Dec 2021, 31 patients have completed the treatment phase. Of the 35 patients treated on study, 20 patients have recurred (7 local, 5 distant, 3 regional, 5 sites unconfirmed), 6 stopped therapy due to adverse effects, and 8 have died. The mean age of patients was 65.8 years and 21 (60.0%) were female. The primary site of disease was vulvovaginal N=12 (32.4%) patients, sinonasal N= 11 (29.7%), anorectal N= 9 (24.3%) and other site N= 5 (13.5%). Adjuvant radiation had been given in 7 pts. Driver mutations were rare, with only 3 (8.6%) patients having a KIT mutation, and one patient (2.9%) each having a NRAS or BRAF mutation. RFS rates at 1 and 2 years were 50% (95% CI 31-66%) and 37% (95% CI 19-55%), with OS rates at 1 and 2 years of 87% (95% CI 68-95%) and 68% (95% CI 46-83%). Median RFS was 10.3 m (95% CI5.7-25.8). Most common grade 3 adverse events were diarrhea (14%), hypertension (14%), hyponatremia (11%), with no grade 4/5 toxicities. **Conclusions:** Flip dose ipilimumab and nivolumab after resection is associated with outcomes improved over previously reported outcomes in the absence of therapy. Long term follow up is ongoing as are subgroup analyses and correlative studies. Clinical trial information: NCT03241186. Research Sponsor: Bristol Myers Squibb.

9574 **Poster Session**

Primary ipilimumab/nivolumab followed by adjuvant nivolumab in patients with locally advanced or oligometastatic melanoma: Update on outcome. *First Author: Emilia Cocorocchio, Istituto Europeo di Oncologia, IRCCS, Milano, Italy*

Background: The aim of neo-adjuvant therapy in locally advanced or oligometastatic melanoma is to facilitate radical resection, improve outcomes and undertake research to identify biomarkers of response and resistance. The optimal schedule to balance efficacy vs toxicity in dual PD1/CTLA4 blockade regimens remains a matter of debate. We initiated an open- label, single arm study to investigate the Nivo 3/ Ipi 1 schedule as primary treatment of locally advanced or oligometastatic melanoma patients (pts). **Methods:** Treatment schedule consists in 4 neoadjuvant cycles of Ipilimumab 1 mg/kg and Nivolumab 3 mg/kg every 3 weeks, followed by surgery and adjuvant Nivolumab 480 mg every 4 weeks for 6 cycles. Primary objective is pathological complete remission (pCR) rate, according to Neoadjuvant Melanoma Consortium criteria. Secondary objectives are: safety, feasibility and efficacy; QoL; identification of molecular and immunological biomarkers of response and resistance (somatic genetic drivers, tumor mutational burden, mutational signatures, predicted neoantigens, germline HLA typing, somatic HLA mutations and liquid biopsy); degree of immune activation; evaluation of microbioma **Results:** From March 2019 to April 2021, 35 pts were included within the trial. All pts completed the treatment program. 6 pts (17%) developed immune-related (IR) G3-4 adverse events (AE): 3 transaminitis, 1 pneumonitis, 1 myocarditis and 1 CPK increase; all of them but one underwent surgery after toxicity resolution. 4 pts (11%) experienced G3-4 non-IR AE. 31 pts underwent surgery after neoadjuvant phase: pCR, near pCR, pathological partial remission (pPR) and pathological no response (pNR) were achieved in 18 (58%), 2 (7%), 4 (13%) and 7 (22%) cases, respectively. 2 pts progressed before surgery and 8 pts progressed during/after adjuvant phase (6/8 in NR at surgery). 4 pts died, 3 after disease progression and 1 for ischemic stroke 5 months after the end of therapy. At 18 months, progression free survival (PFS) and overall survival (OS) were 80 and 85%, respectively (median follow-up: 23 months); non responders (pNR) have a higher risk of relapse or death vs responders (pCR+near pCR+pPR) [HR= 4.11, 95%CI (0.96 -17) adjusted for age, p=0.06]. **Conclusions:** Our study lends further support to the adoption of the Nivo 3/ Ipi 1 schedule as primary treatment for locally advanced/oligometastatic melanoma, as this regimen achieved a pCR/near pCR rate of 65% with a rate of severe IR-AEs (17%) lower than previously reported in CheckMate 511 trial (34%) using Nivo3/ Ipi1 schedule. Available translational data on potential genomic biomarkers of response, gut microbiome and systemic inflammatory landscape evaluated longitudinally during therapy on each patient will be presented. Clinical trial information: 2018-002172-40. Research Sponsor: BMS.

9575 **Poster Session**

Efficacy and safety of "second adjuvant" therapy with BRAF/MEK inhibitors after resection of recurrent melanoma following adjuvant PD-1–based immunotherapy. *First Author: Amelia M. Taylor, Melanoma Institute Australia, Sydney, Australia*

Background: Both anti-PD-1 antibodies and BRAK/MEK inhibitors (BRAF/MEKi) reduce the risk of recurrence for patients with resected stage III melanoma. For patients with V600 BRAF-mutated melanoma who recur with resectable disease on or after adjuvant, many may be suitable for 'second adjuvant' treatment after surgery. We sought to examine the efficacy and safety of 'second adjuvant' BRAF/MEKi in patients who recurred despite adjuvant PD-1 based immunotherapy. **Methods:** Patients with V600 BRAF-mutated melanoma treated with adjuvant PD-1 based immunotherapy for resected stage III/IV disease who recurred, underwent resection of recurrence and were then treated with adjuvant BRAF/MEKi were identified retrospectively from 13 centres. Demographics, disease characteristics, treatment details, and outcome data were examined. **Results:** 55 patients were included; median age at commencement of PD-1 was 53y, most were V600E (91%) and had IIIB (42%) or IIIC (44%) melanoma. PD-1 based adjuvant therapy included nivolumab (71%), nivolumab plus ipilimumab (14%), pembrolizumab (13%) and pembrolizumab plus mRNA-4157 vaccine (2%). Patients had initial recurrence after mean 8.4 months (95% CI 7.4-10.6), mainly while on treatment (65%), in regional nodes (42%), in-transit metastases (ITMs; 38%), both regional nodes and ITMs (7%) and distant metastases (13%). Surgical management included CLND (36%), selected nodal resection (11%), ITM resection (33%) and resection of distant metastasis (13%). A minority had adjuvant radiotherapy (17%). Stage at start of second adjuvant BRAF/MEKi included IIIB (29%), IIIC (53%) IIID (4%) and IV (15%). Patients received dabrafenib and trametinib (95%, N = 52) and encorafenib and binimetinib (5%, N = 3). After a median follow up of 21.4 months (19.7-25.4), 17 (31%) patients have recurred again. Mean duration of treatment was 9 months (95% CI 7.4-10.6); 20% ceased for toxicity, 7% for recurrence and 35% were on treatment at last follow up. The most common toxicity was pyrexia (43%) and 21% patients experienced a severe (G3-4) adverse event. Median RFS was 33.4 months (14.3.7-NR) and median DMFS was not reached. At 12 months, 72% (59-88) of patients were recurrence free and 90% (81-100) were free of distant recurrence. For those whose disease recurred again, most recurred after cessation of second adjuvant BRAF/MEKi (13/17, 76%). 7 (41%) recurred locally and 8 (47%) recurred with new metastatic disease but none had brain metastases. **Conclusions:** This is the first study examining outcomes of patients receiving second adjuvant targeted therapy for melanoma, after failure of adjuvant PD-1 based immunotherapy. While RFS appears shorter compared to first line trials, second adjuvant treatment with BRAF/MEKi appears safe and active in preventing further recurrence. Further data on sequencing adjuvant therapies are needed. Research Sponsor: None.

9576 **Poster Session**

A single-center experience of 98 patients (pts) with regionally metastatic Merkel cell carcinoma (MCC) of known (MCCKP) and unknown (MCCUP) primary at presentation. *First Author: Brandon Cope, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: MCC is a rare skin cancer historically associated with poor survival rates and which is increasing in incidence. A small number of retrospective series suggest that MCCUP may be associated with better prognosis than MCCKP while others report worse outcomes. Recent advances in immunotherapy have changed the multimodal treatment landscape and outcomes of advanced MCC pts. We describe our experience with the management and outcomes of pts presenting with regional MCC metastasis of known and unknown primary origin. **Methods:** A retrospective review of pts with clinical regional disease at MCC diagnosis treated at our institution from 3/2003-3/2021 was performed. Clinicopathologic variables and outcomes were assessed. Overall survival (OS), recurrence-free survival (RFS) and progression-free survival (PFS) were estimated by the Kaplan Meier method. **Results:** Of 98 pts with regional disease on exam at presentation, 56 (57%) had MCCUP and 42 (43%) had MCCKP. Median follow-up from diagnosis to last follow-up or death was 33 months. Pts were generally older (MCCUP vs MCCKP: 68.7 vs 73.1 years), male (MCCUP vs MCCKP: 82% vs 74%) and Caucasian (MCCUP vs MCCKP: 84% vs 83%). Over half the pts had a history of another malignancy (MCCUP vs MCCKP: 52% vs 60%) with 9% and 14% being immunocompromised at diagnosis, respectively. After completion of staging workup, MCCUP pts had earlier stage disease at presentation compared with MCCKP pts (stage IIIA: 80% vs 55%, IIIB: 5% vs 31%, IV: 15% vs 14%, respectively). The cervical nodal basin was most commonly involved in MCCUP pts while regional disease was more varied in MCCKP pts (MCCUP vs MCCKP: cervical 54% vs 28%, axillary 15% vs 33%, inguinal 33% vs 3%, inguinal and pelvic 0% vs 11%, in transit 0% vs 14%). Formal lymphadenectomy (LND) was performed in 27 (48%) and 18 (43%) of MCCUP and MCCKP pts, respectively. Of these pts, 33% and 50% received neoadjuvant systemic therapy, most commonly immunotherapy; 70% and 55% received adjuvant radiotherapy. MCCUP pts had better outcomes compared to MCCKP pts (Table), with longer RFS in pts who underwent LND (not reached [NR] vs 13.1 months) as well as longer PFS in pts who did not undergo LND (17 vs 9 months) with longer OS in both subgroups (LND: NR vs 102.7 months; no LND: 74.4 vs 48.7 months). **Conclusions:** MCCUP patients with regional disease on exam at presentation have improved survival compared to MCCKP. Current stage III survival estimates may underestimate survival in patients with resectable disease. Research Sponsor: None.

Last known status of MCCUP and MCCKP patients presenting with regional disease on exam.

All pts	MCCUP (n=56)	MCCKP (n=42)
Alive, no evidence of disease (NED)	28 (50%)	12 (28.6%)
Alive with disease (AWD)	11 (19.6%)	10 (23.8%)
Deceased	17 (30.4%)	20 (47.6%)
Pts who underwent LND	**MCCUP (n=27)**	**MCCKP (n=18)**
NED	19 (70.4%)	4 (23.5%)
AWD	4 (14.8%)	5 (29.4%)
Deceased	4 (14.8%)	8 (47.1%)

9577 **Poster Session**

Adjuvant treatment of in-transit melanoma: Addressing the knowledge gap left by clinical trials. *First Author: Melissa Melanie de Meza, Leiden University Medical Center, Leiden, Netherlands*

Background: Few clinical trials address the efficacy of adjuvant systemic treatment in patients with ITM. This study describes the efficacy of adjuvant systemic therapy of ITM patients beyond the clinical trial setting. **Methods:** All stage III adjuvant-treated melanoma patients registered in the nationwide Dutch Melanoma Treatment Registry between 01-07-2018 and 31-12-2020 were included. Patients were divided into three groups: patients with ITM only, with ITM and nodal disease, and patients with nodal disease only. Differences in recurrence patterns were analysed. An exploratory analysis was performed for stage III patients who underwent surgical resection without adjuvant treatment. Recurrence-free survival (RFS) and overall survival (OS) at 12-months were assessed. **Results:** A total of 1037 stage III melanoma patients received adjuvant anti-PD-1 therapy, and 260 underwent surgical resection only. Of the adjuvant-treated patients, 16.9% had ITM only, 15.5% had ITM with nodal disease, and 66.8% had nodal disease only. Of the surgical resection only patients 20.4% had ITM only, 12.3% had ITM with nodal disease and 67.3% had nodal disease only. In the adjuvant-treated patients, 12-months RFS was comparable between patients with ITM only and patients with nodal disease only (71.1% vs. 72.2% respectively, p = 0.95), but significantly lower for patients with ITM and nodal disease (57.1%; ITM with nodal disease vs. ITM-only p = 0.01, and ITM with nodal disease vs. nodal disease only p < 0.01). Locoregional metastases occurred as first recurrence site in 72.7% of ITM-only patients, 42.9% of ITM and nodal disease patients and 38.9% of patients with nodal disease only, while distant recurrences occurred in 18.2% of patients with ITM only, in 36.7% of patients with ITM and nodal disease, and in 42.3% of patients with nodal disease only (p = 0.01). OS at 12-months was significantly higher for ITM-only patients compared to patients with ITM and nodal disease (97.7% vs. 90.6%, p < 0.01), and was better compared to patients with nodal disease only (97.7% vs. 94.4%, p = 0.05). OS at 12-months was comparable for patients with ITM and nodal disease and patients with nodal disease only (p = 0.19). In general, surgery-only ITM patients were older and had a worse performance score. 12-months RFS appeared worse compared to adjuvant-treated ITM patients (36.6% vs. 68.3%). In this group of surgery-only ITM patients OS at 12-months also appeared worse compared to adjuvant-treated ITM patients (89.7% vs. 95.5%). **Conclusions:** RFS rates in ITM-only patients are similar to non-ITM patients, while RFS in patients with ITM and nodal disease is shorter. Adjuvant-treated patients with ITM without nodal disease less often experience distant recurrences and have a superior OS compared to other adjuvant stage III patients. Our results suggest that other treatment strategies for ITM patients with nodal disease should be considered. Research Sponsor: None.

9578 **Poster Session**

Adjuvant temozolomide plus cisplatin versus high-dose interferon alpha-2b in resected mucosal melanoma: A randomized, multicenter, controlled, phase III trial. *First Author: Bin Lian, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China*

Background: Mucosal melanoma (MuM) is a rare cancer with an extremely poor prognosis and no established standard adjuvant therapy. A phase II trial showed promising outcomes with adjuvant temozolomide plus cisplatin (Chemo) versus high-dose interferon alpha-2b (HDI) in resected mucosal melanoma. We conducted the phase III trial to definitively compare these two treatments. **Methods:** In this multicenter, randomized, controlled, phase III trial, patients with pathologically confirmed stage I-III mucosal melanoma who had undergone complete resection were stratified by primary site (head and neck vs. non-head and neck) and disease stage (I/II vs. III) and randomized 1:1 to receive Chemo (temozolomide 200 mg/m^2/day orally on days 1 to 5 plus cisplatin 75 mg/m^2 i.v. on days 1-3, repeated every 3 weeks for six cycles) or HDI (15×10^6 U/m^2/day i.v on days 1 to 5 each week for 4 weeks followed by 9×10^6 U three times per week for 48 weeks). Postoperative radiotherapy was recommended for head and neck MuM patients, with a total dose of 65-70 Gy/30-35 fx to GTV and 60 Gy/30 Fx to CTV. The primary endpoint was relapse-free survival (RFS). Secondary endpoints included distant metastasis-free survival (DMFS), overall survival (OS), and safety. The protocol was registered at ClinicalTrials.gov (NCT03435302). **Results:** Between Feb 2014 and Jun 2016, 204 patients were randomized to treatment (Chemo group: n = 103, HDI group: n = 101). Baseline characteristics were generally well balanced between the two groups. Anatomic site of head and neck, gastrointestinal, gynecological were 38.8% vs 49.5%, 35.9% vs 22.8%, 25.2% vs 27.7% in Chemo and HDI group, respectively. Stage of I/II, III were 68.9% vs 73.3%, 31.1% vs 26.7% in Chemo and HDI group, respectively. CKIT, BRAF, NRAS Mutation were 7.0% vs 8.2%, 5.0% vs 8.2%, 13.4% vs 15.8% in Chemo and HDI group, respectively. In the ITT population, At a median follow-up of 64.8 months, patients receiving Chemo had a higher median RFS (15.5 vs. 9.9 months; HR = 0.622; 95% CI, 0.463 to 0.836; P = 0.001), DMFS (19.5 vs. 12.7 months; HR = 0.705; 95% CI, 0.518 to 0.959; P = 0.025) and OS (38.2 vs. 33.5 months; HR = 0.832; 95% CI, 0.598 to 1.155; P = 0.270) versus the HDI group. A subgroup analysis revealed consistent improvements in RFS, DMFS and OS with Chemo versus HDI across multiple subgroups. Toxicities were generally mild to moderate in both groups. The most common adverse events were fatigue, anorexia, nausea/vomiting, leukopenia, Neutropenia, hepatotoxicity, fever and anemia, 23 patients (22.3%) in Chemo group and 57 patients (56.4%) in HDI group had a grade 3 or 4 adverse events. **Conclusions:** Adjuvant temozolomide plus cisplatin led to a significantly lower risk of relapse and distant metastasis in patients with resected mucosal melanoma versus high-dose IFN-a2b and was generally well tolerated. Clinical trial information: NCT03435302. Research Sponsor: National Natural Science Foundation of China, Beijing Municipal Administration of Hospitals' Youth Programme.

9579 **Poster Session**

Leveraging personalized circulating tumor DNA (ctDNA) for detection and monitoring of molecular residual disease in high-risk melanoma. *First Author: Sofia Genta, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: High-risk melanoma has variable prognosis. Adjuvant immuno- (IO) and targeted therapy (TT) are approved for stage III-IV resected disease. However, a significant proportion of patients (pts) are cured by local treatment alone or relapse despite adjuvant therapy. Liquid biopsy with ctDNA assays have been used to predict response to treatment and identify pts at higher risk of progression/death. Personalized ctDNA assays are a highly sensitive approach that may enhance upfront risk stratification and early detection of relapse. **Methods:** Serial ctDNA Monitoring as a predictive Biomarker in advanced neoplAsms (SAMBA) is a Princess Margaret prospective ctDNA kinetics study (NCT03702309) in high-risk melanoma pts. Plasma is collected pre-op (pre-local treatment, if feasible), post-op (after surgery), and every 3-6 months (m) until radiological progressive disease (rPD). Personalized amplicon based NGS assays by Inivata (RaDaR) were used to detect somatic variants in ctDNA identified through whole-exome sequencing of matched tumor tissue. Progression free survival (PFS) and overall survival (OS) from the time of surgery were estimated with the Kaplan Meier and compared with the log-rank test. **Results:** As of December 2021, 82 of 100 planned pts have been enrolled. A total of 191 samples from 47 pts have been analyzed. Median age was 66 years (27-87), 33 were male (70%). Seven (15%), 30 (64%) and 10 (21%) were stage II/III/IV respectively. All pts had surgery and 8 (17%) adjuvant radiation. No systemic therapy was given to 11 pts (23%); 30 (64%) had IO and 6 (13%) TT. rPD occurred in 13 pts (28%). Median follow up was 24 months. A median of 48 variants were included in the personalized ctDNA panel design (35-52). ctDNA was detected (ctDNA+) at any time point in 12/47 pts (26%), of which 5/12 (42%) were *BRAF* and *NRAS* wt on tissue. Median PFS was 4.9 months (m) for ctDNA+ pts and not reached (NR) for ctDNA- pts at post-op (HR = 2.71 CI 0.60-12.31, p = 0.179). Median OS was 23.1 m vs NR in ctDNA+ vs ctDNA- pts (HR = 8.9, CI 1.45-54.77, p = 0.004). Two ctDNA+ pts had neoadjuvant IO and became ctDNA- before surgery. One, free of disease after 12 m, had ctDNA- in 4 follow up samples. The other pt was ctDNA+ in the post-op sample and relapsed within 3 m. Four of 45 (9%) pts had ctDNA+ at post-op. Two of them, including a pt who had neoadjuvant IO, did not receive adjuvant therapy and had rPD within 3 m. The other 2 pts received adjuvant IO; ctDNA cleared and pts remain free of disease at 12 and 34 m. Three pts with rising ctDNA over time experienced rPD after a median of 4 m (2-7). **Conclusions:** Personalized ctDNA analysis with RaDaR may improve risk of death stratification and selection of pts who could benefit from adjuvant treatment. Detection of ctDNA may precede rPD. Follow-up will continue in pts with rising ctDNA who have not yet had rPD. Pts accrual and sample collection are ongoing, and additional data will be presented. Clinical trial information: NCT03702309. Research Sponsor: Princess Margaret Cancer Center institutional founding, Princess Margaret Cancer Foundation.

9580 **Poster Session**

Neoadjuvant dabrafenib and trametinib (D+T) for stage III melanoma: Long-term results from the NeoCombi trial. *First Author: Alexander M. Menzies, Melanoma Institute Australia, The University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, NSW, Australia*

Background: Neoadjuvant D+T has a high pathologic response rate and impressive short-term survival. The NeoCombi trial (NCT01972347) enrolled 35 patients with resectable stage III melanoma, with last patient commencing treatment April 19th 2017. We report 5-year outcomes from this trial. **Methods:** Pts received 12 wks neoadjuvant standard dose D+T, then 40 wks adjuvant D+T. Eligible pts were ≥ 18 yrs, ECOG PS ≤ 1 with clinical stage III BRAF V600E/K melanoma. CT and PET scans were performed at baseline and prior to surgery. Pathologic response was determined as per International Neoadjuvant Melanoma Consortium (INMC) criteria and defined as complete (pCR), near complete, partial (pPR) or no response (pNR). CT monitoring was continued 12 wkly thereafter to 2 yrs, then 6 monthly to 3 yrs, then as standard care. The primary endpoints were the complete pathological response (pCR) and RECIST response rate (rRR) at wk 12. Secondary endpoints included relapse free survival (RFS), OS, and toxicity. **Results:** 35 pts were enrolled, 6 with IIIB, 29 IIIC (7 ITM only) disease (clinical AJCCv7). At data cut August 17th 2021, median F/U was 60 mo (95% CI 56-72). No patients progressed in the neoadjuvant phase, and (49%) had a pCR, 1 near pCR, 6 pPR, 11 pNR. 5-year RFS, DMFS and OS data are shown in the Table. The majority of recurrences occurred within the first 2 years, with no recurrences beyond 3y. 21 patients recurred; 12 (57%) had first recurrence locoregional (6/12 subsequent distant recurrence) and 9 (43%) had first recurrence in distant sites (3/9 in brain). Locoregional recurrence was managed with surgery alone in 4/12, systemic therapy alone in 2/12, or both surgery and systemic therapy in 5/12 (4/5 had adjuvant systemic therapy), 1 pt was observed until distant recurrence. Subsequent systemic therapy in the 15 patients with a distant recurrence included PD-1 based immunotherapy (N=14) and BRAF targeted therapy (N=10). **Conclusions:** Neoadjuvant D+T in clinical stage III melanoma has impressive early activity, however patients remain at high risk of recurrence. Pathologic response can identify patients at the highest risk of recurrence, offering a chance of alternative adjuvant therapy in non-responders. Clinical trial information: NCT01972347. Research Sponsor: GlaxoSmithKline, Novartis, National Health and Medical Research Council, Australia; and Melanoma Institute Australia.

	5y RFS	5y DMFS	5y OS
All (N=35)	40%	57%	80%
pCR (N=17)	53%	59%	88%
Non-pCR (N=18)	28%	55%	71%

9581 **Poster Session**

Health-related quality of life (HRQoL) with pembrolizumab (pembro) in resected high-risk stage II melanoma in the phase 3 KEYNOTE-716 study. *First Author: Muhammad Adnan Khattak, Fiona Stanley Hospital and Edith Cowan University, Perth, Western Australia, Australia*

Background: Adjuvant pembro improved RFS vs placebo (HR, 0.61; 95% CI, 0.45-0.82) and had manageable safety in patients (pts) with resected high-risk stage II melanoma at second interim analysis of KEYNOTE-716 (NCT03553836). HRQoL results are presented. **Methods:** Pts aged ≥12 y with resected stage IIB/C melanoma were randomized 1:1 to adjuvant pembro 200 mg (2 mg/kg for pts ≥12 and < 18 y) Q3W or placebo for ≤17 cycles. Change from baseline in HRQoL was an exploratory end point. EORTC QLQ-C30 and EQ-5D-5L were administered at baseline; cycles 5, 9, 13, and 17 in y 1; every 12 wk in y 2; and every 6 mo in y 3. The HRQoL population included all pts who received ≥1 dose of study treatment and had ≥1 HRQoL assessment available. Least-squares mean (LSM) change from baseline to wk 48 in EORTC QLQ-C30 global health status (GHS)/quality of life (QoL) and physical functioning (PF) and EQ-5D-5L visual analog scale (VAS) were calculated using a constrained longitudinal data analysis model; HRQoL score was the response variable with treatment by time interaction and T stage at baseline as covariates. Empirical mean change from baseline in QLQ-C30 GHS/QoL and PF scores over time was evaluated. A ≥10-point improvement or decline in QLQ-C30 scores was considered clinically meaningful. Data cutoff was June 21, 2021. **Results:** Of 976 pts enrolled, 969 were included in the HRQoL population (483 pembro; 486 placebo). Median follow-up in the ITT population was 20.5 mo (range, 4.6-32.7). At wk 48, compliance (adherence) for EORTC QLQ-C30 was 83.4% for pembro and 89.3% for placebo and completion was 70.6% and 75.7%, respectively. At wk 48, compliance for EQ-5D-5L was 84.1% for pembro and 90.0% for placebo and completion was 71.2% and 76.3%, respectively. QLQ-C30 GHS/QoL and PF and EQ-5D-5L VAS scores were similar between arms at baseline. LSM change from baseline to wk 48 in QLQ-C30 GHS/QoL score was –4.49 (95% CI, –6.19 to –2.79) for pembro and –0.82 (95% CI, –2.47 to 0.83) for placebo (LSM difference: –3.67; 95% CI, –5.91 to –1.44). LSM change from baseline to wk 48 in QLQ-C30 PF score was –3.27 (95% CI, –4.61 to –1.92) for pembro and –1.77 (95% CI, –3.07 to –0.46) for placebo (LSM difference: –1.50; 95% CI, –3.33 to 0.32). LSM change from baseline to wk 48 in EQ-5D-5L VAS score was –2.19 (95% CI, –3.52 to –0.85) for pembro and –0.25 (95% CI, –1.54 to 1.04) for placebo (LSM difference: –1.94; 95% CI, –3.72 to –0.16). LSM change from baseline to wk 48 in other QLQ-C30 functioning and symptom scales was similar in both arms. Empirical mean change from baseline in QLQ-C30 GHS/QoL and PF was similar over 96 wk in both arms. **Conclusions:** No clinically meaningful decreases in EORTC QLQ-C30 or EQ-5D-5L VAS scores were observed for adjuvant pembro or placebo. These results, along with improved RFS and manageable safety, support the use of adjuvant pembro in resected high-risk stage II melanoma. Clinical trial information: NCT03553836. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

9582 **Poster Session**

Successful management of Australian patients with extensive skin field cancerization (ESFC) with widefield volumetric arc radiation therapy (VMAT): Report with 12-month follow-up. *First Author: Walter J Curran, GenesisCare, Atlanta, GA*

Background: Non-melanomatous skin cancer (NMSC) diagnoses are associated with a high risk of developing new skin cancers in adjacent areas. Patients with extensive skin field cancerization (ESFC) have large areas (generally ≥50cm^2) of compromised skin characterized by pre-cancerous actinic keratoses often requiring repeated interventions. Lesion-directed therapies have excellent cure rates, but therapies targeting a wider region have limited durability, including topical agents such as 5-flurouracil. The development of volumetric modulated arc radiation therapy (VMAT) to precisely target large, curved skin surfaces has generated interest in its application to ESFC. This is a report on the efficacy, safety, and cosmetic outcomes of VMAT in the management of patients with ESFC at facilities across five Australian states. **Methods:** Sixty-three ESFC zones on 60 patients were prescribed widefield VMAT and prospectively enrolled in the National (Australian) Dermatology Radiation Oncology Registry (NDROR). Over 80% of patients had received up to 4 prior non-radiotherapy interventions. Fields included lower and upper limb, face, scalp, or trunk regions. Total widefield VMAT RT doses ranged from 45-50 Gy delivered in 25-30 daily fractions across 5-7 weeks. 3-, 6-, and 12-month follow-up assessments rated the percentage of disease clearance, cosmesis using the Lovett's scale, and toxicity based on CTCAE. **Results:** At 12-month follow-up, 97% of treated zones had achieved and maintained clinical success, defined as > 90% field clearance. Five percent of patients exhibited recurrence of original disease, whereas 10% of patients developed a new actinic keratosis or NMSC. Cosmesis was rated as excellent or good in 98% of patients. Most patients exhibited grade 1-2 radiation-induced dermatitis during therapy, which resolved by 3-month follow-up. Grade 3 dermatitis at end of treatment was exhibited in 7% of the patients, which also resolved. Eight percent of patients discontinued treatment due to acute toxicities. The most common persistent toxicity at 12-month follow-up was localized grade 1 xerosis (dryness) at 43% and/or alopecia at 33%. **Conclusions:** Widefield VMAT achieved very promising clinical success in patients with ESFC for whom other therapies had failed. VMAT yielded favorable cosmetic outcomes, and treatment-related toxicity was manageable and transient in most patients. While additional follow up is necessary, these results demonstrate that widefield VMAT may be an excellent option for some patients with increasingly unmanageable presentations of ESFC. Research Sponsor: GenesisCare.

9583 **Poster Session**

Sentinel lymph node biopsy in Merkel cell carcinoma: A multi-institutional study from the Pan-Canadian Merkel Cell Collaborative. *First Author: Megan Delisle, University of Ottawa, Ottawa, ON, Canada*

Background: There is controversy regarding sentinel lymph node biopsy (SLNB) in clinically node-negative Merkel Cell Carcinoma (MCC). We compared MCC recurrence and survival between patients who did versus did not undergo a SLNB. **Methods:** Patients with MCC across 13 Canadian centers were reviewed, from 2000-2018. Of a total cohort of 750 patients, 485 had clinically node-negative disease at presentation. A propensity score was created. The association between SLNB and local, regional and distant recurrence, and cancer-specific and overall survival were evaluated using competing risks and Cox proportional hazards regression. **Results:** 195 patients (40.2%) underwent a SLNB. SLNB was performed more commonly in younger, healthier patients with MCC located in the extremities or torso (Table). The results of 177 SLNBs were available; 60 (33.9%) were positive. SLNB-positive patients underwent completion dissection (n=15, 25%), completion dissection and nodal radiation (n=22, 36.7%), nodal radiation alone (n=18, 30%) or observation (n=5, 8.3%). Patients who did not undergo a SLNB underwent nodal radiation alone (n=40, 13.8%) or observation (n=250, 86.2%). The median follow-up was 2.7 years (range 0.2-14.4). The regional recurrence rate was 14.5% (n=17) among SLNB-negative versus 15% (n=9) among SLNB-positive patients. Among patients who did not undergo a SLNB, the regional recurrence rate was 25.2% (n=63) among those who underwent observation and 15% (n=6) among those who received nodal radiation alone. After propensity score matching, SLNB patients had a lower risk of regional recurrence (sHR 0.54 95% CI 0.34-0.86 p=0.01) and improved overall survival (HR 0.32 95% CI 0.23-0.45 p<0.01), but there was no difference in local recurrence (sHR 0.92 95% CI 0.50-1.69 p=0.79), distant recurrence (sHR 0.88 95% CI 0.52-1.49 p=0.63), or cancer-specific survival (HR 0.67 95% CI 0.31-1.45 p=0.31). **Conclusions:** SLNB is associated with a reduced risk of regional recurrence and improved overall survival. The role of SLNB in selecting patients for emerging therapies, such as immunotherapy, needs to be evaluated. Research Sponsor: None.

Clinicopathologic and treatment factors by SLNB.

	SLNB N (%)	No SLNB N (%)	P-value
Male	122 (62.6)	166 (57.2)	0.24
Age (mean +/- sd)	70 +/-10	79 +/- 10	<0.01
Charlson Co-Morbidity Index [3] [4]	108 (55.4)	228 (78.6)	<0.01
Primary Location			<0.01
Head & Neck	52 (26.7)	178 (61.4)	
Extremities	130 (66.7)	92 (31.7)	
Torso	13 (6.7)	6.9 (20)	
Stage			<0.01
I	84 (43.1)	183 (63.1)	
II	45 (23.1)	100 (34.5)	
III	66 (33.8)	7 (2.4)	

9584 **Poster Session**

Analysis of the effect of systemic corticosteroids on survival from tebentafusp in a phase 3 trial of metastatic uveal melanoma. *First Author: Alexandra Ikeguchi, University of Oklahoma, Oklahoma City, OK*

Background: All immune therapies that rapidly activate T cells, including T cell engagers, can induce cytokine release syndrome (CRS). Tebentafusp (tebe), a T cell receptor bispecific (gp100 x CD3) can also induce skin adverse events (AEs), due to gp100+ cutaneous melanocytes. CRS and skin AEs may require management with short term corticosteroids, which may also be used as premedication for subsequent tebe doses. Here we report the first analysis of systemic corticosteroid use and correlation with efficacy from a Phase (Ph) 3 trial for any T cell engager. **Methods:** Post hoc analyses were performed on the tebe arm of the Ph3 [NCT03070392] study in previously untreated HLA-A*02:01+ metastatic uveal melanoma (mUM) (N = 245). Due to the low rate of severe AEs in Ph1 trials, prophylactic corticosteroids were not mandated. The association between overall survival (OS) and corticosteroid use (new start within 30 days of first tebe dose) was investigated using landmark analyses in the safety population. Multivariate analyses were adjusted for key patient characteristics and AEs of special interest: CRS, rash, and liver function test (LFT) elevation. Steroid type (hydrocortisone vs. others) and treatment duration (1 vs. > 1 day) were also investigated. **Results:** In the Ph3 trial, 64/245 (26%) patients received new systemic corticosteroid within 30 days after the first dose of tebe, mostly for treatment of AEs (56/64, 88%) or pre-medication due to previous AE (14/64, 22%). 25 of the 64 patients received corticosteroids only for a single day. The most frequent AEs (≥15%) were rash (18/64, 28%), CRS (15/64, 23%), and hypotension (12/64, 19%). In a logistic regression model, elevated baseline LDH, the dominant prognostic marker, was most strongly associated with use of corticosteroids (p = 0.01). In the multivariate analysis, corticosteroids were not associated with any significant OS difference (HR 1.41, 95% CI 0.83-2.4, p = 0.2) and this effect did not differ in patients with or without CRS, rash or LFT elevation (all interaction tests p > 0.2). There was no difference in OS according to corticosteroid type or whether administered for 1 vs > 1 day. **Conclusions:** This is the first analysis from a phase 3 trial of the impact of systemic corticosteroids on survival for a T cell engaging cancer therapy. The vast majority of tebe-treated patients (84%) either did not require corticosteroids (74%) or only received them on a single day (10%). The most frequent reason for corticosteroid use was an emergent AE, including CRS and rash. Corticosteroid use following the pre-specified AE guidelines was not associated with any significant impact on OS. Clinical trial information: NCT03070392. Research Sponsor: Immunocore.

9585 **Poster Session**

Treatment with tebentafusp beyond radiographic progressive disease (PD) in metastatic uveal melanoma (mUM). *First Author: Ryan J. Sullivan, Massachusetts General Hospital, Boston, MA*

Background: Tebentafusp (tebe) is the first T cell receptor therapeutic to demonstrate overall survival (OS) benefit in a randomized Phase 3 study vs investigator's choice (IC) [NCT03070392]. OS benefit was also observed in patients (pts) with best objective response (BOR) PD (HR 0.43), and in pts who had tumor growth ≥20% as best change in tumor size (HR 0.41), suggesting tebe-treated pts may exhibit atypical radiological responses and could benefit from treatment beyond radiographic progression (TBP), a well-established concept in immuno-oncology. Here we analyzed tumor kinetics and clinical benefit in pts treated with tebe beyond initial radiographic progression (TBP). **Methods:** 378 mUM pts were randomized 2:1 to tebe vs. IC. BOR was assessed by investigators using RECIST v1.1. TBP was permitted until: 1) additional ≥20% increase in tumor burden with absolute increase of ≥5 mm, or 2) unequivocal PD of non-target lesions; or 3) new non-measurable lesions. A Cox model adjusted for baseline covariates and for covariates at time of progression for TBP-eligible pts was used to compare survival post progression between those who did (TBP) and did not receive TBP (non-TBP). Stepwise selection of covariates (using $p < 0.1$ as the entry and staying criterion) was applied. Analysis performed on data cut-off 13Oct2020. **Results:** 183 tebe pts were eligible for TBP per protocol; 60% (109/183) received TBP with median duration of 8 wks. 21% of all tebe doses were administered as TBP. The proportion of pts with new lesions at initial progression (44% vs 57%) and median time to initial progression (2.9 mo vs 2.9 mo) were similar between TBP and non-TBP pts. Pts receiving TBP were more likely to have favorable key prognostic factors at baseline or at time of progression. After adjusting for these differences, a numerical benefit in post-progression OS favoring TBP was observed (HR 0.67, 95% CI [0.38,1.19]). Serial review of radiographic time points identified initial progression of sum of target lesions followed by stabilization for > 3 months after initial progression in some TBP pts. Safety profile during TBP was consistent with that expected for pts established on tebe and no pts experienced an AE leading to treatment discontinuation. **Conclusions:** An OS benefit observed for tebentafusp among mUM patients who have initial radiographic progression demonstrates that RECIST assessment underestimates benefit. In a post-hoc analysis of OS following initial radiographic progression, continued treatment with tebentafusp was associated with numerically longer OS after adjusting for key prognostic variables. Tebentafusp treatment beyond progression was tolerated without new safety signals and, in some patients, was associated with radiological stabilization of sum of target lesions for > 3 months following the initial progression. Clinical trial information: NCT03070392. Research Sponsor: Immunocore.

9586 **Poster Session**

Randomized phase II study of adjuvant sunitinib or valproic acid in high-risk patients with uveal melanoma: The final analysis of cohort 1. *First Author: Rino S. Seedor, Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA*

Background: Despite successful treatment of primary uveal melanoma (UM), tumors with monosomy 3 and 8q amplification (M3 + 8q amp) or DecisionDx-UM Class 2 have high metastatic death rates. We report the final analysis of Cohort 1 in the randomized phase II clinical trial of 6 months of adjuvant sunitinib or valproic acid (VPA) in high-risk UM patients. **Methods:** High risk for systemic metastasis was defined as the following: A) M3 + 8q amp; B) Class 2. Patients within 6 months of initial treatment of primary UM were randomized 1:1 to receive either sunitinib 25 mg daily or VPA 750 mg daily for 6 consecutive months. The primary endpoint was to evaluate the improvement of 2-year overall survival (OS) rate from 70% (historical references) to 85% in each arm. Secondary endpoints included 1) systemic relapse-free survival (RFS) rate at 18 months, 2) ability to complete adjuvant treatment and, 3) toxicity assessment. **Results:** Eighty-eight patients were included in the final analysis. There were no differences in tumor size or T stage between the two treatment arms. Nine of 45 patients in the sunitinib arm and 4 of 43 patients in the VPA arm could not complete the 6-month treatment due to toxicity (sunitinib n = 6, VPA n = 2) or systemic progression (sunitinib n = 3, VPA n = 2). All but 9 patients (death due to metastasis, sunitinib n =4, VPA n = 5) were followed for at least 2 years. With a median follow-up of 52.6 months, both drugs met the primary end point with 2-year OS rates of 95.6% (sunitinib, 90% CI 86.5-98.6%) and 90.7% (VPA, 90% CI 80.1-95.8%). The 18-month RFS rates were 75.6% (sunitinib, 90% CI 63.1-84.3%) and 62.8% (VPA, 90% CI 49.4-73.5%). Although not statistically significant, there was a trend of superior RFS with sunitinib over VPA in primary UM with T-stage 3-4 (p=0.131) or >12mm (p=0.129). There was no significant difference in median RFS in HLA-A*02:01 positive or negative status (24.6 vs. 24.8 months). It is of note that the potential survival benefit of sunitinib over VPA diminished after 3 years, indicating longer duration of sunitinib administration might be required. In the multivariable Cox analysis, the RFS was not significantly different in the two treatment arms, but increase of tumor diameter was associated with increase hazard of progression (HR=1.23, 95% CI: 1.13, 1.33; p<0.001). **Conclusions:** Six months of adjuvant sunitinib or VPA resulted in 2-year OS of 95.6% and 90.7%, respectively, meeting the primary endpoint of the study. Sunitinib showed a tendency for a better outcome until 3 years after randomization, thus Cohort 2 was created to investigate the safety and prolonged improvement of RFS and OS with 12 months of sunitinib. Additionally, Cohort 3 with adjuvant sunitinib in combination with VPA for 12 months is currently ongoing. The size of primary tumor influenced the survival and should be adjusted for future adjuvant studies. Clinical trial information: NCT02068586. Research Sponsor: Pfizer Inc., Institutional funds at Thomas Jefferson University.

9587 **Poster Session**

The association between mediators of the receptor for advanced glycation end product (RAGE) axis and immune checkpoint inhibitor (ICI)–induced colitis in patients with melanoma. *First Author: Morgan Simons, NYU Grossman School of Medicine, New York, NY*

Background: Colitis and other gastrointestinal (GI) toxicity are a frequent and occasionally severe form of immune-related adverse events (irAEs) in patients treated with ICIs. To date, no definitive mechanism has been identified, and this area remains an active field of investigation. We hypothesized that activation of the RAGE axis, known to be implicated in inflammatory bowel disease through stimulation of signal transduction targeted by pro-inflammatory RAGE ligands, members of the S100 family and High Mobility Group Box 1 (HMGB1), might be associated with irAE- colitis. **Methods:** We examined sera from 111 advanced melanoma patients prospectively accrued and followed up at NYULH (treated with anti-PD-L1, n = 44; antiCTL4, n = 23; and combination, n = 44). 24 (22%) developed GI toxicity grade >2. Serum biomarkers of the ligand-RAGE pathways, soluble (s)RAGE, endogenous secretory (es)RAGE, S100B, and HMGB1, were measured in the patients' sera during ICI treatment. Multivariable ordinal logistic regression analyses with all grades of GI toxicity as the primary outcome for all the recorded covariates (including serum biomarkers, clinical covariates) were performed. We then used ordinal multivariable logistic regression with stepwise variable selection. Similar analyses with GI toxicity as a binary outcome ((≥grade 1 vs no toxicity) were also conducted. Only those variables that jointly contributed to the odds of developing toxicity were included in the final stepwise model. No adjustments for multiplicity were included. As sRAGE and esRAGE are highly correlated (r = 0.86), esRAGE concentrations were not used in the joint models. **Results:** A significant association between GI toxicity and concentrations of sRAGE and S100B was identified. The final stepwise multivariable logistic model includes only sRAGE and S100B. The odds of having a one level increase in GI toxicity grade increase 1.100 times (95% CI: 1.008, 1.199; p = 0.029) for each unit decrease of sRAGE (= sRAGE/100). The odds of a one level increase in GI toxicity increase 1.059 times (95% CI: 1.004, 1.116; p = 0.035) for each unit increase of S100B (= s100B/100). All other analyses yielded comparable results. In contrast, concentrations of HMGB1 and other clinical covariates, including response and treatment category, were not associated with GI toxicity. **Conclusions:** Mediators of the RAGE axis, specifically sRAGE and S100B, might have a role in GI toxicity in patients receiving ICIs. The ligand-RAGE axis may be a novel target for irAE therapies for patients receiving ICIs to mitigate the severity of GI toxicity. Research Sponsor: None.

9588 **Poster Session**

A qualitative exploration of melanoma awareness and prevention among Latinx and non-Latinx White populations in urban and rural California. *First Author: Susan M. Swetter, Stanford University Medical Center and Cancer Institute, Stanford, CA*

Background: Melanoma mortality rates remain high among individuals of lower socioeconomic (SES) status, and racial/ethnic minorities, despite rates declining in non-Latinx whites (NLW). To improve understanding about the factors contributing to inequities in melanoma prevention and care, a qualitative exploratory study was conducted in Northern and Southern California regarding awareness, prevention, and early detection of melanoma in lower SES NLW and Latinx populations living in urban and semi-rural areas. **Methods:** Nineteen focus group (n = 176 individuals: 77% female, 59% self-identified Latinx/Hispanic, and 40% Medi-Cal/state insurance recipients) were conducted with adult participants, stratified by race/ethnicity (Latinx, low-income NLW), geography (semi-rural, urban), and language (English and Spanish). The interview topics included: 1) awareness and views of melanoma risk, prevention, and early detection screening practices; 2) acceptability of primary and secondary prevention strategies in their respective community; and 3) barriers and facilitators of engagement in melanoma prevention and care. Using a hybrid inductive and deductive approach, thematic analysis was used for data analysis. Findings were organized within a socioecological model (individual, interpersonal, community and health system/policy level). **Results:** Individual level findings revealed that many participants were not familiar about melanoma yet were willing to learn through trusted sources. Brown or darker skin tones were perceived as having less risk for skin cancer. Interpersonally, social relationships were important influences for individuals practicing skin cancer prevention. However, for several Latinx and semi-rural participants, conversations about melanoma prevention did not occur with family and peers. At the community level, semi-rural participants reported distance or lack of transportation to a clinic as challenges for dermatology care access. Healthcare systems barriers included burdens of additional medical care costs and obtaining dermatology referral. Many participants were in support of health regulations and education that reduce skin cancer risks for outdoor workers and children. **Conclusions:** Varying and intersecting factors influence melanoma awareness, and behaviors associated with knowledge, prevention, and early detection of melanoma in low-income NLW and Latinx individuals and in those living in semi-rural areas. Our findings promote understanding of how barriers across the socioecological spectrum may affect melanoma prevention and early detection particularly among men, individuals of lower socioeconomic status, and Latinx individuals. The study results have implications for health education interventions, which can involve health navigation strategies for individuals and families. Research Sponsor: Mary E. Brenneisen Fund at Stanford Medicine, U.S. National Institutes of Health.

TPS9589 **Poster Session**

Randomized phase 3 trial of IO102-IO103 plus pembrolizumab versus pembrolizumab alone in patients with previously untreated, unresectable, or metastatic melanoma. *First Author: Inge Marie Svane, National Center for Cancer Immune Therapy, CCIT-DK, Copenhagen University Hospital, Herlev, Denmark*

Background: The treatment of melanoma has improved markedly with the emergence of new immune therapies, and both anti-PD-1 monotherapy and the combination of the anti-PD-1 antibody nivolumab and anti-CTLA-4 therapy ipilimumab are now considered standard-of-care in the unresectable or metastatic (advanced) melanoma setting. However, many patients have primary or acquired resistance to these therapies, thereby underpinning the need for more effective approaches. IO102-IO103 is a potentially first-in-class, dual-antigen, immune-modulatory therapy targeting the key cancer immune resistance pathways mediated by IDO and PD-L1. The ability of IO102 and IO103 to respectively activate the specific T cells that recognize these checkpoint molecules and directly modulate immune regulation has previously been demonstrated both preclinically and in human clinical trials. A synergistic anti-tumor response upon treatment against both IDO and PD-L1 has also previously been demonstrated in a preclinical model where IDO and PD-L1 were expressed by different cells in the tumor microenvironment. Due to the distinctive mechanisms of action of IO102-IO103 and anti-PD-1 antibodies, there may be a further synergistic effect when treatment is combined. A previous Phase 1/2 trial investigating the use of IO102-IO103 plus nivolumab in patients with anti-PD-1-naïve metastatic melanoma has demonstrated promising anti-tumor activity with an overall response rate (ORR) of 80%, median progression-free survival (PFS) of 26 months and a manageable safety profile (NCT03047928; Kjeldsen et al, Nat Med 2021). **Methods:** This is a Phase 3, multicenter, open-label, randomized, 2-arm trial investigating the efficacy and safety of IO102-IO103 plus pembrolizumab versus pembrolizumab alone (EudraCT: 2021-004594-32; ClinicalTrials.gov No: NCT05155254). Inclusion criteria include: adult patients with untreated, unresectable (Stage III), or metastatic (Stage IV) melanoma; > 6 months since last dose of (neo)adjuvant treatment with targeted or immune therapy (in those previously treated); and ≥1 measurable lesion by RECIST v1.1. Primary endpoint is PFS by blinded independent central review. Secondary endpoints include ORR, durable response rate, complete response rate, duration of response, time to response, disease control rate, overall survival, and safety/tolerability. Target enrollment is 300 patients at > 100 sites in 20 countries. Patients are randomized 1:1 to receive either pembrolizumab 200 mg intravenously (IV) every 3 weeks up to 2 years or pembrolizumab 200 mg IV every 3 weeks up to 2 years with dual-antigen IO103-IO102 85-85 μg and Montanide adjuvant subcutaneously on Day 1 and 8 of cycle 1 and 2 and on Day 1 of each cycle thereafter. Enrolment for the study is ongoing. Clinical trial information: EudraCT: 2021-004594-32; ClinicalTrials.gov No: NCT05155254. Research Sponsor: IO Biotech ApS & Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

TPS9590 **Poster Session**

First-in-human clinical trial of an oncolytic adenovirus armed with TNFa and IL-2 in patients with advanced melanoma receiving adoptive cell transfer of tumor-infiltrating lymphocytes. *First Author: Inge Marie Svane, National Center for Cancer Immune Therapy, CCIT-DK, Copenhagen University Hospital, Herlev, Denmark*

Background: The long-term complete remission experienced by some cancer patients after receiving immunotherapies, such as adoptively transferred tumor-infiltrating lymphocytes (ACT-TIL), represent the ideal outcome to pursue for the development of therapies for oncology. At the same time, those responses are limited to a minority of treated patients, and adverse events resulting from preconditioning chemotherapy and postconditioning IL2 are a rather common scenario. TILT-123 is an oncolytic adenovirus (Ad5/3-E2F-D24-TNFa-IRES-IL2) designed to enable T-cell therapies and checkpoint inhibition against cancer. Ultimately, the aim of this approach is to expand the proportion of patients benefiting from immunotherapies. Extensive preclinical studies with this technology showed that the virus repolarizes the tumor's immune microenvironment in a way that favors T-cell presence and their activity against tumor cells. When TILT-123 was used together with TILs in preclinical in vivo models, animals had a higher chance to display curative results while showing reduced toxicity as the use of TILT-123 replaces the pre and post conditioning (Havunen R. et al Mol Ther Oncolytics 2016, Santos J.M. Mol Ther 2018). A Phase I clinical trial (NCT04217473) is ongoing to evaluate safety of the approach in advanced melanoma patients. Extensive biological assays of patient aim to characterize viral transduction of tumors through the intravenous and intratumoral routes, and the recruitment of activated lymphocytes to tumors in order to elucidate the immunological impact of the drug. **Methods:** The primary aim of NCT04217473 is to evaluate safety of TILT-123 in advanced melanoma patients. Refractory or recurrent stage III/IV patients, which cannot be treated with curative intent with available therapies, and are eligible for ACT-TIL therapy, can potentially participate in the study. TILT-123 administration begins while the manufacturing of ACT-TILs takes place and continues after the TIL-therapy is administered to the patient. In contrast with standard ACT-TIL therapy, patients are not conditioned with lymphodepletion or IL-2 in this approach. Patients must present at least one biopsiable/operable tumor for the generation of TILs and another injectable lesion for intratumoral administration of TILT-123. The open label, dose escalation trial has the main endpoint of establishing TILT-123 safety by day 36 (prior to TIL administration), which is based on the incidence of adverse events, severe adverse events, vital signs, ECG, and safety laboratory results. Secondary endpoints include safety and tolerability after TIL therapy has been administered, evaluation of antitumor responses and studies of tumor immune repolarization. Cohorts 1-3 have been completed without DLTs. Enrollment in cohort 4 was initiated in December 2021. Clinical trial information: NCT04217473. Research Sponsor: TILT Biotherapeutics Ltd.

TPS9591 **Poster Session**

A phase II study of biomarker-driven early discontinuation of anti–PD-1 therapy in patients with advanced melanoma (PET-Stop): ECOG-ACRIN EA6192. *First Author: Geoffrey Thomas Gibney, Georgetown-Lombardi Comprehensive Cancer Center, Washington, DC*

Background: In patients (pts) with advanced, metastatic melanoma (aMM) anti-PD-1 monotherapy and anti-PD-1/anti-CTLA-4 combination regimens yield durable responses, yet the optimal therapy duration remains unclear. Most prospective studies have treated responding pts for at least 2 years unless there has been a prohibitive treatment related adverse event (TRAE). Durable treatment-free survival has been observed in pts where anti-PD-1 therapy is discontinued after short courses due to TRAEs. Biomarkers are needed to define which pts may safely discontinue anti-PD-1 therapy in order to reduce financial toxicity and risk of late TRAEs, and to improve quality of life. ^{18}FDG-PET/CT scan and tumor biopsy may better assess for active residual disease and identify pts who can safely discontinue treatment. A retrospective study at G-LCCC demonstrated responding pts with aMM who elected to discontinue their anti-PD-1 therapy (median treatment duration 12 months) after a negative PET/CT scan and/or tumor biopsy had event free survival (EFS) of 95% at 3 years (Gibney et al JITC 2021). We hypothesize that pts with disease control by CT scan after 12 months on anti-PD-1 therapy can be safely discontinued from treatment if no hypermetabolic activity on PET/CT scan or negative biopsy for active disease. **Methods:** EA6192 is a multicenter phase II study to evaluate the EFS after discontinuation of anti-PD-1-based therapy in aMM pts with PET/CT scan and/or biopsy that is negative for active disease. Pts with unresectable stage IIIB-IV aMM treated with nivolumab/ipilimumab (nivo/ipi), nivo, pembrolizumab (pembro), or pembro/ipi are eligible. Pts with uveal melanoma are excluded. Pts must receive 52 weeks of therapy, have disease control (CR, PR or SD by imRECIST) and no prohibitive TRAEs. Eligible pts undergo screening including ^{18}FDG-PET/CT scan at 52 weeks (+/- 2 weeks) from start of anti-PD-1 therapy. Pts with hypermetabolic tumor site(s) undergo biopsy. Pts with non-hypermetabolic PET/CT scan or negative biopsy are assigned to Arm A and are monitored off active treatment. Pts with hypermetabolic PET/CT scan and positive or non-feasible biopsy are assigned to Arm B and remain on active treatment for another 48 weeks. Restaging scans are performed every 12 weeks. Arm B pts with disease control undergo a second PET/CT scan and biopsy, and then are monitored off active treatment. 150 patients are planned for accrual. The primary objective is to accurately define the 12-month EFS rate of Arm A, distinguishing between the null and alternative hypotheses of 12-month EFS rate of 88% and 95% with 92% power and one-sided type 1 error rate of 0.072. Secondary and exploratory objectives include assessment of pathologic response, EFS for Arm B, overall survival, incidence of late TRAEs, and correlative biomarker studies. This study is actively enrolling pts. Clinical trial information: NCT04462406. Research Sponsor: U.S. National Institutes of Health.

TPS9592 **Poster Session**

C-POST protocol update: A phase 3, randomized, double-blind study of adjuvant cemiplimab versus placebo post-surgery and radiation therapy (RT) in patients (pts) with high-risk cutaneous squamous cell carcinoma (CSCC). *First Author: Danny Rischin, Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia*

Background: CSCC is the second most common skin cancer with an estimated incidence of 1 million cases per year in the US. While the surgical cure rate for CSCC is > 95%, some pts have high risk of recurrence as assessed by immune status, primary disease stage, extent of nodal involvement, presence of extracapsular extension (ECE), and prior treatment. Postoperative RT is recommended for these pts but relapse with locoregional recurrence or distant metastases may still occur. C-POST is evaluating the efficacy of cemiplimab as adjuvant therapy for pts with high-risk CSCC. Here, we provide summary of the most recent study protocol amendment. **Methods:** C-POST is a randomized, placebo-controlled, double-blind, multicenter Phase 3 study to evaluate cemiplimab as adjuvant treatment for pts with high-risk CSCC, based on surgical and clinicopathologic findings, who completed surgery and postoperative RT (minimum total dose 50Gy, within 10 weeks before randomization) (NCT03969004). Pts with at least one of the following high-risk features are eligible: (1) nodal disease with (a) ECE and at least one node ≥20 mm or (b) at least three lymph nodes positive on surgical pathology report, regardless of ECE; (2) in-transit metastases; (3) T4 lesion; (4) perineural invasion; and (5) recurrent CSCC with at least one other risk factor. Pts with CSCC involvement in at least three lymph nodes (feature 1b) were added to the eligibility criteria, as this group was found to be at similar risk of CSCC recurrence as the initially planned study population. Protocol amendment now allows patients with chronic lymphocytic leukemia (CLL) who are not on active treatment to be enrolled. The study has two parts. In Part 1 (blinded), pts are randomly assigned 1:1 to receive cemiplimab 350 mg or placebo intravenously every 3 weeks for 12 weeks, followed by cemiplimab 700 mg or placebo every 6 weeks for 36 weeks. In optional Part 2 (unblinded), pts in the placebo arm who experience disease recurrence and pts in the cemiplimab arm who experience disease recurrence ≥3 months after completion of 48-week treatment in Part 1 are eligible to receive open-label cemiplimab for up to 96 weeks. The trial is expected to enrol 412 pts from about 100 sites in North and South America, Europe, and Asia-Pacific regions. Key primary objective is to compare disease-free survival; secondary objectives include evaluating overall survival, freedom from locoregional relapse, and distant relapse with adjuvant cemiplimab versus placebo in patients with high-risk CSCC. This study is once again open for enrolment following interruptions owing to the COVID-19 pandemic. Clinical trial information: NCT03969004. Research Sponsor: Regeneron Pharmaceuticals, Inc., and Sanofi.

TPS9593 **Poster Session**

A randomized, controlled, open-label, phase 2 study of cemiplimab ± RP1 in patients with advanced cutaneous squamous cell carcinoma (CERPASS). *First Author: Andrew Mark Haydon, The Alfred Hospital, Melbourne, VIC, Australia*

Background: RP1 is an oncolytic virus (HSV-1) that expresses a fusogenic glycoprotein (GALV-GP R-) and granulocyte macrophage colony stimulating factor (GM-CSF). In preclinical studies, RP1 induced immunogenic tumor cell death and provided potent systemic anti-tumor activity, which is further improved by combining anti-PD-1 therapy. The prognosis for advanced and metastatic cutaneous squamous cell carcinoma (CSCC) remains poor for many patients despite the adoption of cemiplimab and pembrolizumab as a standard treatment. Preliminary results from IGNYTE, a phase I/II clinical study of RP1 in combination with nivolumab showed a high rate of deep and durable responses in patients (pts) with CSCC. This study is evaluating the efficacy and safety of cemiplimab ± RP1 versus cemiplimab alone in advanced CSCC. **Methods:** This global, multicenter, randomized phase 2 study is enrolling pts with metastatic or unresectable, locally advanced CSCC who are not candidates for/refuse surgery and/or radiation therapy. Key eligibility criteria include no prior treatment with anti-PD1/PD-L1 antibodies or oncolytic viruses. The clinical trial is enrolling approximately 180 pts from centers in the EU, Australia, Canada, and USA. Pts are randomized in a 2:1 ratio to receive combination therapy or monotherapy respectively. Pts receive 350 mg of cemiplimab intravenously (IV) Q3W for up to 108 weeks. In the RP1 + cemiplimab arm, RP1 is injected intratumorally at a starting RP1 dose of 1×10^6 plaque-forming units (PFU)/mL alone, followed by up to 7 doses of RP1 at 1×10^7 PFU/mL Q3W together with the same dose of cemiplimab. Pts in the combination arm may receive up to 8 additional RP1 doses if protocol specific criteria are met. No crossover is allowed. Pts are stratified by disease status (nodal or distant metastatic or locally advanced CSCC) and prior systemic therapy. Tumor assessments are performed every 9 weeks. The dual independent primary endpoints are overall response rate and complete response rate, both by a blinded independent review. Secondary endpoints include safety, progression-free survival, duration of response, and overall survival. Exploratory endpoints include quality of life, and immune biomarker analyses. This trial is currently enrolling pts. Clinical trial information: NCT04050436. Research Sponsor: Replimune Group Inc.

TPS9594 **Poster Session**

DELTA-1: A global, multicenter, phase 2 study of ITIL-168, an unrestricted autologous tumor-infiltrating lymphocyte (TIL) cell therapy, in adult patients with advanced cutaneous melanoma. *First Author: Brian Gastman, Cleveland Clinic Lerner College of Medicine, Cleveland, OH*

Background: Patients (pts) with advanced (unresectable or metastatic) cutaneous melanoma and persistent disease after checkpoint inhibitor therapy have poor outcomes and limited treatment options, highlighting a significant unmet medical need (Schadendorf D et al. *Lancet.* 2018;392:971-984). Investigational autologous TIL cell therapies have shown promise in this population, partly attributable to their intrinsic and patient-specific antitumor activity (Borch TH et al. *J Immunother Cancer.* 2020;8:e000668). Made from each patient's digested and cryopreserved tumor, ITIL-168 is an autologous TIL cell therapy manufactured to offer an unrestricted T-cell receptor repertoire. A single-center, compassionate use clinical series demonstrated the feasibility and clinical utility of an earlier version of ITIL-168, with a high overall response rate among pts previously treated with PD-1 inhibitor (PD-1i) therapy (58%, n = 12; Pillai M et al. *Ann Oncol.* 2021;32[suppl 5]:S882). DELTA-1 (NCT05050006) is a global, multicenter phase 2 study to evaluate efficacy and safety of ITIL-168 in pts with cutaneous melanoma relapsed or refractory to a PD-1i, pts intolerant to a PD-1i, and pts whose current best response to a PD-1i is stable disease. **Methods:** Pts aged ≥18 years with histologically confirmed advanced cutaneous melanoma, ECOG performance status 0-1, and adequate organ function will be enrolled in 1 of 3 cohorts. Cohort 1 (n≈80) will include pts who relapsed after or were refractory to ≥1 prior line of systemic therapy, including a PD-1i and, if *BRAF*-mutated, a BRAFi ± MEKi. Cohorts 2 and 3 (n≈25 each) will include pts intolerant to PD-1i and those with stable disease after ≥4 doses of PD-1i, respectively. After tumor resection for TIL harvest, pts must have ≥1 remaining measurable lesion per RECIST 1.1. Pts with uveal, acral, or mucosal melanoma, prior allogeneic transplant or cell therapy, and with central nervous system (CNS) disorder or symptomatic and/or untreated CNS metastases are ineligible. Pts will receive 5 days of lymphodepleting chemotherapy (cyclophosphamide ×2 days overlapping with fludarabine ×5 days) followed by a single ITIL-168 infusion ($\geq 5 \times 10^9$ cells) and supportive short-course, high-dose IL-2. The primary endpoint is objective response rate (ORR) per central review. Secondary endpoints include duration of response, progression-free survival, overall survival, disease control rate, TIL persistence, and safety. Hypothesis testing of ORR will be performed for cohort 1. The primary analysis will occur when all pts in the cohort 1 modified intent-to-treat population have been followed for ≥6 months after the first posttreatment disease assessment. DELTA-1 opened for enrollment in September 2021. Updated site information will be given at the time of presentation. Clinical trial information: NCT05050006. Research Sponsor: Instil Bio, Inc.

TPS9595 **Poster Session**

Optimization of Voyager V1 (VV1) oncolytic virus systemic delivery in combination with cemiplimab and ipilimumab in patients with melanoma and non–small cell lung cancer (NSCLC). *First Author: Jose Lutzky, University of Miami Sylvester Comprehensive Cancer Center, Miami, FL*

Background: There is a need for novel immunotherapies to address the patient population that never or no longer responds to immune checkpoint inhibitors (CPI). VV1 is an oncolytic vesicular stomatitis virus engineered to express human interferon beta (IFNβ) to enhance cellular anti-tumor immune responses and tumor selectivity. Phase 1 studies demonstrated VV1 anti-tumor activity in several malignancies with or without a CPI. We are exploring ways to optimize VV1 efficacy in combination with cemiplimab, an anti-PD1 antibody approved for lung, basal and squamous cell skin cancers. Recent clinical data support a 5-fold higher dose of VV1 than was previously explored, and pre-clinical data show synergy between the oncolytic and an anti-CTLA4 antibody, in addition to cemiplimab, supporting exploration of a triplet. What was originally a five-arm study of intravenous (IV) VV1 in combination with IV cemiplimab has been amended to focus on 2 means of optimizing efficacy: use of a higher dose of VV1 and triplet combination in proof-of-concept populations. **Methods:** We are now enrolling pts with advanced melanoma (after progression on anti-PD1) and plan to include 1st-line NSCLC pts with PD-L1 expression ≥50%. The study is first exploring the preliminary anti-tumor activity, safety, and immunogenic activity of the combination of IV VV1 at a dose of 1.0×10^{11} $TCID_{50}$ once on D1 followed by IV cemiplimab Q3W starting on D8, or the same regimen with an additional intratumoral injection of VV1 1.0×10^9 $TCID_{50}$ once on D1 for pts with accessible lesions. Pts receive IV cemiplimab Q3W until confirmed disease progression or intolerable toxicity. Once at least 6 pts have been treated with acceptable safety across the 2 melanoma doublet cohorts using this higher dose of VV1, a 3rd melanoma cohort will open to add a single dose of ipilimumab 50 mg on D1 (all IV triplet). Once 6 melanoma pts have received the triplet safely, the 1st-line NSCLC cohort will open. All cohort decisions are guided by a Data Review Committee. Cohorts will be expanded based on a Simon 2-stage design using a type I error rate of 0.05 and power of 85%. Null ORR is 10% with a target of 35% for 2nd line melanoma and null ORR is 40% in 1st line NSCLC with a target of 70%. Each melanoma cohort will require a response in ≥2 of 10 pts in the 1st stage to add 11 more in the 2nd stage, while NSCLC will first need 5/9 evaluable pts to respond, then an additional 13 to complete the design. Response is assessed at week 7 then Q9W per RECIST v1.1. The study includes serial biopsies in ≥3/10 pts in Stage 1 of each of the IV melanoma cohorts (doublet and triplet therapy), all pts in Stage 2 of these IV melanoma cohorts, and all pts in both Stage 1 and Stage 2 of the IV/IT melanoma cohort, to permit a thorough investigation of the impact of the 3 immunotherapies under investigation. The study is currently ongoing in the USA. Clinical trial information: NCT04291105. Research Sponsor: Vyriad and Regeneron.

TPS9596 **Poster Session**

ATTAC-MCC: Phase I/II study of autologous CD8+ and CD4+ transgenic T cells expressing a high affinity MCPyV-specific TCR combined with checkpoint inhibitors and class I MHC-upregulation in patients with metastatic MCC refractory to PD-1 axis blockade. *First Author: Joshua Veatch, Hutchinson Cancer Rsrch Ctr, Seattle, WA*

Background: Merkel cell carcinoma (MCC) is a highly aggressive skin cancer, with an incidence that has doubled in the last 20 years to approximately 3000 cases/year in the US. Over one-third of patients will develop widespread disease, and survival in these patients has been historically poor with a 5-year survival rate of < 10%. MCC is highly immune-sensitive due to the antigenicity of the cancer-causing Merkel cell polyomavirus (MCPyV) expressed in most MCC tumors. Although immune checkpoint inhibitors (ICIs) targeting the PD-(L)1 axis show promising efficacy, most MCC patients will eventually relapse. There is no standard of care for patients that become refractory to ICIs. We hypothesize that cellular immune therapies targeting MCPyV may provide additional clinical benefit to these patients. To test this, we have engineered high-affinity TCR T cells against MCPyV and initiated a clinical trial. **Methods:** NCT03747484 is an ongoing phase I/II, open label, investigator-initiated trial (IIT) of FH-MCVA2TCR in combination with an anti-PD-(L)1 checkpoint inhibitor and an agent to upregulate MHC-I expression on tumor cells. The trial is conducted in patients aged 18 years or older with metastatic or unresectable, histologically confirmed virus-positive MCC whose disease has progressed on or after treatment with a PD-(L)1 axis checkpoint inhibitor. Patients undergo leukapheresis to collect white blood cells (WBCs) for TCR T cell product manufacturing. The cell product is administered on day 0. Patients receive an agent to upregulate MHC-I on tumor cells and continue on an anti-PD-(L)1 checkpoint inhibitor for up to one year. In phase I, three patients receive up to two infusions of dose level 1 of the T cell product. The primary objectives of phase I are to determine safety and tolerability based on dose-limiting toxicities (DLT) during an observation period of 28 days after the first infusion. Phase II enrolls patients at dose level 2. The total sample size of phase II is 12 patients. The first three patients are enrolled in a staggered manner and observed for DLTs. If no DLTs occur, the remaining sample size is accrued in open enrollment. The main objectives of phase II are safety based on number of adverse events and preliminary efficacy based on tumor response according to RECISTv1.1 and iRECIST. Secondary/exploratory objectives include cellular kinetics of TCR T cells, T cell phenotype, tumor infiltration kinetics, and MHC-I expression dynamics over time. After the first 12 months, patients transition to a long-term follow-up (LTFU) study for up to 15 years as per FDA guidelines. Clinical trial information: NCT03747484. Research Sponsor: Affini-T Therapeutics, Inc.

TPS9597 **Poster Session**

An open-label, multicenter, phase 1b/2 study of RP1, a first-in-class, enhanced potency oncolytic virus in solid organ transplant recipients with advanced cutaneous malignancies (ARTACUS). *First Author: Michael Robert Migden, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: RP1 is an oncolytic virus (HSV-1) that expresses a fusogenic glycoprotein (GALV-GP R-) and granulocyte macrophage colony stimulating factor (GM-CSF). In preclinical studies, RP1 induced immunogenic tumor cell death and provided potent systemic anti-tumor activity. Clinical data in combination with nivolumab has demonstrated a high rate of deep and durable response in patients with advanced skin cancer. Solid organ transplantation (SOT) is an important lifesaving procedure for patients with a wide range of end-organ diseases, but requires patients (pts) to undergo lifelong immunosuppression to prevent allograft rejection, and skin cancers (SCs) – including cutaneous squamous cell carcinoma (CSCC) – are common post-transplant malignancies. SC in SOT pts is generally managed with surgical resection, radiation therapy, and chemotherapy or targeted therapy. The use of immune checkpoint inhibitors in SOT recipients has improved outcomes but is associated with a high risk of allograft rejection. Thus, there is a high unmet need for a safe and effective treatment that also protects pts from allograft rejection. The objective of this study is to assess the safety and efficacy of single-agent RP1 in SOT patients with SCs, with a focus on CSCC. **Methods:** This study will enroll up to 65 evaluable SOT pts with locally advanced or metastatic SCs. The study has two parts. In Part A, pts will receive an initial dose of 1 x 10^6 plaque-forming units (PFU) of RP1. Two weeks later they will receive 1 x 10^7 PFU of RP1 and continue every two weeks until pre-specified study endpoints are met. In Part B, after determining the safety and tolerability in the initial cohort with kidney and liver transplants, the study may also enroll heart and lung transplant recipients. RP1 will be administered by intra-tumoral injection, utilizing image guidance as clinically appropriate. Key inclusion criteria are pts with confirmed recurrent, locally advanced or metastatic CSCC and up to 10 pts with non-CSCC SC, stable allograft function and ECOG performance status of ≤1. Pts with prior systemic anti-cancer treatment are allowed. Key exclusion criteria are prior treatment with an oncolytic therapy, active herpetic infections or prior complications of HSV-1 infection and a history of organ graft rejection within 12 months. The primary objective of the trial is to assess efficacy determined by objective response rate and safety of single agent RP1. Additional secondary endpoints include duration of response, complete response rate, disease control rate, progression-free survival and overall survival. Clinical trial information: NCT04349436. Research Sponsor: Replimune Group Inc.

TPS9598 **Poster Session**

Early together: A randomized phase III study of early palliative care in metastatic uveal melanoma (MUM). *First Author: Sophie Piperno-Neumann, Medical Oncology Department, Institut Curie, Paris, France*

Background: Uveal melanoma is a rare cancer. Up to 50% of patients (pts) develop metastasis, mainly hepatic. Overall survival in metastatic pts is 12 months (mo), contrasting with a good overall condition until death. To evaluate the impact of integrating early palliative care on patient needs and self-efficacy, we designed a comparative randomized trial in MUM pts. **Methods:** 162 pts will be randomized (1:2) between the control and the experimental groups in two French centres (Institut Curie-Paris and Centre Antoine Lacassagne-Nice). In the control group, palliative care is introduced according to international guidelines. In the experimental group, it is added earlier, concomitant to the announcement of metastases by the medical oncologist. The main objective is to assess if early supportive care impacts on patient psychological needs at 6 mo, versus standard of care, based on the SCNS-SF34 questionnaire. Secondary objectives include patient's other needs at 6 and 12 mo, quality of life (QLQ-C30), progression-free and overall survival, and partners' needs (SCNS-P&C). MUM pts, suitable for a treatment with no curative intent, ECOG PS 0-1, with no physical or biological sign of disease, and capable of filling questionnaires are eligible. Questionnaires are completed by all pts at each oncological visit (baseline, 3, 6, 9 and 12 mo). Supportive care visits take place every 6 weeks if needed and address patient's information needs, disease and treatment understanding, social and psychological status, symptoms, and partners' involvement. Prognostic uncertainty and disease seriousness in the absence of symptom is addressed depending on pts' expressed needs. Medical oncologists and supportive care physicians from both centres attend communication skill training provided by an expert during the study. Analyses: SCNS-SF34 psychological needs scale scores at 6-mo will be compared with a Student's t-test, in an ITT analysis. For 10 points mean score difference expected between groups (within standard deviation of 20 points) and a two-sided type 1 error of 5%, inclusion of 54 pts (control group) and 108 pts (experimental group) provides the study 85% of power. The planned inclusion period is 3 years, pts will be followed for one year, for a total study duration of 4 years. From July 2020 to January 2022, 63 pts have been enrolled in the trial; 2 pts declined. Five pts were removed early from the study: one for consent retrieval, 4 for early death due to metastasis. COVID-19 delayed enrollment for 5 months. We plan to complete the study Q4 2023 and to analyze the data Q4 2024. Clinical trial information: NCT04728113. Research Sponsor: Cancéropôle Ile-de-France and INCa SHS-E-P 2019 French national grants, Patients donations.

Questionnaires.	
1	Supportive Care Needs Survey (SCNS-SF34)
2	European Organization for Research and Treatment (EORTC) QLQ-C30
3	Hospital Anxiety and Depression Scale (HADS)
4	Prognosis and Treatment Perceptions Questionnaire (PTPQ)
5	Generalized Self-Efficacy scale (GSE)
6	Supportive Care Needs Survey-Partners & Caregivers (SCNS-P& C)

TPS9599 **Poster Session**

A biomarker-guided Bayesian response-adaptive phase II trial for metastatic melanoma: The Personalized Immunotherapy Platform (PIP) trial design. *First Author: Serigne N. Lo, Melanoma Institute Australia, Faculty of Medicine and Health, The University of Sydney, Sydney, Australia*

Background: Anti-PD1-based immunotherapies have been approved for many cancer types and are now a standard therapy for advanced melanoma. Despite this, ~50% of advanced melanoma patients (pts) fail to respond or eventually progress after response. It is therefore critical to identify pts with a low likelihood of response to anti-PD1-based therapy and efficiently assess activity of rationally-selected alternative novel immunotherapies. **Methods:** We designed this investigator-initiated phase II PIP-Trial to evaluate two consecutive biomarker testing platforms, followed by the activity of rationally selected 5 novel agents in pts with advanced melanoma. Two separate pt populations are included: Part-A) treatment-naïve pts predicted to be resistant to either anti-PD-1 alone or combined with ipilimumab using Biomarker Test-1); and Part-B) pts who had progressed on 1 prior line of PD1-based therapy. Part-A) is a Bayesian adaptive multi-arm multi-stage design using response adaptive randomisation after a burn-in period where pts are randomised to the existing arms with equal probability. From then on, regular interim analyses will be carried out with the objective to either drop poorly performing arms or continue. Part-B) is an open platform without control that combined a selection and an expansion phase to identify best novel agent(s) as second-line therapy. Expansion phase decisions will be based on enrichment for biomarker Test-2. Dropping an arm occurs when the posterior probability of observing a clinically significant effect on the primary outcome (i.e. 6-month RECIST objective response rate (ORR)) is low. The operational characteristics of the design were investigated through simulations considering 4 plausible scenarios with 40% ORR in the control arm (anti-PD1 + Anti-CTLA4). Simulations were based on the upcoming R package BATS. Part-A has at least 85% power to detect a 30% absolute improvement in ORR with respect to the control arm (with a max N = 216 – Table below). Part-B will be able to select two promising treatments in the expansion phase and formally test their efficacy against a minimum ORR of 25% at 80% power (max N = 150). Research Sponsor: The Melanoma Institute Australia, Cancer Institute of New South Wales.

Scenario	Probability of declaring a treatment effective					Average N per arm						Maximum N
	Arm A	Arm B	Arm C	Arm D	Arm E	Control	Arm A	Arm B	Arm C	Arm D	Arm E	
1	0.05	0.04	0.05	0.04	0.04	46	29	28	29	29	29	190
2	0.05	0.05	0.24	0.58	**0.91**	48	25	25	33	40	45	216
3	0.04	0.04	0.04	**0.90**	**0.92**	49	26	25	25	45	46	216
4	0.21	0.21	**0.85**	**0.86**	**0.86**	42	29	29	38	39	39	216

TPS9600 **Poster Session**

Tocilizumab in combination with ipilimumab and nivolumab in solid tumors. *First Author: Noha Abdel-Wahab, Assiut University Hospital, Faculty of Medicine, Assiut, Egypt*

Background: Immune checkpoint inhibitors (ICIs) are approved for multiple malignancies, however, durable remission rates with ICI monotherapy remains low. Combined treatment with anti-CTLA-4 and anti-PD1 has shown higher response rates in several cancers but is associated with up to 60% grade 3/4 immune-related adverse events (irAEs) leading to frequent treatment discontinuation. The need for corticosteroids to control irAEs may further diminish anti-tumor activity. A multi-disciplinary approach using clinical, preclinical, and translational analyses implicated the IL-6/Th17 axis in both ICI-related autoimmunity and resistance. Further, preliminary data showed that targeting interleukin 6 (IL-6) could be an effective approach to reduce irAEs while maintaining and possibly boosting the antitumor immune response. **Methods:** We are conducting a phase II, open-label, single center study to evaluate the use of combination treatment with tocilizumab (toci; anti-IL6), ipilimumab (ipi; anti-CTLA4) and nivolumab (nivo; anti-PD1) as a front-line therapy for patients (pts) with treatment-naïve advanced cutaneous melanoma (cohort 1), urothelial carcinoma (cohort 2), and EGFR mutant non-small cell lung cancer after tyrosine kinase inhibitors failure (cohort 3) (NCT04940299). Ten pts per disease site will be enrolled, plus an additional 25 melanoma pts in an expansion cohort. Key inclusion criteria are age ≥18 years (yrs) and histologically confirmed locally advanced or metastatic disease, with specific eligibility criteria defined for each cohort. Patients with interstitial lung diseases, autoimmune diseases, infection, or conditions requiring immunosuppressive therapies are not eligible, but stable asymptomatic brain mets are allowed. Ipi/Nivo dosing is as per approved disease indications: in cohort 1 &2, ipi 3 mg/kg + nivo 1 mg/kg is administered intravenously (IV) every 3 weeks (wks) for 4 doses then nivo 480 mg/4 wks up to 2 yrs. In cohort 3, IV ipi 1 mg/kg/6 wks + nivo 3 mg/kg/2 wks is administered up to 2 yrs. In all 3 cohorts, subcutaneous (SQ) toci 162 mg/2wks is administered up to 12 wks. Imaging is every 12 wks up to 2 yrs or until dose-limiting toxicities or progression. The primary outcome is safety/tolerability of the triple therapy. The secondary outcomes are antitumor efficacy and overall survival. Additionally, tumor and blood samples are being collected for longitudinal immune analysis, including gene expression and multiplex histochemistry to identify predictive biomarkers of response, resistance, and toxicity. The trial opened in October 2021 and has enrolled 14 patients to date. Clinical trial information: NCT04940299. Research Sponsor: The University of Texas MD Anderson Cancer Center Prioritizing Research Innovation and Mentoring Excellence Award, Other Foundation.

TPS9601 **Poster Session**

Design and rationale of a first-in-human (FIH) phase 1/1b study evaluating KIN-3248, a next-generation, irreversible (irrev), pan-FGFR inhibitor (FGFRi), in adult patients with solid tumors harboring FGFR2 and/or FGFR3 gene alterations (NCT05242822). *First Author: Lipika Goyal, Mass General Cancer Center, Harvard Medical School, Boston, MA*

Background: FGFR1-4 gene alterations are observed in approximately 7% of all human cancers. There are currently 3 FDA-approved, reversible FGFRi for treatment of patients w/previously treated, locally advanced or metastatic (met) cholangiocarcinoma (CCA) harboring FGFR2 gene fusions/rearrangements (pemigatinib and infigratinib) or met urothelial carcinoma (UC) w/susceptible FGFR2 or FGFR3 genetic alterations (erdafitinib). A major limitation of approved and clinical-stage FGFRi is emergence of secondary, on-target resistance mutations (mutn) that reduce duration of response. Up to 67% of CCA patients treated with either reversible or irrev FGFRi exhibit secondary FGFR2 kinase domain resistance mutn at the time of relapse. KIN-3248 is a next-generation, selective, irrev, small molecule pan-FGFRi, structurally designed to inhibit primary FGFR oncogenic alterations as well as secondary kinase domain mutn associated w/disease progression. Preclinically, KIN-3248 has favorable pharmaceutical properties, is well-tolerated with continuous, daily oral administration in 28d GLP toxicology studies in rats and beagle dogs and is efficacious against primary FGFR2 and FGFR3 oncogenic driver alterations as well as secondary FGFR2 resistance mutn (e.g., gatekeeper and molecular brake) in human cancer cell and PDX models *in vitro* and *in vivo*. **Methods:** This is a FIH, multicenter, non-randomized Ph1 study of KIN-3248 in adult pts with advanced & metastatic solid tumors (AMST) harboring FGFR2 and/or FGFR3 gene alterations. KIN-3248 is given po qd continuously in 28-day cycles until drug intolerance or disease progression. Planned sample size is approx. 120 pts: Part A is a dose-escalation to MTD for pts w/AMST having either FGFR2 and/or FGFR3 alterations. Part A assesses single agent KIN-3248; Part B will evaluate a selected dose of KIN-3248 in 3 cohorts of pts (ICC, UC, or other AMST), each driven by specified FGFR alterations. Standard Ph1 enrollment criteria are required (ECOG PS 0-1, normal organ function, prior receipt of standard treatment or medical judgment that such is not appropriate). Pts may have measurable or evaluable disease. Key exclusion criteria include known active brain metastases and active/uncontrolled HBV/HCV. FGFRi-naïve & -pretreated patients are both eligible. Primary endpoints are safety/tolerability (Part A), and preliminary antitumor activity: objective response rate, disease control rate, duration of response, & duration of stable disease (Part B). Secondary objectives include pharmacokinetic and pharmacodynamic assessments including measures of FGFR pathway modulation. Enrollment is expected to commence in April 2022. Clinical trial information: NCT05242822. Research Sponsor: Kinnate Biopharma.

TPS9602 **Poster Session**

Evaluating the impact of perioperative antibiotic prophylaxis on the microbiome in patients with cutaneous malignancy. *First Author: Samuel Cass, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Preoperative antibiotic prophylaxis is commonly used to reduce surgical site infections (SSIs). However, the rate of SSIs following surgical procedures classified as clean is only 2-3%. Overuse of antibiotics is associated with several potential adverse effects, including dysregulation of the gut microbiome. Disruption of the composition and function of the native gut microbiota, referred to as dysbiosis, has been implicated in a number of inflammatory and autoimmune disorders, as well as gastrointestinal (GI) and non-GI cancers. Recent studies have demonstrated that antibiotics have a profound and persistent effect on the gut microbiota, as evidenced by diminished overall abundance and diversity, as well as alteration of community composition that includes a decreased relative abundance of bacteria in the Ruminococcaceae family. In melanoma, diversity of gut microbiota and relative abundance of Ruminococcaceae have been linked to improved survival and enhanced response following immune checkpoint blockade. In this study, we seek to determine the impact of preoperative prophylactic antibiotic use on the gut microbiome in patients following surgery for stage I or II melanoma. **Methods:** In this non-comparative randomized pilot trial, the impact of prophylactic antibiotic use at the time of surgical intervention on gut microbiome diversity and composition will be studied. Patients diagnosed with clinical stage I or II melanoma undergoing wide excision with or without lymphatic mapping and sentinel lymph node biopsy are randomized 1:1 to either receive preoperative cefazolin or no preoperative antibiotics. Stool samples and peripheral blood are collected before surgery, the day of surgery (optional), on post-operative day 3 (optional), and 2 weeks and 3 months following surgery. The primary endpoint for the study is change in microbiome alpha diversity at 2 weeks following surgery. Secondary endpoints are change in relative abundance of microbes at 2 weeks and 3 months after surgery and SSI rates according to whether or not prophylactic antibiotics were administered at time of surgery. Exclusion criteria include recent antibiotic use (within 3 months), allergy to beta-lactam or cephalosporin antibiotics, increased risk of infection due to medical comorbidity or use of immunosuppressive medication. Enrollment began in October 2021. As of January 2022, 22 of 30 patients have been accrued to ensure complete sample collection for 20 patients. Study findings may inform a larger trial evaluating interventions to mitigate antibiotic impact. Clinical trial information: NCT04875728. Research Sponsor: None.

TPS9603 **Poster Session**

DETECTION phase II/III trial: Circulating tumor DNA–guided therapy for stage IIB/C melanoma after surgical resection. *First Author: Rebecca Lee, The Christie NHS Foundation Trust, Manchester, United Kingdom*

Background: Circulating tumor DNA (ctDNA; the tumor derived fraction of circulating free DNA in the blood) is a well recognized, minimally-invasive biomarker of tumor burden/progression in many cancers. We have previously shown in retrospective and prospective cohorts of patients with melanoma that ctDNA analysis of serial blood samples following curative intent surgery can identify minimal residual disease (MRD) or molecular relapse. The majority of patients with resected stage II melanoma do not recur, therefore better strategies to identify high risk patients are required. Furthermore, a consistent finding in studies of immune therapy in stage IV melanoma is that patients with small volume disease have the best outcome. We aim to test whether early relapse can be identified by ctDNA analysis and acted upon in a clinically relevant timeframe, and if early treatment of molecular recurrence with immune therapy improves outcomes for patients with resected stage IIB/C melanoma. **Methods:** We designed a phase II/III multicenter study across 21 UK and 4 Australian sites with a tumor informed approach employed for ctDNA detection. Droplet digital assays for *BRAF/NRAS/TERT* promoter mutations were validated for sensitive ctDNA detection across two accredited clinical testing laboratories. Patients with stage IIB/C melanoma, *BRAF/NRAS/TERT* promoter mutant cutaneous melanoma, ECOG 0/1, adequate organ function, with complete resection (including sentinel lymph node biopsy) performed within 12 weeks and radiological/clinical disease-free status confirmed within 4 weeks prior to registration, no prior immune/targeted therapy will be followed up with blinded ctDNA sampling in addition to clinical follow-up. Patients with ctDNA detected will be randomised 1:1 in a double blind fashion to continue routine follow-up with investigators choice treatment if they develop disease recurrence, or unblinded and treated with nivolumab 480mg IV Q4-weekly. Primary objectives include i) whether MRD/molecular relapse following curative intent surgery can be identified earlier than clinical relapse, ii) whether early treatment of molecular recurrence with nivolumab improves overall survival. 1050 patients are planned to be enrolled. The study opened in the UK in November 2021 and will open in Australia in Spring 2022. Clinical trial information: NCT04901988. Research Sponsor: Cancer Research UK, Other Government Agency.

TPS9604 **Poster Session**

Confirmatory trial of narrower side margin excision for head and neck basal cell carcinoma in the Japanese (East Asian) population: JCOG2005 (J-BASE-MARGIN). *First Author: Yasuhiro Nakamura, Department of Skin Oncology/Dermatology, Saitama Medical University International Medical Center, Saitama, Japan*

Background: Basal cell carcinomas (BCCs), the most common type of skin cancer, frequently occur on the head and neck. Because distant metastases are extremely rare, complete excision with clear margins is the standard treatment for BCCs. In the NCCN Guidelines, the recommended surgical treatment strategies include standard excision with wider margins (> 4 mm) or Mohs surgery or other forms of peripheral and deep en face margin assessment (PDEMA) for head and neck BCCs. However, these strategies are based on studies in the Caucasian population, with BCCs mostly arising as non-pigmented lesions and/or with poorly defined clinical borders. Conversely, in East Asians, most BCCs tend to present as pigmented lesions with well-defined clinical tumor borders. Recent retrospective studies from East Asia have reported positive side margin proportions and local recurrence proportions in BCCs excised with narrower margins that are lower than guidelines-recommended margins. Our previous study investigating 1000 East Asian BCCs also indicated that the estimated positive side margin proportions with 2- and 3-mm surgical margin excision in East Asian BCCs were 3.8% and 1.4%, respectively. Those findings may lead to very limited need for Mohs micrographic surgery or PDEMA in East Asian head and neck BCCs; however, there have been no clinical trials regarding fixed narrower margin excision for those cohorts. **Methods:** This is an investigator-initiated, prospective, multicenter, non-randomized phase III confirmatory trial evaluating the efficacy and safety of narrower surgical margins for the treatment of East Asian patients with head and neck, solitary, primary BCCs with sizes ranging from 3 mm to 20 mm. Eligible patients are aged ≥20 years (≤85 years in men or ≤90 years in women). Narrower margin excisions of 2 mm and 3 mm are applied to BCCs with well-defined clinical borders (cohort A) and poorly defined borders (cohort B), respectively. The primary endpoint is the 5-year local recurrence proportion, and the secondary endpoints are positive side margin proportion and incidence of adverse events. We anticipated an expected 5-year local recurrence proportion of 0.8% in both cohorts and a threshold of 3.3% in cohort A and 4.1% in cohort B. The planned sample size is 410 patients (cohort A, 250; cohort B, 160) to provide a power of 80% with one-sided alpha of 5%, assuming a 5% competing risk of death from other diseases. The planned accrual period is 5 years, and the follow-up period is 10 years; primary analysis will be performed at the completion of 5-year follow-up for all registered patients. The trial began in March 2021, and 225 patients (cohort A, 170; cohort B, 55) have already been enrolled as of January 2022. Clinical trial information: UMIN000043511. Research Sponsor: Japan Agency for Medical Research and Development, Other Foundation.

TPS9605 **Poster Session**

The NADINA trial: A multicenter, randomised, phase 3 trial comparing the efficacy of neoadjuvant ipilimumab plus nivolumab with standard adjuvant nivolumab in macroscopic resectable stage III melanoma. *First Author: Minke W. Lucas, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: Adjuvant treatment with anti-PD1 therapy improves the recurrence free survival (RFS) in resectable stage III melanoma. The Checkmate-238 and KEYNOTE-054 trials respectively reported a 4-year RFS of 52.5% for adjuvant nivolumab and a 3-year RFS of 63.7% for adjuvant pembrolizumab. Despite these improved outcomes, a considerable proportion of patients have a relapse in the years after therapeutic lymph node dissection (TLND). The OpACIN trial showed that neoadjuvant treatment with nivolumab (NIVO) plus ipilimumab (IPI) is feasible and induces a stronger and broader T-cell response. The subsequent OpACIN-neo trial identified 2 cycles of NIVO 3mg/kg + IPI 1mg/kg as a neoadjuvant dosing scheme with decreased toxicity and preserved high pathologic response rates (77%), which was confirmed in the PRADO trial. A favorable 2-year RFS (83,6%) was achieved in the overall OpACIN-neo population, although patients with a pathological partial or non-response have a worse prognosis and may therefore benefit from additional adjuvant therapy. The efficacy of neoadjuvant checkpoint inhibition versus the current standard of adjuvant therapy needs to be confirmed in a phase III trial, before neoadjuvant therapy can be considered as a standard option for this patient population. **Methods:** This international, randomized phase 3 trial aims to compare the efficacy of neoadjuvant IPI + NIVO with adjuvant NIVO in macroscopic stage III melanoma. In total 420 patients diagnosed with recurrent or de novo melanoma, with at least one pathologically proven, clinically detectable lymph node (up to 3 in-transit metastases (ITMs) allowed), will be randomized to neoadjuvant or adjuvant treatment. The population will be stratified by BRAF mutation, continent and the presence of ITMs. Patients in arm A will receive 2 cycles of IPI 80mg + NIVO 240mg and will undergo TLND at week 6. In the case of pathological partial response or non-response, surgery will be followed by adjuvant NIVO (11 cycles) or adjuvant dabrafenib + trametinib (46 weeks) if BRAFV600-mutation is present. Patients in arm B will undergo upfront TLND followed by 12 cycles of NIVO 480mg. The primary endpoint will be the event free survival (EFS) defined as the time from randomization until progression to unresectable stage III or stage IV melanoma, recurrent melanoma, a new primary melanoma or death due to melanoma or treatment. Final analysis will be performed after 132 events have been observed, or at latest 2 years after the last patient is included. Baseline biopsies and blood samples (screening, week 0, 3, 6, 9 and 12) will be collected for translational research. Quality of Life questionnaires and electronic Patient Reported Outcomes will be collected using the Kaiku application. The first patient was enrolled on the 23rd of July 2021. Clinical trial information: NCT04949113. Research Sponsor: Bristol Myers Squibb, Other Government Agency.

TPS9606 **Poster Session**

MERLIN_001: A prospective registry study of a primary melanoma gene-signature to predict sentinel node (SN) status and determine its prognostic value for more accurate staging of patients with SN-negative melanoma. *First Author: Tina J. Hieken, Mayo Clinic, Rochester, MN*

Background: For patients with cutaneous melanoma, sentinel lymph node biopsy (SLNB) provides important staging and prognostic information that guides surveillance and adjuvant systemic therapy decisions. At most centers, SLNB is indicated for patients with cutaneous melanoma with at least a 5% risk of having nodal metastases, typically melanomas ≥ 0.8 mm in thickness or thinner lesions with high-risk features such as elevated mitotic rate and/or ulceration. SLNB, generally involving a separate incision, does carry a small but measurable risk of complications including seroma, infection and rarely lymphedema, and most patients have negative sentinel lymph nodes. Currently, there is an unmet clinical need to identify patients who may safely forgo SLNB due to a low (<5%) risk of nodal metastasis, who otherwise meet established criteria for SLNB. Previously, a model consisting of gene expression profile (GEP) of the primary tumor combined with clinicopathological features (CP) has been developed to identify melanoma patients with a low risk of having a positive SLNB. The model has also been validated in multiple retrospective studies. The aim of the MERLIN_001 registry study is to prospectively validate the CP-GEP model in an independent multicenter cohort of primary cutaneous melanoma patients who undergo SLNB for standard indications. **Methods:** In the next two years, a total of 10 centers across the US will enroll 2,340 patients with clinically node-negative cutaneous melanoma undergoing SLNB using current guideline indications and will follow these patients for 5 years (ClinicalTrials.gov identifier: NCT04759781). Enrollment of patients started in September 2021 and 242 patients have been enrolled as of February 1, 2022. FFPE material from the initial melanoma biopsy will be used to assess the GEP of the primary melanoma. The CP-GEP probability scores will be expressed as a binary classification (Low Risk or High Risk for nodal metastasis) and will be compared to SLN pathology. Performance metrics for CP-GEP will be evaluated and will include: Negative Predictive Value, Positive Predictive Value, Sensitivity and Specificity, and the corresponding 95% confidence intervals. Risk for nodal metastasis will be calculated for Low Risk and High Risk CP-GEP patients. Finally, the performance of CP-GEP to stratify patients according to risk of recurrence (local, regional, distant, death) will also be studied, since data will be collected for up to 5 yrs. Clinical trial information: NCT04759781. Research Sponsor: SkylineDx B.V.

TPS9607 **Poster Session**

Neo-adjuvant T-VEC plus nivolumab combination therapy for resectable early-stage or metastatic (IIIB-IVM1a) melanoma with injectable disease: The NIVEC trial. *First Author: Maartje W. Rohaan, Division of Medical Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: The prognosis of patients with melanoma is significantly correlated with disease stage and has greatly improved with the introduction of the currently approved therapies. Trials investigating neo-adjuvant treatment with immune checkpoint inhibitors (ICI) have shown high pathologic response rates up to 25-80%, however, still a large group of patients derive no (durable) clinical benefit. Treatment with talimogene laherparepvec (T-VEC), a modified herpes simplex virus type-1, is approved for patients with unresectable stage IIIB-IVM1a melanoma, with high and durable response rates and a mild toxicity profile. Earlier trials have suggested that T-VEC has the capacity to heighten the immune response and to elicit an abscopal effect in melanoma when given in combination with ICI. Combination ICI and intralesional T-VEC has already been investigated in patients with unresectable stage IIIB-IV disease, however, no data is available yet on the potential benefit of this combination therapy in neo-adjuvant setting. This is the first trial investigating the efficacy and safety of neo-adjuvant treatment of T-VEC in combination with nivolumab (anti-PD-1 antibody), followed by surgical resection in patients with resectable stage IIIB-IVM1a melanoma, with the potential of high pathologic response rates and acceptable toxicity. **Methods:** In this single center, single arm, phase II study, a total of 24 patients ≥18 years of age and a good clinical performance score with treatment naïve, stage IIIB-IVM1a melanoma (AJCC 8th edition) with injectable disease and resectable (sub)cutaneous satellite or in-transit metastases and/or tumor positive lymph nodes, will be included. Patients will receive four courses of T-VEC up to 4mL (first dose as seroconversion dose) and three doses of nivolumab (240mg flatdose) every two weeks, followed by surgical resection in week nine. The primary endpoint of this trial is pathologic response rate, with the aim to show a high major pathologic (near-complete or complete) response rate up to 45%. Secondary endpoints are safety according to CTCAE v5.0, the rate of delay of surgery and event free survival. Additionally, prognostic and predictive biomarker research and health-related quality of life evaluation will be performed. Enrollment started in June 2020 in the Netherlands Cancer Institute, with currently 13 of the 24 planned patients treated. Clinical trial information: NCT04330430. Research Sponsor: Amgen Inc.

TPS9608 **Poster Session**

A first-in-human, phase 1b study to evaluate the safety, tolerability, pharmacokinetics, and anti-tumor activity of neoadjuvant use of ph-762 administered intratumorally in subjects with advanced melanoma. *First Author: Caroline Robert, Gustave Roussy and Paris-Saclay University, Villejuif-Paris, France*

Background: Antibodies targeting immune checkpoints such as PD-1 and CTLA-4 has shown significant benefit in late-stage melanoma. But further improvements in therapeutic options are still required. Two approaches for improving the outcome of immunotherapy with checkpoint inhibitors are neoadjuvant treatment and local intratumoral (IT) injection. IT immunotherapy uses the tumor as its own vaccine to activate the immune system, priming an anti-tumor immune response and generating systemic tumor responses, whilst minimizing systemic exposure and off-target toxicities. Neoadjuvant therapy provides the opportunity for preoperative disease shrinkage with the potential to improve surgical morbidity. There is currently no neoadjuvant standard of care for resectable, advanced melanoma patients. PH-762 is a potent RNAi molecule targeting PD-1 with structural and chemical modifications conferring properties suitable for IT administration, including an optimized cell and tissue uptake profile. Pharmacology studies show potent *in vitro* silencing of PD-1 associated with T cell activation, and robust, dose-dependent *in vivo* inhibition of tumor growth in syngeneic tumor models. **Methods:** The purpose of this study is to evaluate the safety of neoadjuvant use of PH-762 administered by IT injection in subjects with resectable stage IIIB/IIIC/IIID or IV melanoma, to determine the recommended Phase 2 dose, PK after IT injection, and potential immunologic and pathologic tumor responses. Study treatment constitutes of once weekly injections with PH-762 into one designated tumor lesion for 4 weeks prior to surgical excision at 5-6 weeks after the initial injection, with up to 5 dose levels tested in a serial fashion in cohorts of 3 or more subjects. Eligible subjects will have at least one resectable melanoma deposit that is large enough to allow IT injection, and that can undergo repeated biopsy. Subjects with active brain metastases, leptomeningeal disease, uveal melanoma, and auto-immune disease are excluded. The dose of PH-762 will be normalized to tumor volume to ensure an equivalent local dose (tumor tissue concentration). Post tumor excision, subjects will be followed-up for 6 weeks. Primary endpoint is to determine a safe dose of PH-762 assessed by incidence of Dose Limiting Toxicities (DLT) prior to tumor resection. Bayesian optimal interval (BOIN) design will be employed to evaluate escalating doses of PH-762 to determine the Maximum Tolerated Dose based on occurrence of DLT. Tumor changes will be evaluated per RECIST criteria (version 1.1 and iRECIST version adapted for use with IT therapy) and pathological response. Immunological response in tumor tissue and blood samples will be assessed as secondary endpoints. Enrollment commenced in February 2022. Clinical trial information: 2021-002859-10. Research Sponsor: Phio Pharmaceutical.

TPS9609 **Poster Session**

ARTISTRY-6: Nemvaleukin alfa monotherapy in patients with advanced mucosal and cutaneous melanoma. *First Author: Jeffrey S. Weber, Laura and Isaac Perlmutter Cancer Center, NYU Langone Health, New York, NY*

Background: Despite improved outcomes for melanoma patients with the introduction of checkpoint inhibitors (CPIs), ~50% of patients do not respond. A subset of responders ultimately progress and have limited treatment options, underscoring a high unmet need for novel treatments with durable benefit. Patients with mucosal melanoma exhibit response rates and progression-free survival times ~2 times lower than those with cutaneous melanoma. Nemvaleukin alfa (nemvaleukin, ALKS 4230) is a novel, engineered cytokine that selectively binds the intermediate-affinity interleukin-2 receptor complex to preferentially activate $CD8^+$ T and NK cells with minimal expansion of regulatory T cells. Nemvaleukin has been granted Orphan Drug designation for the treatment of mucosal melanoma by the FDA. In ARTISTRY-1, the intravenous (IV) recommended phase 2 dose (RP2D) of 6 μg/kg nemvaleukin monotherapy demonstrated durable antitumor activity in patients with advanced melanoma, including mucosal melanoma, previously treated with a CPI. In ARTISTRY-2, the subcutaneous (SC) RP2D of 3 mg q7d was identified demonstrating pharmacodynamic effects consistent with IV delivery. Data support further evaluation of nemvaleukin monotherapy among patients with advanced mucosal and cutaneous melanoma. **Methods:** ARTISTRY-6 is a phase 2, global, multicenter, open-label study. Eligible patients have had prior treatment with an anti–PD-(L)1 therapy with or without anti–CTLA-4 therapy and have an ECOG performance status of 0 or 1 and adequate hematologic reserve and hepatic and renal function. Patients with advanced cutaneous (Cohort 1) and mucosal (Cohort 2) melanoma will receive nemvaleukin at the SC and IV RP2D, respectively. Patients will receive nemvaleukin until progression or intolerable toxicity. The primary objective is to evaluate the antitumor activity of nemvaleukin monotherapy defined by overall response rate. Additional objectives include the evaluation of safety, health-related quality of life, predictive biomarkers, pharmacokinetics, immunogenicity, and pharmacodynamic effects. Clinical trial information: NCT04830124. Research Sponsor: Alkermes, Inc.

TPS9610 **Poster Session**

Capturing uveal melanoma (UM) global practice patterns and clinical outcomes in the collaborative ocular melanoma natural history (OMNi) study (NCT04588662). *First Author: Joseph J. Sacco, Clatterbridge Cancer Centre, Wirral, United Kingdom*

Background: Geographical differences in the management of primary UM, surveillance for recurrence, and care of metastatic disease have emerged based upon local expertise, treatment availability and insurance coverage. We have initiated accrual to OMNi (NCT04588662), an ambispective database developed to provide contemporary real-world data of UM, capturing its natural history and serving as a virtual biospecimen repository. The overall objectives of OMNi are to characterize regional/international UM management practice patterns and associated clinical outcomes in an effort to inform best practice recommendations. **Methods:** OMNi utilizes the Pulse Infoframe Healthie platform, a globally compliant platform which enables the structured collection of data mapped to Observational Medical Outcomes Partnership. The data fields created permit longitudinal capture of data including baseline patient and tumor characteristics, treatment of primary lesion and outcomes, surveillance patterns, time to disease recurrence, treatment of recurrent disease with outcomes, and survival. Inclusion criteria include a diagnosis of uveal melanoma and the ability to provide written informed consent for participation in the prospective registry or an institutional waiver by the IRB/ethics committee for retrospective data collection without written informed consent. We have initiated data collection at 3 US and 3 Australian centers, with 184 patients enrolled to date. Based upon feasibility assessment, we anticipate retrospective data entry for ~2,000 patients and annual recruitment of ~700 patients once all centers are active. Data collected in this OMNi collaboration, which will include additional US, UK and Australian sites, will facilitate new insights, hypothesis testing, as well as clinical trial development and conduct, and through a governance structure, will be made accessible for research. The OMNi dataset can serve and aid in interpretation of clinical trial outcomes in the real-world, facilitate cutting-edge research, and accelerate the development of diagnostics and therapeutics. Clinical trial information: NCT04588662. Research Sponsor: Immunocore and BMS.

10000 **Oral Abstract Session**

Updated safety and efficacy data from an open-label, phase 1/2 study of frontline brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine (A+AVD) in pediatric patients with advanced-stage classical Hodgkin lymphoma (cHL). *First Author: Anna Rachel Keating Franklin, University of Colorado School of Medicine, Aurora, CO*

Background: A+AVD is approved for treatment of adult patients with previously untreated Stage III or IV cHL. Here we present updated results from a phase 1/2 open-label study of frontline A+AVD in treatment-naïve pediatric patients with advanced stage cHL. **Methods:** Patients aged 5 to < 18 years with CD30+, stage III or IV, newly diagnosed cHL received A+AVD on days 1 and 15 of each 28-day cycle for up to 6 cycles. In phase 1, eight patients were treated with 48 mg/m^2 of brentuximab vedotin combined with doxorubicin, vinblastine, and dacarbazine (AVD). Dose-limiting toxicity (DLT) was evaluated from day 1 of cycle 1 to day 56. In phase 2, a further 51 patients were treated with the same regimen. Results presented here refer to phases 1 and 2 combined. Progression-free survival (PFS) was defined as the time from first dose to disease progression; event-free survival (EFS) was defined as the time from first dose to treatment failure, events included disease progression, treatment withdrawal or death. Data cutoff was September 24 2021, when all patients had been on study for at least 2 years. **Results:** In phase 1, no DLT occurred in the 6 DLT-evaluable patients. The maximum tolerated dose of brentuximab vedotin was not reached and 48 mg/m^2 was determined to be the recommended dose. All 59 patients in phase 1 and 2 completed 6 cycles of A+AVD and all experienced ≥1 treatment-emergent adverse event (TEAE). The most common any-grade TEAEs were vomiting (85%), nausea (75%), and neutropenia (58%). In total, 14/59 patients (24%) developed treatment-emergent peripheral neuropathy (PN); 10 patients had PN resolved by end of treatment (EOT); by last contact, 13 patients had resolved PN and one patient had grade 1 paraesthesia. No patients died on study. The PET-negative rate (Deauville 1, 2, or 3) after cycle 2 was 90%. Objective response rate ([ORR], defined as complete response [CR] + partial response [PR] per independent review facility [IRF] at EOT) was 88%, and 76% of patients achieved a CR. Median duration of response and duration of CR were not estimable. Median PFS and EFS had not been reached, suggesting encouraging efficacy of the combination in this pediatric patient population. Additional PFS, EFS and overall survival data will be presented during the meeting. **Conclusions:** Brentuximab vedotin given at 48 mg/m^2 every two weeks in combination with AVD had an acceptable safety profile and was associated with an efficacy benefit in CD30+, treatment-naïve pediatric patients with advanced cHL, supporting A+AVD as a frontline treatment option for this patient population. Clinical trial information: NCT02979522. Research Sponsor: Takeda Development Center Americas, Inc.

10001 **Oral Abstract Session**

Efficacy and safety of daratumumab (DARA) in pediatric and young adult patients (pts) with relapsed/refractory T-cell acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (LL): Results from the phase 2 DELPHINUS study. *First Author: Laura E. Hogan, Department of Pediatrics, Stony Brook Children's, Stony Brook, NY*

Background: Approximately 15-20% of pediatric pts with ALL or LL will be refractory to/relapse after frontline treatment; relapsed disease is associated with poor outcomes. In a phase 2 study, 2 of 7 (28.6%) pts with T-cell ALL in first relapse achieved a complete response (CR) using the vincristine, prednisone, PEG-asparaginase, and doxorubicin (VPLD) reinduction backbone. DARA, a human IgGκ monoclonal antibody targeting CD38 approved for treating multiple myeloma, has shown preclinical efficacy in ALL models. We report the initial results of DARA plus VPLD in pediatric and young adult pts with relapsed/refractory T-cell ALL or LL enrolled in the phase 2, open-label DELPHINUS study. **Methods:** Eligible pts were aged 1-30 y, had T-cell ALL or LL in first relapse or refractory to 1 prior induction/consolidation regimen, and had a performance status ≥70. DARA (16 mg/kg IV QW) was given with VPLD in Cycle 1 and with methotrexate, cyclophosphamide, cytarabine, and 6-mercaptopurine in Cycle 2. Pts received age/risk-adjusted intrathecal therapy. Response was measured at the end of each cycle by local bone marrow morphology. The primary endpoint for ALL pts was CR rate in pediatric pts at the end of Cycle 1. Pts achieving CR after Cycles 1 or 2 could proceed to allogeneic HSCT off study. Overall response rate (ORR) was defined as CR or CR with incomplete hematological recovery (CRi) at any time before start of subsequent therapy or HSCT. Minimal residual disease (MRD) negativity (< 0.01%) at any time before disease progression, start of subsequent therapy, or HSCT was centrally reviewed by flow cytometry. **Results:** Twenty-four pediatric (age 1-17 y) and 5 young adult (age 18-30 y) ALL pts and 10 LL pts (age 1-30 y) received ≥1 DARA dose. Median (range) age was 10.0 (2-25) y (ALL) and 14.5 (5-22) y (LL); median (range) time from initial diagnosis to first study treatment was 2.0 (0.1-6.1) y (ALL) and 0.8 (0.5-6.0) y (LL). Pediatric ALL pts received a median (range) of 2 (1-3) treatment cycles; young adult ALL pts and LL pts each received 2 (1-2). Among pediatric ALL pts, 10 (41.7%) pts (90% CI, 24.6-60.3) achieved CR at the end of Cycle 1. ORR was 83.3% (CR, 13 [54.2%] pts; CRi, 7 [29.2%] pts) in pediatric and 60.0% (all CR) in young adult ALL pts and 40.0% (all CR) in LL pts. Ten (41.7%) pediatric ALL pts achieved MRD negativity. All pediatric ALL pts had a grade 3/4 TEAE. No pediatric ALL pt discontinued DARA primarily due to AEs and 1 (4.2%) died due to TEAEs (brain edema and hepatic failure) attributed to study treatment but unrelated to DARA. **Conclusions:** The addition of DARA to VPLD in pediatric and young adult pts with relapsed/refractory T-cell ALL or LL showed initial activity, generating improved response rates compared to those achieved with backbone therapy alone, with a manageable safety profile. Clinical trial information: NCT03384654. Research Sponsor: Janssen Research & Development, LLC.

10002 **Oral Abstract Session**

BEACON-Immuno: Results of the dinutuximab beta (dB) randomization of the BEACON-Neuroblastoma phase 2 trial—A European Innovative Therapies for Children with Cancer (ITCC–International Society of Paediatric Oncology Europe Neuroblastoma Group (SIOPEN) trial. *First Author: Juliet Gray, University of Southamtpon, Southampton, United Kingdom*

Background: The BEACON phase II trial (NCT02308527) addressed a number of questions in children with relapsed/refractory high-risk neuroblastoma (RR-HRNB). Here we report the chemo-immunotherapy randomisation, assessing if anti-GD2 (dB) demonstrates activity when added to chemotherapy. **Methods:** Patients aged 1-21 years with RR-HRNB with adequate organ function and performance status were randomised in a 1:2 ratio to receive chemotherapy alone or with dB, given concurrently as a 7 day continuous infusion (10 mg/m^2/24hr). As the trial had a factorial design, some patients were also randomised between chemotherapy regimens (temozolomide (T) versus Temozolomide-Topotecan (TTo); this randomisation closed soon after the dB randomisation opened and all patients subsequently received TTo chemotherapy. Cross-over to dB with topotecan and cyclophosphamide was allowed for patients randomised to chemotherapy alone who experienced disease progression. The primary outcome measure was best response (complete or partial) at any point during the first 6 courses of treatment, by RECIST or International Neuroblastoma Response Criteria for patients with measurable and evaluable disease respectively. Progression free and overall survival (PFS & OS) and safety were secondary outcomes. The success criterion for proceeding to a Phase 3 trial was a one-sided p-value (1p) less than 0.23 for Objective Response Rate (ORR). **Results:** From Aug 2019 to Feb 2021, 65 patients were randomised to chemotherapy alone (3 T, 19 TTo) or with dB (6 dBT, 37 dBTTo). Median age was 4 years; 48 and 17 had measurable and evaluable disease respectively; 29 and 36 had refractory and relapsed disease respectively; 19 had MYCN amplification. Baseline characteristics were balanced between arms. Response was assessable in all patients. The ORR was 18% with chemotherapy alone and 35% for patients receiving chemotherapy with dB (risk ratio 1.66, 80% confidence interval (CI) 0.9 to 3.06, 1p = 0.19). 1-year PFS was 27% for chemotherapy alone, and 57% for those receiving chemotherapy +dB (HR 0.63, 95% CI 0.32 to 1.25, p = 0.19). Twelve patients in the chemotherapy only arm crossed over to receive dB at progression. OS did not differ between the arms: HR = 0.99, 95% CI 0.42 to 2.36, p = 0.99. Nine (41%) patients receiving chemotherapy alone and 13 (30%) receiving chemotherapy plus dB had grade ≥3 toxicities (CTCAE v4.0). Neurotoxicities were more common in patients receiving dB compared to chemotherapy alone (Grade 1-2: 67.4% vs 13.6%, Grade 3: 9.3 vs 0%). Other toxicities were similar with and without dB. **Conclusions:** The Phase 2 success criterion for ORR was met and PFS is also encouraging. The addition of dB to temozolomide-based chemotherapy shows promising activity in patients with RR-HR-NB. Clinical trial information: NCT02308527. Research Sponsor: Solving Kids Cancer, Imagine for Margo, Cancer Research UK.

10003 **Oral Abstract Session**

A pilot induction regimen incorporating dinutuximab and sargramostim for the treatment of newly diagnosed high-risk neuroblastoma: A report from the Children's Oncology Group. *First Author: Sara Michele Federico, St. Jude Children's Research Hospital, Memphis, TN*

Background: The addition of dinutuximab (DIN) in the post-consolidation setting led to improved event-free survival rates for patients with high-risk neuroblastoma. Chemoimmunotherapy including irinotecan, temozolomide, DIN and sargramostim (GM-CSF) in patients with recurrent or refractory neuroblastoma results in robust objective clinical responses. Evaluation of chemoimmunotherapy in the induction setting for patients with newly-diagnosed high-risk neuroblastoma (HR-NBL) warrants investigation. **Methods:** Children's Oncology Group (COG) ANBL17P1 is a prospective, single arm, limited institution pilot study to assess the tolerability and feasibility of administering DIN (17.5mg/m^2/dose, IV Days 2-5) and GM-CSF (250mcg/m^2/dose, subcutaneous Days 6-count recovery) with COG Induction chemotherapy Cycles 3-5 for patients with newly-diagnosed high-risk neuroblastoma. The primary endpoint of tolerability included the number of toxic deaths and number of patients experiencing predefined unacceptable toxicities during Induction Cycles 3-5. Unacceptable toxicities included: hypotension requiring pressors > 24 hours, respiratory toxicity requiring ventilatory support > 24 hours, Grade 4 neuropathy that did not resolve prior to the next cycle, and failure to recover the ANC to > 750 mm^3 by day 35. Feasibility was assessed as being able to receive > 75% of planned DIN doses administered during Induction Cycles 3-5. Revised International Neuroblastoma Response Criteria (INRC) were used to assess end of Induction (EOI) response. **Results:** Forty-two eligible and evaluable patients with newly-diagnosed high-risk neuroblastoma enrolled at 8 sites (22 [52.4%] males; median age 3.3 years at diagnosis) from January 14, 2019 to June 4, 2020. The most common DIN related Grade >3 toxicities observed during Induction Cycles 3-5 included fever (31.0%) and pain (9.5%). None of the patients experienced a toxic death or unacceptable toxicity during Induction Cycles 3-5. Thus, the regimen was deemed tolerable. Patients received 97.4% - 101.8% of the total DIN dose expected to be administered during Induction Cycles 3-5. Therefore, the regimen was deemed feasible. Thirty-eight of 42 patients completed the EOI evaluations, including 11 with complete response, 22 with partial response, 0 with minor response, 3 with stable disease and 2 with progressive disease. The overall EOI objective response rate (CR+PR+MR) was 86.8%. **Conclusions:** The administration of DIN and GM-CSF to COG Induction Cycles 3-5 for patients with newly-diagnosed high-risk neuroblastoma was tolerable and feasible. The objective response rate at EOI appears encouraging. This therapeutic regimen will be studied in a randomized phase 3 trial to further evaluate the efficacy of Induction phase chemoimmunotherapy for high-risk neuroblastoma. Clinical trial information: NCT03786783. Research Sponsor: NCTN Operations Center Grant U10CA180886, Other Foundation, Other Government Agency, Pharmaceutical/Biotech Company.

10004 **Oral Abstract Session**

Poverty, race, ethnicity, and survival among U.S. children with non-metastatic osteosarcoma treated on EURAMOS-1: A report from the Children's Oncology Group. *First Author: Lenka Ilcisin, Boston Children's Hospital Department of Surgery, Boston, MA*

Background: Children living in poverty and those who identify as a race/ethnicity other than non-Hispanic White experience higher rates of relapse and lower overall survival across many pediatric cancers. Racial, ethnic and socioeconomic disparities have not been comprehensively investigated in osteosarcoma. We leveraged data from US-enrolled patients on the recent international EURAMOS-1 trial to investigate disparities in survival outcomes. Aim: Identify if race/ethnicity, household or neighborhood poverty exposure are associated with event-free survival (EFS) or overall survival (OS) in patients with non-metastatic osteosarcoma enrolled at a US-center on EURAMOS-1. **Methods:** Retrospective cohort study of US patients aged 5-21 years enrolled on EURAMOS-1 with a diagnosis of non-metastatic, primary osteosarcoma. Poverty was the primary exposure defined at the household- (sole coverage with Medicaid or CHIP public insurance versus other) and neighborhood- (Census-defined high-poverty ZIP code with >20% of residents living at <100% Federal Poverty Level vs other) levels. Race and ethnicity were categorized to reflect structural inequities and historically marginalized populations, as Hispanic, non-Hispanic Black (NHB), non-Hispanic Other (NHO), and non-Hispanic White (NHW). OS and EFS as a function of time from trial enrollment were estimated using the Kaplan-Meier method. Hypotheses of associations between risks for EFS-event, death and post-relapse death with poverty-exposures and race/ethnicity were assessed using log-rank tests. Statistical comparisons were performed excluding patients with missing values for the exposures considered. P-values <=0.05 were considered significant. **Results:** Among 758 patients, 27% were household poverty-exposed and 29% were neighborhood-poverty exposed. Twenty-one percent of children identified as Hispanic, 17% NHB, 5% NHO and 57% NHW. Neither household- or neighborhood-poverty, nor race/ethnicity were significantly associated with risks for EFS-event or death. Post-relapse risk for death differed significantly across race/ethnicity with NHB at greatest risk compared to others (4-Year post-relapse survival 35.7% Hispanic vs. 13.0% NHB vs. 43.8% NHO vs 38.9% NHW; p=0.0046). **Conclusions:** Neither poverty-exposures nor race/ethnicity were associated with EFS or OS in this COG trial-enrolled cohort, suggesting equitable outcomes following standardized therapy. Despite this, non-Hispanic Black children experienced significantly inferior post-relapse survival. Investigation of mechanisms driving these post-relapse disparities, including inequities in health care delivery and access to post-relapse trial-enrollment, are paramount to ensure equity in outcomes for all children with cancer. Research Sponsor: None.

10005 **Oral Abstract Session**

Racial, ethnic, and socioeconomic survival disparities among children with high-risk neuroblastoma treated on upfront Children's Oncology Group clinical trials. *First Author: Puja J Umaretiya, Dana-Farber and Boston Children's Cancer and Blood Disorders Center, Boston, MA*

Background: Racial and socioeconomic disparities have not been comprehensively investigated in high-risk neuroblastoma (HR NBL). Prior Children's Oncology Group (COG) investigations have demonstrated population-based disparities in late relapse rates among Black children, and trial-based disparities in relapse and survival among children living in poverty receiving post-consolidation immunotherapy. It is unknown whether these disparities persist in upfront trials for newly diagnosed patients. We leveraged COG data to investigate race, ethnicity, and socioeconomic disparities in a cohort of children with HR NBL treated on upfront clinical trials from 2007-2016. **Methods:** Retrospective cohort study of children enrolled on upfront COG HR NBL trials ANBL0532, ANBL09P1, and ANBL12P1. Race and ethnicity were the primary exposures categorized as: Black Non-Hispanic (BNH); Hispanic; Other Non-Hispanic (ONH); or White Non-Hispanic (WNH). Poverty was the secondary exposure, defined as household (public insurance only vs others), area (census-defined high-poverty ZIP code with >20% of population living below 100% Federal Poverty Level (FPL) vs <20% below 100% FPL), and rural (Census-defined rurality measures linked to ZIP code). Overall (OS) and event-free (EFS) survival from time of trial enrollment were plotted by Kaplan-Meier methods; associations with race/ethnicity and poverty were evaluated by log-rank tests. **Results:** Among 696 children, 16% were BNH, 11% Hispanic, 4% ONH, and 69% WNH. One-third (33%) of children were household poverty-exposed, 26% area poverty-exposed, and 15% rural-exposed. Tumor stage and biology did not differ by race/ethnicity or poverty measures. Five-year OS differed significantly by race/ethnicity (47% Hispanic vs. 50% ONH vs. 61% WNH vs. 62% BNH; p=0.047). Five-year OS was inferior among children exposed to household-poverty (53% vs. 63%; p=0.036) and neighborhood-poverty (54% vs. 62%; p=0.050) compared to unexposed children. There was no difference in OS by rurality. Similar directionality in 5-year EFS outcomes by race/ethnicity and poverty were observed without statistical significance. **Conclusions:** Race/ethnicity and poverty-exposure are associated with inferior OS outcomes among children with HR NBL despite uniform planned treatment on upfront COG trials. Investigation of mechanisms driving these disparities, including disparate early phase trial enrollment are ongoing to inform targeted health equity interventions to improve outcomes. Research Sponsor: None.

10006 **Oral Abstract Session**

Securing access to innovative anticancer therapies for children, adolescents, and young adults outside clinical trials: The SACHA study of the French Society of Pediatric Oncology (SFCE). *First Author: Pablo Berlanga, Gustave Roussy Cancer Campus, Villejuif, France*

Background: Access to innovative anticancer therapies for children, adolescents and young adults within clinical trials in France is steadily increasing in the last years. However, current clinical trials portfolios are still inadequate and thus pediatric hemato-oncologists regularly prescribe innovative medicines outside their marketing authorization, and/or experimental drugs through compassionate use. **Methods:** The Secured Access to innovative medicines for CHildren with cAncer (SACHA) is a French prospective observational study developed by the French Society of Pediatric Oncology (SFCE) with Gustave Roussy as the legal sponsor to prospectively collect real-world safety and activity data of innovative therapies administered to patients ≤ 25 years-old with pediatric malignancies (solid tumor or leukemia) or other related conditions, either on compassionate use of experimental drugs or off-label use of anti-cancer medicines that have been first approved in adults after 2007. Prior to SACHA inclusion, multicenter tumor board discussion defining best available therapeutic options for each patient with a relapsed malignancy is mandatory. **Results:** The SACHA study opened in March 2020 and by February 2022, 283 patients have been included from 29/31 SFCE recruiting centers; median age: 11.0 years (range: 0.3-24.4). Main cancer types were central nervous system (CNS) tumors (47%), followed by non-CNS tumors (40%) and leukemias (13%). Innovative therapies prescribed in > 10 patients with reported objective response rate (ORR) and related CTCAE v.5 grade ≥2 clinical and/or grade ≥3 biological adverse drug reactions (ADRs) are described in Table. **Conclusions:** SACHA confirms the feasibility of this type of prospective real word registry, with a high participation of French centers. Based on this French experience, the Innovative Therapies for Children with Cancer (ITCC) consortium is currently developing a "SACHA International Project" to be opened in ITCC and collaborating countries. Research Sponsor: Imagine for Margo, Association Hubert Gouin, Fondation du LEEM and the SFCE.

Innovative drug	N	Reported ORR / evaluable patients*	Patients with at least 1 reported ADR / evaluable patients*	Serious ADR*
Trametinib	64	9/40	30/64	3
Trametinib/Dabrafenib	36	11/20	2/33	2
Pazopanib	16	3/12	9/16	0
Cabozantinib	16	0/12	7/16	0
Regorafenib	15	0/9	7/15	0
Tazemetostat	14	1/14	4/14	1

ORR: objective response rate; ADR: adverse drug reaction. *Data cut-off: 4th February 2022.

10007 **Oral Abstract Session**

Late mortality and morbidity among adult survivors of childhood glioma treated over three decades: A report from the Childhood Cancer Survivor Study. *First Author: Peter de Blank, University of Cincinnati, Cincinnati Children's Hospital Medical Center, Cincinnati, OH*

Background: Therapy for pediatric low-grade glioma has evolved to delay or eliminate the need for cranial radiation. The impact of this change in approach on long-term outcomes remains unknown. **Methods:** Cumulative incidence of late mortality (death ≥5 years from diagnosis), subsequent neoplasms (SNs), and chronic health conditions (CHCs, graded using CTCAE criteria) were evaluated in the Childhood Cancer Survivor Study among 5-year survivors of glioma diagnosed between 1970 and 1999. Outcomes were evaluated by diagnosis decade (1970s, 1980s, 1990s) and by treatment exposure in the first five years from diagnosis [surgery only, chemotherapy (with or without surgery), and cranial radiation (with or without surgery or chemotherapy)]. Relative Risk (RRs) with 95% CIs estimated long-term outcomes using multivariable piecewise exponential models. **Results:** Among 2,684 eligible survivors (median age at diagnosis, 7 years [range, 0 to 20 years]; median time from diagnosis, 24 years [range, 5 to 48 years]), the proportion exposed to cranial radiation decreased from 51% (1970s) to 45% (1980s) and 25% (1990s) while the rate of recurrence within > 5 years but ≤15 years of diagnosis decreased from 9.8% (1970s) to 8.8% (1980s) and 5.0% (1990s). The 15-year cumulative incidence rate of all-cause late mortality was 10.3% (1970s), 6.5% (1980s), and 6.0% (1990s) ($p < 0.001$, comparison of cumulative incidence curves). The 15-year cumulative incidence rates of severe, disabling or life-threatening (grade 3-5) CHCs also decreased between 1970 and 1999: 19.7% (1970s), 17.8% (1980s), and 14.2% (1990s) ($p < 0.0001$). Lower rates of SN were not observed. In a multivariable analysis adjusted for age at diagnosis, attained age, race, sex and diagnosis decade, later diagnosis (1990s vs. 1970s) was associated with lower risk of late mortality (RR 0.86, 95% CI 0.74-0.99), grade 3-5 CHCs (RR 0.65, 95% CI 0.51-0.82) and SN (RR 0.64, 95% CI 0.44-0.94). In addition, when treatment exposure was added to the multivariable model, the effect of diagnosis decade was attenuated and no longer significant. Exposure to radiation or chemotherapy both increased risk compared to surgery alone: all-cause mortality (radiation RR 4.95, 95% CI 3.79-6.47; chemotherapy RR 2.88, 95% CI 1.85-4.48), grade 3-5 CHCs (radiation RR 4.02, 95% CI 3.28-4.94; chemotherapy RR 1.66, 95% CI 1.13-2.45), SNs (radiation RR 4.02, 95% CI 3.06-6.13, chemotherapy RR 2.08, 95% CI 1.03-4.23)). The effect of delayed radiation (> 1year to ≤5 years from diagnosis) on all-cause late mortality, grade 3-5 CHCs, or SNs was not different compared to radiation within one year of diagnosis. **Conclusions:** Late mortality and CHCs decreased in childhood glioma survivors diagnosed from 1970-1999 largely due to therapy changes, particularly avoidance of cranial radiation, without increased late recurrence. Research Sponsor: Other Foundation, U.S. National Institutes of Health.

10008 **Oral Abstract Session**

Joint effects of general population polygenic risk scores (PRS) and radiation treatment on subsequent neoplasm risk among childhood cancer survivors: A report from the Childhood Cancer Survivor Study (CCSS). *First Author: Todd M. Gibson, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD*

Background: We examined whether PRS from general population studies are associated with risk of subsequent neoplasms (SNs) in childhood cancer survivors and evaluated joint associations between PRS and radiation treatment (RT), an established SN risk factor. **Methods:** Common genetic variants associated with risk of basal cell carcinoma (BCC), breast cancer, thyroid cancer, squamous cell carcinoma (SCC) or melanoma in general population studies were used to calculate cancer specific PRS among 5,911 5 year cancer survivors diagnosed < 21 years of age and between 1970-1986 in the CCSS. We examined associations between each PRS and SN risk using conditional logistic regression in nested case control studies, with incidence density sampling and matching on childhood cancer type, age at diagnosis, sex, RT dose to the SN site, and chemotherapy exposure. Further analyses matching only on non-treatment factors assessed joint associations considering potential combinations of PRS and RT exposure. We calculated the relative excess risk due to interaction (RERI) to determine whether joint associations were consistent with additivity of the individual risk factors (RERI > 0 indicates a more-than-additive joint association). **Results:** Among survivors (median age at follow-up 40 years, range 3-67; 62% exposed to RT), cancer specific PRS were associated with risk of subsequent BCC (N = 626; quartile 4 versus 1, OR [95% CI] = 1.9 [1.5-2.4]), breast cancer (N = 277; 4.5 [2.8-7.1]), thyroid cancer (N = 149; 1.9 [1.2-3.1]), and melanoma (N = 76; 2.7 [1.3-5.6]). Both PRS and RT were independently associated with SN risk, but joint analyses using a common reference group (PRS < median, RT < 1 Gy) found that both risk factors together resulted in more-than-additive increases in risk of BCC (RERI [95% CI] = 6.9 [2.0-11.8], breast cancer (6.6 [2.2-10.1], and thyroid cancer (4.8 [0.5-9.2]). Specifically, BCC risk was increased 28.8-fold for both PRS ≥ median and RT ≥ 1 Gy together, but only 3.3-fold for PRS ≥ median alone and 19.7-fold for RT ≥ 1 Gy alone. Similarly, breast cancer risk was increased 14.1-fold for both risk factors together, 2.5-fold for PRS ≥ median alone, and 6.5-fold for RT ≥ 1 Gy alone, and thyroid cancer risk was increased 12.3-fold for both risk factors together, 2.4-fold for PRS ≥ median alone, and 6.0-fold for RT ≥ 1 Gy alone. In joint analyses using more detailed RT categories, we found more-than-additive joint associations at both low and high RT doses. **Conclusions:** General population PRS were associated with SN risks after childhood cancer. More-than-additive increased risks with the combination of PRS and RT suggest that established markers of genetic susceptibility remain important in the context of treatment-related risks and may be useful in further refining risk assessment and follow-up guidelines for survivors. Research Sponsor: U.S. National Institutes of Health, American Lebanese-Syrian Associated Charities provided funding to St. Jude Children's Research Hospital.

10009 **Poster Discussion Session**

Tazemetostat in patients with tumors with alterations in EZH2 or the SWI/SNF complex: Results from NCI-COG Pediatric MATCH trial Arm C (APEC1621C). *First Author: Susan N. Chi, Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA*

Background: The NCI-Children's Oncology Group (COG) Pediatric Molecular Analysis for Therapy Choice (MATCH) trial assigns patients, age 1-21 years, with relapsed or refractory solid tumors, lymphomas, and histiocytic disorders to phase 2 treatment arms based on genetic alterations detected in their tumor. Arm C evaluated the EZH2 inhibitor tazemetostat in patients whose tumors harbored *EZH2* hotspot mutations or SMARCB1 or SMARCA4 loss by immunohistochemistry. **Methods:** Tazemetostat 1200 mg/m^2/dose PO BID was administered to the first 13 patients; after study amendment due to second malignancy noted in the pediatric phase 1 trial, the dose for patients with non-CNS tumors was reduced to 520 mg/m^2/dose PO BID. Patients were treated for 28-day cycles until PD or intolerable toxicity (max 26 cycles); response assessments occurred every 2-3 cycles. Primary and secondary endpoints were ORR and PFS, respectively. **Results:** Twenty eligible and evaluable patients (median age 5 years; range 1-21) were enrolled between Nov 2017 and Sept 2020. SMARCB1 loss was detected in 16/20 (80%) tumors: atypical teratoid rhabdoid tumor (ATRT, n = 8), malignant rhabdoid tumor (MRT, n = 4), epithelioid sarcoma (ES, n = 2), renal medullary carcinoma (RMC, n = 1) and hepatocellular carcinoma (HCC, n = 1). *EZH2* mutations were identified in 3/20 (15%) tumors: Ewing sarcoma (n = 2), ependymoma (n = 1). One patient with Langerhans cell histiocytosis (LCH) had SMARCA4 loss. Centrally reviewed, one objective response (PR) was observed (LCH [SMARCA4], 26 cycles at 1200 mg/m^2/dose BID). Five other patients had a best response of stable disease (ES [SMARCB1], 26 cycles, 520 mg/m^2/dose BID; ATRT [SMARCB1], 13 cycles,1200 mg/m^2/dose BID; RMC [SMARCB1], 12 cycles, 520 mg/m^2/dose BID; ES [SMARCB1], 9 cycles,1200 mg/m^2/dose BID; ATRT [SMARCB1], 6 cycles, 1200 mg/m^2/dose BID). No other patients received > 2 cycles. Six-month PFS was 35% (95% CI 15.7%, 55.2%); OS was 45% (95% CI 23.1%, 64.7%). Treatment-related adverse events were consistent with AEs previously reported with tazemetostat, including anemia, thrombocytopenia, elevated LFTs, abdominal pain, dyspnea, infection, and intracranial hemorrhage. Three patients had bromide elevations. **Conclusions:** In this cohort of children with relapsed tumors harboring EZH2 mutations or loss of SMARCB1 or SMARCA4, tazemetostat did not produce significant objective responses (ORR: 5%, 90% CI 1%, 20%). However, we observed prolonged stable disease of > 6 months (range: 6-26 cycles) in 33% of patients across different histologic diagnoses, including two patients who received the full two years of study therapysuggesting a potential effect of tazemetostat on disease stabilization. Future studies will incorporate tazemetostat in combination with chemotherapy or immunologic agents for patients with these aggressive and difficult to treat tumors. Clinical trial information: NCT03213665. Research Sponsor: U.S. National Institutes of Health.

10010 **Poster Discussion Session**

Matched external control analysis of event-free survival (EFS) in patients with high-risk neuroblastoma (HRNB) receiving eflornithine (DFMO) maintenance. *First Author: Javier E. Oesterheld, Levine Children's Hospital at Carolinas Medical Center, Charlotte, NC*

Background: Long term survival in HRNB patients remains a challenge with relapse as the primary cause of mortality. DFMO has been evaluated as a chemopreventative therapy in a single arm study designed to compare EFS outcomes with published rates for the Phase 3 Children's Oncology Group ch14.18 immunotherapy trial, ANBL0032. In order to address the limitations associated with comparison to a historical control group, we used ANBL0032 patient-level data and propensity-score matching (PSM) to simulate a randomized study comparing EFS of patients treated with DFMO after ch14.18 (treated) to ANBL0032 patients who did not subsequently receive DFMO (control). **Methods:** A phase 2 trial enrolled a total of 140 HRNB patients in remission at the completion of disease treatment from 2012 to 2016. Patients received 2 years of continuous treatment with DFMO 750 ±250 mg/m^2 BID and were followed for up to 7 years. ANBL0032 enrolled a total of 1328 HRNB patients from 2001 to 2015 who were assigned to treatment with ch14.18 immunotherapy and followed for up to 10 years. With FDA input, we defined selection rules to identify like groups of treated and control patients eligible for matching, covariates of potential prognostic importance, and matching algorithm details. PSM was used to balance cohorts on their baseline demographic and characteristics, matching each treated patient with the 3 most closely scored control patients with an exact match on MYCN. The Kaplan-Meier method and Cox regression analyses were used to compare EFS (primary) and overall survival (OS) (key secondary) endpoints. Multiple sensitivity analyses were performed to further investigate the primary comparison. **Results:** A total of 92 treated patients and 852 control patients met selection criteria, with 91 and 516, respectively, having complete covariate data required for the analysis. Eighty-seven (94.6%) of the treated group had verified participation in ANBL0032 immediately prior to enrollment in the DFMO trial. EFS from end of immunotherapy was significantly improved in the matched DFMO group (n=90) vs. control group (n=270), with a hazard ratio of 0.48 (95% CI: 0.27, 0.85) and a p-value of 0.0114. Four-year EFS was 84.4% (95% CI 75.2, 90.5) in the DFMO group versus 72.8% (95% CI 67.0, 77.7) in the control group. OS rates were also higher for DFMO group in the matched population, with a hazard ratio of 0.36 (95% CI: 0.16, 0.79) and a p-value of 0.0105. EFS sensitivity analyses demonstrated consistent results, including those challenging selection criteria for the control population. **Conclusions:** Patients in remission after standard upfront therapy treated with DFMO had approximately half the risk of relapse compared to matched control patients. The PSM comparisons represent the most statistically robust findings to date supporting the benefit of DFMO as a maintenance treatment for HRNB. Clinical trial information: NCT02395666, NCT00026312. Research Sponsor: Beat Childhood Cancer Foundation, Pharmaceutical/Biotech Company.

10011 **Poster Discussion Session**

STRIVE-02: A first-in-human phase 1 trial of systemic B7H3 CAR T cells for children and young adults with relapsed/refractory solid tumors. *First Author: Navin R. Pinto, Seattle Children's Hospital, Seattle, WA*

Background: B7H3 (CD276) has limited expression in normal tissues and high cell-surface expression in pediatric solid malignancies providing rationale for immunologic therapeutic targeting. We present a first-in-human experience of B7H3 chimeric antigen receptor T cells (CAR-T) for children and young adults (CYA) with relapsed or refractory solid tumors (R/RST). **Methods:** CYA patients with R/RST were enrolled onto a Phase 1 trial (NCT04483778) to examine the safety of autologous T cells genetically modified to express scFV-IgG4hinge-CD28tm-4-1BB-zeta B7H3-specific CAR with the methotrexate resistance/selection cassette DHFRdm and the tracking/suicide construct EGFRt. All patients received lymphodepleting fludarabine and cyclophosphamide prior to infusion of cryopreserved CAR-T at the prescribed dose level. The maximal tolerated dose or biologically effective dose (BED) was determined based upon observed toxicity through day 28 from initial CAR-T infusion and using a 3+3 statistical design. **Results:** Sixteen subjects (age 11-24, median 17 years) enrolled and received dose level (DL) 1 (0.5 x 10^6 CAR-T/kg, n = 3) or DL2 (1 x 10^6 CAR-T cells/kg, n = 6). No dose limiting toxicity was observed following first infusion, most common toxicities were fatigue and cytokine release syndrome (CRS) (n = 2, maximum CTCAE grade 2). Maximum circulating CAR-T expansion on first infusion was 4.98 cells/uL (range 0.23-4.98 cells/uL) with median persistence of 28 days (range 14-90). Best overall response of Stable Disease was observed in 3 of the 9 subjects infused. Given observed expansion and persistence, DL2 was determined to be the BED. A second infusion at DL2 in one subject demonstrated CAR T expansion to 1590 cells/uL (86% of circulating CD3 cells) with CTCAE grade 2 CRS and transient dose limiting CTCAE grade 4 liver enzyme elevation. A partial metabolic response on FDG-PET by PERCIST criteria was observed in this subject at Day 28. **Conclusions:** B7H3 CAR T cells are safe and demonstrate anti-tumor activity in CYA with R/RST. CAR-T cell expansion and persistence may be necessary to achieve objective responses. STRIvE-02 Arm B will explore dual expression of CD19 CAR with B7H3 CAR, using lymphocytic CD19 expression to drive CAR expansion and persistence. Clinical trial information: NCT04483778. Research Sponsor: Seattle Children's Therapeutics.

10012 **Poster Discussion Session**

Pediatric EBV-negative monomorphic post–solid organ transplant lymphoproliferative disorders [EBV(-)M-PTLD]: Characteristics, treatment, and outcome from 11 pediatric academic centers. *First Author: Zeinab A.M. Afify, Primary Children's Hospital, University of Utah, Salt Lake City, UT*

Background: Pediatric EBV(-)M-PTLD comprises < 15% of M-PTLD. Two-year-overall survival of pediatric EBV(+) PTLD is 83%. No large multi-institution pediatric-specific reports are available for EBV(-)M-PTLD. **Methods:** Retrospective study of characteristics, treatment, and outcome of pediatric solid organ recipients diagnosed with EBV(-)M-PTLD at age ≤21 years (y) in 11 pediatric transplant centers in US and UK. **Results:** Thirty-three patients transplanted with solid organs between 1991-2017 developed EBV(-)M-PTLD. Twenty-two (66%) were male. Median age (range) at organ transplantation was 2.6y(0.1-17), diagnosis of EBV(-)M-PTLD 14y(3-20), interval from transplant to PTLD 8.3y (2.3-18). Transplanted organs were heart (n = 10), kidney (n = 17), liver (n = 4), small bowel (n = 1), liver and small bowel (n = 1). Immunosuppressive therapy at the time of diagnosis of PTLD was available on 31 patients. All were receiving a calcineurin inhibitor except one who was on sirolimus alone. Tacrolimus was given in 27 patients, alone (n = 3), or in various combination with mycophenolate (n = 8), azathioprine (n = 9), prednisone (n = 8), or everolimus (n = 1). Four of these receiving tacrolimus received 3 immunosuppressive drug combinations. Cyclosporine was given in 3 patients, with mycophenolate (n = 1), prednisone (n = 1), or both (n = 2). Murphy stages were I (n = 1), II (n = 7), III (n = 22), and IV (n = 3). Lactate dehydrogenase was elevated in 19/31 (61%) and > 2X upper limit of normal in 10/31 (32%) tested. Pathological diagnoses were diffuse large B-cell lymphoma (n = 30) and B-NHL NOS (n = 3). Treatment included: rituximab alone (n = 1), low-dose cyclophosphamide, prednisone, and rituximab (CPR; n = 9), pediatric mature B-NHL-specific regimen [FAB/LMB with (n = 12) or without (n = 1) rituximab], EPOCH-R (n = 2), R-CHOP (n = 3), modified R-CHOP (n = 2), COP (n = 1), and R-COP (n = 2). At a median 2.9y (0.3-11y) from diagnosis, 26/33 (79%) were alive and in complete remission (CR). Three experienced relapses at 1, 3, and 6.5y after CPR, rituximab alone, and B-NHL therapy, respectively. All achieved a sustained second CR with additional B-NHL therapy. Of the 7 deaths: 6 were from progressive disease despite escalation to intensive B-NHL therapy following initial COP (n = 1), R-COP (n = 1), CPR (n = 2), and B-NHL therapy (n = 2), and one cardiac transplant recipient from presumed cardiotoxicity. There was one graft rejection that was successfully treated. **Conclusions:** This collaboration represents the first multi-institution series of pediatric EBV(-)M-PTLD. Overall survival was comparable to that reported for pediatric EBV(+) PTLD, but inferior to DLBCL in immunocompetent children. These preliminary data reflect a wide range of therapeutic regimens used over 20 years and strongly support an organized collaborative effort to collect data prospectively. Research Sponsor: None.

10013 **Poster Discussion Session**

Survival of patients with neuroblastoma before versus after reduction of therapy due to the change in age cut-off from 12 to 18 months in Children's Oncology Group (COG) risk stratification. *First Author: Wendy B. London, Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA*

Background: In 2006, COG reclassified subgroups of toddlers diagnosed with neuroblastoma from high-(HR) to intermediate-risk (IR), when the age cut-off for increased risk was raised from 365 days (12 mo) to 547 days (18 mo) (London, *J Clin Onc* 2005). The aim of this retrospective study was to determine if excellent outcome was maintained after a reduction of therapy. **Methods:** Children < 3 yrs old at diagnosis, enrolled on a COG biology study from 1990-2018, were eligible (n = 9,189). Therapy was reduced for two "cohorts of interest" based on the age cut-off change: 365-546 days old with INSS stage 4, *MYCN* not amplified, favorable INPC, hyperdiploid tumors (12-18mo/Stage4/FavBiology); and, 365-546 days old with INSS stage 3 tumors with non-amplified *MYCN* and unfavorable INPC (12-18mo/Stage3/NotAmp/UnfavINPC). Log rank tests compared event-free (EFS) and overall survival (OS) curves. **Results:** In the cohorts of interest, patient (pt) characteristics were similar for ≤2006 vs > 2006. For 12-18mo/Stage4/FavBiology, 5-year EFS and OS (± std error) before (≤2006; n = 40) versus after (> 2006; n = 55) the reduction in therapy were similar: 89±5.1% versus 87±4.6% (p = 0.7), and 89±5.1% versus 94±3.2% (p = 0.4), respectively (Table). For 12-18mo/Stage3/NotAmp/UnfavINPC, the 5-year EFS and OS were both 100%, before (n = 6) and after (n = 4) 2006. For the combined cohorts for ≤2006 versus > 2006, EFS and OS were 91±4.4% versus 88±4.3% (p = 0.6), and 91±4.5% versus 95±2.9% (p = 0.5), respectively. Within HR pts diagnosed ≤2006, EFS/OS were 91±4.4%/91±4.5% for (12-18mo/Stage4/FavBiology plus 12-18mo/Stage3/NotAmp/UnfavINPC) vs 38±1.3%/43±1.3% for all other HR pts < 3 yrs old (p < 0.0001; Table). Within IR pts diagnosed > 2006, EFS/OS were 88±4.3%/95±2.9% for (12-18mo/Stage4/FavBiology plus 12-18mo/Stage3/NotAmp/UnfavINPC) vs 88±0.9%/95±0.6% for all other IR pts < 3 yrs old (p = 0.9). **Conclusions:** Our 19 year study demonstrates that excellent outcome is maintained among toddlers with Stage4/FavBiology and Stage3/Not Amp/Unfav INPC neuroblastoma with a significant reduction of therapy from high- to intermediate-risk treatment. Importantly, pts were likely spared acute toxicity and late effects known to be associated with HR therapy. Efforts to identify additional pt cohorts who may not require HR therapy to achieve long-term survival are critical to improve the long-term health of children with neuroblastoma. Research Sponsor: Little Heroes Pediatric Cancer Research Foundation, Other Foundation, U.S. National Institutes of Health.

	5-yr EFS±SE % (n)	5-yr EFS±SE % (n)	EFS p-val	5-yr OS±SE % (n)	5-yr OS±SE % (n)	OS p-val
	≤2006	> 2006		≤2006	> 2006	
A = 12-18mo Stage 4 Fav Biology	89±5.1 (40)	87±4.6 (55)	0.7	89±5.1 (40)	94±3.2 (55)	0.4
B = 12-18mo Stage 3 Not Amp Unfav INPC	100 (6)	100 (4)	1.0	100 (6)	100 (4)	1.0
< 3 yrs old	A+B	All others		A+B	All others	
HR ≤2006	91±4.4 (46)	38±1.3 (1535)	< 0.0001	91±4.5 (46)	43±1.3 (1535)	< 0.0001
IR > 2006	88±4.3 (59)	88±0.9 (1385)	0.9	95±2.9 (59)	95±0.6 (1385)	0.9

10014 **Poster Discussion Session**

Modifiable risk factors for late mortality among five-year survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. *First Author: Stephanie B Dixon, St. Jude Children's Research Hospital, Memphis, TN*

Background: The impact ofmodifiable lifestyle and cardiovascular risk factors (CVRFs) on risk for late mortality in adult survivors of childhood cancer is not well established. **Methods:** All-cause and health-related late (>5 years from cancer diagnosis) mortality (HRM; excludes death from primary cancer and external causes) were evaluated in five-year survivors diagnosed <21 years of age using the National Death Index through 2017. Modifiable lifestyle (smoking status, alcohol use, physical activity, body mass index [BMI]; combined to create a score [0-4] and categorized as unhealthy [0-2], moderate [2.5 or 3], healthy [3.5 or 4]) and CVRFs (hypertension [HTN], diabetes [DM], dyslipidemia) were assessed as time-varying covariates. Standardized mortality ratios (SMRs) and absolute excess risk of death per 1000 person-years (AER) with 95% confidence intervals (CIs) were estimated. Multivariable models estimated the relative risk (RR) of death adjusted for demographic and socioeconomic variables. **Results:** Among 20,051 adult survivors (median age 40.0 years, range 18.7 – 67.7), 19% reported ≥1 CVRF (13% HTN, 9% dyslipidemia, 5% DM) and few reported a healthy lifestyle (29% healthy, 40% moderate, 31% unhealthy). There were 1476 deaths due to health-related causes. While all survivors experienced an increased risk of HRM compared to the US population, risk was lower among those with a healthy vs. unhealthy lifestyle (SMR 3.5, 95% CI 3.1-3.9 vs. 6.2, 5.7-6.7) and very high among underweight survivors (11.1, 9.3-13.3) and those with both HTN and DM (13.0, 9.2-18.0). Stratified by lifestyle score, the excess risk of HRM was lowest in those with a healthy lifestyle across survival time (Table). Similar trends were seen when stratified by 0, 1 and 2 CVRFs. In multivariable models, compared to survivors with no CVRFs and healthy lifestyle, no CVRFs and unhealthy lifestyle was associated with a 50% increased risk of HRM (RR 1.5, 95% CI 1.2-1.8) and unhealthy lifestyle plus HTN a 2-fold increased risk of HRM (2.2, 1.6-2.8). Regardless of lifestyle group, ≥2 CVRF increased risk for HRM at least 2-fold (p-values <0.001). **Conclusions:** A reduction in excess deaths is observed among adult survivors of childhood cancer with a healthy lifestyle and no CVRFs as they age. Interventions that target improved lifestyle choices and prevention or aggressive treatment of modifiable CVRFs may reduce risk for late mortality. Research Sponsor: U.S. National Institutes of Health, American Lebanese Syrian Associated Charities.

AER (95% CI) of health-related death.

	Survival Time (yrs)			
Lifestyle	6-14	15-24	25-34	≥35
Healthy	0.6 (0.0-1.9)	1.4 (1.0-1.9)	3.2 (2.5-4.0)	6.5 (4.5-9.0)
Moderate	2.0 (0.8-3.7)	2.3 (1.8-2.8)	4.9 (4.2-5.7)	12.1 (10.1-14.4)
Unhealthy	1.6 (0.3-3.9)	2.9 (2.3-3.7)	6.4 (5.5-7.4)	15.7 (13.3-18.3)
CVRF				
0	1.3 (0.7-2.2)	1.9 (1.6-2.2)	4.1 (3.6-4.6)	9.7 (8.3-11.3)
1	0.7 (0.0-5.6)	3.8 (2.6-5.2)	7.2 (5.8-8.8)	15.4 (12.2-19.2)
≥2	8.8 (0.0-50.5)	5.1 (2.6-8.6)	10.8 (8.2-13.9)	20.5 (15.8-26.0)

10015 **Poster Discussion Session**

Benefits, harms, and burden of colorectal cancer screening among childhood cancer survivors previously treated with abdominal-pelvic radiation. *First Author: Jennifer M Yeh, Boston Children's Hospital and Harvard Medical School, Boston, MA*

Background: Survivors of childhood cancer treated with abdominal-pelvic radiation are at increased risk for colorectal cancer (CRC). The Children's Oncology Group recommends early initiation of CRC screening at age 30, yet the benefits and burden are unknown. **Methods:** We used incidence and mortality data from the Childhood Cancer Survivor Study to modify the SimCRC model from the Cancer Intervention and Surveillance Modeling Network (CISNET) to reflect high CRC and competing mortality risks among survivors, assuming the elevated cancer risk arises from higher adenoma onset. Strategies evaluated varied by modality (no screening, colonoscopy, multitarget stool DNA [mtsDNA] testing, fecal immunochemical testing [FIT]), screening start age (25, 30, 35, 40, 45) and screening interval (every 3, 5 or 10 yrs for colonoscopy; every 1, 2 or 3 yrs for mtsDNA and FIT). Abnormal stool test results were followed up with colonoscopy. Screening performance and complication rates were based on published studies. Analyses assumed full uptake and adherence to all screening and follow-up procedures. To identify the optimal strategy for each modality, we estimated the number of colonoscopies required per additional life-year gained and compared it to benchmarks for screening strategies recommended by the US Preventive Services Task Force for average-risk individuals. **Results:** Among a simulated cohort of 20-yr-old 5-yr survivors with a history of abdominal-pelvic radiation, the cumulative CRC risk at age 50 was 0.8%, approximately twice that predicted among general population average-risk individuals (0.4%). In the absence of screening, 73 per 1000 survivors would be diagnosed with CRC in their lifetime and 29 would die from the disease. All screening strategies evaluated were estimated to yield substantial reductions in the lifetime number of CRC cases (45-71 cases averted per 1000) and deaths (23-28 deaths averted per 1000). The estimated lifetime number of colonoscopies ranged from 1781 to 14,625 per 1000. The lifetime number of colonoscopy complications was relatively low at 9 to 20 per 1000. Based on the burden-to-benefit ratios, colonoscopy every 10 yrs starting at age 30, mtsDNA every 3 yrs starting at age 30, or FIT every 3 yrs starting at age 25 were the optimal screening strategies identified (Table). **Conclusions:** Early initiation of screening may substantially reduce CRC mortality among high-risk childhood cancer survivors. These estimates of the balance of screening benefits and burden can inform follow-up care guidelines. Research Sponsor: American Cancer Society, U.S. National Institutes of Health.

Model results per 1000 survivors for optimal screening strategies*.

	Benefits			Burden	Harms
Strategy	**CRC cases averted**	**CRC deaths averted**	**Life-years gained**	**Colonoscopies**	**Colonoscopy complications**
Colonoscopy, age 30, every 10y	61	26	342	4373	10
mtsDNA age 30, every 3y	53	25	333	2457	9
FIT age 25, every 3y	53	26	334	2190	9

*Compared to no screening

10016 **Poster Discussion Session**

Outcomes of Hispanic and non-Hispanic white pediatric and young adult patients with B-cell acute lymphoblastic leukemia after commercial tisagenlecleucel. *First Author: Panayiotis Vandris, Stanford University School of Medicine, Stanford, CA*

Background: Population-level data show significantly inferior outcomes for Hispanic children, adolescents, and young adults (CAYA) diagnosed with B-cell acute lymphoblastic leukemia (B-ALL) relative to non-Hispanic whites (NHW). Here, we compare outcomes between Hispanic and NHW CAYA patients with relapsed and/or refractory (RR) B-ALL receiving tisagenlecleucel, a CD19-specific chimeric antigen receptor (CAR) T cell therapy. **Methods:** We used data from the Pediatric Real World CAR Consortium retrospective cohort of 200 patients who underwent cell shipment for standard-of-care tisagenlecleucel between August 2017 and March 2020 (N=15 US institutions). Race/ethnicity was identified by medical record review. Patients reported as belonging to more than one racial/ethnic group were classified as multiracial and excluded from analysis. Baseline factors, outcomes, and safety post-infusion were characterized for Hispanic vs. NHW infused patients. Outcomes included complete response (CR) rate, overall survival (OS), duration of response (DOR), and duration of B-cell aplasia (DBA). A multivariate Cox model for OS was constructed, including all baseline factors. **Results:** Among 185 infused patients, 90 (48.6%) were NHW and 70 (37.8%) were Hispanic. Among 15 non-infused patients, 3 (20.0%) were NHW and 5 (33.3%) were Hispanic. Hispanic patients were significantly older at diagnosis (mean: 10.7 vs. 8.3 years, p=0.02) and had significantly shorter time from diagnosis to infusion (mean: 34.4 vs. 46.4 months, p=0.04). Hispanic and NHW patients did not significantly differ across sex, leukemia type, number of prior lines of therapy, receipt of prior CD19-directed therapy, level of disease burden pre-infusion, and number of relapses pre-infusion. Hispanic and NHW patients did not significantly differ across 1-month CR, 6-month OS, 1-year OS, 18-month OS, 6-month DOR, 1-year DOR, 6-month DBA, and 1-year DBA (Table). On multivariate analysis including the above covariates, OS did not significantly differ for Hispanic patients (HR=1.04, p=0.92). Hispanic and NHW patients did not significantly differ across grade ≥ 3 cytokine release syndrome, grade ≥ 3 neurotoxicity, grade 4 neutropenia, tumor lysis syndrome, or number of infections post-infusion. **Conclusions:** Outcomes were similar between Hispanic and NHW CAYA RR B-ALL patients receiving tisagenlecleucel in the real-world setting. Increasing access to CAR therapy among Hispanic CAYA B-ALL patients could help mitigate population-level disparities in outcomes observed after receipt of conventional therapies. Research Sponsor: None.

Outcomes for Hispanic vs. NHW patients.

Outcome (%)	Hispanic	NHW	P-value
1-month CR	81.4	88.8	0.19
6-month OS	89.7	83.4	0.82
1-year OS	71.9	71.2	0.62
18-month OS	68.2	71.2	0.62
6-month DOR	74.2	72.8	0.34
1-year DOR	62.3	60.7	0.42
6-month DBA	59.5	64.7	0.87
1-year DBA	52.1	50.0	0.85

10017 **Poster Discussion Session**

Racial and ethnic differences in presentation and clinical outcomes for pediatric rhabdomyosarcoma (RMS). *First Author: Princess Ekpo, Pediatric Oncology Branch, National Cancer Institute, Bethesda, MD*

Background: Race and ethnicity are recognized risk factors for many cancer types, including several pediatric cancers. Though racial and ethnic disparities in the presentation, treatment, and survival of certain cancers have been widely demonstrated, there is conflicting evidence about whether such disparities exist in RMS, the most common pediatric soft tissue sarcoma. Understanding the role of race and ethnicity in the presentation, treatment, and prognosis of RMS is important to promote improved survival in patients of all racial and ethnic groups. **Methods:** Patient, tumor, and treatment characteristics of patients enrolled on Children's Oncology Group studies D9602, D9802, D9803, ARST0331, ARST0431, ARST0531, and ARST08P1 were compared across racial and ethnic groups using a chi-square test. Significant characteristics underwent pairwise analysis, comparing the Non-Hispanic Black (NHB) and Non-Hispanic White (NHW) groups. Outcome analyses were performed using the Kaplan-Meier method and Wilcoxon signed-rank test. **Results:** Race and ethnicity incidence among the 2157 study patients were as follows: 8 (0.4%) American Indian or Alaska Native, 56 (2.6%) Asian, 271 (12.6%) Hispanic, 4 (0.2%) Native American or other Pacific Islander, 275 (12.8%) Non-Hispanic Black, 1335 (61.9%) Non-Hispanic White, and 208 (9.6%) unknown. Thirteen patient and tumor factors relating to presentation and treatment were evaluated for differences by race and ethnicity; the following five were significant: age, IRS group, tumor invasiveness, metastatic disease, and FOXO1 fusion partner. Pairwise comparison of NHB and NHW patients for these factors demonstrated that NHBs are more likely than NHWs to present at age 10 years or greater ($p = 0.002$) and that NHB patients are more likely to present with invasive tumors ($p = 0.012$). Incidence of metastatic disease at diagnosis was not significantly different between the groups ($p = 0.202$). No differences in treatment, including extent of surgical resection ($p = 0.259$) or use of radiation therapy ($p = 0.920$), were found. Neither event free survival nor overall survival were significantly different across the entire cohort (EFS $p = 0.457$, OS $p = 0.159$) or in subset analysis by risk group (low risk: EFS $p = 0.856$, OS $p = 0.558$; intermediate risk: EFS $p = 0.907$, OS $p = 0.493$; high risk: EFS $p = 0.218$, OS $p = 0.397$), by age (< 1y: EFS $p = 0.489$, OS $p = 0.546$; 1-9y: EFS $p = 0.417$, OS $p = 0.112$; ≥10y: EFS $p = 0.556$, OS $p = 0.609$), in invasive tumors (EFS $p = 0.704$, OS $p = 0.872$), or in metastatic disease (EFS $p = 0.270$, OS $p = 0.373$). **Conclusions:** These data indicate that while differences in the presenting features of RMS exist between racial groups, with NHB patients exhibiting higher risk features, patients treated on these clinical trials did not experience differences in outcomes by racial group. This suggests NHB patients may experience a survival benefit from clinical trial enrollment. Research Sponsor: U.S. National Institutes of Health.

10018 **Poster Discussion Session**

Barriers to effective childhood cancer control in Kenya (BECK) study, 2019-2020: A mixed methods study in a national tertiary facility and 10 regional cancer treatment centers. *First Author: Valerian Mwenda, National Cancer Control Program, Ministry of Health, Nairobi, Kenya*

Background: Globally, 80,000 children die from cancer annually; 80% in low- and middle-income countries (LMICs). Childhood cancer cure is possible in more than 80% of cases, in all economic settings. This study aimed to identify barriers to effective management of childhood cancers in Kenya, for program and policy intervention. **Methods:** We reviewed childhood cancer cases diagnosed at Kenyatta National Hospital in the period 2015-2019. We also assessed capacity of ten recently established regional cancer centres for childhood cancer diagnosis and treatment. We conducted focused group discussions among childhood cancer survivors' caregivers and key informant interviews among childhood cancer specialists and policy makers from the Ministry of Health and the National Cancer Institute of Kenya. We estimated diagnostic delays, mapped service availability and deductively summarized the qualitative data into main themes. **Results:** We abstracted 1,764 cases; median age 6 years (IQR 9); 1013 (57.5%) were male. Most affected age group was 0-4 years (47.3%). Most common cancer types were retinoblastoma (23.3%), nephroblasoma (10.4%) and acute lymphoblastic leukaemia 10.3%). Cases managed at KNH decreased between 2015 and 2017, and then recovered. The median total delay (symptoms onset to treatment initiation) was 32 days (range 0-3666). Regional cancer centres lacked specialized workforce for childhood cancer care. Caregivers identified inadequate cover by National Health Insurance and disorganized care process as major challenges. At health system and policy level, low awareness, fragmented referral systems and in-effective policy implementation are major challenges to childhood cancer control. **Conclusions:** Increasing number of specialized personnel, creation of a differentiated financing package for childhood cancer and restructuring of referral and the care process can improve childhood cancer outcomes in Kenya. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

10019 **Poster Discussion Session**

Identifying trends for high symptom burden across the care continuum in adolescents and young adults (AYA) with hematologic malignancies. *First Author: Sarah Elizabeth Monick, University of Chicago Medicine, Chicago, IL*

Background: Cancer in adolescence and young adulthood is a non-normative life event associated with profound long-term physical and psychosocial consequences. Prior studies specifically demonstrate AYA patients with hematologic malignancies experience high symptom burden with poor quality of life. Here, we describe trends and factors associated with high symptom burden in patients treated at a multi-disciplinary AYA leukemia clinic at an academic medical center. **Methods:** The Edmonton Symptom Assessment Scale [ESAS] (measuring physical symptoms) and Brief Symptom Inventory-18 [BSI-18] (measuring psychological distress) were administered at baseline, 3 months, and 6 months from initial survey. Baseline demographic and treatment characteristics were collected. All patients had leukemia or lymphoma, were on treatment or in survivorship, and had access to a palliative care provider who was integrated into the clinic. Data was analyzed using Wilcox ranked sum test and linear mixed-effects model testing. **Results:** Of the 31 patients (median age 29 years, range 18-43) who completed surveys, 25 (80%) completed surveys at 6 months; 48% were female, 58% were white, 16% lived alone, 28% were single, 37% had children, 54% completed college, and 35% had an annual household income ≥ $75,000. Phases of care included 52% on intensive frontline/salvage treatment, 19% in maintenance (i.e. lower intensity) therapy, 16% as recent stem cell transplant (SCT) recipients (< 1 year since date of transplant), and 13% in survivorship. Overall, ESAS scores among patients were similar regardless of care phases; however, patients on frontline/salvage therapy reported higher fatigue than those in maintenance ($p = 0.01$). Moderate-severe symptoms (defined as ESAS > 3), including tiredness, anxiety, poor appetite, and poor feeling of well-being, were reported regardless of phase of care. At 6 months, there was no significant change in BSI-18 scores compared to baseline, while tiredness ($p = 0.02$), depression ($p = 0.01$), and constipation ($p = 0.02$) improved; no ESAS scores worsened. Age ≥ 30 was associated with worsening anxiety ($p = 0.01$) at 6 months vs baseline, while no statistically significant differences in ESAS scores were observed among race, education, relationship status, presence of children, living arrangement, or income. **Conclusions:** AYA patients with hematologic malignancies experience high symptom burden independent of demographic characteristics or phase of care. These findings highlight the need for standard symptom screening at each visit and the importance of incorporating supportive care throughout the continuum. Research Sponsor: None.

10020 **Poster Discussion Session**

Neuropathy and neurocognitive impairment in long-term survivors of pediatric cancer treated without central nervous system (CNS) directed therapy. *First Author: AnnaLynn Williams, St. Jude Children's Research Hospital, Memphis, TN*

Background: Survivors of pediatric cancer, including those without CNS-directed treatment, are at risk of neurocognitive impairment and peripheral or autonomic neuropathies; conditions that co-occur in non-cancer populations. Using the St. Jude Lifetime Cohort, we investigated associations between these sequelae to inform contributors to long-term cancer-related neurocognitive impairment. **Methods**: Clinically assessed survivors of pediatric cancer (N=2,138, mean age 31 [SD 13], 23[11] years from diagnosis, 51% male) not treated with CNS-directed therapy completed neurocognitive testing. Modified total neuropathy score peripheral sensory and motor subscales were combined with functional tasks and severity graded using a modified NCI CTCAE. Cardiac autonomic neuropathy was defined as impaired heart rate reserve (<80% age-sex-predicted or ≤62% with beta blocker). Separate log binomial regression models estimated risk of neurocognitive impairment (age adjusted z-score <10^{th} percentile) associated with grade 2+ sensory, motor or autonomic neuropathy. Path analysis examined if pain with daily interference mediated associations between motor or sensory neuropathy and neurocognitive impairment. **Results**: 838 (39%) survivors had autonomic, 115 (5.4%) had motor and 162 (7.6%) had sensory neuropathy. Compared to those with no neuropathy, survivors with motor or sensory neuropathy had a higher risk of impairment in sustained attention, visual-motor processing speed, short- and long-term memory, and executive function (Table, p's<0.01). Autonomic neuropathy was associated with a higher risk of impairment in visuo-motor processing speed (p=0.03). Pain partially mediated associations between sensory neuropathy and sustained attention (10% mediated, p=0.04), visual-motor processing speed (8% p=0.02), and executive function (14% p=0.02). Pain was not related to motor neuropathy. **Conclusions**: Peripheral and autonomic neuropathies are associated with significant risk of neurocognitive impairment in adult survivors of pediatric cancer. Research is needed to further understand shared mechanisms (e.g., pain, inflammation) to design targeted interventions to improve neuropathic symptoms and neurocognitive function. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

Relative risk (95% confidence interval) of neurocognitive impairment associated with neuropathy (vs. none).[1]

	Motor	Sensory	Autonomic
Sustained Attention	3.0 (1.7,5.4)	3.1 (1.8,5.3)	1.1 (0.7,1.7)
Visual-Motor Processing Speed	2.8 (1.7,4.6)	3.6 (2.3,5.6)	1.7 (1.2,2.4)
Short-term Verbal Recall	1.9 (1.1,3.2)	2.1 (1.3,3.5)	1.2 (0.8,1.8)
Long-term Verbal Recall	1.8 (1.2,2.8)	1.8 (1.1,2.7)	1.3 (0.9,1.8)
Executive Function	2.1 (1.4,3.1)	2.1 (1.4,3.1)	1.2 (0.9,1.6)

[1]Models adjusted for age at diagnosis, sex, race/ethnicity, high-dose methotrexate, high-dose cytarabine, and physical activity (MetHrs).

10021 **Poster Session**

Vitamin A and association with asparaginase-associated pancreatitis in children with acute lymphocytic leukemia. *First Author: Cheng-Yu Tsai, Stanford University, Palo Alto, CA*

Background: Asparaginase is a key component of treatment of acute lymphoblastic leukemia (ALL), which is the most common cancer in the pediatric population. However, asparaginase is associated with many toxicities, including pancreatitis, which is observed in up to 10% of patients and can lead to severe sequelae. **Methods:** We performed analysis of (1) transcriptomic data from (a) asparaginase-treated leukemic cells, and (b) the pancreas of mice that were induced with a chemical form of pancreatitis; (2) the US FDA Adverse Reporting System (FAERS) and electronic health records (TriNetX); (3) global plasma metabolomic screen and dietary intake evaluation from ALL patients; and (4) experimental animal studies to identify factors that impact asparaginase-associated pancreatitis (AAP). **Results:** Connectivity map analysis showed that asparaginase-induced gene signatures are potentially reversed by the retinoids (vitamin A and its natural and synthetic analogs). Analysis of TriNetX and FAERES demonstrated a 2-fold reduction in AAP risk with concomitant exposure to vitamin A. Further, we performed a case-control metabolomic study of 50 subjects with ALL enrolled in the Dana-Farber Cancer Institute DFCI ALL clinical trial protocols 05-001 (NCT00400946) and 11-001 (NCT01574274). All subjects were given a single dose of pegylated *E. Coli* asparaginase during induction therapy. Twenty-four subjects developed pancreatitis within 9 months from the start of induction therapy and were considered cases. The median time to develop pancreatitis among cases was 3.68 months (interquartile range: 3.58 months). Twenty-six control subjects were identified among patients who did not develop pancreatitis within the same evaluation period. The controls were matched for age, sex, and initial ALL risk. The screening revealed that the plasma levels of carotene diol isomers, from the start of induction to its end, were reduced by about 60% in the cases compared to the controls. A detailed 30-day dietary recall showed that the cases had received less dietary vitamin A than the controls during induction therapy. Notably, the median value for the composite intake of vitamin A constituents, termed the RAE (retinol activity equivalents) was 656.92 mcg per day among the controls, but was 34.6% lower among in the cases (median of 429.40 mcg per day, which is just above the recommended dietary allowance level of 400 mcg per day for the 4–8 year-old age group). In mice, asparaginase administration as a single agent was sufficient to reduce circulating and hepatic retinol levels. **Conclusions:** Based on these data, we propose that circulating retinoids maintain pancreatic health, that asparaginase reduces circulating retinoids, and AAP is more likely to develop with reduced dietary vitamin A intake. The systems approach provides the impetus to examine the role of dietary vitamin A supplementation for preventing or treating AAP. Research Sponsor: Servier Pharmaceuticals, U.S. National Institutes of Health.

10022 **Poster Session**

ADVL1514, a phase 1 study of ABI-009 (nab-sirolimus) in pediatric patients with recurrent or refractory solid tumors, including CNS tumors as a single agent and in combination with temozolomide and irinotecan: A Children's Oncology Group pediatric early-phase clinical trial network study. *First Author: Stuart Cramer, Prisma Health Children's Hospital- Midlands, Columbia, SC*

Background: nab-Sirolimus (formerly know ABI-009 and nab-rapamycin) is a novel human albumin-bound preparation of sirolimus, a potent mTOR inhibitor. We report results of a Phase I study of ABI-009 alone and in combination with irinotecan and temozolomide in children with relapsed/refractory solid or CNS tumors. **Methods:** Patients (age 1-21 years) with relapsed/refractory solid or CNS tumors were eligible. Using a rolling 6 design, ABI-009 was administered intravenously as a single agent on Days 1 and 8 of cycle 1 (cycle = 21d), then subsequent cycles ABI-009 was administered in combination with temozolomide (125 mg/m^2/dose, maximum 250 mg/dose) orally once daily x 5 on Days 1-5 and irinotecan 90 mg/m^2/dose orally once daily x 5 on Days 1-5. Three dose levels (DL) of ABI-009 were investigated (DL1: 35mg/m^2/dose, DL-1: 20mg/m^2/dose, and DL-2: 15mg/m^2/dose). The maximum tolerated dose (MTD) or Recommended Phase 2 Dose (RP2D) was established based on dose limiting toxicity (DLT) observed during Cycle 1 and 2. At the RP2D, additional patients were enrolled for pharmacokinetics (PK). **Results:** 33 patients were enrolled (32 eligible and 1 ineligible); 11 did not experience DLT but were not evaluable for toxicity due to progressive disease or physician decision to discontinue protocol therapy prior to completion of cycle 2; 17 [median age 13 (2-20) years] were evaluable for determination of MTD during dose escalation, 6 were enrolled on the PK cohort, of which 3 were evaluable to toxicity. At DL1, 2/5 patients experienced DLT (thrombocytopenia during cycle 1 (n = 1) and cycle 2 (n = 1)); at DL-1, 2/6 patients experienced DLT (thrombocytopenia in cycle 1); at DL-2, 1/6 patients experienced DLT (thrombocytopenia in cycle 1). PK expansion enrolled at DL-2 and 1/3 participants evaluable for toxicity had a DLT (mucositis). Overall, at DL-2, 2/9 patients (22%) had DLT. One patient with Ewing Sarcoma had a partial response and remained on study for 35 cycles; Patients (one each) with Ewing Sarcoma, Wilms Tumor, and Pineoblastoma had stable disease, ranging from 3-6 cycles. **Conclusions:** Thrombocytopenia was dose limiting for ABI-009 alone and in combination with temozolomide and irinotecan. The MTD for ABI-009 is 15mg/m^2/dose days 1 and 8 in combination with 5 daily doses of temozolomide 125 mg/m^2/dose and oral irinotecan 90 mg/m^2/dose. One patient had a partial response, 3 patients had prolonged stable disease. Pharmacokinetics and pharmacodynamics are pending and will inform future trials. Clinical trial information: NCT02975882. Research Sponsor: Pediatric Early Phase Clinical Trial Network (PEP-CTN): PEP-CTN Grant UM1CA228823; Phase I/Pilot Consortium Grant UM1CA097452; Cookies for Kids' Cancer; Solid Malignancy Integrated Translational Science Center: NCTN ITSC-Solid Malignancy Grant U10C.

10023 **Poster Session**

Minimal residual disease comparison between Ig/TCR PCR versus NGS assays in children with Philadelphia chromosome-positive acute lymphoblastic leukemia: A report from the COG AALL1631 study. *First Author: Thai Hoa Tran, CHU Ste-Justine, University of Montreal, Montreal, QC, Canada*

Background: Minimal residual disease (MRD) assessment by immunoglobulin/T-cell receptor (Ig/TCR) polymerase chain reaction (PCR) is currently being used in the international pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph$^+$ALL) trial EsPhALL2017/AALL1631 for risk stratification. MRD concordance has previously been demonstrated between Ig/TCR PCR and flow cytometry in Ph$^+$ALL. We sought to assess concordance of MRD assessment between conventional Ig/TCR PCR and next-generation sequencing (NGS) assays. **Methods:** MRD was assessed in all pts on AALL1631 by Ig/TCR PCR at end-induction IB; those with MRD <5x10^{-4} were classified as standard-risk (SR) and randomized to treatment with imatinib and one of two chemotherapy regimens without hematopoietic stem cell transplant (HSCT), whereas pts with end-induction 1B MRD ≥ 5x10^{-4} were considered high-risk (HR) and assigned to HSCT after consolidation chemotherapy. Residual diagnostic and end-induction IB samples from consenting pts were assessed for NGS MRD by the clonoSEQ assay (Adaptive Biotechnologies) in blinded fashion and subsequently compared to Ig/TCR MRD to determine concordance as related to MRD-based HSCT recommendations (*ie*, MRD ≥ 5x10^{-4} consistent with HR group assignment). MRD values were calculated using the kappa statistic for agreement above chance. **Results:** Sixty-seven pts had matched samples available for MRD assessment at end-induction 1B by both Ig/TCR PCR and NGS (Table). NGS MRD was evaluable for all 67 pts and stratified as 62 SR (<5x10^{-4}) and 5 HR (≥5x10^{-4}). In contrast, Ig/TCR PCR results were inevaluable for 3 pts (unsatisfactory sample quality) and indeterminate (positive, but not quantifiable) in 4 pts. Of the remaining 60 pts, 55 met SR and 5 HR criteria using Ig/TCR PCR. There was only 1 discordant case between the two methods for MRD-based HSCT recommendation among these 60 pts with a kappa statistic for agreement above chance of 0.88. **Conclusions:** NGS and Ig/TCR PCR assays were highly concordant in MRD assessment for risk stratification at a threshold of 5x10^{-4} in pediatric pts with Ph$^+$ALL enrolled on AALL1631. Of note, the NGS assay yielded MRD results amenable for risk stratification in 100% pts compared to 89.6% for the Ig/TCR PCR methodology. These data support the use of NGS MRD testing for risk stratification in pediatric Ph$^+$ALL. Research Sponsor: Heme-ITSC grant.

End-Induction IB MRD by Ig/TCR PCR versus NGS assays and HSCT recommendation concordance.

	MRD assays	
End-induction IB MRD results (n=67)	**NGS**	**Ig/TCR PCR**
Undetectable	34 (50.7%)	41 (61.2%)
Detectable - <1 x 10^{-5}	12 (17.9%)	1 (1.5%)
1 x 10^{-5} - <1 x 10^{-4}	11 (16.4%)	7 (10.4%)
1 x 10^{-4} - <5 x 10^{-4}	5 (7.5%)	6 (9.0%)
>5 x 10^{-4}	5 (7.5%)	5 (7.5%)
Inevaluable	0	3 (4.5%)
Indeterminate	0	4 (6.0%)
HSCT recommendation (n=60)	**Ig/TCR vs. NGS**	**Ig/TCR vs. NGS**
Concordant	Yes/Yes	4
	No/No	55
Discordant	Yes/No	1
	No/Yes	0

10024 **Poster Session**

Menin inhibitors as targeted therapeutics in KMT2a rearranged infant leukemia and the identification of effective treatment combinations. *First Author: Ritul Sharma, University of Calgary, Calgary, AB, Canada*

Background: *KMT2a* rearrangements are a hallmark of infant (less than 1 year of age) leukemia and are associated with poor prognosis. Menin is a ubiquitous protein that binds to the N-terminal of the KMT2a-fusion protein to mediate the oncogenic activity of *KMT2a*-rearranged leukemia cells. In this study, we evaluated the effect of multiple menin inhibitors and effective drug combinations for the treatment of KMT2A-rearranged infant leukemia. **Methods:** FISH analysis and immunoblotting confirmed the presence of *KMT2a*-fusion in the primary patient samples and cell lines studied. Lymphocytes from healthy donors were used as controls. Cells were treated with various concentration of multiple menin inhibitors for 72 hours and growth inhibition was measured using alamar blue assay. Infant leukemia cells were treated with a panel of FDA-approved agents (n = 221) to identify potential synergy, additive- and antagonistic-effects with specific menin inhibitors. Therapeutic drug interaction properties were established by calculating combination indices (CI) using the Chou-Talalay method. Mode of cell death and cellular target modulations were determined by western blot analysis. The effect of targeting menin in the context of the leukemogenic bone marrow microenvironment was determined through stromal cell co-cultures. **Results:** A comprehensive analysis of menin inhibitors on infant leukemia cell lines and primary patient cells exhibited significant and quantitatively diverse responses in cells with distinct molecular properties. Within the panel of menin inhibitors, infant B-ALL cells were found to be more sensitive to MI-463, MI-503 and MI-136 with a mean IC_{50} of 5.9μM, 6.1μM and 10.2μM, respectively. On the other hand, MI-3 exhibited an IC_{50} of 35.6μM. The cytotoxic effect of menin inhibitors on normal lymphocytes was minimal, suggesting a favourable therapeutic window ($p < 0.0001$). High-throughput screening with a library of > 200 FDA-approved drugs revealed significant sensitivity of distinct infant leukemia cells to proteasome, HDAC and CDK9 inhibitors. Among these, substantial drug synergy was observed between menin and proteasome inhibitors. For example, carfilzomib synergised with menin inhibitors over a broad range of concentrations with a CI value of 0.7. **Conclusions:** In this study, we present and discuss the initial proof-of-concept preclinical data for the effective anti-leukemic activity of menin inhibition against KMT2A-rearranged infant leukemia cells. Furthermore, the comprehensive drug screen and drug combination studies identified a spectrum of mechanistically-validated synergies, providing usable data for the formulation of multi-agent clinical studies for this currently unmet need in pediatric oncology. Research Sponsor: Alberta Children's Hospital Foundation.

10025 **Poster Session**

Progression-free survival and patterns of response in patients with high-risk neuroblastoma (HR-NB) treated with irinotecan/temozolomide/dinutuximab/granulocyte-macrophage colony-stimulating factor (I/T/DIN/GM-CSFS) chemoimmunotherapy. *First Author: Benjamin Lerman, Children's Hospital of Philadelphia, Philadelphia, PA*

Background: Encouraging responses to chemoimmunotherapy with I/T/DIN/GM-CSF have been observed in trials for patients (pts) with relapsed/refractory HR-NBL, but factors associated with response have not been identified and duration of response has not been assessed. We aimed to evaluate timing and duration of response among pts with relapsed HR-NBL treated with I/T/DIN/GM-CSF and identify factors associated with response. **Methods:** We performed a multicenter retrospective cohort study of pts treated with I/T/DIN/GM-CSF. Eligibility criteria included: diagnosis of relapsed HR-NBL prior to age 30; objective response [OR; complete, partial, or minor response (CR, PR, or MR) by International Neuroblastoma Response Criteria (INRC)] or stable disease (SD) after initial therapy; receipt of I/T/DIN/GM-CSF for relapse or progression outside a clinical trial from 1/1/15-6/1/20. Logistic regression was used to identify factors associated with OR. Kaplan Meier analysis was used to determine progression-free survival (PFS). **Results:** We enrolled 143 pts with a median age at diagnosis of 51 months. Tumors were MYCN amplified in 52 (36%) and ALK was wild type in 73/94 (78% of tumors in which ALK status was known). 79 (55%) had received prior anti-GD2 therapy. I/T/DIN/GM-CSF comprised first relapse therapy in 96 pts (67%), second relapse therapy in 23 (16%) and subsequent therapy in 24 (17%). 70 (49%) achieved OR following I/T/DIN/GM-CSF therapy [29% CR, 15% PR, 5% MR], 30 (21%) achieved SD and 43 (30%) progressed. Median cycles received was 5 (range 1-31). 121 patients (85%) had their best response upon first disease evaluation. Later disease evaluations showed improved INRC classification in 14% of pts with initial SD, 33% with MR, and 41% with PR. Median time to OR was 2 months (range 1-21). Of the 105 relapse/progression events after starting I/T/DIN/GM-CSF (73% of pts), 59 (56%) occurred during therapy. Of the 42 pts who achieved CR with I/T/DIN/GM-CSF, 5 (12%) relapsed during I/T/DIN/GM-CSF and 17 (40%) relapsed after discontinuation. I/T/DIN/GM-CSF was discontinued in 83 pts (58%) due to suboptimal response or PD, and in 19 (13%) for toxicity. Median PFS among objective responders was 15.5 months. Among those in CR, median PFS after discontinuation of I/T/DIN/GM-CSF was 11.8 months (range 0.7-70.6). Multivariable models did not identify clinical or biologic factors associated with OR. **Conclusions:** 49% of pts receiving I/T/DIN/GM-CSF for relapsed HR-NBL achieved OR. Among responders, median response duration was 15.5 months. Pts with SD on first disease evaluation were unlikely to achieve OR, but > 1/3 of pts with MR/PR on first evaluation ultimately achieved CR. No identifiable clinical or biologic factors were associated with OR. Research Sponsor: None.

10026 **Poster Session**

Modulation of radiation biomarkers in a randomized phase II study of ^{131}I-MIBG with or without radiation sensitizers for relapsed or refractory neuroblastoma: A report from the NANT Consortium. *First Author: Kevin M. Campbell, Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA*

Background: ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) has demonstrated efficacy as a single agent for patients with neuroblastoma. Recent trials have focused on ^{131}I-MIBG combination strategies, though little is known about the impact of combination agents on markers of radiation exposure. **Methods:** NANT11-01 (NCT02035137) was a multicenter, open label, randomized phase II clinical trial that evaluated ^{131}I-MIBG therapy alone (Arm A) or in combination with vincristine/irinotecan (Arm B) or vorinostat (Arm C) for patients with resistant/relapsed neuroblastoma. We collected blood samples at baseline, 72 hours, 96 hours, and 15 days after ^{131}I-MIBG infusion and determined levels of plasma FLT3 ligand, serum amylase, and gene expression for selected RNA transcripts (apoptosis, DNA damage response and cell cycle related). We evaluated marker association with treatment arm, clinical response using NANT response criteria, toxicity, and whole-body radiation dose. **Results:** The cohort included 99 patients who had at least one biomarker available for analysis (32 Arm A; 35 Arm B; 32 Arm C). We observed both positive and negative significant modulation in most biomarkers between baseline, 72 hours, and 96 hours following ^{131}I-MIBG. Patients in Arm C had the lowest degree of modulation in FLT3 ligand. Elevated baseline levels of FLT3 ligand were significantly associated with improved Curie response but not overall response. Lower baseline BCL2 levels were associated with higher overall and Curie response. Patients with increased FLT3 ligand at 96 hours after ^{131}I-MIBG therapy were significantly more likely to have grade 4 thrombocytopenia .Peripheral blood gene expression of the BCL2 family of apoptotic markers (BCL2/L1 and BAX) was significantly associated with grade 4 hematological toxicity. Whole-body radiation dose and PRKDC fold change at 72 hours were significantly correlated. No other individual biomarkers were correlated with whole body radiation dose at 72 or 96 hours post ^{131}I-MIBG. **Conclusions:** Peripheral blood biomarkers relevant to radiation exposure demonstrate significant modulation over time after ^{131}I-MIBG treatment. Biomarkers related to hematopoietic damage and apoptosis were associated with hematological toxicity. Patients treated with vorinostat and ^{31}I-MIBG had differential modulation of FLT3-ligand Further use of these biomarkers may improve our ability to care for patients treated with ^{131}I-MIBG. Research Sponsor: Alex's Lemonade Stand Foundation.

10027 **Poster Session**

Impact of diagnostic and end-of-induction Curie scores in tandem autologous hematopoietic cell transplant for patients with high-risk neuroblastoma: A report from the Children's Oncology Group. *First Author: Keri A. Streby, Nationwide Children's Hospital/The Ohio State University, Columbus, OH*

Background: Diagnostic mIBG (meta-iodobenzylguanidine) scans are an integral component of response assessment in children with high-risk neuroblastoma. The role of end of induction (EOI) Curie Scores (CS) has been previously described in patients undergoing a single autologous hematopoietic cell transplant (AHCT) as consolidation therapy. We now examine the prognostic significance of CS in patients randomized to tandem or single AHCT on the Children's Oncology Group (COG) trial ANBL0532. **Methods:** A retrospective analysis of mIBG scans obtained from patients enrolled in COG ANBL0532 (n = 652) was performed. Evaluable patients (n = 179) had mIBG-avid, International Neuroblastoma Staging System (INSS) stage 4 disease, did not progress during induction therapy, consented to consolidation randomization, and received either a single (n = 99) or tandem AHCT (n = 80). In addition, evaluable patients had paired mIBG scans at time of initial diagnosis and EOI. Optimal CS cut points maximized the outcome difference (≤ vs > CS cut-off) according to the Youden index. Log-rank tests compared EFS subgroups, with $p < 0.05$ considered statistically significant. 3-year EFS is presented ± standard error. EFS was estimated for relative reductions in CS of 50% and 75% from diagnosis to EOI. **Results:** For recipients of tandem AHCT, the optimal cut point at diagnosis was CS = 12, with superior EFS from study enrollment for patients with CS<12 (74.2±7.9%; n = 31) vs CS > 12 (59.2±7.1%; n = 49) ($p = 0.002$). At EOI, the optimal cut point was CS = 0, with superior EFS from EOI for patients with CS = 0 (72.9±6.4%; n = 48) vs CS > 0 (46.5±9.1%; n = 32) ($p = 0.002$). The cut point at diagnosis for recipients of single AHCT was CS = 21 ($p = 0.04$), while the EOI CS had an optimal cut point of 2, but without a significant difference in EFS ($p = 0.29$). Absolute CS at diagnosis and at EOI had a greater impact on outcome than the relative reduction in CS between diagnosis and EOI, for both single and tandem AHCT. **Conclusions:** In the setting of tandem transplantation for children with high-risk neuroblastoma, Curie scores at diagnosis and end-induction may identify a more favorable patient group. Patients treated with tandem AHCT who exhibited a CS<12 at diagnosis or CS = 0 at EOI had superior EFS compared to those with CS above these cut points. Similar to prior reports, a CS<2 was the optimal cut point for single transplant recipients. Clinical trial information: NCT00567567. Research Sponsor: U.S. National Institutes of Health.

10028 **Poster Session**

Naxitamab-based chemoimmunotherapy for resistant high-risk neuroblastoma: Results of "HITS" phase II study. *First Author: Shakeel Modak, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Chemoresistant disease is an obstacle for cure of high-risk neuroblastoma (HR-NB). Anti-GD2 monoclonal antibodies (MoAb) dinutuximab and naxitamab in combination with cytokines are FDA-approved to consolidate remission and for chemorefractory osteomedullary HR-NB, but responses in progressive disease (PD) are rare. We investigated the combination of Humanized anti-GD2 MoAb naxitamab (Hu3F8), Irinotecan, Temozolomide and Sargramostim (GMCSF) in a phase II "HITS" protocol against resistant HR-NB (NCT03189706). Noteworthy differences between HITS and COG protocol ANBL 1221 included higher MoAb and temozolomide dosage and overlap of naxitamab with GMCSF. **Methods:** Patients were treated at Memorial Sloan Kettering (MSK) on protocol and at Hospital Sant Joan de Déu (HJSD) per protocol on compassionate basis. Salient eligibility criteria included evaluable or measurable chemoresistant disease. Prior anti-GD2 MoAb or irinotecan/temozolomide (IT) therapy was permitted. Each cycle, administered 3-5 weeks apart, comprised irinotecan 50 mg/m^2/day intravenously (IV) plus temozolomide 150 mg/m^2/day IV or orally (days 1-5); naxitamab 2.25 mg/kg/day IV, days 2,4,8 and 10, and GMCSF 250 mg/m^2/day subcutaneously, days 6-10. Toxicity was measured by CTCAE v4.0 and responses by International Neuroblastoma Response Criteria. Objective responses (OR) were also noted. The primary endpoint of the phase II trial was complete (CR) and partial response (PR) after 4 cycles with a desirable rate of 40%; type I and II errors of 10% (undesirable=20%). **Results:** Of 90 heavily prior-treated patients (38 at MSK evaluated on trial, 52 at HJSD), 8 had HR-NB refractory to induction chemotherapy while 82 had up to 6 prior relapses (median=1). 503 cycles (median 5/patient) were administered. Toxicities included myelosuppression and diarrhea expected with IT, pain and hypertension expected with naxitamab, plus febrile neutropenia in 4%. No other >grade 2 unexpected toxicities occurred; treatment was outpatient. Primary endpoint was reached in the phase II trial: INRC response = 30.6%, lower boundary = 20.4%. In the entire cohort, best responses were CR (26%), PR (11%), mixed response (9%), stable disease (27%) and PD (27%). OR were noted in 64%, with soft tissue (48%) and skeletal MIBG uptake (66%). CR in BM was seen in 57%. OR occurred in patients with *MYCN*-amplified (25%), refractory (100%) and relapsed (61%) HR-NB; and patients who had previously received I/T (64%) or naxitamab (68%). In patients who had previously received dinutuximab/IT, OR rate to HITS was 42% (5/12). Human anti-human antibody did not develop in any patient (n=50). **Conclusions:** Naxitamab-based chemoimmunotherapy was safe without immunogenicity. It was effective against chemoresistant HR-NB in all disease compartments even in patients with multiple prior relapses, and in patients who previously received anti-GD2 MoAbs and/or IT. Research Sponsor: Band of Parents, Pharmaceutical/Biotech Company.

10029 **Poster Session**

Phase 1 clinical trial of durvalumab in children with solid and central nervous system tumors. *First Author: Leo Mascarenhas, Cancer and Blood Disease Institute, Children's Hospital Los Angeles, Keck School of Medicine, University of Southern California, Los Angeles, CA*

Background: Immune checkpoint inhibitors targeting PDL-1 have shown clinical benefit in adults with cancer. We conducted a first in pediatrics, phase 1 clinical trial to assess safety, pharmacokinetics (PK), and pharmacodynamics of durvalumab in children with solid and central nervous system malignancies. **Methods:** This single center investigator-initiated trial enrolled eligible patients considered incurable with measurable/evaluable disease (exception: osteosarcoma in 3rd remission), no prior exposure to checkpoint inhibitors and adequate organ function on 2 dose levels: 10 mg/kg (DL1) and 15 mg/kg (DL2), utilizing a standard 3+3 design. The primary objectives were to assess safety and PK of durvalumab. Durvalumab was administered intravenously (IV) Q2 weeks for a maximum of 24 doses (12 cycles) on study or until disease progression/unacceptable toxicity. Patients were assessed for dose-limiting toxicity (DLT) in the first 28 days. The tolerable dose level was expanded to obtain PK on at most 6 patients age ≥12 years (yrs) and 6 patients < 12 yrs weighing < 35 kg). Soluble PDL-1 (sPDL1) and anti-drug antibody (ADA) levels were also assessed. **Results:** Fifteen patients (8M/7F) were enrolled (3 DL1, 12 DL2) with median age of 12.7 (2.9-16.6) yrs. Diagnoses included 5 osteosarcoma, 4 ependymoma and 1 each of glioblastoma, astrocytoma, rhabdomyosarcoma, synovial sarcoma, hepatoblastoma and adrenocortical carcinoma. Of the 14 patients evaluable for DLT, 3 were on DL1 and 11 on DL2. Only 1 DLT was observed, Grade (Gr) 3 intracranial hemorrhage (ICH). Median number of cycles administered was 3 (1-12). There were no treatment related deaths. There were 72 treatment-related adverse events (TRAEs) observed in 11 patients in a total of 73 cycles administered on the trial. The most common TRAE was AST elevation (7 instances in 4 patients). All TRAEs were < Gr 3 except for 1 instance each of Gr 3 AST elevation, anemia, and ICH. All 15 patients had PK, sPDL1 and ADA samples analyzed. PK for DL2 in patients ≥35 Kg and < 35 Kg were comparable to PK in adults dosed with durvalumab 10 mg/kg IV Q2W. Mean (SD) DL2 Cmax 292 (102) mg/mL, Ctrough 85.1 (27.7) mg/mL, AUC 2220 (986) day*mg/mL in pts ≥35 Kg and Cmax 442 (338), Ctrough 120 (123), AUC 2470 (1870) in pts < 12 yrs weighing < 35 kg. sPDL1 was completely suppressed in all patients 2 weeks after a single dose of durvalumab. No ADA were detected in any patients. Five patients (2 osteosarcoma, 3 ependymoma) completed > 6 cycles and 3 (1 osteosarcoma, 2 ependymoma) completed all 12 cycles of treatment. One objective response (PR) was seen in a patient with anaplastic ependymoma by RECIST1.1. Four patients were alive at the time of data cut-off with a median follow up of 30.5 (8.8-58.1) months. **Conclusions:** Durvalumab at 15 mg/kg IV Q2W was well tolerated in children with drug exposures comparable to adults receiving10 mg/kg IV Q2W. A signal for activity was noted in ependymoma where 3 of 5 children benefitted clinically. Clinical trial information: NCT02793466. Research Sponsor: AstraZeneca.

10030 **Poster Session**

Efficacy and safety of larotrectinib in pediatric patients with tropomyosin receptor kinase (TRK) fusion-positive cancer: An expanded dataset. *First Author: Leo Mascarenhas, Cancer and Blood Disease Institute, Children's Hospital Los Angeles, Keck School of Medicine, University of Southern California, Los Angeles, CA*

Background: Neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions are oncogenic drivers in various tumor types across all ages. Larotrectinib is a first-in-class, central nervous system (CNS)-active, highly selective tropomyosin receptor kinase (TRK) inhibitor approved for pediatric and adult patients (pts) with TRK fusion-positive cancer, demonstrating an objective response rate (ORR) of 88% across 78 pediatric pts with non-CNS cancers (van Tilburg et al, SIOP 2021). We report an analysis of the efficacy and safety of larotrectinib in an expanded dataset of pediatric pts with TRK fusion-positive cancer. **Methods:** Pediatric pts (< 18 years) with non-CNS TRK fusion-positive cancer in larotrectinib clinical trials (NCT02637687, NCT02576431) were included and ORR (RECIST v1.1) was investigator (INV)-assessed. Data cut-off was July 20, 2021. **Results:** A total of 94 pts were included in this analysis. Tumor types included infantile fibrosarcoma (52%), other soft tissue sarcoma (40%), congenital mesoblastic nephroma (2%), thyroid cancer (2%), bone sarcoma (1%), breast cancer (1%), and melanoma (1%). Pts had gene fusions involving *NTRK1* (43%), *NTRK2* (3%), or *NTRK3* (54%). Median age was 2.2 years (range 0–18 years). Of the 62 (66%) pts who received prior systemic therapy, 32 (52%) received ≥2 lines. The INV-assessed best ORR for the 93 evaluable pts was 84% (95% confidence interval [CI] 75–91): 35 (38%) complete response (CR; including two pending confirmation and 10 pathological CR), 43 (46%) partial response (two pending confirmation), 11 (12%) stable disease, two (2%) progressive disease, and two (2%) not determined. The median time to response was 1.8 months. Overall, median duration of response was 43.3 months (95% CI 23.4–NE); median follow-up was 26.0 months. Median progression-free survival and overall survival (OS) were 37.4 months (95% CI 22–NE) and not reached, respectively; median follow-up was 21.2 and 30.3 months, respectively. The 36-month OS rate was 93% (95% CI 86–99). Treatment duration ranged from 1+ to 63+ months. At data cut-off, 31 pts had progressed; 18 continued treatment post-progression for ≥4 weeks. There were no treatment-related deaths. Treatment-related adverse events (TRAEs) occurred in 81% of pts (23% were Grade [G] 1, 28% G2, 25% G3, and 5% G4). The most common TRAE was increased aspartate aminotransferase (31 pts [33%]). Four pts (4%) discontinued treatment due to TRAEs. Neurological TRAEs occurred in 12% of pts (5% were G1, 4% G2, and 2% G3). The most common neurological TRAE was headache (5 pts [5%]). **Conclusions:** In this expanded dataset, larotrectinib continues to demonstrate rapid and durable tumor-agnostic efficacy, extended survival, and a favorable safety profile in pediatric pts with TRK fusion-positive cancer. These results highlight the importance of identifying *NTRK* gene fusions in pediatric solid tumors. Clinical trial information: NCT02576431, NCT02637687. Research Sponsor: Bayer HealthCare and Loxo Oncology.

10031 **Poster Session**

Risk-adapted local therapy and intensive chemotherapy in patients with high-risk rhabdomyosarcoma. *First Author: Michael W. Bishop, St. Jude Children's Research Hospital, Memphis, TN*

Background: Outcomes for patients with metastatic RMS remain poor. Dose escalation of radiation may reduce risk of local failure, and maintenance therapy has prolonged survival in intermediate risk patients. We investigated a multimodal chemotherapeutic regimen with risk adapted local therapy and the addition of maintenance therapy following intensive chemotherapy to improve the outcome for patients with high-risk RMS. **Methods:** We conducted a phase 2 multi-center trial for patients with newly diagnosed high-risk (stage 4) RMS. Patients received 54 weeks of chemotherapy (vincristine/irinotecan, interval compressed vincristine/doxorubicin/cyclophosphamide and ifosfamide/etoposide, and vincristine/dactinomycin/cyclophosphamide) followed by 4 cycles of anti-angiogenic maintenance therapy (bevacizumab, sorafenib, cyclophosphamide). Primary tumor local control consisted of surgery and photon/proton radiation therapy (RT) dependent on the degree of resection (negative margin – no RT, positive margin – 36 GyRBE, unresected ≤5cm – 50.4 GyRBE, unresected > 5cm – 59.4 GyRBE). RT was administered at Week 4 or 20 based on size/location, and to radiographically visible (non-CR) sites of metastatic disease at end of treatment. **Results:** Thirty-nine eligible patients with high-risk RMS (64% *FOXO1* fusion positive, 74% with nodal disease, 67% Oberlin score > 1) were enrolled. Two of 13 patients with Oberlin score ≤ 1 were *FOXO1* fusion positive whereas 23 of 26 patients with Oberlin score > 1 were fusion positive. Seventeen patients received maintenance therapy as planned (progression, n = 12; received alternate maintenance regimen, n = 4; other, n = 6) with a median of 4 cycles (range 1-4). Common toxicities of maintenance included palmar-plantar erythrodysesthesia (n = 9), rash (n = 7), and cystitis (n = 6). At a median follow-up of 43.5 months for survivors, 3-year EFS was 29.5% (95% CI 15.4-45.1%). Fusion positive status significantly predicted EFS (negative, 60.6% vs. positive, 9.6%, p = 0.019), whereas low Oberlin score approached significance for EFS (≤1, 56.6% vs. > 1, 16.4%, p = 0.064). The cumulative incidence of local failure was 17.5% (95% CI 6.9-32.2%). Twenty-one patients achieved CR of all metastatic sites and did not receive metastatic site RT. Of those, 7 experienced disease recurrence in a pre-existing metastatic soft tissue site. Among 4 patients who received metastatic site RT at the end of treatment, one patient experienced disease recurrence in a pre-existing metastatic site. **Conclusions:** The addition of maintenance therapy to intensive chemotherapy and risk adapted radiotherapy did not improve EFS in this population. Consolidative radiation should be considered for soft tissue metastatic sites regardless of radiographic response. Clinical trial information: NCT01871766. Research Sponsor: American Lebanese Syrian Associated Charities.

10032 **Poster Session**

Predictors of differential outcomes according to response to induction chemotherapy in high-risk neuroblastoma. *First Author: Elizabeth Sokol, Ann & Robert H Lurie Children's Hospital of Chicago, Chicago, IL*

Background: Response to induction chemotherapy has been shown to predict outcome in patients with high risk neuroblastoma, with those achieving a complete response (CR) having superior outcomes. Little is known about what factors impact survival within groups of patients with favorable and unfavorable end-induction response. We evaluated whether conventional prognostic factors remain prognostic in subsets of patients defined by response to induction. **Methods:** Patients from four COG high risk trials (A3973, ANBL02P1, ANBL0532, and ANBL12P1) were included. End-induction response was determined according to the 1993 International Neuroblastoma Response Criteria (INRC). Patients were categorized as having end-induction responses of CR, partial response (PR) or better, less than PR without progressive disease (PD), and PD. Univariate Cox models calculated OS hazard ratios for clinical and biological variables in subsets defined by response category. **Results:** 1,244 patients were included. Among all patients, age >5 years, INSS stage 4 disease, adrenal primary site and unfavorable histology by INPC were associated with inferior OS (see Table). Among patients who achieved a CR, stage 4 disease was the only factor that remained significantly associated with worse OS. Among those who achieved PR or better, age >5 years, stage 4 disease and unfavorable histology remained significantly associated with inferior OS. For those with less than PR but without PD, adrenal primary site, *MYCN* amplification and 1p LOH were significantly associated with inferior OS. For those with PD, *MYCN* amplification and 1p LOH were associated with worse OS, but older age was associated with better OS. **Conclusions:** Specific prognostic factors in neuroblastoma are associated with differential survival in groups defined by response to induction. Age, stage, and histology appear to be associated with OS for patients with more favorable response to induction, whereas *MYCN* and 1p LOH play a greater role in patients with unfavorable response to induction. These data can help to further define prognosis for patients with variable responses to induction. Research Sponsor: None.

Hazard ratios for death (95% CI) according to clinical and biological variables for all high risk patients and for subsets defined by response to induction.

Variable	All Patients (n=1244)	CR (n=258)	PR, VGPR, or CR (n=992)	MR or NR (n=139)
INSS Stage 4	2.63* (1.91,3.63)	2.82* (1.54,5.16)	3.11* (2.10,4.59)	1.10 (0.35,3.49)
Unfavorable Histology	2.40* (1.28,4.49)	0.88 (0.22,3.57)	2.03* (1.01,4.09)	4.00 (0.56,28.81)
Age >5 years	1.29* (1.07,1.55)	1.14 (0.68,1.90)	1.39* (1.10,1.74)	0.95 (0.62,1.47)
Adrenal Primary	1.25* (1.06,1.47)	1.18 (0.78,1.78)	1.18 (0.97,1.44)	1.57* (1.01,2.43)
***MYCN* Amplified**	1.17 (0.99,1.40)	0.85 (0.55,1.30)	1.08 (0.88,1.33)	1.93* (1.10,3.39)
LOH/Aberration at 1p	1.29 (0.98,1.68)	0.88 (0.45,1.72)	1.21 (0.87,1.67)	2.50* (1.29,4.87)

* $p<0.05$

10033 **Poster Session**

Metronomic oral maintenance chemotherapy in patients with localized high-risk rhabdomyosarcoma (RMS) and RMS-like tumors: A report from a randomized, multicenter, phase III trial CWS-2007HR. *First Author: Ewa Koscielniak, Klinikum Stuttgart-Olgahospital, Stuttgart Cancer Center, Zentrum für Kinder-, Jugend- und Frauenmedizin, Pediatrics 5 (Oncology, Hematology, Immunology), Stuttgart, Germany*

Background: Low dose maintenance therapy as consolidation after multimodal standard therapy has been shown to improve survival in patients with sarcoma. It is however unclear which drugs and how long would be optimal. We investigated whether adding oral maintenance chemotherapy after standard multimodal therapy (ST) in patients with localized RMS and RMS-like sarcoma defined as high and very-high risk (HR and VHR), according to CWS stratification, would improve survival. **Methods:** Patients (pts) age > 6 months < 21 years, with 1. embryonal RMS N0, incompletely resected, (Group II or III), tumor size > 5cm and/or ≥10 years, in unfavorable primary sites and all N1 (HR RMS Group), 2. alveolar RMS N0/N1 (VHR RMS Group) 3.Unidfferentiated sarcoma (UDS), extraskeletal Ewing sarcoma (EES) and primary non resectable (Group III) synovial sarcoma (SS) (HR RMS-like Group) in complete remission after ST including 9 cycles of ifosfamide, vincristine and actinomycin D +/- doxorubicin, surgery and/or radiotherapy were eligible for randomization to stop treatment (S-arm) or receive maintenance chemotherapy (M-arm) with eight 10-days courses consisting of trofosfamide (2x 75mg/m^2/day) and idarubicine (1 x 5mg/m^2/day 1,4,7,10) alternating with trofosfamide and etoposide (2x 25mg/m^2/day). The study was designed with 80% power and a two-sided alpha level of 5% to detect an increase in 3 yr EFS from 60 to 75%. Randomisation was stratified according to risk groups. To reduce possible imbalances in the number of treatment assignments, a permuted block design was used. The initial calculated sample size was 145 pts in each group (recruitment period six years). Due to the lower than planned recruitement rate, the accrual was extended to 10 years and sample size recalculated to 98 pts in each group. **Results:** Between 1.7.2009 and 30.6.2019, 441 pts were eligible at diagnosis and 337 at the end of ST. 195 pts were randomized: 99 were assigned to the S-arm and 96 to M-arm. The distribution of the following clinical features:age, gender, tumor size, IRS-Group, T-Status, N-Status, histology and localisation showed no significant difference between the treatment groups. In the intent to treat population, with a median follow up of 4.9 years (IQR 3.0-5.7) in surviving pts, 3yr EFS and OS in M-arm vs S-arm were respectively: EFS 66.2% (95% IC 57.1-76.79) vs 75.0% (95% IC 66.8-84.3) (p 0.07) and OS 81.9% (95% IC 74.2-90.4) vs 84.6 (95% IC 77.5-92.4) (p 0.15). Toxicity grade 3 (no grade 4) in the M-arm was: hematological in 51 %, febrile infection 5%, sensory neuropathy in 1% pts. **Conclusions:** The addition of maintenance therapy with trofosfamide, etoposide and idarubicine after ST does not improve EFS and OS in patients with high risk RMS and RMS-like sarcomas. Clinical trial information: 2007-0001478-10. Research Sponsor: Kinderkrebstiftung Germany.

10034 **Poster Session**

Phase I results of the INFORM2 combination study of nivolumab and entinostat in children and adolescents: INFORM2 NivEnt. *First Author: Cornelis Martinus van Tilburg, Hopp Children's Cancer Center Heidelberg (KiTZ), German Cancer Research Center (DKFZ) and Heidelberg University Hospital, Heidelberg, Germany*

Background: Pediatric patients with relapsed or refractory high-risk solid and CNS tumors have dismal survival. To date treatment with immune checkpoint inhibitors in this population has been disappointing. This study exploits the immune enhancing effects of entinostat on nivolumab in biomarker enriched subpopulations. The study aims to determine the pediatric recommended phase II dose (pRP2D) and to evaluate activity and safety. **Methods:** This is an exploratory non-randomized, open-label, multinational seamless phase I/II trial in children and adolescents with relapsed / refractory or progressive high-risk solid and CNS tumors. The phase I is divided in 2 age cohorts: 12–21 years (y) and 6–11y and follows a 3 + 3 design with two dose levels for entinostat (dose level 1: 2 mg/m^2 and dose level 2: 4 mg/m^2 once per week) and fixed dose nivolumab (3 mg/kg every 2 weeks). Patients entering the trial on pRP2D can seamlessly enter phase II which consists of a biomarker defined four group basket trial: high mutational load (group A), high PD-L1 mRNA expression (group B), focal MYC(N) amplification (group C), low mutational load and low PD-L1 mRNA expression and no MYC(N) amplification (group D). **Results:** The first patient was enrolled in May 2020 and at the time of the data cut (21-JAN-2022), 19 patients were treated. The median age at enrollment was 14 y. In the 12 – 21y cohort 15 patients were enrolled and four patients in the 6 – 11y cohort. The most frequent treatment-related AEs to date were thrombocytopenia in six (32%), nausea and vomiting both in four (21%), and neutropenia in three patients (16%). Five patients (26%) experienced grade 3/4 mostly reversible treatment-related AEs, e.g. neutropenia/leukopenia. No treatment related deaths were reported. In the 6 – 11y cohort dose escalation is ongoing. In the 12 – 21y cohort, one DLT (CTCAE grade 3 thrombocytopenia) was observed in six patients on dose level two, which was determined as the pRP2D of the combination. At the time of the data cut, 10 patients (six in arm D and four patients in which the biomarker group was not yet determined) had received at least one RECIST/RANO response evaluation by central review in phase II. One patient (17%) in arm D with metastatic relapsed renal cell carcinoma (RCC) harboring a typical PRCC-TFE3 fusion showed a PR after two cycles and finally achieved an ongoing CR. Extensive explorative analyses of immune signatures derived from INFORM RNA-Seq and WES data revealed that both the primary diagnosis and the current relapse samples harbored a remarkable high immune cell infiltration, especially CD8+ T-cells. **Conclusions:** The first and ongoing global INFORM2 trial has identified the pRP2D for the nivolumab and entinostat combination in the older age cohort with good tolerability. A patient with metastasized relapsed RCC experienced a CR. The role of immune infiltration as a potential predictive biomarker is currently being explored. Clinical trial information: NCT03838042. Research Sponsor: DKFZ intramural NCT 3.0 POC grant, Other Foundation.

10035 **Poster Session**

A fully automated MRI-based deep-learning algorithm for classifying germinomas and nongerminomatous germ cell tumors. *First Author: Yanong Li, Beijing Tiantan Hospital, Beijing, China*

Background: Intracranial germ cell tumors (iGCTs) are classified into two pathological subtypes (Germinomas [GEs] and nongerminomatous germ cell tumors [NGGCTs]), with distinct treatment strategies and prognosis. Accurate preoperative determination of iGCT subtypes is essential for clinical decision-making and prognosis assessment. We aim to develop and validate a deep-learning algorithm to automatically segment the iGCTs and classify their subtypes using preoperativeT2-weighted (T2W) images. **Methods:** Brain MR imaging and corresponding pathologic information were retrospectively obtained for 594 iGCTs, including 269 GEs and 325 NGGCTs from Beijing Tiantan Hospital (between January 1, 2008, and October 31, 2020). The retrospective set was subdivided into the training (n = 416) and test (n = 178) sets to develop and test a 3D nnU-Net using T2W images (here we named iGCT-net) for iGCT segmentation and its subtypes (GEs and NGGCTs) classification, simultaneously. A prospective cohort (n = 73, 56 GEs and 17 NGGCTs) was designed as a simulation set to test the model in a simulated clinical application. Dice scores were computed to assess tumor segmentation. Accuracy, sensitivity, specificity, and area under the curve (AUC) were used to assess the GEs and NGGCTs classification. Sensitivity analysis on subgroups with tumor locating at suprasellar, pineal, and basal ganglia in test and simulation set, respectively. **Results:** For tumor segmentation, the iGCT-net achieved a dice score of 0.73 and 0.80 in test and simulation sets, respectively. For GEs and NGGCTs classification in the test set, the iGCT-net achieved an accuracy of 90.96%, sensitivity of 86.84% and specificity of 82.26%, and AUC of 84.87%. The iGCT-net showed 83.65% accuracy in the simulation set, with sensitivity of 83.56% and specificity of 83.72%, and AUC was 81.17%. In sensitivity analysis, the accuracies of the iGCT-net presented for the suprasellar region, pineal region, and basal ganglia region were 86.84%, 92.92%, and 61.73% in the test set, and 92.31%, 88.89%, and 72.27% for suprasellar region, pineal region, and basal ganglia region in the simulation set. **Conclusions:** We developed and validated a fully automatic deep learning algorithm to segment iGCT and classify GEs and NGGCTs with a high accuracy using only T2W images based on a large dataset. Research Sponsor: Grant number: 2020-2-1072.

10036 **Poster Session**

Multiomics analysis of pediatric solid tumors within the INFORM precision oncology study: From functional drug profiling to biomarker identification. *First Author: Dina ElHarouni, Hopp Children's Cancer Center Heidelberg (KiTZ), Faculty of Biosciences, Heidelberg University, Clinical Cooperation Unit Pediatric Oncology, German Cancer Research Center (DKFZ) and German Consortium for Translational Cancer Research (DKTK), Heidelberg, Germany*

Background: Within the INFORM (INdividualized Therapy FOr Relapsed Malignancies in Childhood) registry over 1200 childhood malignancies were molecularly profiled using next generation sequencing to identify therapeutic targets. Nevertheless, high evidence targets were only detected in 5% of cases and only 50% of the patients were identified with druggable pathways, while the remaining cases lacked druggable alterations. Thus, an ex-vivo functional drug response profiling platform for pediatric solid tumors has been established within the INFORM program to identify novel biomarkers and unravel molecular mechanisms associated with drug response profiles for clinical translation. **Methods:** Solid tumors from 97 paediatric patients were screened against a library of 76 drugs. A quality control classification decision tree was designed to select the samples for further analysis. Whole exome sequencing, low-coverage whole genome sequencing, and RNA-seq were used to analyze the molecular profiles of the samples. Molecular features were filtered to retain oncogenic and druggable events. Five data feature views (mutations, mRNA, gene fusions, CNVs, and drug responses) were used to train a Multi-Omics Factor Analysis (MOFA) model to identify prominent latent factors. **Results:** 81 samples passed the quality control inclusion criteria of which 76 samples had available omics data profiles. Quantitative drug profiling measurements were reported using the selective asymmetric drug sensitivity score.The multi-omics analysis captured five entity-specific omics signatures of Ewing sarcoma, Wilms tumor, BCOR sarcoma, neuroblastoma and ependymoma. Moreover, the analysis revealed sensitivity to navitoclax in neuroblastoma samples with PHOX2B-GATA3 overexpression, and an association between MEK inhibitor sensitivity and an expression signature in Wilms tumors. **Conclusions:** The combination of functional drug and multi-omics profiling enabled the identification of novel biomarkers for drug sensitivities in pediatric solid tumors. As we continue to expand the number of patient samples evaluated with our drug sensitivity platform, this dataset will provide insights for novel drug targets, and could unravel key molecular events and mechanisms acting towards personalized therapies. Research Sponsor: German Cancer Consortium (DKTK), the German Cancer Aid (DKH), the German Childhood Cancer Foundation (DKS), the German Cancer Research Center (DKFZ) and "Ein Herz für Kinder", Other Foundation.

10037 **Poster Session**

Combined IL-6 and IL-8 inhibition to overcome mesenchymal stem cell (MSC)-induced resistance to antimetastatic drugs in osteosarcoma. *First Author: S. Rubina Baglio, Amsterdam UMC, location VUMC, Amsterdam, Netherlands*

Background: Mesenchymal stem cells (MSCs) play a key role in the progression of osteosarcoma (OS). In response to tumor-associated signals, including tumor-secreted extracellular vesicles (EVs), MSCs increase the expression of inflammatory cytokines promoting tumor cell aggressiveness. Previous data has demonstrated that IL-6 and IL-8 signaling mediate metastasis in OS. The aim of this study was to evaluate tumor EV-induced alterations of MSCs and identify combination therapies that can counteract MSC-induced resistance to antimetastatic drugs. **Methods:** Tumor EV-induced alterations of the MSC transcriptome were analyzed by RNA-seq. Gene set enrichment analysis (GSEA) was applied to discriminate TGFβ-dependent and independent pathways. EV RNA-induced expression changes were identified by transfecting purified EV-RNA in MSCs and by using a selective dsRNA antagonist. We selected candidate targets to block MSC-induced drug resistance and evaluated their effect in an orthotopic xenograft model of OS. Ladarixin (an allosteric inhibitor of the CXCL8/IL-8 receptors CXCR1 and CXCR2; 30 mg/kg 6x per week i.p.) and tocilizumab (anti-IL6 receptor antibody; 100 µg/mouse every other day i.p.) were administered starting from day one until the experimental endpoint. Metastasis were quantified by histological examination. This study was funded by the Dutch Cancer Society (KWF), POR FESR Campania 2014-2020 and Dompé Farmaceutici SpA. **Results:** EVs from aggressive cancer cell lines induced an inflammatory MSC (iMSC) phenotype, characterized by increased expression of chemokines, including IL-8 as the most upregulated. Apart from IL-6, these alterations were mostly independent from TGFβ signaling and related to pattern recognition receptor (PRR) activation. We demonstrated that tumor EV-associated non-coding RNAs trigger TLR3 signaling in MSCs activating an innate immune response leading to high induction of IL-8 and other chemokines. Ladarixin and tocilizumab combination significantly reduced metastasis formation in a spontaneous metastasis model and overcame iMSC-induced resistance observed with single antimetastatic treatments. No effect was observed on primary tumor growth. **Conclusions:** EV-associated TGFβ together with EV-RNA induce iMSCs development in OS. Ladarixin in combination with tocilizumab reduced metastasis formation in a xenograft mouse model of OS, and, importantly, may prevent the occurrence of iMSC-induced tumor resistance to antimetastatic drugs. Research Sponsor: KWF Kankerbestrijding, Pharmaceutical/Biotech Company, POR FESR Campania 2014-2020.

10038 **Poster Session**

Phase I study of ^{131}I-MIBG with dinutuximab for patients with relapsed or refractory neuroblastoma: A report from the new approaches to neuroblastoma therapy (NANT) consortium. *First Author: Thomas Cash, Aflac Cancer & Blood Disorders Center, Children's Healthcare of Atlanta, Emory University School of Medicine, Atlanta, GA*

Background: ^{131}I-metaiodobenzylguanidine (MIBG) is one of the most active salvage therapies for patients with relapsed or refractory (R/R) high-risk neuroblastoma (HRNB). Preclinical neuroblastoma studies show cooperative effects when radiation is combined with anti-GD2 monoclonal antibody (mAb). We hypothesized that MIBG would synergize with the anti-GD2 mAb dinutuximab to provide improved anti-tumor responses. The primary aims of Part A of this study were to determine the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D) of MIBG administered with dinutuximab in children with R/R HRNB and to define and describe the toxicities. **Methods:** Patients 1-29 years of age with R/R HRNB who had MIBG uptake in ≥ 1 site were eligible. Prior anti-GD2 mAb therapy was allowed provided it was not administered with MIBG and not permanently discontinued due to toxicity. One prior MIBG therapy was allowed. MIBG was administered on day 1 at one of three dose levels (DLs): 12, 15, and 18 mCi/kg (DL1-DL3, respectively) with an expansion cohort at the RP2D. Doses were escalated using a rolling six design starting at DL1. The primary endpoint was dose-limiting toxicity (DLT) during course 1. Dinutuximab (17.5 mg/m^2/dose) was administered intravenously on days 8-11 and 29-32 and GM-CSF (250 mcg/m^2/dose) subcutaneously on days 8-17 and 29-38. Autologous peripheral blood stem cells were infused to all patients on day 15 (+/- 2 days). A maximum of 2 courses per patient were allowed. Response rate was defined as the proportion of patients with a complete or partial response. **Results:** Thirty-one patients were enrolled. Fourteen were evaluable for dose escalation (4 on DL1, 4 on DL2, and 6 on DL3); 5 evaluable patients were treated in the DL3 expansion. The median age was 7.4 years (range: 3.1 – 22.0) and 20 (65%) were male. Twenty-seven (87%) patients had previously received a median of 8.5 cycles of chemoimmunotherapy (range: 2 – 21). Eight patients previously progressed while receiving anti-GD2 mAb including 7 in DL3. Five (16%) patients had previously received MIBG. No patient at any dose level experienced DLT. Common grade 3/4 treatment-related toxicities were expected hematologic toxicities attributable to MIBG and non-hematologic toxicities attributable to dinutuximab or GM-CSF. Among 26 response-evaluable patients, the centrally-confirmed response rate was 31% across all dose levels: 2/6 (33%) in DL1, 3/5 (60%) in DL2, and 3/15 (20%) in DL3. There were 3 minor responses, 1 in DL2 and 2 in DL3. **Conclusions:** The RP2D of MIBG in combination with standard doses of dinutuximab and GM-CSF is 18 mCi/kg. This radioimmunotherapy regimen is well-tolerated without additive toxicity. Preliminary efficacy data are encouraging in this heavily pre-treated patient population. A phase 2 trial of this regimen is planned in patients with R/R HRNB. Clinical trial information: NCT03332667. Research Sponsor: United Therapeutics Corporation, Other Foundation, Aflac Cancer & Blood Disorders Center.

10039 **Poster Session**

Predicting outcomes with circulating adrenergic neuroblastoma mRNAs in children with relapsed and refractory neuroblastoma: A BEACON-Neuroblastoma biomarker study. *First Author: Lucas Moreno, Division of Pediatric Oncology & Hematology, Vall d'Hebron University Hospital, Barcelona, Spain*

Background: Children with relapsed and refractory neuroblastoma (RR-NBL) have poor outcomes. Early identification of children at greatest risk of relapse could mean timelier modifications of treatment to improve outcomes. High levels of adrenergic neuroblastoma mRNAs in blood of children with stage M neuroblastoma receiving frontline treatment predict poor outcome (Viprey PMID: 24590653). Since these markers have not been thoroughly studied in the RR-NBL population, we have prospectively evaluated the prognostic potential of the adrenergic neuroblastoma mRNAs paired-like homeobox 2B *(*PHOX2B*)* and tyrosine hydroxylase (TH) in blood from children with RR-NBL treated in the BEACON-Neuroblastoma trial (NCT02308527). **Methods:** Blood samples collected at baseline from 88 children were analysed by reverse transcriptase polymerase chain reaction (RTqPCR) for PHOX2B and TH mRNAs. The prognostic power of these mRNAs was evaluated using Kaplan-Meier survival curves and Cox proportional hazards regression. Progression-free (PFS) and overall survival (OS) were calculated from the date that the blood sample was taken at screening to the date of an event; progression, disease recurrence, death or censored alive at the last clinical evaluation. **Results:** Of the children in this cohort, 58 (66%) had relapsed and 30 (34%) had refractory disease. Twenty-three (26%) had *MYC-N* amplified tumours. TH and PHOX2B mRNAs were detected in 55% and 60% of blood samples respectively; the correlation coefficient between TH and PHOX2B was 0.75. Higher levels of TH, PHOX2B mRNAs or both combined were associated with reduced PFS and OS (Table). For TH, median PFS for children with TH levels below the median was 12 months (95%CI, 4.6–13 months) versus 5.5 months (95%CI, 1.8–9.4 months) for those children with TH levels above the median. For PHOX2B, median PFS for children with PHOX2B levels below the median was 11.5 months (95%CI, 7.6–34 months), compared to 5.7 months (95%CI, 1.8–10.5 months) where levels were above the median. **Conclusions:** TH and PHOX2B mRNAs in blood collected at baseline identify children with refractory or relapsed neuroblastoma at greatest risk of progression or death. In the RR-NBL setting, this simple blood test could be used to stratify treatment strategies. Clinical trial information: NCT02308527. Research Sponsor: Cancer Research UK, Imagine for Margo, Solving Kids Cancer.

Summary of RTqPCR data for TH and PHOX2B mRNAs in blood (n=87) taken at baseline from children treated in BEACON-Neuroblastoma.

	PFS			OS		
	TH	PHOX2B	TH and PHOX2B	TH	PHOX2B	TH and PHOX2B
Number PCR positive/Total (% positive)	48/88 (55)	52/88 (59)	40/88 (46)	48/88 (55)	52/88 (59)	40/88 (46)
Hazard Ratio	1.45	1.46	2.68	1.47	1.47	2.84
95% confidence interval of Hazard Ratio	1.25-1.69	1.25-1.70	1.65-4.35	1.22-1.77	1.22-1.77	1.71-4.72
P value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

10040 **Poster Session**

Update on phase 1 study of tazemetostat, an enhancer of zeste homolog 2 inhibitor, in pediatric patients with relapsed or refractory integrase interactor 1–negative tumors. *First Author: Susan N. Chi, Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA*

Background: A defining feature of malignant rhabdoid tumors (MRTs), epithelioid sarcoma (ES), and poorly differentiated chordomas (PDC) is loss of integrase interactor 1 (INI1) expression, which induces dependence on enhancer of zeste homolog 2 (EZH2). Tazemetostat (TAZ) is a selective EZH2 inhibitor approved by the US Food and Drug Administration for patients (pts) aged ≥16 y with metastatic or locally advanced ES ineligible for complete resection. Pediatric dose escalation and interim efficacy and safety data for the dose expansion were previously reported. Updated efficacy, safety, subgroup analyses, and translational results are reported here. **Methods:** NCT02601937 is a phase 1 multicenter study evaluating TAZ monotherapy ≤2400 mg/m^2 daily in pediatric pts with relapsed or refractory INI1$^-$ tumors (MRT, atypical teratoid rhabdoid tumor [ATRT], select tumors with rhabdoid features, other INI1$^-$ tumors, and SS18-SSX synovial sarcoma). Primary endpoint for dose expansion was objective response rate (ORR). Secondary endpoints included safety/tolerability, duration of response (DOR), progression-free survival (PFS), and overall survival. Selected exploratory flow data using 250,000 cells from peripheral blood were available for up to 25 pts. **Results:** Phase 1 enrolled 109 pts (escalation, n=46; expansion, n=63; Table) with mean ages of 5.4 y in the dose escalation and 7.4 y in the dose expansion. ORRs were 7% (3/46) in the dose escalation and 14% (9/63) in the dose expansion. Per tumor category in the dose expansion, ORRs were 24% (5/21) ATRT, 33% (2/6) PDC, 22% (2/9) ES, and 0% in non–CNS RTs (n=21) and other tumors (n=6). ORR for pts with prior radiotherapy was 14% (11/80) vs 3% (1/29) with prior radiotherapy (P>0.05). In the dose expansion, median PFS was 8 wk (95% CI: 8–13), OS was 21 wk (95% CI: 13–38), and DOR was 35 wk (95% CI: 24–121). Grade 3–4 treatment-related treatment-emergent adverse event rates were 15% (7/46) in the dose escalation and 22% (14/63) in dose expansion. Differences between responders (R) and nonresponders (NR) at C1D1 for neutrophil counts were significant (P<0.05). All R (6/6) had <125,000 total neutrophils at C1D1 vs 42% (8/19) of NR; 50% (3/6) of R had >50,000 total CD3 T cells vs 0% (0/19) of NR. **Conclusions:** TAZ showed promising antitumor activity in ATRT, ES, and PDC. Potential synergism between prior radiotherapy and TAZ requires further investigation. TAZ was generally well tolerated. The biological/clinical significance of differences in peripheral blood cell counts between R and NR at C1D1 needs further investigation. Clinical trial information: NCT02601937. Research Sponsor: Epizyme, Inc.

Escalation and expansion phase dosing.

Dosing phase, n	240 N=8	300 N=6	400 N=6	520 N=33	700 N=6	800[a] N=6	900 N=6	1200 N=38	Total N=109
Escalation	8	6	6	7	6	0	6	7	46
Expansion	0	0	0	26	0	6	0	31	63

Dosed (mg/m^2) twice daily unless otherwise noted. [a]Three times daily.

10041 **Poster Session**

Phase I trial of lorlatinib in combination with topotecan/cyclophosphamide in children with ALK-driven refractory or relapsed neuroblastoma: A new approaches to neuroblastoma therapy consortium study. *First Author: Kelly C. Goldsmith, Children's Healthcare of Atlanta, Emory University, Atlanta, GA*

Background: Lorlatinib, a macrocyclic ATP-competitive ALK inhibitor, exerts potent activity against neuroblastoma (NB) xenograftsharboring the most common *ALK* mutations. We performed a first-in-child phase 1 study of lorlatinib for patients with refractory/relapsed (R/R) ALK aberrant high-risk NB. We previously reported on Part A of the study, where safety of single agent lorlatinib was determined, showing complete responses (CR) to lorlatinib at the recommended phase 2 dose (RP2D) of 115 mg/m2 in pts < 18 years and 150 mg in pts > 18 yrs. Part B of the study aimed to determine the safety, pharmacokinetics (PK), RP2D, and explore the anti-tumor activity of lorlatinib in combination with topotecan and cyclophosphamide in pts with R/R ALK-driven NB. **Methods:** Patients with R/R NB ages 1-17 years with *ALK* mutations or amplification were eligible; prior ALK inhibitor (ALKi) treatment was allowed. Lorlatinib was orally administered once daily on days 1-28 with topotecan (0.75 mg/m^2/day) and cyclophosphamide (250 mg/m^2/day) administered intravenously days 1-5 and GCSF starting day 6. Two lorlatinib dose levels (DL) of 95 mg/m^2/day (DL4B) and 115 mg/m^2/day (DL5B) were assessed using a 3+3 dose escalation design with the primary endpoint of dose limiting toxicity (DLT) in Course 1. We report lorlatinib safety, PK, and objective response rate (ORR) for patients enrolled on Part B. **Results:** Between 10FEB2020 and 03DEC2021,9 eligible pts enrolled on Part B with a median age of 6.7 years (3.7-12.7). Three pts were enrolled onto DL4B and six onto DL5B (2/3 pts on DL4B and 4/6 pts on DL5B had received prior ALKi therapy) with no DLT's observed in course 1. One patient on DL5B experienced a neuropsychological DLT in Course 3. Most common treatment-related adverse events were hematological, febrile neutropenia, high cholesterol, hypertriglyceridemia, and neuropsychological effects. The median number of courses received was 6 with a range of 1-8 on DL4B and 1-7 on DL5B. Of the 8 patients evaluable for response, ORR was 50%: 2/3 pts on DL4B and 2/5 pts on DL5B. Preliminary PK data demonstrate comparable dose level-associated lorlatinib steady state exposure between Part B chemotherapy combination and Part A monotherapy cohorts, supporting that chemotherapy had no effect on lorlatinib exposure that there are no overlapping toxicities. **Conclusions:** Lorlatinib in combination with topotecan and cyclophosphamide is well tolerated, and early data suggest encouraging objective anti-tumor activity. These data support the current integration of lorlatinib into up-front high risk neuroblastoma therapy for patients with ALK-driven neuroblastoma. Clinical trial information: NCT03107988. Research Sponsor: U.S. National Institutes of Health, Other Foundation, Pharmaceutical/Biotech Company.

10042 **Poster Session**

Phase II trial of gemcitabine and nab-paclitaxel for recurrent osteosarcoma: A report from the National Pediatric Cancer Foundation. *First Author: Lars M. Wagner, Duke University Medical Center, Durham, NC*

Background: The combination of gemcitabine and docetaxel is often used to treat patients with recurrent osteosarcoma. A retrospective study of 35 such patients has reported an objective response rate of 17% and 4-month progression-free survival (PFS) of 56% with this combination (BMC Cancer 2016;16:280). Nab-paclitaxel is a nanoparticle taxane that has activity against osteosarcoma xenografts and may have less myelosuppression than docetaxel. The combination of gemcitabine and nab-paclitaxel is now frontline therapy for pancreatic cancer. We conducted a prospective multi-institutional phase II trial of this drug combination for patients with recurrent osteosarcoma. **Methods:** Patients with relapsed/refractory osteosarcoma with measurable disease and age ≥ 12 years and adequate organ function were included. A Simon's two-stage design was used to identify a 4-month progression-free survival (PFS) of > 35%. Patients received nab-paclitaxel 125 mg/m^2 and gemcitabine 1000 mg/m^2 weekly x 3 in 4-week cycles. **Results:** Eighteen patients with a median age 16 years (range 12- 26) received a total of 56 total cycles.(median 2, range 1 - 12). The median number of prior treatment regimens was 3 (range 1-7). Two patients (11%) experienced a partial response, and 6 (33%) received more than 2 cycles. The 4-month PFS was 30% (95% CI 14-62 %). Six patients required dose reductions for neutropenia (n = 4), pleural effusion (1), or neuropathy (1). Two patients were removed from study secondary to neutropenia despite dose reduction and myeloid growth factor support, and one patient came off study due to severe peripheral edema. **Conclusions:** In this prospective study, the combination of gemcitabine and nab-paclitaxel administered on this schedule showed only limited activity for patients with heavily pretreated recurrent osteosarcoma. Toxicity led to dose modifications in 33% and discontinuation in 17% of patients. When compared to a historical retrospective study, the substitution of nab-paclitaxel for docetaxel did not appear to increase activity or decrease toxicity for this patient population. Clinical trial information: NCT02945800. Research Sponsor: National Pediatric Cancer Foundation.

10043 **Poster Session**

Patterns of relapse after immunotherapy in patients with high-risk neuroblastoma. *First Author: Scott Moerdler, Department of Pediatrics, Rutgers Cancer Institute of New Jersey, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ*

Background: While the addition of anti-GD2 immunotherapy led to improvement in outcomes in patients on the Children's Oncology Group (COG) ANBL0032 study, relapse remains a concern. Prior studies demonstrated the prognostic importance of time to first relapse, however, the effect of immunotherapy on timing and patterns of relapse in neuroblastoma (NBL) have yet to be evaluated. The purpose of this exploratory analysis was to describe the impact of immunotherapy on patterns of relapse in patients with high-risk NBL, including a descriptive comparison of sites of relapse based on post-consolidation treatment received [dinutuximab with cytokines and isotretinoin (DIN) vs isotretinoin alone (ISO)]. **Methods:** A retrospective, descriptive analysis of patients on ANBL0032 was performed, including patients randomized to DIN or ISO and those non-randomly assigned to DIN after ISO arm closure. Pt characteristics including age, stage, *MYCN* amplification status, tumor grade, mitosis-karyorrhexis index (MKI) and ploidy were summarized descriptively and relapse sites were tabulated. For DIN patients who subsequently relapsed, overall survival (OS) was calculated starting from the time of first relapse after enrollment on ANBL0032 ("post-relapse OS"). Kaplan-Meier OS curves were generated based on site of relapse. **Results:** The analytic cohort included 1,431 (DIN = 1,327; ISO = 104) patients. Among DIN patients, 492 relapsed, many in > 1 site. In the randomized cohort (n = 248), 122 relapsed (DIN = 68/144; ISO = 54/104). The frequencies (DIN; ISO) by site of relapse in the randomized cohort were: bone (53%; 54%), CNS (16%; 11%), lymph node (13%; 17%), abdominal (10%; 17%), paraspinal (6%; 2%), liver (3%; 4%), other soft tissue (22%; 7%). A higher proportion of ISO patients had marrow relapse (29.4% DIN; 48.2% ISO); however, the proportion of DIN patients with lung relapses appeared higher (9% vs 2%). Among all relapsed patients, the proportion with bone relapse did not appear to differ between treatment groups, regardless of *MYCN* status. Among patients with *MYCN* amplified disease, the proportion with marrow relapse did not appear to differ based on treatment [21/149 (14.1%) DIN; 3/20 (15.0%) ISO]; however, among patients with *MYCN* non-amplified disease, the proportion with marrow relapse appeared higher in the ISO group [16/23; 69.6%] vs the DIN group [52/193 (26.9%)]. **Conclusions:** In this exploratory analysis of patients on COG ANBL0032, the pattern for site of relapse appears to differ between patients treated with DIN vs ISO. While immunotherapy remains the treatment of choice in this population, the findings from this retrospective exploratory analysis warrant further investigation to decrease the risk for post-immunotherapy relapse. Clinical trial information: NCT00026312. Research Sponsor: NCTN Operations Center Grant U10CA180886 NCTN Statistics & Data Center Grant U10CA180899.

10044 **Poster Session**

Clinical and biological features prognostic of survival after relapse of INRGSS-stage MS pattern neuroblastoma: A report from the International Neuroblastoma Risk Group (INRG) project. *First Author: Kevin M. Campbell, Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA*

Background: Neuroblastoma (NB) presenting with INRGSS MS metastatic pattern highlights the extreme heterogeneity within NB and subsequent difficulty in risk assignment. Depending on tumor biology, patients with stage MS disease may be classified as very-low risk or as high-risk. While outcomes at initial diagnosis have been well-described, outcomes after relapse are less well defined. **Methods:** From the INRG Data Commons, we investigated clinical and biological characteristics of patients diagnosed 1984-2021 with stage MS pattern NB (INSS stage 4s, INSS stage 4 or INRG stage MS) who subsequently experienced disease relapse or progression, excluding patients whose first event was death. Using Kaplan-Meier methods, post-relapse overall survival (OS)± standard error (SE) was calculated from the time of first relapse/progression until death or last contact, overall and by era of diagnosis: < 2000 vs ≥2001. Univariate Cox models were used to identify factors prognostic of post-relapse OS. **Results:** 209 patients met eligibility criteria,103 diagnosed < 2001 and 106 ≥2001. Of patients diagnosed ≥2001, 89% (n = 94) were < 365 days old at diagnosis; tumors were *MYCN* amplified in 21% (21/102) and diploid in 31% (20/64). Of this same cohort, time from initial diagnosis to relapse was < 6 months in 40% (n = 42), 6-12 months in 25% (n = 26), and > 12 months in 36% (n = 38) of patients. Of 60 patients with known site of relapse/progression diagnosed ≥2001, 73% (44) were metastatic (29) or primary plus metastatic (15). Among these, 16% (5/32) remained stage MS pattern while 84% (27/32) had metastatic sites beyond MS sites. Five-year post-relapse OS±SE was 53±3.5% overall (n = 209), and higher for those diagnosed ≥2001 (62±5.0%; n = 106) compared to those diagnosed < 2001 (44±4.9%; n = 103) (p = 0.0046). In patients diagnosed ≥2001, factors prognostic of superior post-relapse OS included: age < 365 days; not Hispanic; *MYCN* non-amplified; no 1p loss/aberration, hyperdiploidy; low/intermediate MKI; LDH < 1400 U/L, favorable INPC histology; and < 12 months from initial diagnosis to first relapse. **Conclusions:** Most patients with relapsed stage MS NB have metastatic relapse and these relapses more commonly occur at sites outside liver, skin, and bone marrow. Patients diagnosed ≥2001 with MS pattern NB have substantially better post-relapse OS compared to those diagnosed < 2001. In the cohort of patients with MS pattern NB diagnosed ≥2001, most of the well-accepted prognostic factors for OS at diagnosis are also prognostic of post-relapse OS. Research Sponsor: None.

10045 **Poster Session**

Outcomes of patients with bilateral retinoblastoma: A report from the RIVERBOAT Consortium. *First Author: Debra L. Friedman, Vanderbilt University Medical Center/Vanderbilt-Ingram Cancer Center, Nashville, TN*

Background: Retinoblastoma (RB) is the most common tumor of the eye in childhood. Intraocular RB cure rates approach 100%. Therefore, treatment advances have focused on globe salvage preserving functional vision. The Research Into Visual Endpoints and RB Health Outcomes After Treatment (RIVERBOAT) consortium was established to examine patient health outcomes, including vision, in the contemporary therapy era. **Methods:** Patients with RB treated at consortium centers from 2007 to the present were identified. Medical record abstraction was performed for disease presentation, treatment, and outcomes. A subset of the patients returned to centers and completed functional vision questionnaires (Child Vision Function Questionnaire for ages 0 – 7 and Cardiff Visual Ability Questionnaire for Children for ages >8) and had visual acuity assessed. For participants who could not yet return for a study evaluation, medical record abstraction alone was performed. **Results:** Among 463 participants enrolled to date, 193 (42%) had bilateral disease. Two each had metastatic RB, trilateral RB, and secondary osteosarcoma. One patient each with metastatic RB and trilateral RB is deceased, with overall survival for the cohort of 99%. The eye group distribution (International Intraocular Retinoblastoma Classification) was 14% A, 22% B, 14% C, 28% D, 19% E and 3% not classified. Primary enucleation was performed in 43 (22%), secondary enucleation in 48 (25%) and bilateral enucleation in 1(0.5%). Intravenous chemotherapy (IV) alone was administered in 58%, intra-arterial chemotherapy (IAC) alone in 4%, with 31% receiving both. Among 145 patients who did not require secondary or bilateral enucleation, the distribution was 16% A, 21% B, 16% C, 28% D, 15% E, and 4% non-classified eyes. This salvage was achieved with IV alone, IAC alone, or both in 55%, 5% and 30% respectively and with ophthalmic therapy only in 10%. The mean percentage of patients receiving IAC per year increased from 6% in 2008 – 2013 to 11% in 2014 – 2022 and was stable at 11% in 2018 – 2022. Among 53 patients who have reported functional vision to date, the mean scores were 0.81 for < 3 years 0.80 for 3-7 years and -1.31 for those >8 years, all considered to be good functional vision. Among 50 eyes in 37 of these 53 patients, 33 had normal vision (20/20-20/40) across A to E groups. Moderate vision loss (> 20/40 – 20/70) was noted in 1 C and 1 B eye and low vision (> 20/70 - < 20/200) in 6 group B, C or D eyes. Nine B or D eyes were legally blind (>20/200). No patients had two legally blind eyes. **Conclusions:** In this cohort of RB patients with bilateral disease treated between 2007 and 2022, 52% have been successfully treated without enucleation. Self-reported functional vision in 53 of these patients with all group eyes was good. Only 6 of 50 eyes in 37 patients met criteria for legal blindness and 66% of eyes had normal vision. With cohort accrual ongoing, we will determine if these promising outcomes continue. Research Sponsor: U.S. National Institutes of Health.

10046 **Poster Session**

Outcomes of patients with unilateral retinoblastoma: A report from the RIVERBOAT Consortium. *First Author: Debra L. Friedman, Vanderbilt University Medical Center/Vanderbilt-Ingram Cancer Center, Nashville, TN*

Background: Retinoblastoma (RB) is the most common tumor of the eye in childhood. Intraocular RB cure rates approach 100%. Therefore, treatment now focuses on globe salvage preserving functional vision. The Research Into Visual Endpoints and RB Health Outcomes After Treatment (RIVERBOAT) consortium was established to examine patient health outcomes, including vision, in the contemporary therapy era. **Methods:** Patients with RB treated at consortium centers from 2007 to present were identified. Medical record abstraction was performed for disease presentation, treatment, and outcomes. A subset of the patients returned to centers and completed functional vision questionnaires (Child Vision Function Questionnaire - ages 0 – 7 and Cardiff Visual Ability Questionnaire for Children - ages > 8) and had visual acuity assessed. For participants who could not yet return for a study evaluation, medical record abstraction alone was performed. **Results:** Among 463 participants enrolled to date, 270 (58%) had unilateral disease. One patient with metastatic RB did not survive, resulting in overall survival of 99.6. There was one case of secondary leukemia. The eye group distribution (International Intraocular Retinoblastoma Classification) was 0.4% A, 5.6% B, 7.0% C, 36.0% D, 49.0% E and 2.0% not classified. 131 (49%) patients underwent primary enucleation and are not included in further analyses. Among the remaining 139 patients, 3% were treated with local ophthalmic therapy only, 22% with intravenous chemotherapy (IV) only, 53% with intra-arterial chemotherapy (IAC) only, 22% with IV and IAC, and 35% required secondary enucleation. Globe salvage after chemotherapy was successful in 100% A, 93% B, 82% C, 72% D, and 48% E eyes. This salvage was achieved with IV only, IAC only, or both in 22%, 58% and 20% respectively. The mean percentage of patients receiving IAC per year increased from 13% (2008 – 2013) to 21% (2014 – 2017) to 28% (2018 – 2022). In 29 patients without enucleation who reported functional vision to date, the mean scores (survey theoretical ranges) were 0.72 for < 3 years (0.57 to 0.87), 0.82 for 3 -7 years (0.56 to 0.94) and -2.72 for > 8 years (-2.53 to -0.51), all considered good functional vision. In 20 of these 29 patients, 4 eyes had normal vision (20/20-20/40) across A to D groups. Moderate vision loss (> 20/40 – 20/70) was noted in 3 D eyes and low vision (> 20/70 - < 20/200) in 1 D eye. Twelve B through E eyes met criteria for a legally blind eye (>20/200). **Conclusions:** In this cohort of RB patients with unilateral disease treated from 2007 - 2022, 66% required primary or secondary enucleation. Among 29 patients with globe salvage, self-reported functional vision was good, but 12 eyes in 20 of the patients were legally blind. IAC only or IV plus IAC was most used in those who avoided secondary enucleation. With ongoing cohort accrual and increased IAC use, it will remain to be determined if globe salvage with functional vision will improve. Research Sponsor: U.S. National Institutes of Health.

10048 **Poster Session**

Informatics tools to implement late cardiovascular risk prediction modeling for population health management of high-risk childhood cancer survivors. *First Author: David H Noyd, The University of Oklahoma Health Sciences Center, Oklahoma City, OK*

Background: Marked improvements in outcomes for children with cancer and robust cohort studies with longitudinal follow-up inform evidence-based guidelines for survivors at risk for late cardiomyopathy. Clinical informatics tools to integrate data from multiple sources have the potential to catalyze population health management. **Methods:** The Oklahoma Childhood Cancer Survivor cohort was constructed from an institutional cancer registry of survivors diagnosed between 2005 and 2014 (n=382). Data elements (cumulative anthracycline, cumulative chest-directed radiotherapy, alkylator, and platinum exposures) were extracted from Passport for Care (PFC) to implement previously validated late cardiovascular risk prediction modeling from the Childhood Cancer Survivor Study (CCSS) for cardiomyopathy. Risk groups were compared to the Children's Oncology Group (COG) Long-Term Follow-up Guidelines. Standard query language facilitated extraction of echocardiogram data from the electronic health record to determine adherence, defined as an echocardiogram within 27 months and 63 months from the last day of therapy for high and moderate risk survivors, respectively. **Results:** Sixty-nine percent (n=264) of survivors from the cancer registry were documented in PFC, of whom 29%, 56%, and 15% were classified as low, moderate, high risk, respectively, based on the CCSS late cardiomyopathy risk calculator. Concordance was modest for high and moderate risk groups (Kappa = 0.42 and 0.46, respectively) and good for the low risk group (Kappa = 0.77) compared to COG risk groups. There was excellent adherence to echocardiogram guidelines with 93% and 81% of moderate and high-risk survivors, respectively. There were significant differences based on risk group (p=0.02) and age at diagnosis (p<0.01). **Conclusions:** Clinical informatics tools represent a feasible approach to leverage discrete data elements regarding key treatment exposures from PFC to successfully implement previously validated late cardiovascular risk prediction models on a population health level. PFC promotes adherence to echocardiogram surveillance and serves as a platform for future interoperability to generate real-world data to improve survivorship-focused care. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

Children's Oncology Group Echocardiogram Guideline Adherence.

	Adherence		
	Yes	No	P-Value
Total	233 (88%)	32 (12%)	
COG Guideline			0.02
Every 5 Years	167 (72%)	15 52%)	
Every 2 Years	64(28%)	14 (48%)	
Age, in years (SE)	6.7 (0.4)	10.6 (1.2)	<0.01
Adolescent at Diagnosis			<0.01
Yes	46 (20%)	15 (52%)	
No	185 (80%)	14 (48%)	
Sex			0.95
Male	126 (55%)	16 (55%)	
Female	105 (45%)	13 (45%)	
Race			0.58
White, Non-Hispanic	145 (63%)	20 (69%)	
Black, Non-Hispanic	20 (9%)	2 (7%)	
Hispanic	38 (16%)	5 (17%)	
American Indian	18 (8%)	0 (0%)	
Other	10 (4%)	2 (7%)	
RUCA			0.69
Urban	158 (69%)	17 (61%)	
Large Town	33 (14%)	5 (18%)	
Small Town/Isolated Rural	39 (17%)	6 (21%)	

10049 **Poster Session**

Thyroid gland definitive ultrasound screening in childhood cancer survivors following radiotherapy. *First Author: Julia A. Baran, Division of Endocrinology and Diabetes, The Thyroid Center, Children's Hospital of Philadelphia, Philadelphia, PA*

Background: Childhood cancer survivors (CCS) are at risk for radiotherapy (RT) late effects, including second malignancies. Optimal screening for thyroid cancer (TC) in CCS post-RT remains controversial. We assessed the clinical benefit of thyroid ultrasound (US) surveillance in CCS exposed to RT. **Methods:** 316 CCS (175 males) were prospectively surveilled with thyroid US between 2002 and 2021 at the Children's Hospital of Philadelphia. Patients were screened upon referral to the Survivorship Program. Thyroid US, clinicopathologic features, and endocrine-related outcomes were ascertained. Outcomes were compared using primary CCS diagnosis age cohorts of ≤ 3, > 3 to ≤ 10, and > 10 years. Risk factors for thyroid nodule(s) and TC were evaluated using Kruskal Wallis and ANOVA [OR (95% CI)]. **Results:** The most common CCS diagnoses were leukemia (32%), CNS tumor (26%), and neuroblastoma (18%). Patients received TBI (43%) and/or RT to craniospinal (43%), chest (13%), and neck regions (7%). About 48% (n = 152) of patients presented thyroid nodule(s) (Table). Forty-six patients underwent surgery, and 28 had TC, including 19 with ATA low-risk, 2 with ATA intermediate-risk, and 7 with ATA high-risk disease. Of the 9 patients with intermediate- or high-risk disease, 5 were ≤ 3 years, 3 were > 3 to ≤ 10 years, and 1 was > 10 years at the time of RT exposure. Eight patients with TC demonstrated pathogenic variant(s). RT exposure at ≤ 3 years old conferred 2-fold increased risk for nodule(s) compared to RT at > 10 years [OR = 2.14 (1.44-2.84) p = 0.03]. Female sex [OR = 1.73 (1.25-2.21) p = 0.02] and greater interval between RT and first US [OR = 1.10 (1.04-1.15) p = 0.001] were additional independent risk factors. **Conclusions:** Younger age at RT exposure is associated with increased risk of and shorter latency for developing TC. Thyroid US surveillance appears most beneficial in CCS exposed to RT ≤ 3 years old in an effort to diagnose TC at an earlier stage prior to metastasis. Research Sponsor: Children's Hospital of Philadelphia Frontier Program Grant for the Thyroid Center.

Age at CCS Diagnosis (yrs)	≤ 3 N = 97	> 3 to ≤ 10 N = 155	> 10 N = 64	*p*-value
Interval from CCS Diagnosis to First US (yrs), Median (IQR)	12.0 (8.3-14.9)	9.0 (6.5-12.4)	7.3 (5.4-10.2)	**< 0.001**
Patients Presenting Nodule(s) on US, N (%)	62 (64)	66 (43)	24 (38)	**< 0.001**
Age at Initial Presentation of Nodule(s) on US (yrs), Median (IQR)	15.8 (14.2-18.5)	17.7 (14.9-20.1)	22.2 (21.0-24.3)	**< 0.001**
Interval from CCS Diagnosis to Initial Presentation of Nodule(s) on US (yrs), Mean ± SD	14.2 ± 3.7	11.9 ± 4.0	9.1 ± 4.6	**< 0.001**

10050 **Poster Session**

Improvements in life expectancy among childhood cancer survivors: Uneven gains and remaining challenges. *First Author: Jennifer M Yeh, Boston Children's Hospital and Harvard Medical School, Boston, MA*

Background: Childhood cancer survivors are at risk for shortened lifespan. Projections of life expectancy (LE) by diagnosis can provide benchmarks for assessing improvements over time. **Methods:** We developed a simulation model to project risk for common, life-threatening chronic health conditions (CHCs; heart failure, myocardial infarction, valvular disease, stroke, secondary breast cancer, colorectal cancer, glial tumors, sarcomas) and excess mortality among 5-year survivors, based on patient characteristics (sex, age at diagnosis, diagnosis) and treatment exposures (chemotherapy, radiation dose). Risk was estimated using statistical models and Childhood Cancer Survivor Study data. Age-related CHC risks (SEER, NHLBI) and competing mortality (CDC Wonder) were based on national databases. We used model calibration to identify parameter sets that generated outcomes consistent with observed data. Model outcomes included conditional LE and 10-year survival probability at age 40. For comparisons to the general population, we simulated age-, sex-, and diagnosis year-matched individuals who faced only competing mortality rates. **Results:** Among a cohort representative of the CCSS (mean diagnosis age, 7.4 yrs), compared to the general population, the gap in LE among survivors diagnosed in the 1970s vs. 1990s decreased from 17 yrs (25%) to 11 yrs (17%). Changes in LE among survivors diagnosed in the 1990s vs. 1970s varied by diagnosis, with leukemia, lymphoma, and CNS tumor survivors estimated to live an additional 8 to 11 yrs (Table). In contrast, considerably smaller gains were estimated for sarcoma and renal tumor survivors (1–3 yrs) and a loss for neuroblastoma (-3 yrs). Among survivors who reached age 40, the probability of surviving an additional 10 years increased from 89% to 92% between 1970s vs. 1990s, with the greatest gains for lymphoma and CNS tumors. **Conclusions:** Although temporal changes in pediatric oncology are projected to result in LE gains among survivors, considerable variation is projected across diagnoses. These findings highlight the uneven success of improving treatments for all cancers. Research Sponsor: American Cancer Society, U.S. National Institutes of Health.

	Conditional LE, yr			Conditional 10-year survival probability at age 40, %		
Cohort	Diagnosed 1970s	Diagnosed 1990s	Δ	Diagnosed 1970s	Diagnosed 1990s	Δ
General population	65 (64–65)	67 (66–67)	2 (1–2)	97 (97–97)	97 (97–98)	0 (0–0)
5-yr survivors	48 (46–49)	55 (53–57)	7 (6–9)	89 (88–90)	92 (91–93)	3 (2–5)
Leukemia	53 (47–56)	61 (55–64)	8 (5–11)	93 (90–95)	94 (91–96)	1 (-1–4)
Lymphoma	39 (38–41)	51 (47–56)	11 (8–15)	84 (81–86)	93 (91–95)	9 (6–12)
CNS tumors	37 (35–40)	46 (41–51)	9 (5–12)	80 (75–85)	86 (82–90)	7 (1–12)
Bone tumors	47 (46–49)	48 (47–50)	1 (-2–3)	92 (89–94)	93 (90–95)	1 (-2–5)
Neuroblastoma	61 (59–63)	58 (57–60)	-3 (-5–0)	92 (89–95)	92 (89–94)	-1 (-5–3)
Renal tumors	59 (57–61)	62 (61–63)	3 (1–5)	92 (89–95)	94 (92–96)	2 (-1–6)
Soft tissue sarcoma	51 (49–52)	53 (51–55)	2 (0–5)	90 (88–93)	91 (87–94)	0 (-4–5)

10051 **Poster Session**

The relationship between chronic health conditions and employment transitions among survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS). *First Author: Neel S. Bhatt, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: Chronic health conditions are prevalent among adult survivors of childhood cancer. The impact of health on maintaining full-time (FT) employment, a common indicator of socioeconomic independence, has not been studied in this population. **Methods:** Self-reported employment status (FT, part-time [PT], unemployed [any reason], not in labor force) was assessed at two timepoints (2002-04 [T1] and 2015-16 [T2]) in adult (≥25y old) survivors of childhood cancer diagnosed between 1970-86. Sex-stratified Poisson regression, adjusted for race and ages at diagnosis and T2, was used to study associations between timing and severity of chronic health conditions (graded per the CTCAE v4.03) and transitions from FT to PT or unemployed. **Results:** Survivors employed FT at T1 (males=1712, median age [min-max]: 34y [25-53]; females=1337, 33y [25-53]) who reported employment status at T2 were included. At T2 (median time from T1 11.5y [9.4-13.8]), 83% males and 70% females remained employed FT, but 4% and 10% transitioned to PT, and 11% and 12% to unemployed (additional 2% and 8% left the labor force), respectively. Male and female survivors with grade 2 or 3-4 neurologic conditions acquired before T1 or between T1-T2 were at a higher risk of moving from FT to PT or unemployed compared to those with grade 0-1 conditions. Males and females with grade 3-4 respiratory conditions prior to T1 and cardiac and musculoskeletal conditions acquired between T1-T2 were also at higher risk for moving to PT or unemployed (Table). Additional predictors for males included grade 2 vision (before T1 RR 2.3, 95% CI 1.5-3.3; between T1-T2 RR 1.7, 95% CI 1.1-2.7) and endocrine (before T1 RR 1.4, 95% CI 1.1-1.9; between T1-T2 RR 1.7, 95% CI 1.3-2.3) conditions. **Conclusions**: A substantial portion of adult survivors of childhood cancer with health conditions of varying severity leave FT employment. Increased awareness of all stakeholders may facilitate access to clinical counseling and occupational provisions for flexible and supportive work accommodations to reduce work-related barriers for childhood cancer survivors. Research Sponsor: U.S. National Institutes of Health.

Multivariable relative risks (95% CI) for transition from FT employment (at T1) to PT or unemployment (at T2) associated with chronic health conditions (*=not estimable).

Condition	Maximum grade (vs. grade 0-1)	Prior to T1		Acquired between T1-T2	
		Male	Female	Male	Female
Neurological	2	1.8 (1.3-2.5)	1.7 (1.2-2.2)	2.2 (1.6-3.1)	2.5 (1.7-3.5)
	3-4	1.6 (1.1-2.3)	1.8 (1.3-2.6)	3.8 (2.8-5.2)	2.9 (2.0-4.0)
Respiratory	2	1.0 (0.6-1.6)	1.4 (1.0-2.0)	0.6 (0.1-2.8)	1.1 (0.7-1.9)
	3-4	2.1 (1.2-3.5)	2.5 (1.5-4.1)	2.9 (1.4-5.8)	1.3 (0.6-2.6)
Cardiac	2	0.9 (0.7-1.2)	1.0 (0.7-1.3)	1.0 (0.7-1.3)	0.9 (0.7-1.2)
	3-4	1.2 (0.9-1.7)	0.8 (0.5-1.1)	1.9 (1.5-2.4)	1.8 (1.4-2.3)
Musculoskeletal	2	2.5 (0.9-6.9)	2.5 (0.4-14.6)	*	*
	3-4	1.0 (0.6-1.7)	1.0 (0.7-1.5)	2.7 (1.8-4.1)	1.7 (1.0-2.8)

10052 **Poster Session**

Associations between global longitudinal strain (GLS), N-terminal-prohormone brain natriuretic peptide (NT-proBNP) and subsequent cardiomyopathy (CM) in a clinically assessed cohort of childhood cancer survivors exposed to cardiotoxic therapy. *First Author: Matthew J. Ehrhardt, St. Jude Children's Research Hospital, Memphis, TN*

Background: Among survivors exposed to anthracycline or chest radiation (RT) who have an ejection fraction (EF) of ≥50%, the utility of GLS and NT-proBNP to identify survivors who are at highest risk for future CM is unknown. **Methods:** Survivors participating in the St. Jude Lifetime Cohort, ≥5 years from cancer diagnosis and at risk for CM per the International Guideline Harmonization Group (IGHG), underwent baseline surveillance echocardiography. A baseline GLS and NT-proBNP was also performed for survivors with an EF ≥50%. Multivariable Cox regression models estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for risk of CM (graded per modified Common Terminology Criteria for Adverse Events v4.0) based on abnormal baseline GLS (≥ -18) and/or NT-proBNP (>age-sex-specific 97.5th percentiles) adjusted for age at baseline assessment, age at diagnosis, sex, race, hypertension, diabetes, obesity, and IGHG risk group (Table footnote). **Results:** Among 1598 at-risk survivors (median age 35.1, range 9.4-68.8 years), all had GLS and 1110 NT-proBNP at baseline. 165 (10.3%) developed CM ≥ grade 2 at a median follow-up of 5.2 (0.7-10.0) years. IGHG moderate- and high-risk survivors exposed to anthracyclines were at increased risk of CM at follow-up if both baseline GLS and NT-proBNP were abnormal (HR=3.4, 95% CI: 1.9-5.8; Table) or GLS was abnormal and NT-proBNP not assessed (HR=3.8, 95% CI: 2.0-7.2), or when GLS was normal and NT-proBNP was abnormal (HR=1.9, 95% CI: 1.1-3.4). Abnormal GLS and/or NT-proBNP were not associated with increased risk of CM in IGHG low-risk survivors or in those defined as moderate- to high-risk due to chest RT only. **Conclusions:** Among long-term survivors of childhood cancer exposed to >100 mg/m^2 anthracycline, abnormal GLS and NT-proBNP identified those survivors at increased risk of future CM despite an EF ≥50% on surveillance echocardiography. Conditional surveillance strategies utilizing GLS and NT-proBNP may benefit moderate- to high-risk survivors. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

			Any Anthracycline + Chest RT[b] (N=289) or Anthracycline[c] Only (n=605)							
IGHG Low-Risk[a] (n=512)			Chest RT[b] Only (n=192)			IGHG Moderate- and High-Risk				
GLS		NT-proBNP	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Cardiomyopathy, n (%)			23 (4.5%)			25 (13.0%)			117 (13.1%)		
Variables											
N	+	N	1.0			1.0			1.0		
A	+	N	1.1	0.3 - 3.5	0.89	0.8	0.3 - 2.1	0.65	1.1	0.6 - 2.0	0.69
N	+	A	0.0	0.0 - 1.6	0.98	0.9	0.3 - 2.6	0.87	**1.9**	**1.1 - 3.4**	**0.02**
A	+	A	0.0	0.0 - 1.8	0.99	1.1	0.4 - 2.6	0.89	**3.4**	**1.9 - 5.8**	**<0.001**
N	+	NA	1.2	0.5 - 3.3	0.67	1.5	0.2 - 11.6	0.68	1.7	0.9 - 3.1	0.11
A	+	NA	1.0	0.2 - 4.8	0.97	1.1	0.2 - 8.0	0.94	**3.8**	**2.0 - 7.2**	**<0.001**

N=normal; A=abnormal; NA=not assessed.

Adjusted for race, sex, age, age at cancer diagnosis, hypertension, diabetes, obesity, and IGHG risk group.

[a]anthracycline <100 mg/m^2 and RT <15 Gy; [b] ≥15 Gy; [c] ≥100 mg/m^2.

10053 **Poster Session**

Long-term medical and functional outcomes of medulloblastoma survivors: A population-based, matched cohort study. *First Author: Hallie Coltin, Division of Haematology/Oncology, The Hospital for Sick Children, Toronto, ON, Canada*

Background: Most medulloblastoma survivors suffer from late treatment-related sequelae. There are no population-based studies examining such late effects in a dedicated cohort of medulloblastoma survivors. **Methods:** Using a provincial pediatric cancer registry, all 5+ year medulloblastoma survivors diagnosed between 1987-2015 at <18 years of age in Ontario, Canada were identified and matched to cancer-free population controls based on age, sex, and geographical location. Cases were followed from the index date (five years from latest of diagnosis, or relapse/subsequent malignancy prior to age 18 years) until December 31, 2020 or censorship (death, or relapse/new cancer after age 18 years). Clinical data were linked to administrative health databases to estimate the cumulative incidences and cause-specific hazard ratios (HR) of mortality, hospitalizations, strokes, hearing loss requiring a hearing aid, and receipt of homecare services between cohorts, accounting for matching and competing risks. We evaluated demographic, disease, and treatment predictors of mortality using Cox proportional hazards models. **Results:** Of 389 medulloblastoma diagnoses in the study period, 159 (40.9%) were excluded, most commonly due to early death prior to the index date. Two hundred thirty cases were matched to 1150 controls (Table). Ten-year survival probability after index was 92.4% in cases and 99.4% in controls (HR 21.5, 95% CI 9.8-54.0). Cases were at higher risk for hospitalizations (HR 3.4, 95% CI 2.7-4.3), stroke (HR 45.6, 95% CI 12.8-289.8), hearing loss (HR 96.3, 95% CI 39.7-317.3), and requiring homecare services (HR 7.9, 95% CI 5.8-10.9). By 10 years after index, 4.8% (95% CI 2.2-9.0) of survivors had experienced a stroke compared to 0.1% (95% CI 0.01-0.7) of controls. None of the candidate predictors were significantly associated with mortality on univariate analyses. **Conclusions:** Survivors of childhood medulloblastoma experienced an increased risk of mortality and serious morbidity compared to population controls. Consideration for mitigation strategies or early interventions for preventing neurovascular sequelae and hearing loss is warranted, as is dedicated supports for survivors. Research Sponsor: Garron Family Cancer Centre.

Characteristics of cases and controls.

Characteristic	Cases No. (%) (n=230)	Controls No. (%) (n=1150)
Female	151 (65.7)	755 (65.7)
Age at diagnosis (years), median (IQR)	7 (4-10)	7 (4-10)
Attained age (years), median (IQR)	24 (18-31)	25 (18-33)
Follow-up time from index (years), median (IQR)	11 (5-17)	13 (6-19)
Death during follow-up	26 (11.3)	7 (0.6)
Craniospinal irradiation	187 (81.3)	–
Focal irradiation	19 (8.3)	
Cyclophosphamide equivalent dose ≥8000mg/m^2	162 (70.4)	–
Cumulative cisplatin exposure ≥400mg/m^2	54 (23.5)	–

–: not applicable; IQR: interquartile range.

10054 **Poster Session**

Long-term medical and functional outcomes of ependymoma survivors: A population-based, matched cohort study. *First Author: Hallie Coltin, Division of Haematology/Oncology, The Hospital for Sick Children, Toronto, ON, Canada*

Background: Ependymoma is the third most common pediatric central nervous system tumour. Treatment approaches are intensive and may include surgery, radiation, and chemotherapy. There are no longitudinal population-based cohort studies evaluating the long-term medical and functional outcomes of survivors of childhood ependymoma. **Methods:** Using a provincial pediatric cancer registry, all 5+ year ependymoma survivors diagnosed between 1987-2015 in Ontario, Canada were identified and matched to cancer-free population controls based on age, sex, and geographical location. Cases were followed from the index date (5 years from latest of diagnosis, or relapse/subsequent malignancy prior to age 18 years) until December 31, 2020 or censorship (death, or relapse/ new cancer after age 18 years). Clinical data were linked to administrative health databases to estimate the cumulative incidences and cause-specific hazard ratios (HR) of mortality, hospitalizations, strokes, hearing loss requiring a hearing aid, receipt of homecare services, and subsequent malignant neoplasms (SMNs) between cohorts, accounting for matching and competing risks. **Results:** Of 166 ependymoma diagnoses in the study period, 70 (42.2%) were excluded, most commonly due to early death prior to the index date. Ninety-six cases were matched to 480 controls (Table). The 10-year survival probability after the index date was 92.8% in cases and 99.6% in controls (HR 9.3, 95% CI 2.3-45.2, p=0.002). Compared to controls, cases were at higher risk of hospitalization (HR 3.2, 95% CI 2.2-4.6, p<0.0001), stroke (HR 33.3, 95% CI 5.7-629.1, p<0.0001), and receiving homecare services (HR 4.1, 95% CI 2.5-6.5, p<0.0001). Cases were at high risk of hospitalizations, strokes, hearing loss, and SMNs, with cumulative incidences of 64.7% (95% CI 46.6-78.0), 9.7% (95% CI 3.4-19.9), 13.5% (95% CI 5.3-25.5), and 12.8% (95% CI 4.7-24.9) at 20-years post index date, respectively. **Conclusions:** As survival of pediatric ependymoma improves, establishing the burden of late morbidity is critical. Dedicated screening programs for late sensory and neurovascular sequelae are warranted, as are interventions during and following treatment to mitigate the risk of developing such complications. Research Sponsor: Garron Family Cancer Centre.

Characteristics of cases and controls.

Characteristic	Cases No. (%) (n=96)	Controls No. (%) (n=480)
Female	59 (61.5)	295 (61.5)
Age at diagnosis (years), median (IQR)	7 (2-11)	7 (2-11)
Attained age (years), median (IQR)	22 (15-30)	25 (15-34)
Follow-up time from index (years), median (IQR)	8 (4-16)	10 (5-19)
Death during follow-up	<6	<6
Craniospinal irradiation	25 (26.1)	–
Focal irradiation	49 (51.0)	–
Cyclophosphamide equivalent dose ≥8000mg/m^2	13 (13.5)	–
Cumulative cisplatin exposure ≥400mg/m^2	<6	–

–: not applicable; IQR: interquartile range.

10055 **Poster Session**

Protein, fat, and animal food intakes and premature aging in adult survivors of childhood cancer: St. Jude Lifetime (SJLIFE) cohort. *First Author: Yikyung Park, Washington University School of Medicine, St. Louis, MO*

Background: Childhood cancer survivors are a growing population who appear to be at higher risk for premature aging and age-related chronic health conditions than their peers with no history of cancer. Diet affects many hallmarks of aging, such as inflammation, metabolic dysfunctions, and molecular and epigenetic changes, leading to impairment in physical and cognitive functions and premature death. High consumption of animal foods that are high in protein and fat increase risk for many age-related chronic diseases. However, some studies found protein intake was beneficial for physical frailty in elderly and cancer survivors. **Methods:** Adult survivors (> = 18 years old) of childhood cancer survivors enrolled in the SJLIFE Cohort between 2007 and 2017 completed a 110-item food frequency questionnaire at study entry (n = 3,322). Survivors' sociodemographic, cancer, cancer treatments, and medical history data were abstracted from medical records. Health conditions self-reported after cancer diagnosis were clinically validated. Premature aging was assessed using the Deficit Accumulation Index (DAI) based on 45 aging-related health conditions. DAI is categorized into low (< 0.2), medium (0.2-0.34) and high (> 0.35) aging risk groups. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using multinomial logistic regressions adjusting for potential confounders. **Results:** The average age of survivors at baseline was 31 years. Approximately half of the survivors were women, and 82% were white, non-Hispanic. 20% and 8% of survivors were at medium and high risk for aging, respectively. Survivors at high risk for aging tended to be female, smokers, have low socioeconomic status, and received radiation therapy to head and neck, chest, spine or abdomen compared to those at low aging risk. Higher protein intake was associated with a less risk of premature aging (OR = 0.74, 95% CI: 0.58-0.95 for high aging risk group; OR = 0.91, 95% CI: 0.78-1.07 for medium aging risk group, per increment of 5% of total energy intake). On the other hand, higher fat intake was related to an increased risk of premature aging (OR = 1.14, 95% CI: 1.01-1.29 for high aging risk group; OR = 0.99, 95% CI: 0.91-1.08 for medium aging risk group, per increment of 5% of total energy intake). However, substituting monounsaturated fat for other types of fat was associated with a lower risk of premature aging (OR = 0.81 95% CI: 0.70-0.95 for high aging risk group). Red meat (OR = 1.11, 95% CI: 0.87-1.42 for high aging risk group) and dairy intake (OR = 0.99, 95% CI: 0.72-1.38 for high aging risk group) was not related to risk of premature aging. **Conclusions:** Consuming protein and fat from healthy foods may lower the risk of premature aging in childhood cancer survivors. Research Sponsor: St. Jude Children's Research Hospital-Washington University St. Louis Implementation Sciences Collaborative.

10056 **Poster Session**

Treatment exposure-based risk-stratification for care of survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. *First Author: Michaela Ann Dinan, Yale Cancer Center, New Haven, CT*

Background: Treatment exposure-based risk-stratification oflong-term cancer survivors is needed to allocate tailored health care in survivorship clinics. Investigators from the United Kingdom (UK) developed a treatment exposure-based algorithm that stratifies survivors into low, medium, and high risk groups. Because this algorithm has not been validated, we sought to use the large, diverse population of the Childhood Cancer Survivor Study (CCSS) to validate risk for poor outcomes. **Methods:** Five-year survivors of childhood cancer (diagnosed between 1970-1999 at < 21 years of age) were categorized into low, medium, and high risk groups based on treatment exposures and diagnoses (Table). Primary endpoints included cumulative health-related (i.e., non-recurrence, non-external) late mortality and cumulative incidence of grade 3-5 chronic conditions (CTCAEv4.03) conditional on reaching age 20 without the outcome. Siblings were a comparison group for chronic conditions. Cox proportional hazards models among survivors estimated hazard ratios (HRs) and 95% confidence intervals (CI) adjusted for sex and race. **Results:** A total of 21,504 survivors were analyzed with a median follow-up of 22 years. Application of the risk stratification algorithm resulted in 3,152 low risk, 6,443 medium risk, and 11,909 high risk survivors. Among those who survived to age 20 without any grade 3-5 conditions, the risk of developing one by age 35 was 12.2% (95% CI 1.0-14.7%), 14.2% (12.8-15.7%) and 25.4% (24.2-26.6%) for low, medium, and high-risk patients, respectively, and 6.9% (6.1-7.9%) for siblings. HRs of grade 3-5 conditions for medium (HR 1.8, 95% CI 1.6-2.1) and high (HR 3.9, 95% CI 3.5-4.4) risk relative to low risk survivors, respectively, were elevated. Cumulative health-related mortality was similarly associated with risk categories; conditional on being alive at age 20, survivors within low, medium, and high risk groups had cumulative incidences of 2.3% (95% CI 1.7-3.1%), 3.3% (2.8-3.9%) and 6.1% (5.6-6.6%), respectively, by age 35. **Conclusions:** Risk categorizations based on treatment exposures were effective at providing generalized risk stratification within the CCSS with respect to risk of grade 3-5 conditions and health related mortality, particularly for identifying high risk survivors. These risk groups may be useful to physicians in determining follow-up intervals and guiding management and long-term surveillance of these survivors. Research Sponsor: U.S. National Institutes of Health.

Risk Stratum	Diagnosis	Treatments
Low	ALL	Chemo only with DED < 100 mg/m^2
	Wilms Tumor	No RT & DED = 0
	Non-CNS tumors	Surgery Only
Medium	Anyone not in Low or High Risk	
	CNS	No RT
High	Any	Auto or Allo Transplant
		Cranial RT > 24Gy; direct RT to neck, chest, abdomen, or pelvis
		CED > = 10 g/m^2; Cisplatin > 400 mg/m^2, DED > 250

RT = Radiation Therapy; DED = Doxorubicin Equivalent Dose; CED = Cyclophosphamide Equivalent Dose.

10057 **Poster Session**

The impact of clinical trial enrollment on specialty palliative care utilization in pediatric patients with high-grade gliomas. *First Author: Holly Roberts, University of Michigan Medical School, Ann Arbor, MI*

Background: In pediatric oncology patients, palliative care has been shown to provide numerous benefits, including less intense clinical care in the last month of life, improved symptom management, and dedicated family communication. Pediatric patients with high grade glioma (HGG) represent a patient population particularly well suited for early involvement of palliative care given their high symptom burden and relatively poor prognosis. However, a recent study revealed that pediatric patients with primary malignant central nervous system (CNS) tumors missed multiple opportunities for appropriate palliative care involvement throughout their disease courses. We hypothesize that clinical trial enrollment may lead to a lack of or delay in involvement of palliative care in children and young adults with HGG. **Methods:** We identified a cohort of 43 deceased pediatric patients with HGG who received care at our institution. IRB exemption was obtained. For each patient, the electronic medical record was reviewed to collect patient demographics, cancer diagnoses and outcomes, clinical trial enrollment, non-clinical trial treatments, and palliative care involvement. Statistical analysis was performed comparing patients enrolled in trials to those not enrolled, employing Fisher's exact tests for categorical data and t tests for numerical data. **Results:** Overall, 72% (31/43) of patients had at least one visit with a specialty palliative care provider. 56% (24/43) of patients enrolled in a clinical trial with HGG-directed therapy. 71% (17/24) of patients who enrolled in a clinical trial received specialty palliative care compared to 74% (14/19) of non-trial participants ($p = 1.000$). Similarly, among patients who received palliative care there was no statistically significant difference in the timing of palliative care involvement, measured from the date of first palliative care contact to date of death, for patients who enrolled in a clinical trial (mean = 177 days) compared to those who did not (mean = 113 days, $p = 0.180$). Of the 24 patients enrolled in clinical trials, only 7 (29%) had palliative care involvement prior to initiation of study treatment. **Conclusions:** As our understanding of the genomic landscape of pediatric brain tumors increases, it can be expected that patients electing to enroll in targeted therapy clinical trials will also increase. As such, it is reassuring that our data suggest that trial participation does not interfere with the receipt of specialty palliative care in children with HGG. While not statistically significant, initial palliative care involvement trends toward occurring in closer proximity to death in the patients who are not enrolled on a clinical trial. Overall, it is encouraging that in our pediatric HGG patient cohort, enrollment in clinical trials does not appear to have an adverse impact on specialty palliative care involvement. Research Sponsor: U.S. National Institutes of Health.

TPS10058 **Poster Session**

Erdafitinib in pediatric patients with advanced solid tumors with fibroblast growth factor receptor (*FGFR*) gene alterations: RAGNAR study pediatric cohort. *First Author: Olaf Witt, Hopp Children's Cancer Center (KiTZ), University Hospital of Heidelberg and German Cancer Research Center, Heidelberg, Germany*

Background: *FGFR* gene alterations have been observed in pediatric patients with cancers and represent potentially targetable genomic variants. Gliomas (high- and low-grade) and soft tissue sarcomas are among the pediatric solid tumors that may harbor *FGFR* alterations. Erdafitinib is a selective pan-FGFR inhibitor approved in patients with locally advanced or metastatic urothelial carcinoma with susceptible *FGFR2/3* alterations. RAGNAR (NCT04083976) is an ongoing single-arm, open-label, phase 2 histology-agnostic study investigating the efficacy and safety of erdafitinib in patients with advanced solid tumors exhibiting *FGFR* alterations after failure of standard systemic therapies. Here we describe the pediatric study cohort. **Methods:** The pediatric cohort (n = 26, planned) includes patients (≥ 6- < 18 y) with advanced solid tumors (measurable disease per RECIST v.1.1 or RANO [brain tumors]) with *FGFR* mutations, gene fusions, or internal tandem duplication (patients with *FGFR* amplification are not eligible) identified via local test reports or central molecular testing. Eligible patients will have received ≥ 1 lines of prior systemic therapy, have exhausted or be unable to tolerate standard-of-care therapies, and have documented disease progression and measurable disease. In addition, up to 6 patients in this cohort will be allowed to be treatment naive. Children and adolescents will be treated with oral erdafitinib, allowing pharmacodynamically guided uptitration based on serum phosphate levels to maximize efficacy. Treatment will continue until progressive disease. The primary end point is overall response rate (ORR) assessed by an independent review committee. Secondary efficacy end points include ORR assessed by the investigator, duration of response, disease control rate, clinical benefit rate, progression-free survival, and overall survival. Other secondary end points are pharmacokinetic exposure parameters, incidence/severity of adverse events, and change from baseline in patient-reported health status. End-of-treatment visit will occur 30 days after the last dose of erdafitinib. A follow-up phase will continue until death, withdrawal of consent, loss to follow-up, or end of study. As of January 2022, 3 patients have been enrolled. Clinical trial information: NCT04083976. Research Sponsor: Janssen Research & Development.

TPS10059 **Poster Session**

Trial in progress: A phase I trial of dual EZH 1/2 inhibitor valemetostat tosylate (DS-3201b) in pediatric, adolescent, and young adult patients with malignant solid tumors. *First Author: Ayumu Arakawa, Department of Pediatric Oncology, National Cancer Center Hospital, Tokyo, Japan*

Background: Enhancer of zeste homolog enzymes (EZH1 and EZH2) form parts of the polycomb repressive complex 2 and regulate gene expression by catalyzing the tri-methylation of lysine 27 residue of histone H3. SMARCB1/INI1 is one of the core components of the SWI/SNF chromatin remodeling complex, with the loss of SMARCB1/INI1 causing the oncogenic activation of EZH2 and EZH1. The inhibition of EZH2 or both EZH2 and EZH1 can be effective against various hematological malignancies and SMARCB1/INI1-deficient solid tumors. Valemetostat tosylate (DS-3201b; valemetostat) is a potential first-in-class dual inhibitor of EZH1 and EZH2 that targets epigenetic regulations by inhibiting both EZH1 and EZH2 enzymes. A phase 2 single-arm study showed that valemetostat demonstrated promising response rates in Japanese patients with relapsed or refractory adult T-cell leukemia/lymphoma (Yoshimitsu M et al., presented at ASH Annual Meeting, 2021). Tumors characterized by SMARCB1/INI1 deficiency (a SWI/SNF mutation), such as malignant rhabdoid tumors, epithelioid sarcoma, or synovial sarcoma are quite frequently observed during childhood and adolescence, among whom valemetostat is expected to show antitumor effects. **Methods:** This open-label multi-center phase I trial evaluates the safety and efficacy of valemetostat in pediatric, adolescent, and young adult patients with refractory/relapsed solid tumors. The inclusion criteria are relapsed, refractory, or progressive metastatic disease; >3 and <19 years of age during the dose escalation cohort and < 29 years of age in the expanded cohort; performance status of >50 (assessed by Karnofsky Performance score in patients >16 years old, and Lansky Performance score in patients <15 years old); and adequate organ function. Valemetostat is administered orally once a day without interruption. Three dose levels (150, 200, and 250 mg/1.7 m^2) are assessed using a 3+3 design during the dose escalation cohort. After determining the recommended phase 2 dose (RP2D) during dose escalation cohort, up to 30 patients will be further enrolled, and the safety and efficacy data of valemetostat are determined in the expanded cohort. The primary endpoint is the incidence of dose limiting toxicity, whereas the secondary endpoints include safety, pharmacokinetics, overall response rate, progression-free survival. The overall response rate of the tumors with SMARCB1/INI1 deficiency or SWI/SNF mutation is also evaluated as a secondary endpoint. Exploratory endpoint includes overall survival. Enrollment into this trial began in March 2020, and enrollment into the dose escalation cohort was completed. Enrollment into the expanded cohort began in November 2021. Clinical Trial Information: jRCT2031190268. Research Sponsor: Japan Agency for Medical Research and Dvelopment.

TPS10060 **Poster Session**

CaboMain: A phase 2 study of cabozantinib as a maintenance agent in patients with ultra-high risk pediatric solid tumors. *First Author: Nilay Shah, Nationwide Children's Hospital, Columbus, OH*

Background: Patients with relapsed or refractory pediatric solid tumors have one-year progression-free survival (PFS) <25% even if a remission is achieved [1-9]. Maintenance treatments may extend survival for these patients but have not been tested. Many tyrosine kinase inhibitors (TKIs) target oncogenic pathways active in pediatric cancers and are being evaluated in children with cancer. The multitargeted TKI cabozantinib inhibits MET, VEGFR, AXL, RET, ROS1, KIT, TRKB, FLT3, and TIE2. Preclinical studies and clinical use suggest that cabozantinib may be active against childhood cancers [10-20]. A pediatric Phase 1 study defined a dose of 40 mg/m^2/day[21], currently used in an ongoing pediatric Phase 2 study for measurable relapsed/refractory solid tumors, NCT02867592 . However, cabozantinib has not been tested as a maintenance agent against cancers in children. We hypothesize that cabozantinib, in patients with ultra-high-risk pediatric solid tumors with minimal disease burden, can prevent recurrent tumor formation or induce a durable remission. **Methods:** Trial Design: Single arm, open-label, multisite investigator-initiated Phase 2 trial for patients with a "best response," defined as no progression at least 28 days after end of prior therapy. Primary objective: Evaluate the effect of cabozantinib administered for up to 12 months on 1-year PFS. Statistical design and measure: Bayesian time-to-event optimal phase 2 design with a single interim analysis designed to detect 20% increase in PFS at 1 year with 80% power. Secondary objectives include 2- and 5-year PFS; 1-, 2-, and 5- year OS, duration of response, and safety and tolerability. Exploratory objectives include patient-reported outcomes, predictive biomarkers, PK and PD measurements. Treatment: Patients will take cabozantinib tablets on a continuous dosing schedule, partitioned into 28-day cycles, at an initial dose of 40 mg/m2/day (per dosing nomogram), for up to 365 days. Assessments are defined; radiographic assessment every 3 cycles. Dose modifications will be based on toxicities per protocol. Patients will continue on therapy until progression, toxicities not relieved by dose reduction, or end of planned therapy. Major eligibility criteria: Three strata: Neuroblastoma with residual disease at end of upfront therapy ("Best Response 1", BR1) or after any relapse, n=36. Pediatric CNS tumors, defined in the protocol, n=30. Other pediatric solid tumors, as defined in the protocol, n=36. Patients must be ≥ 18 months and ≤40 years of age at enrollment, have completed prior therapy ≥ 4 weeks and ≤ 12 weeks prior to enrollment and demonstrate radiographic BR at time of enrollment. Measurable or evaluable disease is not required. Enrollment: Protocol is open to enrollment as of February 12, 2022. At time of abstract submission, we have not yet enrolled the first patient. Clinical trial information: NCT05135975. Research Sponsor: Exelixis.

TPS10061 **Poster Session**

Naxitamab and granulocyte macrophage colony stimulating factor (GM-CSF) in combination with irinotecan and temozolomide in patients with high-risk neuroblastoma with primary refractory disease or in first relapse: An international, single-arm, multicenter phase 2 trial. *First Author: Godfrey Chi-Fung Chan, Hong Kong Children's Hospital, The University of Hong Kong, Hong Kong, Hong Kong*

Background: Neuroblastoma (NB) is the commonest extracranial solid tumor in children. At diagnosis, > 50% have high-risk (HR) disease with poor prognosis despite intensive therapy; thus, there is a high unmet medical need. Naxitamab is an anti-GD2 monoclonal antibody indicated under accelerated approval in the US with GM-CSF for the treatment of relapsed/refractory HR NB in the bone and/or bone marrow in patients (pts) ≥1 year of age with a partial response, minor response, or stable disease to prior therapy. Irinotecan and temozolomide (IT) are commonly used salvage chemotherapies following failure of frontline therapy. The objective of this study is to investigate the efficacy and safety of naxitamab plus IT in pts with HR NB with primary refractory disease or first relapse. **Methods:** Trial 203 (NCT04560166) is an international, single-arm, multicenter phase 2 trial for HR NB patients ≥12 mo of age, with either evaluable primary refractory disease or first relapse following induction and consolidation therapy. The primary endpoint of the study is the centrally-assessed overall response rate (ORR) (complete [CR] or partial response) at or before completion of 4 cycles of treatment. Key secondary endpoints include ORR after 2 cycles of treatment, duration of response (DoR), CR rate, time to first subsequent therapy or death, progression-free survival (PFS), and overall survival (OS). 52 pts will be enrolled to provide 82% power to demonstrate that response rate is significantly higher than 20%. Key inclusion criteria are documented HR NB at time of diagnosis; received frontline induction/consolidation therapy; active disease despite previous aggressive chemotherapy; and measurable tumor (CT/MRI) that is either MIBG-avid/PET-positive or have MIBG scan with uptake at ≥1 site. Key exclusion criteria include prior treatment with duration ≤3 wks (chemotherapy), ≤6wks (autologous stem cell transplant or therapeutic ^{131}I-MIBG), ≤4wks (radiation therapy), or progressed while on anti-GD2; residual NB in the bone marrow only; and CNS/leptomeningeal disease in the prior 6 mo. In addition, there should not be < 50% performance status per Lansky or Karnosky scale and life expectancy < 6 mo. Pts will receive irinotecan 50 mg/m^2/day IV and temozolomide 100 mg/m^2/day orally (both on Days 1-5) in combination with naxitamab 2.25 mg/kg/day IV (Days 2, 4, 8 and 10) and GM-CSF 250 ug/m2/day sc (Days 6-10) in 21 days cycle. Response rates will be assessed using the 2-sided binomial test at the 5% significance level; DoR, PFS, and OS will be estimated using Kaplan-Meier analysis. Adverse events will be graded per CTCAE. Clinical trial information: NCT04560166. Research Sponsor: Y-mAbs Therapeutics.

TPS10062 **Poster Session**

FIREFLY-1 (PNOC 026): A phase 2 study to evaluate the safety and efficacy of tovorafenib (DAY101) in pediatric patients with *RAF*-altered recurrent or progressive low-grade glioma or advanced solid tumors. *First Author: Daniel Landi, Department of Neurosurgery, Duke University, Durham, NC*

Background: *RAF* gene fusions (*BRAF* and *RAF1*) and BRAF V600E mutations are oncogenic drivers found on a mutually exclusive basis in most pediatric low-grade gliomas (LGGs). In addition, *RAF* fusions (*BRAF* and *RAF1*) have also been identified in other pediatric solid tumors. Tovorafenib (DAY101) is an investigational, oral, highly selective, CNS-penetrant, small molecule, type II pan-RAF inhibitor. In contrast to type I BRAF inhibitors, tovorafenib does not induce RAS-dependent paradoxical activation of the MAPK pathway. In the phase 1 PNOC014 study in pediatric patients with recurrent/progressive LGG, tovorafenib was well tolerated and 7/8 patients with tumor harboring *RAF* fusions had meaningful clinical benefit. Recently, a child with a novel *SNX8-BRAF* fusion spindle cell sarcoma demonstrated a rapid and deep response when treated with tovorafenib. **Methods:** FIREFLY-1 (NCT04775485) is an open-label, multicenter, phase 2 study evaluating the safety and efficacy of tovorafenib monotherapy in pediatric patients with *RAF*-altered recurrent or progressive LGG or advanced solid tumors. The initial design included only patients with LGG (arm 1). Two new arms have now been added; arm 2 will allow tovorafenib treatment for patients with LGG harboring an activating *RAF* alteration after completion of enrollment to arm 1 and prior to tovorafenib regulatory approval; arm 3 will enroll patients with advanced solid tumors harboring an activating *RAF* fusion. Eligible patients are 6 months to 25 years of age, who have received ≥1 prior line of systemic therapy with documented radiographic progression, have evaluable and/or measurable disease by appropriate criteria, a Karnofsky or Lansky performance score of at least 50, and adequate organ function. Patients are excluded if their tumor has other driver mutations, they have neurofibromatosis type 1, central serous retinopathy, retinal vein occlusion, clinically significant active cardiovascular disease, or are currently being treated with a strong CYP2C8 inhibitor or inducer other than those allowed per protocol. Approximately 140 patients in total will be enrolled including 60 in arm 1, 60 in arm 2 and 20 in arm 3. Tovorafenib will be administered at 420 mg/m^2 (not to exceed 600 mg) weekly (days 1, 8, 15 and 22) for 26, 28-day cycles (in the absence of disease progression or unacceptable toxicity). They may then continue tovorafenib or enter a drug holiday period. The primary endpoint is overall response rate, as defined by the RANO criteria (arm 1) or RECIST v1.1 (arm 3) and as determined by an independent radiology review committee. Secondary endpoints (arms 1 and 3) include safety and tolerability, pharmacokinetics, duration of response, time to response and progression-free survival. Tovorafenib is available in tablet or liquid suspension formulations. Clinical trial information: NCT04775485. Research Sponsor: Day One Biopharmaceuticals.

TPS10063 **Poster Session**

A pilot clinical study of VAL-413 (oral irinotecan HCl) in patients with recurrent pediatric solid tumors. *First Author: Dennis Brown, Edison Oncology Holding Corp., Menlo Park, CA*

Background: Intravenous irinotecan hydrochloride (IRN-IV) is approved for the treatment of adult colorectal cancer. IRN-IV is also widely used off-label for a range of adult and pediatric solid tumors including recurrent Ewing sarcoma, rhabdomyosarcoma, neuroblastoma, hepatoblastoma, Wilms tumor, gynecologic cancers, lung cancer and medulloblastoma. Previously, a regimen of IRN-IV administered as a 60-min i.v. infusion daily for 5 days, every 21 days has been recommended use in treating children with solid tumors *(*Blaney. *ClinCanRes,* 2001*).* Protracted administration schedule of intravenous irinotecan is inconvenient for patients, so oral regimens utilizing IRN-IV have been developed *(*Wagner. *ClinSarcRes,* 2015*).* Unfortunately, the palatability of the intravenous preparation is poor, leading to reduced compliance especially in younger pediatric patients. Development of an advanced formulation to improve tolerability and patient compliance is an important unmet clinical need. VAL-413 is a novel formulation developed to improve palatability of oral irinotecan. **Methods:** Eligibility: Up to 20 patients ≥ 1 year and ≤ 30 years of age with recurrent pediatric solid tumors and adequate bone marrow, renal and liver function, for whom irinotecan therapy is a treatment option will be enrolled. Trial Design: Two different dose levels of VAL-413, 90mg/m2/day or 100mg/m2/day will be studied in combination with a fixed-dose of temozolomide using a standard 3 + 3 phase I design. In the event that the starting dose of 90 mg/m2/day is not tolerable due to toxicity, a lower dose of 75 mg/m2/day may be implemented. Treatment: During the first cycle of treatment, each patient will receive 4 daily doses of VAL-413 and one daily dose of the intravenous preparation of irinotecan taken orally (IRN-IVPO). During all subsequent cycles, only VAL-413 will be given with temozolomide in 5-day courses administered every 21 days, as tolerated. Outcome Measures: Toxicity is assessed by NCI CCTCAEv5; tumor response is assessed by RECIST 1.1. A palatability survey instrument will assess palatability of VAL-413 vs. IRN-IVPO; and comparative intrapatient pharmacokinetics of irinotecan and its metabolites will be assessed in all patients. This trial is ongoing (CT.gov: NCT04337177). Enrolment of the first dose level is ongoing, with no DLT observed to date. Clinical trial information: NCT04337177. Research Sponsor: Edison Oncology Holding Corp.

10500 **Oral Abstract Session**

Democratizing germline genetic testing and its impact on prostate cancer clinical decision-making. *First Author: Neal D. Shore, Carolina Urologic Research Center, Myrtle Beach, SC*

Background: Approximately 10-15% of prostate cancer (PCa) patients (pts) have a pathogenic germline variant (PGV). Identification of a PGV has important implications affecting decisions regarding cancer screening, treatment selection, and family cascade testing. There exists limited data documenting real world recommendations post germline genetic testing (GGT). This study was designed to collect clinician reported outcomes from PCa pts who underwent GGT. **Methods:** An IRB-approved, nationwide, prospective registry recruited unselected PCa pts from 15 community and academic urology practices. Pts underwent an 84-gene panel test, with clinical outcomes collected via clinician-completed case report forms > 1-month post GGT. Statistical significance was determined by two-tailed Fisher's exact test. **Results:** 982 predominantly white (75.9%), non-metastatic (80.7%) males with PCa were recruited; 56.9% met National Comprehensive Cancer Network (NCCN) GGT criteria. Average age was 65.3 years at PCa diagnosis. PGVs, most commonly *CHEK2* (17) and *BRCA2* (10), were identified in 100 (10.2%) pts; 34 (34%) of these did not meet NCCN GGT criteria. Among PGV positive pts, 241 recommendations were made (Table). They were more likely to have changes to treatment ($p < 0.0001$), follow up ($p < 0.0001$) and cascade testing recommendations ($p < 0.0001$) than those with negative/variant of uncertain significance (VUS) results. There were no significant differences in changes to treatment ($p = 0.4471$) or follow up ($p = 0.861$) for pts who met NCCN criteria versus those who did not. 7 pts with PGVs received targeted therapy or were referred to a clinical trial. 5 pts with VUS results were also referred to a clinical trial. Among these 12 pts, 6 (50%, 2 *CHEK2* PGV, 1 *ATM* PGV, 1 VUS each *ATM*, *BLM*, *CHEK2*) did not meet NCCN GGT criteria. Referral to a genetic counselor was the most common follow up recommendation for those with PGV (38 patients, 38%) and VUS results (66, 13.7%). The most commonly reported impact to health outcomes for those with negative results was knowledge/reassurance (38, 7.88%). **Conclusions:** This study showed that GGT did influence PCa pts care. Appropriately, pts with PGVs received a greater number of recommendations for relatives, changes to follow up and treatment. Research Sponsor: Invitae.

# pts	# positive	%	# negative	%	# vus	%	total	%
	100	10.2%	400	40.7%	482	49.1%	982	100%
# yes, GGT impacted pt health outcome	67	67.0%	100	25.0%	188	39.0%	356	36.3%
# pts, change to treatment recommendations	18	18.0%	1	0.3%	10	2.1%	29	3.0%
# changes to treatments recommendations	21	-	1	-	11	-	33	-
# pts, change to follow up	62	62.0%	7	1.8%	92	19.1%	161	16.4%
# changes to follow up	82	-	7	-	92	-	181	-
# pts, GC recommended for family	67	67.0%	4	1.0%	35	7.3%	106	10.8%
# pts, GGT recommended for family	71	71.0%	7	1.8%	41	8.5%	119	12.2%
Total # health outcome evaluations	241	-	19	-	179	-	439	-

GC, genetic counseling; GGT, germline genetic testing; pt(s), patient(s); VUS, variant of uncertain significance.

10501 **Oral Abstract Session**

Rates of germline genetic testing and DNA damage response mutations found through population-based recruitment of men with incident metastatic prostate cancer. *First Author: Hiba Khan, University of Washington, Seattle, WA*

Background: Approximately 10% of men with metastatic prostate cancer (mPC) have germline DNA damage response gene mutations (gDDRm), indicating candidacy for precision treatment. Consequently, national guidelines recommend germline genetic testing be offered to all men with mPC. It is currently unclear what the rates of testing are in the community, and barriers to testing are not well understood. We conducted a population-based study to better understand current rates of germline genetic testing in men with newly diagnosed mPC, and to determine whether removing major barriers of cost and access could expand uptake of germline genetic testing. **Methods:** This is a prospective observational study that identifies men ages 35-79y with mPC residing in a 13-county area of Washington State through the Surveillance, Epidemiology, and End Results (SEER) program (NCT04254133). Men with new diagnoses of mPC are contacted by mailed invitation and follow-up phone inquiry. Interested men are then invited to provide informed consent and complete a questionnaire about personal and family health history. A saliva collection kit for a 30-gene targeted panel of cancer predisposition genes (Color Genomics) is mailed to participants' homes free of charge. Results are issued by phone and/or email with genetic counseling support, including discussion about cascade genetic testing if relevant. **Results:** As of Feb 9, 2022, 484 men with incident mPC diagnosed 1/2018-6/2021 were identified through SEER. 430 men were reached via a letter to their home address sent > 3 months after diagnosis. 175 of 430 (40.6%) men expressed interest and completed the questionnaire, the majority preferring to complete testing through mail after a phone-initiated introduction to the study. 164 of 175 men completed the consent process and were eligible. Of these 164 men, 45 (27.4%) reported prior genetic testing, and reports were requested and reviewed to ensure adequate testing. Ultimately, 121 of 164 (73.8%) participants initiated and 101/121 (83.5%) have completed genetic testing through the study. Nine percent (9/101) of participants completing testing as part of the study were found to have gDDRm. **Conclusions:** We used a population-based approach to understand the proportion of men with mPC undergoing germline genetic testing through clinical care, and the subsequent uptake of genetic testing when access and cost barriers are removed. The uptake of guideline-based germline genetic testing among men with mPC in the community prior to study enrollment is only 27.4%. With study interventions in the form of free testing through mail, and phone-based support, 83.5% of men in this community successfully completed testing. Further work in this study will aim to elucidate and attempt to eliminate other barriers in germline genetic testing to further improve testing rates in this community. Research Sponsor: U.S. National Institutes of Health.

10502 **Oral Abstract Session**

Mutation spectrum and rates of variants of uncertain significance among African American males undergoing prostate cancer germline testing: Need for equity in genetic testing. *First Author: Veda N. Giri, Departments of Medical Oncology, Cancer Biology, and Urology, Cancer Risk Assessment and Clinical Cancer Genetics Program, Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA*

Background: Germline testing (GT) for prostate cancer (PCA) is central to metastatic disease management, PCA screening strategies, and hereditary cancer assessment. African American (AA) males have a higher burden of PCA, yet have lower engagement in germline testing which limits understanding of genetic contribution to PCA. Here we evaluated the germline spectrum of AA and White males with PCA undergoing clinical multigene panel testing (MGPT) to inform germline testing strategies with attention to equity. **Methods:** Study participants included AA men and White men with PCA who underwent a 14-gene MGPT between April 2012 - December 2020 at a clinical diagnostic laboratory (Ambry Genetics). Exclusions were men with known pathogenic variants reported in their families or who had prior genetic testing. MGPT included: *ATM, BRCA1, BRCA2, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, RAD51D, TP53.* Sanger or next generation sequencing analysis was performed per standard clinical testing protocol. Variant classification was per ACMG 5-tier system. Descriptive statistics summarized results with counts and percentages for categorical variables and mean and standard deviation for continuous variables. Data were compared with Fisher's exact, Chi-squared, two proportion z-test, or two sample t-test, as appropriate. Significance level was set a priori at 0.05. **Results:** The dataset included genetic and clinical data from 427 males who had undergone MGPT: White males (n = 190; 45.5%) and AA males (n = 237; 55.5%). Mean age at diagnosis was 59 + 9.3 years. Among men whose Gleason score was indicated (72%), 47% had Gleason > = 8. Majority of men indicated having a $1^{st}/2^{nd}$ degree relative with PCA (68.97%) or $1^{st}/2^{nd}$ degree relative with any cancer (99.2%). In the entire cohort, 8.2% tested positive for a pathogenic/likely pathogenic variant; AA males (n = 14, 5.91%) and White males (n = 21, 11.05%). VUS only was reported in 21.31% of the overall cohort with a significant difference noted between AA and White males (25.32% vs. 16.32%, respectively; $p = 0.0238$). Mutation spectrum in AA males included: *BRCA2* (n = 7), *PALB2 (n = 3), ATM* (n = 3), and *BRCA1* (n = 1). Among White males, a wider spectrum of mutations was observed: *BRCA2* (n = 6), *ATM* (n = 5), *HOXB13* (n = 5), *CHEK2* (n = 2), *TP53* (n = 1), and *NBN* (n = 2). The proportion of AA males with multiple VUS was significantly higher than for Caucasian males (5.1% vs. 0.53%, $p = 0.003$). **Conclusions:** Clinical germline testing among AA males reveals a narrow spectrum of mutations in key DNA repair genes, with important implications for precision therapy and hereditary cancer assessment. Furthermore, AA males had significantly higher rates of multiple VUS, indicating critical need for greater inclusion of diverse populations in genetic studies to discern the pathogenic spectrum contributing to PCA aggressiveness and risk. Research Sponsor: None.

10503 **Oral Abstract Session**

Implementing systematized patient-facing Lynch syndrome (LS) risk assessment in oncology using the electronic health record (EHR) system. *First Author: Chinedu Ukaegbu, Dana Farber Cancer Institute, Boston, MA*

Background: Lynch syndrome (LS) is the most common inherited cause of colorectal (CRC) and endometrial cancers. Significant provider and institutional level barriers limit LS detection, even in oncology patients with LS-associated cancers. PREMM5 is a validated tool based on personal and family cancer history that is recommended by national professional societies for LS risk assessment. This project's goal was to study the feasibility of patient-facing LS risk assessment using a PREMM5 screener embedded in an electronic health record (EHR) system, as a means of improving LS identification. **Methods:** The PREMM5 LS screener intake questions were adapted to be completed by patients rather than healthcare providers. Screener adaptation and implementation involved iterative review by multidisciplinary experts and multilevel stakeholder engagement. The patient-facing PREMM5 LS screener was embedded in the EHR (Epic) at the Dana-Farber Cancer Institute (DFCI) to enable remote (via the EHR patient portal) and on-site completion (in clinic waiting rooms). All new gastrointestinal (GI) cancer patients seen at DFCI for initial oncology consultation from 6/2020-12/2021 were invited through the portal to complete the screener. PREMM5 scores ≥2.5% were considered "positive", with genetics referral recommended. Beginning 2/2021, the EHR generated an automated provider-facing alert for positive screens. **Results:** 35% (1504/4262) of new GI cancer patients completed the screener. 367/1504 (24%) had a positive PREMM5 screen (mean age 53 years), of whom 66% were male, and 62%, 12% and 10% had CRC, neuroendocrine and pancreas cancer respectively. 97% (357/367) of screen positives completed the PREMM5 screener remotely through the portal. 102/367 (28%) received a genetics referral as a result of their positive PREMM5 screen (not including 75 genetics referrals outside this workflow), 13 of whom had a pathogenic variant (PV) on germline testing, including 4 with LS (*MSH2, MSH6, PMS2*), and others with PVs in *ATM, BRCA2*, *CHEK2*, *NTHL1*, *RAD50* and *RECQL4*. **Conclusions:** A practice-wide patient-facing EHR-integrated PREMM5 risk assessment workflow is feasible and identified nearly 1 in 4 general GI oncology patients as warranting genetic evaluation, resulting in the identification of numerous actionable germline PVs. This method of deployment could make genetic risk assessment more accessible to non-genetics providers. The suboptimal screener completion rate and 28% genetics referral rate among positive screens suggest the need for additional refinements, including patient and provider engagement and outreach to positive screens who do not follow up with appointments for genetic evaluation. Research Sponsor: None.

10504 **Oral Abstract Session**

Clinical implications of germline genetic testing stratified by ethnicity in a large colorectal cancer cohort. *First Author: Brandie Heald, Invitae, San Francisco, CA*

Background: Germline genetic testing for patients (pts) with colorectal cancer (CRC) is currently recommended for those diagnosed prior to age 50, as well as other select cases based on personal and/or family history criteria. Whether universal germline multi-gene panel testing (MGPT) should be performed in all pts with CRC remains uncertain given the lack of large-scale studies examining MGPT in CRC across a diverse population. The present study aims to determine the yield, and potential clinical impact, of MGPT across a large CRC cohort. **Methods:** We conducted a de-identified retrospective cohort study of all pts with CRC who underwent MGPT (excluding patients who underwent testing limited to ≤10 genes) at a commercial laboratory between 03/2015-05/2021. We collected pts demographics from test requisition forms and results of germline MGPT. Clinically actionable PGVs were defined as variants in genes with reported CRC or polyposis risk, as well as other actionable genes associated with clinical management and/or therapeutic implications. **Results**: A total of 34,210 pts with a history of CRC underwent germline MGPT. These pts were primarily female (60.7%), White (70.6%), and 50 or older (68.8%), with 35.5% reporting an extra-colonic malignancy. Of this cohort, 4,577 (13.4%) were found to carry at least one PGV, with 2,925 (8.6%) having a PGV associated with increased risk of CRC or polyposis. Of all positive pts, 3,038 (66%) had PGVs with precision therapy or clinical trial implications while another 33% had PGVs with published management implications. Among pts under the age of 30 when tested, 23.3% had a clinically actionable PGV compared to 14.7% at age 30-39, 11.7% at 40-49, 12.9% at 50-59, 11.6% at 60-69, 8.9% 70-79, and 7.8% over the age of 80. When compared to pts identified as White, PGVs were more frequently identified in pts of Ashkenazi Jewish descent ($p < 0.001$) and less frequently identified in those who identified as Hispanic ($p < 0.001$). VUS was more frequently identified in pts identified as Black, Asian, or Hispanic ($p < 0.001$). **Conclusions**: This is the largest study to date examining MGPT in CRC, where we demonstrate high rates of clinically actionable variants across all age groups, self-reported racial/ethnic groups, and panel sizes, with 13% of all CRC pts having a PGV with precision therapy, clinical trial and/or published management implications.- This is likely an underestimate as patients with strong clinical suspicion of hereditary CRC (Lynch, FAP) often receive a targeted panel of <10 genes and were excluded. The lower rate of PGVs in Hispanic pts and higher rate of VUS in Black, Asian and Hispanic pts underscores the historical underrepresentation of these pts and ongoing need to mitigate the associated healthcare disparities. Overall, this work supports consideration of broadening germline genetic testing criteria for patients with CRC. Research Sponsor: None.

10505 **Oral Abstract Session**

The frequency of second primary malignancies and colonic polyps in Lynch syndrome with MSI tumors following immune checkpoint blockade. *First Author: Emily Harrold, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Lynch syndrome (LS) is caused by germline mutations in DNA mismatch repair genes and is characterized by microsatellite instability (MSI) status of associated tumors. MSI sensitizes tumors to immune checkpoint inhibition (ICI). The incidence of second primary malignancies and colonic polyps in LS patients with MSI tumors following ICI has not been evaluated. **Methods:** The Memorial Sloan Kettering LS database was queried for all patients with cancer who received ≥1 cycle of ICI using an IRB approved protocol. LS was confirmed by presence of a germline pathogenic/likely pathogenic alteration in a DNA mismatch repair gene (*MLH1, MSH2, MSH6, PMS2, EPCAM*). Tumor and matched normal DNA sequencing was performed via MSK-IMPACT, an IRB approved protocol (NCT01775072). MSI status was assessed using MSIsensor. **Results:** At our center, 131 patients with LS received ICI mostly (73.3%) in the context of metastatic cancer. While 108 patients received ICI for an MSI tumor, 23 LS patients received ICI for a MSS (Microsatellite Stable) tumor (4 hepatobiliary, 3 colorectal, 3 CNS, 2 endometrial, 2 gastroesophageal, 2 renal, 2 sarcoma, 5 other). Five patients (3.8%) developed ≥1 second primary malignancy while on or following ICI comprised of an MSI small bowel adenocarcinoma, MSI upper tract urothelial cancer, 2 MSS prostate cancers, MSS HCC and MSI sebaceous neoplasm; 1 patient developed both MSS prostate cancer and MSI urothelial cancer on ICI. All five patients' primary malignancy was MSI. Only a minority of patients underwent surveillance colonoscopies post completion of ICI (31.3%, (41/131)). Of these 41, nine (22%, (9/41)) were identified to have polyps including 8 tubular adenomas and 1 tubulo-villous adenoma. Median time to development of a polyp was 22 months (95% CI 16.82-27.18) from last colonoscopy and 13 months (95% CI 4-25 months) from last ICI. Notably amongst the 23 LS patients whose tumors were MSS, 14 had progression on ICI. **Conclusions:** Herein, we demonstrate that in LS-patients in receipt of ICI for cancer treatment, the risk of a second primary cancer and polyps remain high following treatment with ICI. Biological mechanisms underlying immune escape warrant further investigation. Surveillance strategies should be continued for LS patients post ICI. Research Sponsor: None.

10506 **Oral Abstract Session**

Effect of lung cancer screening on the incidence of advanced lung cancer in the United States: A SEER database analysis. *First Author: Maxwell Oluwole Akanbi, McLaren Flint, Flint, MI*

Background: In 2013, the USPSTF recommended screening for lung cancer with low-dose chest computed tomography (LDCT). This was based on the results of the National Lung Screening Trial which showed a 20% relative reduction in mortality from LDCT compared with chest radiography. In Feb/March 2015, the Centers for Medicare and Medicaid (CMS) provided screening guidelines and they and private insurers started covering the cost of LDCT. The impact of this recommendation in the real-world setting is unknown. We investigated the impact of LDCT recommendations on the incidence of advanced lung cancer (a-LCa) in the US general population. We sought to verify that the implementation of LDCT will yield an earlier lung cancer diagnosis and thereby reduce the incidence of later stages of lung cancer. **Methods:** From the Surveillance, Epidemiology, and End Results (SEER) 18 registries database, we identified adults 55-80 years diagnosed with regional or metastatic (advanced) lung cancer from 2004 to 2018. Age-adjusted incidence rates (AAIR) of advanced lung cancer in 2004-2014 (Pre-LDCT) and 2015-2018 (Post-LDCT) were compared using interrupted time series (ITS) regression analyses. Analyses were stratified by sex, race, and residence. **Results:** A total of 400,343 patients who met the study criteria were included. Of these, 219,828 (55%) were women and 76% (n = 304,801) were non-Hispanic White. At all periods, the AAIR of a-LCa was highest in non-Hispanic Blacks. Overall, there was a 41% decline in the AAIR of a-LCa in the post-LDCT period compared to the pre-LDCT era (Annual decline of 7.6 vs 4.5 /100,000 person-years (PY) for 2015-2018 vs 2004-2014, $p < 0.01$). Women experienced a more accelerated decline in the AAIR of a-LCa compared to men (53% versus 30%). By race, the annual rates of a-LCa declined most rapidly among non-Hispanic Blacks (55%, 9.5/ 100,000 PY, 2015-2018 vs 4.7/100,000 PY, 2004-2014, $p < 0.01$), and the slowest rate of decline was among Hispanics (41%, 4.6/100,000 PY,2015-2018 vs 2.7/100,000 PY, 2004-2014, $p < 0.01$). By residence, non-metropolitan dwellers experienced a greater decline in annual rates of a-LCa compared with metropolitan dwellers (non-Metropolitan: 69%, 10.1/100,000 PY, 2015-2018 vs 3.2/100,000 PY 2003-2014, $p < 0.01$: Metropolitan dwellers: 37%, 7.2/100,000 PY 2015-2018 vs 4.5/100,000 PY, $p < 0.01$). **Conclusions:** Using population-based data we found a significant decline in rates of a-LCa following the adoption of LDCT for lung cancer screening in the US. Rates of decline in the incidence of a-LCa, however, varied among subgroups. Non-Hispanic Blacks, women, and rural dwellers experienced the most decline in annual rates of a-LCa from 2015 to 2018. Our study shows the overall benefit of LDCT in marginalized communities. However, the impact of our findings on lung cancer mortality will still need further study. Research Sponsor: None.

10507 **Oral Abstract Session**

Clinical validation of a deep-learning–based model to predict lung cancer risk from chest X-rays. *First Author: Anika Walia, Boston University, Boston, MA*

Background: Screening with chest CT prevents lung cancer death, but only 5% of eligible Americans are screened. The updated 2022 Centers for Medicare and Medicaid Services (CMS) criteria expand eligibility to 50-77 year-olds, current or former (<15 years) smokers, with a ≥20 pack-year history. However, smoking quit date and pack-years are often not available in the electronic medical record (EMR), stymying identification of high-risk smokers for lung cancer screening (LCS). We previously developed a free, open-source deep-learning model (CXR-LC) that identifies smokers at high risk of lung cancer better than the 2015 CMS criteria, based on a chest X-ray (CXR) image automatically extracted from the EMR. CXR-LC was developed in the PLCO trial, an asymptomatic LCS population. The present study externally validates CXR-LC using existing CXRs obtained through usual care and compares CXR-LC to the expanded 2022 CMS lung screening eligibility criteria. **Methods:** Current or former smokers who had a routine clinical CXR in 2013-2014 were included. Patients with known lung cancer or who were undergoing LCS were excluded. Smoking status and 2022 CMS LCS eligibility were determined by manual review of the EMR. The primary outcome was 6-year incident lung cancer, identified using International Classification of Disease (ICD) codes and confirmed through discharge summaries and pathology reports. The CXR-LC model and the 2022 CMS eligibility criteria were compared for prediction of 6-year incident lung cancer. **Results:** Among 10,784 patients (mean age 63.1± 6.8 years; 61.0% male), CMS eligibility could be determined in 45% (4,886/10,784), with 55% missing pack-year or quit date data. In this population, 3.9% (191/4,886) developed lung cancer. The 2022 CMS criteria missed 57% (109/191) of lung cancers, while CXR-LC missed 8.9% (17/191, $p < 0.001$). After adjusting for sex, race, and prevalent COPD, the hazard ratio for CXR-LC eligibility (3.6, 95% CI [2.2,6.0]) was greater than for CMS eligibility (2.7, 95% CI [2.0,3.7]). In the 5,897 patients for whom CMS eligibility could not be determined, CXR-LC eligible patients had a 3-fold higher rate of lung cancer than CXR-LC ineligible patients (3.8% vs. 1.3%, $p < 0.001$). All CXR-LC eligible groups had 6-year lung cancer incidence >3.5%, above accepted screening risk thresholds of >1.5% and >2%. **Conclusions:** Using routine CXRs from the EMR, CXR-LC identified high-risk smokers who may benefit from LCS with CT, complementary to the 2022 CMS eligibility criteria. Research Sponsor: None.

Six-year incident lung cancer (number of cancers/number of patients) by CXR-LC and 2022 CMS eligibility.

	CMS Eligible, % (n/N)	CMS Ineligible, %(n/N)	CMS Eligibility Unknown, % (n/N)	Total, % (n/N)
CXR-LC Eligible	8.9 (77 / 861)	3.7 (97/2,633)	3.8 (193/5065)	4.3(367/8559)
CXR-LC Ineligible	6.2 (5 / 81)	0.9 (12/ 1,311)	1.3 (11/833)	1.3 (28 / 2,225)
Total	8.7 (82/942)	2.8 (109/3944)	3.5 (204 / 5897)	3.7 (395/10784)

10508 **Oral Abstract Session**

Trends in stage I lung cancer. *First Author: Aashray Singareddy, Washington University in St. Louis, St. Louis, MO*

Background: The American Cancer Society has recently reported an increase in the percentage of patients with localized lung cancer from 2004 to 2018 with a corresponding improvement in survival for all patients combined. We analyzed the recent trends in stage distribution for lung cancer including tumor and demographic factors. **Methods:** We selected patients with lung cancer from the National Cancer Database (NCDB) public benchmark report diagnosed between 2010 and 2017. Patients with unknown stage were excluded. Stage distribution using the AJCC 7th edition of the TNM system was evaluated according to year of diagnosis, histology, age, gender, race, insurance and income. **Results:** Among the 1,447,470 patients from 1,384 hospitals identified in the database, 56,382 (3.9%) were excluded due to unknown stage or incorrect histology, leaving 1,391,088 patients eligible. The percentage of patients with stage I progressively increased from 23.5% in 2010 to 29.1% in 2017 while stage IV decreased from 45.5% to 43.1% during the same period (Table). The increased in percentages of stage I from 2010 to 2017 were 25.9% to 31.8% in non-small cell lung cancer (NSCLC) and 5.0% to 5.4% in small cell lung cancer (SCLC). Although the increased percentage of stage I lung cancer was observed in all subsets of patients, there were significant imbalances according to demographic and socio-economic factors. In the year 2017, the major gaps in stage I included insurance (31.4% for Medicare, 26.4% for private insurance, and 12.9% for uninsured), income (32.4% for the highest annual income and 25.4% for the lowest) and race (29.9% in whites and 24.3% in blacks). **Conclusions:** There has been a significant increase in the percentage of stage I lung cancer at diagnosis from 2010 to 2017 which occurred mostly in NSCLC. Disparities in diagnosis and access to treatment may account for the differences in the percentage of patients with stage I among selected demographic populations. The staging trends and recent treatment improvements may lead to better survival for lung cancer. Research Sponsor: None.

	Stage I	Stage II	Stage III	Stage IV
2010	37,757 (23.5%)	15,270 (9.5%)	34,437 (21.5%)	72,910 (45.5%)
2011	39,077 (24.2%)	15,071 (9.3%)	34,640 (21.4%)	72,817 (45.1%)
2012	40,729 (24.5%)	15,291 (9.2%)	35,538 (21.4%)	74,580 (44.9%)
2013	43,279 (25.2%)	15,838 (9.2%)	35,462 (20.7%)	76,859 (44.8%)
2014	45,211 (25.7%)	15,926 (9.0%)	36,661 (20.8%)	78,441 (44.5%)
2015	48,855 (26.9%)	16,393 (9.0%)	37,055 (20.4%)	79,605 (43.8%)
2016	51,928 (28.1%)	16,242 (8.8%)	36,006 (19.5%)	80,722 (43.7%)
2017	54,793 (29.1%)	16,278 (8.6%)	36,258 (19.2%)	81,159 (43.1%)
Total	361,629 (26.0%)	126,309 (9.1%)	286,057 (20.6%)	617,093 (44.3%)

10509 **Clinical Science Symposium**

Constitutional *BRCA1* methylation and risk of incident triple-negative breast cancer and high-grade serous ovarian cancer. *First Author: Per Eystein Lonning, K.G. Jebsen Centre for Genome-Directed Cancer Therapy, Department of Clinical Science, University of Bergen, and Department of Oncology, Haukeland University Hospital, Bergen, Norway*

Background: About 25% of all triple-negative breast cancer (TNBC) and 10–20% of high-grade serous ovarian cancers (HGSOC) harbor *BRCA1* promoter methylation. While constitutional *BRCA1* promoter methylation has been observed in normal tissues of some individuals, the potential role of normal tissue methylation as a risk factor for incident TNBC or HGSOC risk is unknown. **Methods:** The objective of this study was to assess potential correlation between white blood cell (WBC) *BRCA1* promoter methylation and subsequent risk of incident TNBC and HGSOC. To do so, we analyzed samples from women participating in the Women's Health Initiative (WHI) study who had not been diagnosed with either breast or ovarian cancer prior to study entrance. A total of n = 636 women developing incident TNBC and 509 women developing incident HGSOC were matched with cancer-free controls (n = 1838 and 2979) in a nested case-control design. Cancers were confirmed after central medical record review. Blood samples, collected at entry, were analyzed for *BRCA1* promoter methylation by massive parallel sequencing. Associations between *BRCA1* methylation and incident TNBC and incident HGSOC were analyzed by unconditional logistic regression. **Results:** Age at entry was 62 (median; range 50 to 79) years, with median interval to diagnosis of 9 (TNBC) and 10 (HGSOC) years. The presence of methylated *BRCA1* alleles was significantly associated with higher risk of incident TNBC (OR 2.44, 95% CI 1.79–3.33; P < .001) and incident HGSOC (OR 1.87, 95% CI 1.32–2.61; P < .001). Restricting analyses to individuals with > 5 years between sampling and cancer diagnosis yielded similar results (> 5 years; TNBC: OR 2.53, 95% CI 1.81–3.54; P < .001; HGSOC: OR 1.81, 95% CI 1.21–2.63; P = .003). Across individuals, methylation was not haplotype-specific, arguing against an underlying *cis*-acting factor. Within individuals, *BRCA1* methylation was observed on the same allele, indicating clonal expansion from a single methylation event. **Conclusions:** Constitutional normal tissue *BRCA1* promoter methylation is significantly associated with risk of incident TNBC and HGSOC with implications for prediction of these cancers not associated with germline mutations. These findings warrant further research to determine if constitutional methylation of tumor suppressor genes are pan-cancer risk factors. Research Sponsor: NIH, Norwegian Research Council.

10510 **Clinical Science Symposium**

Whole genome germline sequencing: Its role in general health screening in family practice, the first study in the UK. *First Author: Ros A. Eeles, Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom*

Background: Whole genome sequencing (WGS) is now possible due to improvements in next generation sequencing technology. This gives the opportunity to incorporate genetic data into family practice health screening. The fulfilment of the potential of WGS lies in its future implementation into family practice. This study aimed to set up a model pathway to undertake WGS for actionable findings and assess its potential role in enhancing health screening. **Methods:** A pilot study comprised of 100 healthy participants from 2020-2022, recruited from a family practice, consented to routine baseline blood tests, cardiac assessment (ECG and echocardiogram), abdominopelvic ultrasound, all performed at the practice. Review of past medical, and family history was done from electronic health records (EHR). Germline genetic testing consisted of 84 cancer and 77 cardiac genes and whole genome sequencing (566 actionable genes reported), including higher penetrance monogenic mutations, recessive carrier alterations and pharmacogenomics. A multidisciplinary clinical team reviewed integrated results through an iterative process, which fed back to participants. **Results:** Twenty of 100 individuals (20%) had an actionable genetic variant in either cancer (10 individuals), thrombophilia (8) or cardiac rhythm disorder genes (2). Eighty percent of the participants had a variant in an autosomal recessive gene. Pharmacogenomics results yielded significant variants in 30%. **Conclusions:** The majority of patients had a significant change in management for themselves or their families. Whole genome sequencing as part of health screening in family practice is feasible and is likely to have significant beneficial health management implications. This study is the first of its kind in family practice and shows how this can be implemented. Research Sponsor: Oppenheimer Foundation, Other Government Agency.

10511 **Clinical Science Symposium**

Multicenter retrospective study of clinical genetic testing in patients with sarcoma. *First Author: Helen Catherine Wilbur, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Hospital, Baltimore, MD*

Background: Sarcomas are rare and diverse malignancies with a subset developing in the context of heritable cancer predisposition syndromes. Data surrounding the frequency of inheritance and patient/genomic findings are limited. We aimed to describe the characteristics of patients with sarcoma referred for clinical genetic testing and to determine the prevalence of pathogenic/likely pathogenic germline variants (PGV/LPGV). **Methods**: We performed retrospective chart reviews of patients with sarcoma referred to Michigan Medicine Cancer Genetics Clinic between 12/2006 and 1/2020 and Vanderbilt Hereditary Cancer Clinic between 1/2005 and 1/2019. Reviewers obtained medical/family history, cancer phenotype, and results of germline genetic testing. Descriptive analyses were performed to assess the prevalence of germline variants classified as pathogenic/likely pathogenic according to American College of Medical Genetics criteria. Associations with clinical factors were tested for using Fisher's exact test or Wilcoxon rank-sum test. **Results**: One-hundred sixteen patients with sarcoma underwent genetic evaluation during a 15-year period. Mean age at time of visit was 46 years (SD, 17.6 years; range, 1-80 years). Sixty-nine patients (59%) were female. The most common reasons for referral were personal history of multiple malignancies (n = 69, 59.4%), first degree relative (FDR) with malignancy (n = 67, 57.7%) and young age at diagnosis (age ≤ 18, n = 18, 15.5%). Forty-eight patients (41.4%) had both a history of multiple malignancies and a FDR with a malignancy. Eight patients had a FDR with sarcoma (6.9%). Of the 110 patients who underwent germline testing, 53 patients (48.2%) had a PGV/LPGV. Identified germline variants and frequencies are listed in the Table. There was no statistical significance between young age at diagnosis, history of personal malignancies, FDR with sarcoma, FDR with one or more malignancies, or multiple FDRs with malignancy and presence of a PGV/LPGV. **Conclusions**: In this multicenter study, approximately half of patients with sarcoma referred for cancer genetic testing had a PGV/LPGV associated with hereditary predisposition to cancer. There was no identified positive predictive factor for germline variants. Though *TP53* was the most common, over 20 genetic variants were identified, supporting the consideration of multigene panel testing. Our study is limited to patients who were both referred to and attended genetic evaluation. Yet, the high frequency of pathogenic germline variants observed highlights the necessity for further investigation of the prevalence of and predictive factors for germline mutations in all sarcoma patients. Identified germline variants. Research Sponsor: None.

Germline Variant	Number of Patients (%)
TP53	11 (10.0)
MSH2	6 (5.5)
BRCA2, ATM	5 (4.5) each
FLNC	3 (2.7)
BARD1, MSH6, MUTYH, FH, RB1, CDKN2A	2 (1.8) each
CHEK2, MITF, PTEN, SDHB, NTHL-1, RECQL4, SCN5A, SMAD4, PMS2, POLE, POT1	1 (0.9) each

10512 **Poster Discussion Session**

A multicenter study of clinical impact of variant of uncertain significance reclassification in breast, ovarian, and colorectal cancer susceptibility genes. *First Author: Sukh Makhnoon, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Up to 10% of all cancers are attributable to germline mutations and identifying mutation carriers is critical for cancer prevention. Clinical interpretation of genetic test results is complicated by variants of uncertain significance (VUS) with unknown impact on health, which can be clarified through reclassification. However, there is little empirical evidence regarding VUS reclassification in oncology care settings, including the prevalence and outcomes of reclassification, racial/ethnic differences, and the proportion of patients who undergo cancer preventive healthcare management as a result of VUS reclassification. **Methods:** Retrospective analysis of persons carrying VUS (with or without an accompanying pathogenic or likely pathogenic [P/LP] variant) in breast, ovarian, and colorectal cancer genes who underwent genetic counseling at four geographically dispersed cancer care settings (in Texas, Florida, Ohio, and New Jersey) between 2013 and 2019, and followed until 2020. **Results:** Among 2,715 individuals, 3,261 VUS and 313 P/LP variants were reported and 11% (300/2,715) had a P/LP in addition to VUS. In total, 8.1% of all individuals with VUS experienced reclassifications, 87.1% of which were downgraded to benign or likely benign and 12.9% were upgraded to P/LP. Reclassification rates varied significantly among cancer care settings from 4.81% to 20.19% (overall $p < 0.001$). The reclassification pattern across genes suggests that VUS in most genes underwent reclassification at a rate proportional to their prevalence in the overall sample and occurred commonly in *ATM, BRCA2, BRCA1*, and *CHEK2*. Compared to their prevalence in the sample, reclassification rates were higher for Blacks (13.6% vs 19.0%), lower for Asians (6.3% vs 3.5%), and proportional for Whites and Hispanics. Median time to reclassification decreased steadily between 2014 and 2019 from 3.08 to 0.91 years. Overall, 11.3% of all reclassified VUS resulted in clinically actionable findings and 4.6% subsequently changed individuals' clinical managements including prophylactic surgeries and intensive screenings for cancer prevention and early detection. **Conclusions:** In this large multisite study, VUS reclassification changed clinical management for 0.4% of all individuals. VUS reclassification may alter clinical management, has implications for precision cancer prevention, and highlights the need for standardized clinical practice guidelines and policies for returning reclassified results to patients. Research Sponsor: U.S. National Institutes of Health.

10513 **Poster Discussion Session**

Cascade testing of first-degree relatives of patients with pancreatic cancer with confirmed germline genetic mutations: A simulation modeling study. *First Author: Mary Linton Bounetheau Peters, Division of Medical Oncology, Beth Israel Deaconess Medical Center, Boston, MA*

Background: Universal germline genetic testing is recommended for all patients with pancreatic ductal adenocarcinoma (PDAC). In addition to treatment implications for the patient, it is valuable for family members of the PDAC patient to undertake germline testing to understand their familial cancer risk. We evaluated the potential effectiveness of cascade testing of first-degree relatives (FDRs) of PDAC patients to guide MRI-based screening for PDAC. **Methods:** We used a microsimulation model of PDAC to estimate the potential life expectancy (LE) benefit of cascade genetic testing of FDRs of PDAC patients. Analysis was performed for eight mutations of interest (ATM, BRCA1, BRCA2, PALB2, Lynch, TP53, CDKN2A, STK11) with relative risk of PDAC ranging from 1.6 – 24. FDRs were defined by their sex, age, and information state (not informed, informed but not tested, test negative, or test positive). Family size and composition, communication of genetic testing results, and uptake of cascade testing were based on published studies. For each FDR group, we simulated multiple MRI-based screening strategies, defined by starting age (FDR age at patient diagnosis to age 75) and frequency (once or annual until age 75), and identified the strategy that resulted in the highest LE. **Results:** Each PDAC patient would have an average of 4.35 living FDRs. 1.32 of these living FDRs would be informed of the patient's test results but not undergo testing themselves, and 1.03 would test positive for the mutation of interest. For lower risk mutations (ATM, BRCA2, PALB2), FDRs would only undergo screening if they test positive. For Lynch syndrome, not tested FDRs would undergo screening starting at age 65 or 70, whereas FDRs who test positive would start at 50 or 55. For STK11, the highest risk mutation, FDRs would start screening annually as soon as they are informed of the patient's test results. The total LE gain for cascade testing of FDRs ranged from 0 (BRCA1) to 1.05 years (STK11). **Conclusions:** For each PDAC patient identified to have a germline genetic mutation, cascade testing of FDRs could add up to a year life expectancy for the family, in addition to the value of the germline information to the PDAC patient's care. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

Screening selection and life expectancy gain in days for *CDKN2A* family.

	Brothers	Sisters	Sons	Daughters	Total Family LE Gain (days)	Total Family LE Gain (days) given Genetic Testing for all FDRs
Test Positive for *CDKN2A* (RR 12.7)	Annual screening, start at notification (6.8 days)	Annual screening, start at notification (11.8 days)	Annual screening, start at notification (35.2 days)	Annual screening, start at notification (33.9 days)	135.02	226.87
Informed but not Tested (RR 6.8)	Annual screening, start at notification (5.4 days)	Annual screening, start at notification (0.3 days)	Annual screening, start age 50 (24.5 days)	Annual screening, start age 55 (17.1 days)		

10514 **Poster Discussion Session**

Double jeopardy? A closer look at cancer histories of individuals with multiple germline pathogenic variants. *First Author: Carolyn Horton, Ambry Genetics, Aliso Viejo, CA*

Background: Germline multigene panel testing has led to the increased detection of multiple co-occurring pathogenic variants (PV) in the same individual. As this occurrence is still relatively rare, reports of these individuals have been limited. Therefore, we sought to describe the clinical features of individuals with multiple PV identified at a single high-volume diagnostic laboratory. **Methods:** We performed a retrospective review of demographics and clinical data for individuals with > 1 pathogenic or likely pathogenic variant (PV) who underwent hereditary cancer panel testing (5-67 genes) between May 2012 and April 2017. In recessive genes (i.e. *MUTYH*), PV were only included when biallelic. PVs with reduced penetrance (*APC* p.I1307K; *CHEK2* p.I157T, p.S428F, p.T476M) were excluded. In individuals with the most common combinations of genes, personal cancer history and age at cancer diagnosis was evaluated. **Results:** A total of 555 individuals were identified with multiple PVs. Most individuals were female (85.1%), had a personal history of cancer (73.3%) and 26.3% had two or more primary cancers. *CHEK2* was most often seen in co-occurrence with a PV in a different gene (137 observations), followed by *ATM* (120 observations), *BRCA2* (110 observations), and *BRCA1* (88 observations). Among cases in which clinical information was provided (n = 545), the five most frequent co-occurring combinations were in *ATM/CHEK2* (25), *ATM/BRCA2* (23), *BRCA1/CHEK2* (19), *CHEK2/CHEK2* (16), and *BRCA2/CHEK2* (14). Individuals with co-occurring PVs in *CHEK2/CHEK2* had the youngest age at first cancer diagnosis (mean = 41.5y; median = 42y), the highest rate of breast cancer diagnoses and other cancer diagnoses (100.0% and 70.6% of individuals, respectively), and the highest proportion of individuals with > 1 primary cancer (52.9%). **Conclusions:** Our results indicate that individuals with two PVs in *CHEK2* have an average age of cancer onset that is similar to individuals with either a *BRCA1* or *BRCA2* concurrent PV. Additionally, individuals with two PVs in *CHEK2* were more likely to have multiple primary cancers as compared to others in the cohort with concurrent PVs including those with either a *BRCA1* or *BRCA2* concurrent PV (Table). Continued studies, including comparisons to individuals with one PV, will provide valuable insight to aid in counseling and management of individuals with multiple germline PV. Research Sponsor: None.

PV Gene Combination	Total individuals	n Female (%) *n Male (%)*	Mean age 1st cancer diagnosis (median)	n breast cancer (%)	n other cancer (%)	n > 1 primary cancer (%)
ATM/CHEK2	25	23 (92.0%) *2 (8.0%)*	42.5 (44)	20 (80.0%)	7 (28.0%)	5 (20.0%)
ATM/BRCA2	23	18 (78.3%) *5 (21.7%)*	47.9 (49)	13 (56.5%)	7 (30.4%)	4 (17.4%)
BRCA1/CHEK2	19	17 (89.5%) *2 (10.5%)*	42.1 (43)	10 (52.6%)	7 (36.8%)	4 (21.1%)
CHEK2/CHEK2	17	17 (100.0%) *0 (0.0%)*	41.5 (42)	17 (100.0%)	12 (70.6%)	9 (52.9%)
BRCA2/CHEK2	14	14 (100.0%) *0 (0.0%)*	43.1 (45)	9 (64.3%)	2 (14.3%)	2 (14.3%)

10515 **Poster Discussion Session**

Rates of pathogenic variants in common cancer genes among different racial/ethnic groups. *First Author: Peter D. Beitsch, Dallas Surgical Group, Dallas, TX*

Background: Racial/ethnic disparities have been well-documented in access to cancer screening and treatment, as well as treatment outcomes. Less is known regarding the proportion of higher and lower penetrance genetic pathogenic variants (PVs) in these populations. **Methods:** Patient data was obtained from the Informed Genetics Annotated Patient Registry (iGAP), an IRB-approved multi-center longitudinal, observational study designed to capture genetic and genomic lab agnostic test results and their utilization and impact on treatment practices and outcomes from patients at Breast Clinics. 1323 patients self-declared race/ethnicity and underwent germline genetic testing at any lab. Analyses were limited to 24 cancer susceptibility genes (*ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, NBN, PALB2, PTEN, STK11, TP53, APC, BMPR1A, CDK4, EPCAM, MLH1, MSH2, MSH6, MUTYH* biallelic, *PMS2, RAD51C, RAD51D, SMAD4*), 21 of which have clinical management guidelines from the NCCN (excluding *NBN, BARD1, CDK4*). Descriptive statistics were used to assess and compare data from these populations and germline genetic testing results. **Results:** The PV rate among racial/ethnic groups were as follows: Caucasian 110/991 (11.1%), Asian 5/93 (5.4%), Hispanic 26/87 (29.9%), African/Black 6/59 (10.2%), Ashkenazi 5/25 (20%), Other 1/17 (5.9%). There are significant differences in PV rates between Hispanic ethnicities and all other categories (p-value < 0.001 for all) and significant differences in PV rates between Asian race and all other categories (p-value 0.05 Caucasian, 1.9e-7 Hispanic, 0.03 Ashkenazi, 0.05 Other) except African/Black (p-value 0.06). The *BRCA1/2* PV rates were: Caucasian 30/991 (3.0%), Asian 1/93 (1.1%), Hispanic 12/87 (13.8%), African/Black 3/59 (5.1%), Ashkenazi 1/25 (4.0%), Other 1/17 (5.9%). There are significant differences in *BRCA1/2* PV rates between Hispanic ethnicities (p-value < 0.001 for all) and all other categories, and between Asians and Caucasians (p-value 0.04). **Conclusions:** Racial/ethnic groups varied by PV rate and proportion of both *BRCA1/2* and overall PV rate. The higher proportion of PVs in Hispanics could be due to the greater representation of Hispanics from New Mexico which may harbor Ashkenazi ethnicity. Further studies are needed to understand whether these differences are a result of disparate access to testing, true population differences, lack of data in non-Caucasian populations skewing variant classification, or other factors. Research Sponsor: Medneon, Invitae.

10516 **Poster Discussion Session**

Racial and regional disparities in metastatic breast cancer. *First Author: Sachi Singhal, Propesct CCMC, LLC dba Crozer Chester Medical Center, Chester, PA*

Background: Breast cancer is the most commonly diagnosed malignancy in American women, with about 281,500 new reported cases this year, 3.8 million women living with an active or history of breast cancer, and a lifetime occurrence of 1 in 8 women in this nation. Racial disparities persist despite the advent and implementation of screening by national agencies. AA females are less likely to be diagnosed with breast cancer, and yet bear an arbitrarily high burden of mortality of this malignancy. Socioeconomic variables and lifestyle are the most plausible explanations of this discrepancy. Even in clinical trials, there remains an underrepresentation of all ethnic minorities. Encouragement of guideline based screening for all along with constant follow ups, access to health insurance and a more uniform representation in trials are the cornerstone of eliminating these disparities. **Methods:** Data for this study was obtained from the 2016-18 Nationwide Inpatient Sample (NIS) which comprises 20% of the total US hospital discharges. We identified all patients with a primary diagnosis of Malignant Neoplasms of Breast. In-hospital mortality, race and hospital regions for the given patients were studied. Baseline characteristics of participants were summarized using descriptive statistics. The patient population was stratified as per race, hospital region, gender, therapy they received and family history. Logistic regression was performed to derive the odds ratio while adjusting for different variables. Further details: https://www.hcup-us.ahrq.gov/. **Results:** 99, 543 patients with metastatic breast cancer were identified, and almost 99% of them were females. 67% of the population was comprised of Caucasians, 16.91% African Americans (AA), 9.14% Hispanics and 3.28% Asians and Pacific Islanders (API). AAs had the most reported deaths at 5.54%, followed by APIs at 4.80% and Caucasians 4.09% ($p < 0.0001$). The odds of dying were significantly higher in AA population when compared to Caucasian population (OR 1.391 (1.286-1.504)), and the odds were consistently higher across all regions of the US. In terms of regional variation, it was seen that races identifying as "others' " had significantly higher odds of dying in the North East (OR 1.646 (1.238-2.189)) and the West (OR 1.503 (1.059-2.133)). **Conclusions:** It is crucial to identify racial disparities in diagnosis, treatment and mortality before we devise a blueprint to tackle this incongruity. This highlights the significance of universal screening and better health insurance coverage in addition to recognition of reasons behind these differences. Research Sponsor: None.

10517 **Poster Discussion Session**

Ancestry-specific risk of triple-negative breast cancer (TNBC) associated with germline pathogenic variants (PV) in hereditary cancer (CA) predisposition genes. *First Author: Michael J. Hall, Fox Chase Cancer Center, Philadelphia, PA*

Background: TNBC represents ~15% of invasive BC. Ancestry-specific variabilities in TNBC risk are well-described, with African American (AA) women experiencing higher incidence and mortality from TNBC than women of other races/ethnicities. Increased risk of TNBC has been associated with both rarer (e.g. *RAD51C/D, BARD1*) and more commonly detected (e.g. *BRCA1/2, PALB2*) germline PV in hereditary CA predisposition genes, but less is known about ancestry-specific TNBC risks for PV carriers. **Methods:** We examined clinical and genetic records from women referred for multigene CA panel testing (9/2013-5/2020). Multivariable logistic regression was used to test associations of PV in 13 genes with risk of TNBC after accounting for age, ancestry, and personal/family CA history. We analyzed each gene in the full cohort, and in subcohorts defined by self-reported ancestry. Effect sizes are expressed as odds ratios with 95% confidence intervals. Seven genes are not reported in ancestry-stratified analyses due to small numbers of PV carriers with TNBC. **Results:** From 627,219 individuals referred for multigene panel testing, 115,337 (18.4%) women with personal history of BC were identified, of whom 17,951 (15.6%) reported TNBC. Personal history of TNBC was reported more frequently in women of African ancestry (26.9%) than in women of European (13.9%) or Asian (11.7%) or Latinx ancestry (14.9%). Ancestry-stratified risks of TNBC associated with germline PVs are seen in the Table. **Conclusions:** While small samples sizes limit some gene-specific analyses, comparable ancestry-specific risks of TNBC were seen across the racial/ethnic groups examined here. Research Sponsor: None.

Gene	Ancestry	N positive	N positive w/TNBC	OR	95% CI	p
BRCA1	All	7228	1193	21.23	(19.70, 22.87)	< 10-260
	Asian (A)	275	49	26.27	(17.58, 39.24)	2.7x10-57
	Black (B)	688	161	19.40	(15.56, 24.19)	4.5x10-153
	Latinx (L)	958	155	25.23	(20.34, 31.30)	1.5x10-189
	White (W)	3625	582	22.84	(20.57, 25.36)	< 10-260
BARD1	All	898	125	7.02	(5.68, 8.68)	5.9x10-73
	A	29	7	19.81	(6.75, 58.11)	5.4x10-08
	B	94	22	5.92	(3.37, 10.40)	5.9x10-10
	L	49	4	-	-	-
	W	549	71	7.61	(5.79, 10.02)	1.1x10-47
PALB2	All	2604	231	5.29	(4.57, 6.12)	4.0x10-110
	A	65	7	7.79	(3.14, 19.34)	9.7x10-06
	B	284	43	5.14	(3.57, 7.40)	1.3x10-18
	L	298	15	3.46	(2.00, 5.99)	9.4x10-06
	W	1398	115	5.71	(4.66, 7.00)	4.1x10-63
RAD51C	All	846	86	4.93	(3.87, 6.27)	3.4x10-38
	A	22	0	-	-	-
	B	78	22	9.50	(5.31, 16.98)	3.1x10-14
	L	88	9	5.66	(2.66, 12.04)	7.0x10-06
	W	483	47	5.24	(3.80, 7.23)	6.5x10-24
RAD51D	All	506	45	4.66	(3.35, 6.48)	5.4x10-20
	A	25	2	-	-	-
	B	64	14	6.34	(3.18, 12.62)	1.5x10-07
	L	33	3	-	-	-
	W	269	21	5.15	(3.22, 8.25)	9.2x10-12
BRCA2	All	8077	488	4.43	(4.01, 4.88)	9.1x10-193
	A	294	14	3.93	(2.19, 7.05)	4.6x10-06
	B	850	101	4.85	(3.84, 6.12)	2.1x10-40
	L	732	44	5.68	(4.08, 7.91)	9.7x10-25
	W	4407	243	4.68	(4.08, 5.37)	7.2x10-107

10518 **Poster Discussion Session**

Association of germline genetic testing results with chemotherapy regimens received by women with early-stage breast cancer. *First Author: Allison W. Kurian, Stanford University School of Medicine, Stanford, CA*

Background: Germline genetic testing is widespread after breast cancer diagnosis and increasingly informs treatment decisions; however, guidelines do not advise selecting chemotherapy regimens based on genetic testing results. It is unknown whether women with pathogenic variants (PVs) in *BRCA1, BRCA2* (*BRCA1/2*) or other cancer risk genes receive different chemotherapy regimens than women with negative genetic testing results. **Methods:** We linked Surveillance, Epidemiology and End Results (SEER) registry records from Georgia and California to clinical germline genetic testing results from four participating laboratories (Ambry, Bioreference/GeneDx, Invitae, and Myriad). For this analysis, we included patients who: 1) were diagnosed with stages I-III breast cancer, either hormone receptor-positive and HER2-negative (HR+HER2-) or triple-negative, in Georgia or California from 2013-2017; 2) received chemotherapy based on SEER records; and 3) linked to a genetic testing result. We further selected cases by genetic testing results: 50% PVs in *BRCA1/2* or another cancer risk gene, 25% variant of uncertain significance (VUS) only and 25% negative. We extracted details of chemotherapy regimens from SEER text fields completed by registrars. We categorized regimens by drug classes reported (anthracycline, taxane, platinum, nitrogen mustard, other). We used multivariable models that controlled for age, race/ethnicity, stage, grade, surgical procedure, radiotherapy receipt and geographic site to test whether PV carriers received a more intensive chemotherapy regimen. For HR+HER2-, a more intensive regimen was defined as at least three drugs including an anthracycline and for triple-negative, as at least four drugs including an anthracycline and a platinum (versus fewer drugs). **Results:** 2,293 women were included, 1,451 with HR+HER2- and 842 with triple-negative disease. On multivariable analysis, receipt of a more intensive chemotherapy regimen was associated with having a *BRCA1/2* PV among women with HR+HER2- disease (odds ratio 1.22, $p = 0.036$), but not among women with triple-negative disease. Moreover, platinum use was elevated in *BRCA1/2* PV carriers with HR+HER2- disease (from an adjusted model: *BRCA1/2* PV 10.9%, other PV 3.6%, VUS 5.6%, negative 5.7%), while in *BRCA1/2* PV carriers with triple-negative disease, platinum use did not vary significantly by genetic results (*BRCA1/2* 27.7%, other PV 27.7%, VUS 20.9%, negative 20.7%; $p = 0.025$ for interaction between genetic result and subtype). **Conclusions:** Compared to women with negative genetic testing results, women with *BRCA1/2* PVs more often received a platinum and/or an anthracycline in chemotherapy regimens for early-stage, HR+HER2- breast cancer. This suggests potential over-treatment. No differences in chemotherapy regimen by genetic testing result were observed in triple-negative disease. Research Sponsor: U.S. National Institutes of Health.

10519 **Poster Discussion Session**

Heart toxicity effects (HTE) of anthracyclines-containing regimens (ACRs) in patients with breast cancer (BC) carrying mutational signature of homologous recombination deficiency (HRD). *First Author: Lorena Incorvaia, Dept.of Surgical,Oncological and Oral Sciences,Section of Medical Oncology,University of Palermo,Italy, Palermo, Italy*

Background: *BRCA1/2* genes (*BRCA*) play a prominent role in the Homologous Recombination Repair (HRR) pathway. Following the technological progress and deeper knowledge on *BRCA*-related cancers, the demand for genetic testing is rapidly increasing. Beyond *BRCA1/2*, other genes are involved in the HRR, including *ATM*, *PALB2*, *RAD51*, and *BARD1*. Due to the important role in the cellular repair process, deleterious variants in HRR genes may cause inadequate DNA damage repair in cardiomyocytes. The role of *BRCA1/2* as predisposing condition to cardiac dysfunction is debated, and the contribution by no-*BRCA* genes is still unknown. **Methods:** This is a multicenter, retrospective, study to investigate the risk of heart-insults from anthracyclines on adjuvant setting in BC patients carrying germline pathogenic or likely pathogenic variant (PV) (classes IV and V) in *BRCA* and no-*BRCA* HRR pathway genes. We collected genetic and clinical data, and evaluated the left ventricular ejection fraction (LVEF) at cardiac ultrasound, before starting ACR therapy, and at subsequent time points, according to clinical indications. **Results:** Three hundred and sixty (360) BC patients, aging 22 to 80, were included in this study; 131 patients were carriers of germline PVs in HRR pathway genes: 52 in *BRCA1* gene (39.7%), 48 in *BRCA2* gene (36.6%), and 31 harbored PVs in no-*BRCA* HRR pathway genes (23.7%), including PVs in *PALB2*, *CHEK2*, *ATM*, *RAD51C*, *RAD50* and *BARD1* genes. In the cohort of 229 patients without PVs, 47 showed variant of uncertain significance (VUS, class III), and 173 had genetic testing not informative. When LVEF between the groups was compared, the difference was not significant for the pre-treatment values. Notably, individuals carrying *BRCA* or other HRR gene deleterious variants, showed a statistically significant reduction of LVEF > 5% at the second timepoint (3 month), compared to the LVEF pre-treatment values ($p = 0.001$). A marked LVEF reduction was in mutated patients treated with risk-reducing bilateral salpingo-oophorectomy prior to age 40, body mass index > 25, and type-II diabetes mellitus. The latter risk factor was probably related to increased risk developing insulin-resistance reported for *BRCA*-mutated patients. **Conclusions:** Our data suggest that PVs in *BRCA* or other genes involved in HRR pathway, can lead to impaired homologous recombination, thus increasing sensitivity of cardiac cells to DNA damaging chemotherapy in BC patients. In this subgroup of patients, other measurements such as the global longitudinal strain (GLS), and a more in-depth assessment of risk factors, could be proposed to optimize cardiovascular risk-management and to improve long-term survival. Research Sponsor: None.

10521 **Poster Discussion Session**

Germline mutational landscape of non-highly penetrant Fanconi anemia genes unveiled from sequencing of 5,044 patients with solid tumor cancer. *First Author: Kevin J. McDonnell, City of Hope, Duarte, CA*

Background: Nearly two dozen Fanconi anemia (FA) genes work in concert to mediate critical DNA repair steps. Previous investigations have well described germline pathogenic variation and associated solid tumor cancer predisposition in the highly penetrant (HP)-FA genes, *BRCA1 (FANCS), BRCA2 (FANCD1)* and *PALB2 (FANCN)*. To date, understanding of pathogenic variation and cancer association among non-HP-FA genes remains incomplete. In this study we investigated the germline mutational landscape of non-HP-FA genes in patients with a personal/family history of a solid tumor. **Methods:** Unselected, consented patients with a personal/personal history of solid tumor cancer underwent germline testing through a sponsored program of universal access. Testing used a custom panel to detect pathogenic single nucleotide variants, short insertions/deletions and exon-level deletions/duplications of 155 cancer-predisposition genes including 15 non-HP-FA genes [*FANCA, FANCB, FANCC, FAND2, FANCE, FANCF, FANCG, FANCI, FANCJ (BRIP1), FANCL, FANCM, FANCO (RAD51C), FANCP (SLX4), FANCQ (ERCC4)* and *FANCU (XRCC2)*]. Here we summarize germline pathogenic variant frequency in non-HP-FA genes and describe the mutational landscape across solid tumors. Additionally, we report the clinical actionability (on- and off-label FDA approved drug availability and/or clinical trial eligibility) of identified variants. **Results:** 5044 patients consented and completed germline genetic testing. 1014/5044 (20.1%) of patients carried a pathogenic variant in a cancer predisposition gene. 116/1014 (11.4%) of germline positive patients carried a pathogenic variant in a non-HP-FA gene. Non-HP-FA genes with highest frequencies included: *FANCA* (28 patients), *FANCM* (19 patients), *BRIP1* (FANCJ) (19 patents) and *FANCC* (14 patients). Testing identified germline non-HP-FA pathogenic variants in eighteen different tumor types. The tumor types associated with the highest percentages of associated germline non-HP-FA pathogenic variants included: squamous cell cancers (8.2%), bladder/urothelial cancer (5.0%), breast cancer (3.5%) and ovarian/fallopian tube cancers (3.5%). Moreover, 19 patients carrying a non-HP-FA germline pathogenic variant qualified for an on- or off-label FDA-approved drug; 101 patients achieved clinical trial eligibility by virtue of their non-HP-FA variant. **Conclusions:** Our study offers a landscape view of germline pathogenic variants in non-HP-FA genes in patients with a history of a solid tumor. Furthermore, this investigation provides a basis for further examination of associations between these germline pathogenic variants and solid tumor cancer predisposition. Finally, importantly, our work underscores the value of expanded germline non-HP-FA gene testing to optimize therapeutic and clinical trial opportunities for cancer patients. Research Sponsor: City of Hope National Medical Center.

10522 **Poster Discussion Session**

Comparison of characteristics and outcomes of young onset versus average onset pancreatobiliary adenocarcinoma. *First Author: Thejus Jayakrishnan, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH*

Background: Young-onset gastrointestinal malignancies appear to be increasing in incidence but most investigations have focused on colorectal cancer and there are limited data on young-onset pancreatobiliary cancers (YO-PBA). We evaluated trends and characteristics of YO-PBA in comparison to average-onset disease (AO-PBA). **Methods:** The study cohort comprised patients with PBA (pancreatic adenocarcinoma, intra- and extra-hepatic cholangiocarcinoma) diagnosed between 2004 and 2017 from the National Cancer Database. YO-PBA was defined as diagnosis at age < 50 years and AO-PBA as >50 years. Logistic regression was used to assess factors associated with YO-PBA status, and cox proportional hazards modeling was performed to associate demographic and clinical factors with overall survival. **Results:** Of 360,764 patients analyzed, 20,822 (5.8%) were YO-PBA with a median age at diagnosis of 45 years (IQR 42 – 48) vs 70 (62-78) years for AO-PBA. The number of patients with YO-PBA increased by 33.3% during the study period compared to 111.8% for AO-PBA. Characteristics associated with YO-PBA were (p-values<0.001 for all): male sex (6.3% YO-male out of all male patients vs 5.2% YO-female out of all female patients, OR 1.2), Black race (7.9% YO-Black vs 5.0% YO-White, OR 1.4), lower income (6.4% YO-lowest household income based category vs 5.5% highest, OR 1.3), and lower education (6.9% YO-lowest educational status category vs. 4.9% highest, OR 1.4). YO-PBA were more likely to present with stage-IV disease (6.4% YO-Stage IV of all stage IV vs 5.4% YO-Stage I-III, OR 1.2, p-value<0.0001), but more likely to undergo surgery (7.4% YO-surgery patients vs 5.4% YO no-surgery patients). Median OS was YO 11.0 (95% CI 10.8 – 11.3) vs. AO 7.1 months (95% CI 7.0 – 7.1). Effects of patients' characteristics on OS differed significantly between YO and AO-PBA cohorts (interaction p-values < 0.001), and were analyzed separately (table). Notably, Black patients experienced worse outcomes in both age groups. **Conclusions:** Young-onset pancreatobiliary cancers (YO-PBA) reported in NCDB have increased over the years. YO-PBA is associated with better survival compared to AO-PBA. Socioeconomic disparities significantly impact incidence and outcomes. More work is needed to help address these health disparities, especially for those with young-onset cancer. Research Sponsor: None.

Characteristics	YO – HR (95% CI)*	AO – HR (95% CI)*
Sex – Male vs Female	1.11 (1.09-1.15)	1.01 (1.00-1.09, p=0.005)
Race – Black vs Others	1.23 (1.07-1.42,p=0.005)	1.25 (1.20-1.31)
Insurance – Government vs Private	1.34 (1.30-1.39)	1.30 (1.29-1.31)
Income category – Lowest vs Highest income group	1.33 (1.27-1.39)	1.18 (1.17-1.19)
Education – Lowest vs Higher	1.20 (1.15-1.26)	1.09 (1.08-1.11)
Treatment center – Academic vs Non-academic	0.87 (0.85-0.90)	0.77 (0.76-0.77)

*p-value < 0.001 unless specified. HR higher than 1 means worse prognosis.

10523 **Poster Discussion Session**

Germline predisposition in oncologic and dermatologic melanoma cohorts. *First Author: Pauline Funchain, Cleveland Clinic Foundation - Taussig Cancer Institute, Cleveland, OH*

Background: Melanoma has recently been suggested to be a highly heritable cancer with high twin-twin concordance. In contrast, prior studies on patients with familial atypical multiple mole melanoma (FAMMM) syndrome, multiple primary melanomas and early age of onset, all known to be associated with germline *CDKN2A/CDK4* pathogenic variants, suggest that individuals with melanoma who carry germline alterations are rare. We studied the overall prevalence of germline cancer predisposition in a large prospective oncologic cohort with comparison to other defined cohorts of individuals with melanoma with available germline data. **Methods:** Individuals who presented to medical oncology clinic with a diagnosis of melanoma and personal or family history of multiple cancers were offered germline testing with a commercially available next generation sequencing panel (Invitae, San Francisco, CA). Eligibility criteria required ≥ 2 melanomas in an individual or family; melanoma and other cancer(s) in an individual; melanoma and at least 2 other cancers in 1st- or 2nd-degree relatives; age ≤35 at diagnosis; or limited family structure. Comparative analysis of germline NGS data from 3 additional selected and non-selected melanoma datasets was performed. **Results:** In a cohort of 400 oncology patients with melanoma who consented to commercial germline testing of 85 cancer-associated genes, a germline pathogenic/likely pathogenic (gP/LP) positive rate of 15.3% (n = 61) was observed. Genes previously associated with inherited melanoma (*BAP1, BRCA1/2, CDKN2A, MITF, TP53*) comprised less than one-third of gP/LP variants (20, 32.7%); the majority of germline variants were in cancer predisposition genes not traditionally associated with melanoma (e.g. *BRIP1, CHEK2, MSH2, PMS2, MLH1, RAD51C, BLM*). Family history of non-cutaneous cancer (42, 69%) and personal history of melanoma with ≥ 1 non-cutaneous cancer (22, 36%) were the most common eligibility criteria met in gP/LP variant carriers. Analysis of germline data from other large oncologic and dermatologic melanoma datasets yielded gP/LP variant positive rates of 10.6% in an unselected oncologic melanoma cohort (TCGA, n = 470), 15.8% in a selected commercial testing cohort (Invitae, n = 12,571), and 14.5% in a highly selected, primarily dermatologic subset (Boston-Athens, n = 289). **Conclusions:** In oncologic and dermatologic cohorts, germline testing of selected individuals with melanoma yields rates of clinically impactful P/LP variant detection which exceed consensus standards for pretest probability. Most P/LP variants were found in genes associated with non-cutaneous cancers. Obtaining a family and personal history of cancer, particularly non-cutaneous cancers, and referring for broad panel-based germline testing in all individuals with melanoma are recommended. Research Sponsor: Gross Family Melanoma Registry.

10524 **Poster Session**

Increase in incidence of advanced-stage breast cancer in Asian women versus White women: Can this be explained by the lower utilization of mammograms? *First Author: Cheng-I Liao, Department of Obstetrics and Gynecology, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan*

Background: To examine trends in postmenopausal breast cancer and mammogram utilization in Asian and White women in the United States. **Methods:** Data on postmenopausal breast cancer was obtained from the United States Cancer Statistics Public Use Database from 2001 and 2018. Rates of mammogram screening for women ages 18 and older were evaluated using the Behavioral Risk Factor Surveillance System (BRFSS) between 2000 and 2018. Obesity rates for women ages 18 and older were extracted from BRFSS between 2001 and 2016. SEER*Stat 8.3.8 and Joinpoint regression program 4.8.0.1 were used to calculate incidence trends. Breast cancer incidence and trends were described using average annual percent change (AAPC). Mammogram screening trends were described using average biennial percent change (ABPC). Obesity trends were described using AAPC. Age groups were divided into five-year or ten-year intervals. **Results:** The incidence of metastatic postmenopausal breast cancer in women was 19.48/100,000 in 2018 has increased by 1.03% annually over the past eighteen years (p = 0.000). In 2018, the incidence of advanced-stage breast cancer in Asian and White women was 12.17/100,000 and 19.17/100,000 respectively. Over time, the incidence of advanced-stage breast cancer has increased in Asian women by 2.19% annually (p = 0.000), but remained stable in White women. In a subset analysis of early-stage breast cancer, there was no difference in both Asian and White women. Using the BRFSS data, we evaluated the utilization of mammograms. In the overall population, 20.92% were newer screened and this was higher in Asian women at 40.99% compared to 18.17% in White women in the year 2018. Given the potential association of obesity and breast cancer, we then evaluated the rate of obesity in these two groups. Our data showed that the incidence of obesity was low in Asian women at 12.8% compared to 28.13% in White women. **Conclusions:** There is an increased incidence of advanced-stage breast cancer in Asian women in the U.S. Although Asian women are less obese but they are also less likely to undergo screening compared to White women. Research Sponsor: None.

10525 **Poster Session**

Simulation modeling as a tool to support clinical guidelines and care for breast cancer prevention and early detection in high-risk women. *First Author: Jinani Jayasekera, Lombardi Cancer Center MedStar Georgetown University Hospital, Washington, DC*

Background: To evaluate the incremental short- and long-term benefits and harms of primary prevention with risk reducing medication in high-risk women receiving screening mammography. **Methods:** We adapted an established, validated Cancer Intervention and Surveillance Modeling Network (CISNET) breast cancer discrete event microsimulation model developed to synthesize data the impact of using risk-reducing medication and annual mammography among women with a 3% or higher five-year risk of developing breast cancer. We also examined the effects of supplemental MRI. The model follows a simulated cohort of millions of US women from birth to death. We used large observational and clinical trial data to derive input parameters for cohort-specific birth rates, breast cancer risk, incidence and stage, screening performance, survival by age, stage, and subtype, treatment efficacy, and other cause mortality. Breast cancer risk was modeled based on family history, breast density, age and history of past breast biopsy. We compared two strategies, annual 3D mammography alone vs. annual 3D mammography and a 5-year course of risk reducing medication at various starting ages, and adding MRI to each approach. Outcomes included the benefits of risk-reducing drugs (avoiding breast cancer) and screening (stage, breast cancer death). Harms included drug side effects and screening false positives and overdiagnosis. Sensitivity analysis tested the impact of uncertainty in model inputs and assumptions on results. **Results:** Compared to mammography alone, adding risk reducing medication could decrease invasive breast cancer incidence by 30%, and breast cancer deaths by 30% (Table). However, due to reduction in breast cancer incidence, risk reducing medication could result in a 3% increase in false positive results; adding MRI increases benefits but also increases false-positive results. Benefits and harms of risk reducing medication and breast cancer screening strategies for women at high-risk of developing breast cancer. **Conclusions:** Risk-reducing mediation reduces the risk of hormone-receptor positive breast cancer, and combining this with mammography (and/or MRI) improves earlier detection. Additional work is ongoing to incorporate adverse effects of therapy. Simulation modeling can be used to provide individualized data to facilitate discussions about breast cancer prevention and early detection among high-risk women seen in clinical practice. Research Sponsor: U.S. National Institutes of Health.

	Strategy		
Screening Outcomes Per 100,000 Women Screened	Annual 3D Mammography Screening	Annual 3D Mammography Screening + 5-years of Risk Reducing medication	% Incremental Effects of Risk Reducing Medication
Invasive breast cancer incidence	518	365	30% decrease
De-novo Stage IV diagnosis	15	11	27% decrease
Breast cancer deaths	109	76	30% decrease
False positives	6927	7145	3% increase
Overdiagnosis	33	34	-

10526 **Poster Session**

Characterization of time to diagnosis indicates shorter interval for screenable versus symptom-driven cancers. *First Author: Vladimir Gainullin, Exact Sciences Corporation, Madison, WI*

Background: Cancer screening provides a straightforward diagnostic path compared to non-screening, which often requires complex evaluation for patients with non-specific symptoms. The time to diagnosis (from clinical presentation or screening event to definitive diagnosis) captures the clinical efficiency of the journey. The study characterizes time to diagnosis for cancers with and without USPSTF Grade A/B screening recommendations. This could inform the value of screening in diagnostic management and care efficiency improvements. **Methods:** The Geisinger Health System Phenomics Initiative Database provides deidentified EHR and tumor registry data. Patients aged 50-74 with encounters at least biennially for six years prior to a cancer diagnosis were frequency-matched to a non-cancer control group by diagnosis year. From 18 months prior to diagnosis, equally-sized random samples were drawn (with replacement) from a time-bounded sliding window at monthly intervals. Aggregated procedure and diagnostic code counts for cancer and non-cancer samples were used to calculate the Bray-Curtis dissimilarity (BCd) statistic. The start of the diagnostic path was defined as the earliest date with a monotonically-increasing statistically-significant difference in BCd (95% CI), and was stratified into cancers with and without screening and by stage. **Results:** 8188 new cancer cases were identified between 2010-2019; 40% had an established screening modality (breast, lung, colorectal, cervical), 55% of which were screened prior to diagnosis. The time to diagnosis for non-screenable cancers was 6 months versus 3 months for screenable cancers. The BCd for procedures differed by 0.029 (95% CI: 0.021-0.037) between the two groups at 6 months prior to diagnosis. Stages I and IV had a time to diagnosis of 3 months across all cancers versus 7 and 6 months for stages II and III, respectively. **Conclusions:** We report the first known quantification of time to diagnosis across multiple cancers. Screenable cancers were associated with shorter time to diagnosis than non-screenable cancers. Stage II and III cancers took longer to diagnose than stage I and IV, likely related to early detection by screening in the former and severe symptom presentation in the latter. These novel data highlight improved time to diagnosis as another achievable benefit from expanded, multi-cancer screening. Research Sponsor: Exact Sciences.

10528 **Poster Session**

Renal cell carcinoma in renal transplant recipients: Is there a role for screening? *First Author: Binoy Yohannan, U. Texas Medical School, Houston, TX*

Background: Renal transplant (RT) recipients are at an increased risk of developing renal cell carcinoma (RCC), mainly due to iatrogenic immunosuppression and changes in immune surveillance. Most RCCs in RT recipients arises from the native kidney, but rarely may arise from the allograft. RCC post-RT can adversely affect allograft function and long-term survival. Screening for RCC in RT recipients is controversial and is not routinely done. **Methods:** We performed a retrospective chart review of RT recipients who underwent transplantation between January 1, 1999, and December 31, 2019. The following data were collected: Baseline demographic variables, cause of end-stage renal disease (ESRD), duration of dialysis prior to RT, type of RT (cadaveric vs. living donor), immunosuppressive regimen, site of RCC (native kidney vs transplanted kidney), time from RT to diagnosis of RCC, stage and Fuhrman grade, tumor histology, RCC treatment, and RCC-related mortality. RCC stage at diagnosis and survival were compared between patients who were screened versus those who were not. **Results:** Among 1998 RT recipients who underwent transplantation at Memorial Hermann Hospital (MHH) Texas Medical Center (TMC); 16 patients (0.8%) developed RCC. An additional 4 patients with RCC who underwent RT elsewhere but received follow up at MHH TMC were also included. Therefore, a total of 20 patients with post-RT RCC were identified, of whom 75% were men. Subject races included White (20%), Black (50%), Hispanic (20%), and Asian (10%). The median age was 56 years. Median duration of dialysis prior to RT was 36 months (range, 1–120). Median time to RCC diagnosis post-RT was 96 months (range, 16–312). Histologies included clear cell (75%), papillary (20%), and chromophobe (5%) RCC. RCC developed in the native kidney in 60% and in the allograft in 40% of the patients. Post-RT RCC patients were divided into those who underwent regular screening (n = 12) and no screening (n = 8). The regular screening group (n = 12) underwent ultrasound or computerized tomography annually or every 2 years. All of these patients had early-stage disease at presentation: stage I (n = 11) or II (n = 1). All patients who had RCC detected by screening were cured by nephrectomy (n = 10) or cryotherapy (n = 2). In patients who had no screening post RT, 37.5% had stage I, 25% had stage III, and 37.5% had stage IV RCC. Two patients with stage IV RCC died from metastatic disease. The RCC-related mortality was 0% in patients who were screened, compared to 25% in patients who had no screening. **Conclusions**: All RT recipients who had RCC diagnosed based on screening had an early diagnosis and no RCC-related mortality. Screening for RCC in RT recipients is an effective tool for early diagnosis and to reduce RCC-related mortality. Further research into the cost-effectiveness of screening is imperative. Research Sponsor: None.

10529 **Poster Session**

Comparison of simulated outcomes between stool- and blood-based colorectal cancer screening tests. *First Author: A. Fendrick, University of Michigan, Ann Arbor, MI*

Background: The Centers for Medicare & Medicaid Services (CMS) recommends covering blood-based biomarker tests with proposed minimum performance thresholds for colorectal cancer (CRC) screening test every 3 years for average-risk, asymptomatic Medicare beneficiaries ages 50–85 years. A blood-based test is a non-invasive screening method to detect CRC but is limited by low sensitivity to detect adenomas. Using the CRC-AIM microsimulation model, predicted life-years gained (LYG) and CRC incidence and mortality reduction were compared between a blood-based test meeting the CMS minimum thresholds and stool-based screening tests (fecal immunochemical test [FIT], fecal occult blood test [FOBT], and multitarget stool DNA [mt-sDNA]). **Methods:** Outcomes of blood- and stool-based tests were simulated for average-risk individuals free of diagnosed CRC at age 40 and screened between ages 45–75 years per USPSTF recommendations. Per CMS proposed criteria, CRC sensitivity and specificity for a blood-based test were set at 74% and 90%, respectively, and adenoma sensitivity was set at 10%. Published adenoma and CRC sensitivity and specificity were used for each stool test. For the primary analysis, adherence was assumed to be 100%. For secondary analysis, adherence was set at 30–70%, in 10% increments. Outcomes were per 1000 individuals. **Results:** At 100% adherence, LYG was 229 for a blood test and ≥305 for stool tests, corresponding to at least 25% lower LYG for a blood test relative to all stool tests (Table). Absolute CRC incidence and mortality reductions were at least 19% and 18% lower, respectively, for a blood test vs all stool tests. Secondary analysis indicates that at identical adherence rates that are less than 100%, a blood test had lower LYG vs all stool tests (Table). When the adherence of any test was 50%–70%, a blood test resulted in at least 20% lower LYG vs any stool test, and absolute reductions in CRC incidence and mortality were at least 9% and 10% lower, respectively, vs any stool test. **Conclusions:** This model suggests that if blood-based CRC screening tests do not sufficiently detect advanced adenomas, clinical outcomes will be inferior to stool-based testing due to lack of cancer prevention. Further discovery efforts to identify blood-based markers associated with both invasive and preinvasive neoplasia are needed to address this deficiency. Research Sponsor: Exact Sciences Corporation.

LYG with each screening modality and differing adherence rates.

Adherence	Annual FIT	Annual FOBT	Triennial mt-sDNA	Triennial blood test
100%	332	305	312	229
70%	308	273	299	210
60%	295	257	292	200
50%	277	234	282	187
40%	252	207	270	172
30%	218	171	248	150

10530 **Poster Session**

Lung cancer risk prediction nomogram in Chinese female non-smokers. *First Author: Guo Lan-Wei, The Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China*

Background: About 53% of lung cancers in females are not attributable to smoking worldwide. The aim was to develop and validate a simple and non-invasive model which could assess and stratify lung cancer risk in female non-smokers in China. **Methods:** A large-sample size, population-based study was conducted under the framework of a population-based Cancer Screening Program in Urban China (CanSPUC). Data on the lung cancer screening in Henan province, China, from October 2013 to October 2019 were used and randomly divided into the training and validation sets. Related risk factors were identified through multivariable Cox regression analysis, followed by establishment of risk prediction nomogram. Discrimination [area under the curve (AUC)] and calibration were further performed to assess the validation of risk prediction nomogram in the training set, and then validated by the validation set. **Results:** A total of 151,834 eligible subjects were included, with a mean age of 55.34 years. Subjects were randomly divided into the training (75,917) and validation (75,917) sets. Elder age, history of chronic respiratory disease, first-degree family history of lung cancer, menopause, and history of benign breast disease were the independent risk factors for lung cancer. Using these five variables, we plotted 1-year, 3-year, and 5-year lung cancer risk prediction nomogram. The AUC was 0.762, 0.718, and 0.703 for the 1-, 3- and 5-year lung cancer risk in the training set, respectively. In the validation set, the model showed a good predictive discrimination, with the AUC was 0.646, 0.658, and 0.650 for the 1-, 3- and 5-year lung cancer risk. **Conclusions:** We developed and validated a simple and non-invasive lung cancer risk model in female non-smokers. This model can be applied to identify and triage patients at high risk for developing lung cancers in female non-smokers. Research Sponsor: None.

10531 **Poster Session**

Designing a decision aid for cancer prevention. *First Author: Shakira R Milton, Centre for Cancer Research, The University of Melbourne, Melbourne, VIC, Australia*

Background: Australian guidelines recommend those aged 50 to 70-years-old without contraindications, consider taking low-dose aspirin (100 mg – 300 mg per day) for at least 2.5 years to reduce their risk of colorectal cancer. To increase uptake of the new guidelines, we hypothesized that a decision aid (DA) would help facilitate a discussion between clinicians and patients about aspirin chemoprevention. We aimed to design a DA with clinician and consumer input including state-of-the-art expected frequency trees (EFTs). We aimed to explore clinicians' opinions about using EFTs with their patients during consultations and gain consumers feedback on DAs including their understanding and their hypothetical decision to take aspirin or not. **Methods:** Semi-structured interviews were conducted with relevant clinicians including familial cancer clinic staff (geneticists, oncologists and genetic counsellors), gastroenterologists, pharmacists, and general practitioners (GPs). Focus groups were conducted with consumers in the target age range of the guidelines. DAs were developed through an iterative process. The clinician and focus group interview schedules covered ease of comprehension, design, potential effects on decision making, and approaches to implementation of the DA. Coding was inductive and the focus group interviews were independently coded by two researchers. Themes were developed through consensus between the authors. Final versions of the DAs were proposed to consumers for their final approval after all changes were made. **Results:** Sixty-four interviews were completed with clinicians between March and October 2019. Twelve consumers, aged 50 to 70 years, participated in two focus groups in February and March 2020. The clinicians agreed that the EFTs would be helpful to facilitate a discussion with patients but suggested including an additional estimate of the effects of aspirin on all-cause mortality. Clinicians agreed that patients would benefit from being shown the EFT in a consultation. The consumers felt favorable about the DA, especially if used with a clinician, and suggested some additional changes to the design and wording to improve ease of comprehension. **Conclusions:** We have designed a DA using novel approaches to communicate risks and benefits of low dose aspirin for cancer and cardiovascular disease prevention. The DAs are currently being trialled in the SITA trial in general practice to determine its impact on informed decision-making and aspirin uptake. Research Sponsor: Department of Health and Human Services, Victorian Cancer Agency Grant CPSRG19011.

10533 **Poster Session**

Robust artificial intelligence-powered imaging biomarker based on mammography for risk prediction of breast cancer. *First Author: Eun Kyung Park, Lunit Inc., Seoul, South Korea*

Background: Accurate risk assessment allows the precise personalized screening of breast cancer. Conventional statistical risk models have been used that estimate the probability of breast cancer incidence with patient demographics, detailed personal and family history. The purpose of this study was to investigate the feasibility of the AI-powered Imaging Biomarker in mammography (IBM) which was developed to predict the risk of future breast cancer beyond the mammographic breast density. **Methods:** We trained and developed the deep learning risk model, the AI-powered IBM, using a total of 36,955 examinations from 21,438 patients, who underwent at least one mammogram using Hologic or Siemens machines and pathology-confirmed breast cancer outcomes. To discover the feasibility of the AI-powered IBM, mammograms and various clinical information including pathology-confirmed breast cancer outcomes were collected, which were only used for external validation. C-indices and receiver operating characteristic (ROC) curves for 1- to 5-year outcomes were obtained. We compared 5-year ROC area under the curves (AUCs) of our AI-powered IBM and statistical risk models including the Tyrer-Cuzick model and the Gail model, which were most commonly used and widely known, using DeLong's test. **Results:** A total of 16,894 mammograms were collected for external validation, of which 4,002 were followed by a cancer diagnosis within 5 years. Our AI-powered IBM obtained C-index of 0.758, and the model demonstrated the risk of breast cancer with AUC of 0.895 (95% CI: 0.880, 0.909) at 1-year, 0.839 (0.824, 0.852) at 2-year, 0.807 (0.794, 0.819) at 3-year, 0.783 (0.7947, 0.819) at 4-year. The 5-year AUC of our AI-powered IBM was 0.808 (0.792, 0.822). Our AI-powered IBM showed significantly higher 5-year AUC than the Gail model (AUC: 0.572, $P< 0.001$) and the Tyrer-Cuzick model (0.569, $P< 0.001$). **Conclusions:** A deep learning AI-powered IBM using mammograms has a substantial potential to advance toward the robust risk prediction of breast cancer over conventional risk models. This approach for risk stratification of breast cancer might be feasible to improve personalized screening programs. Research Sponsor: Lunit Inc.

10534 **Poster Session**

Factors associated with the decreasing rate of oropharyngeal cancer in young adults in the United States. *First Author: John K Chan, Palo Alto Medical Foundation, Palo Alto, CA*

Background: To evaluate trends of HPV-associated oropharyngeal cancers and HPV infections in the United States. **Methods:** Data was extracted from the United States Cancer Statistics Public Use Database (USCS) between 2001 and 2017 and the National Health and Nutrition Examination Survey (NHANES) between 2011 to 2016. Data on oropharyngeal squamous cell carcinoma (OSCC) was obtained from the USCS database. HPV vaccination and screening (oral washings) data were obtained from NHANES. Based on CDC guidelines, HPV strains were further subdivided into high-risk strains (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68). **Results:** Based on USCS, oropharyngeal cancer incidence rates have increased in males by 1.64% every year ($p < 0.001$) while remaining stable in females over the last 17 years. Oropharyngeal cancers have increased for all age groups over the age of 55, with the largest increase seen in those between the ages of 65-69 years old ($p < 0.001$). However, individuals between the ages of 30-34 had the largest decrease in oropharyngeal cancers over the same time period ($p = 0.016$). Based on race, Whites had the highest incidence rates at 5.12/100,000 followed by 2.99 in Blacks, 2.32 in Hispanics, and 1.11 in Asians. By geographical region, the incidence was found to be the highest in the Midwest with 4.68/100,000 and the lowest in the West at 3.78. Our intersectional analysis showed that White males in the South aged 65-69 had the highest incidence of oropharyngeal cancers at 40.57/100,000 and this same group aged 60-64 had the highest annual increase at 4.65% ($p < 0.001$). Using the NHANES database, we showed that those with greater than 4 lifetime sexual partners have a 3-fold higher risk of high risk HPV infection compared to those with 4 or under (7.1% vs 1.9%, $p < 0.0001$). 8.8% of current smokers are infected with high risk oral HPV compared to only 3.9% of non smokers ($p < 0.001$). The incidence of any HPV infection for those <39 years old was 5.9% in 2011 and 4.7% in 2016 ($p = 0.4723$). In contrast, the incidence in those > 39 years old was 6.6% in 2011 and 6.4% in 2016 ($p = 0.99$). On multivariate analysis, males have a 4-fold higher risk of high risk HPV infections compared to females (4.45, 95% CI: 2.94 - 6.74, $p < 0.0001$). Those with five or more sexual partners have 7-fold higher rate of high risk oral HPV infections compared to those without any sexual partners (7.15, 95% CI: 1.94 - 26.3, $p = 0.0039$). Furthermore, current smokers (1.81, 95% CI: 1.17 - 2.77, $p = 0.0081$) and three to four drinks per day (1.63, 95% CI: 1.05 - 2.55, $p = 0.0312$) have an increased risk of high risk oral HPV infections. **Conclusions:** Over the last 18 years, oropharyngeal cancers are increasing in individuals over the age of 55, particularly White males residing in the South. Individuals with greater than 4 lifetime sexual partners, current smokers, and those who consume three to four drinks per day have increased HPV infectivity rates. Research Sponsor: None.

10535 **Poster Session**

The role of health information technology in improving awareness of HPV and HPV vaccine among U.S. adults: Insights from the health information national trends survey. *First Author: Gideon T Dosunmu, University of South Alabama Medical Center, Mobile, AL*

Background: Despite advances in cancer prevention and wide-spread availability of Human papilloma virus (HPV) vaccines, US adults continue to have suboptimal HPV vaccination uptake with less than 50% vaccinated. Strategies aimed at enhancing HPV-related awareness are considered one of the most effective ways to improve HPV vaccine adoption and potentially eliminate HPV-related cancers. Health information technology (HIT) may influence HPV-related awareness and subsequently drive vaccine adoption. This study assessed the impact of HIT utilization on HPV and HPV vaccine awareness. **Methods:** Data was obtained from Health Information National Trends Survey (HINTS 5 cycles 1 and 2). Cross-sectional sample of 6,522 individuals aged 18 years or more was analyzed. The independent variables were use of smartphone, computer, or electronic means to (i) look up health information, (ii) fill a prescription online, (iii) communicate with a doctor or doctor's office, (iv) look up test results of and (v) track health care charges. The dependent variables were HPV and HPV vaccine awareness. Chi-square analysis was used to evaluate group differences, and a multiple logistic regression was used to analyze the association between HIT utilization and HPV-related awareness controlling for sociodemographic and health-related factors. **Results:** Of the total sample, awareness of HPV and HPV vaccine was 62.7% and 61.8% respectively. In adjusted multivariable logistic regression analysis, those who utilized a smartphone, computer, or electronic means to look up health information (aOR 2.23; 95% CI 1.68 – 2.97, $p < 0.001$), communicate with healthcare provider (aOR 1.53; 95% CI 1.23 – 1.91, $p < 0.001$), look up test results (aOR 1.67; 95% CI 1.35 – 2.08, $p < 0.001$), and track health care charges (aOR 1.61; 95% CI 1.26 – 2.05, $p < 0.001$), were more likely to endorse HPV awareness than those who did not. Similar positive associations were observed for HIT utilization and HPV vaccine awareness. **Conclusions:** Our findings showed a positive association between HIT utilization and HPV-related awareness. Amid a background of sub-optimal HPV vaccination and explosion in technology, these results emphasize the potential for the role of HIT in preventive medicine. Strategies that integrate HIT into vaccine interventions and communications should be encouraged as a medium to expand HPV awareness and vaccine coverage. Research Sponsor: None.

10536 **Poster Session**

Cost-effectiveness of targeted genomic risk provision to prevent skin cancer: Results of a randomized trial. *First Author: Chi Kin Law, NHMRC Clinical Trials Centre, University Of Sydney, Camperdown, NSW, Australia*

Background: Many melanomas and keratinocyte cancers (KC) are preventable by reducing sun exposure and improving sun protection behaviors. Recent evidence indicates a melanoma prevention program involving personalized genomic risk information provision can reduce self-reported sunburns at 12 months in Australian adults with no history of melanoma. This was alongside genetic counselling and educational materials on skin cancer prevention and early detection. However, the economic impact of this approach was unclear. This study aimed to determine the cost-effectiveness of the program to prevent melanoma and KC. **Methods:** A decision-analytic Markov model was developed to simulate the lifetime cost-effectiveness of personalized genomic risk provision compared with standard prevention advice alone, from a health system perspective. We used data from the Melanoma Genomics Managing Your Risk Study Randomized Control Trial. Traditional risk was measured by a validated melanoma risk prediction model involving hair color, nevus density, history of non-melanoma skin cancer, family history of melanoma, level of sunbed sessions. Quality-adjusted life years (QALY) gained was the primary outcome measure used to estimate an incremental cost-effectiveness ratio (ICER). Both deterministic and probabilistic sensitivity analyses (PSA) were undertaken. **Results:** The cost of the genomic testing and risk counselling program was AUD$189 (USD$132) per participant. Genomic risk provision targeting high-traditional risk individuals was the most cost-effective lifetime strategy with an ICER of AUD$23,033 (USD$16,059) per QALY gained and an 80% probability of being cost-effective at a willingness-to-pay threshold of AUD$50,000, compared with standard preventive advice (Table). When genomic risk provision was extended to low-traditional risk groups the ICER was $43,746 (USD30,500) per QALY gained with a 45% probability of being cost-effective. **Conclusions:** Genomic risk provision targeted to individuals at high-traditional risk of melanoma is a cost-effective strategy for the prevention of melanoma and KCs. Long-term sustainability of the program's effect should be examined in future research. Clinical trial information: ACTRN12617000691347. Research Sponsor: Australian National Health and Medical Research Council.

Modelled strategies for comparison	Total lifetime costs (AUD)	Incremental costs (AUD)	QALYs	Incremental QALY	ICER	Probability of being cost-effective
Standard prevention advice alone	3507		19.194			
Genomic risk provision targeting high traditional-risk individuals	3586	79	19.198	0.004	23033	0.8024
Genomic risk provision targeting high traditional-risk individuals	3586		19.198			
Genomic risk provision to low and high traditional risk individuals	3672	86	19.200	0.002	43746	0.4467

10537 **Poster Session**

Increase in postmenopausal women with distant stage breast cancer in the United States over the last 18 years: Who is the most at risk? *First Author: Arya Aliabadi, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of California Los Angeles, Los Angeles, CA*

Background: In the United States, Asian women have traditionally been considered at low risk for breast cancer; yet it is unknown how distant stage disease has trended by geographic, demographic, and modifiable risk factors since 2001. **Methods:** Data were obtained from the United States Cancer Statistics (USCS) program from 2001-2018, the Behavioral Risk Factor Surveillance System (BRFSS) from 2000-2018. SEER*Stat 8.3.9.2 and the Joinpoint regression program 4.9.0.0 were used to calculate the incidences and trends of distant stage breast cancer per 100,000 women. The trend was presented as average annual or biennial percent change (AAPC or ABPC). **Results:** Using the USCS program, the overall incidence of postmenopausal breast cancer decreased from 367.90 to 345.07 (per 100,000); however, the incidence of distant stage cancer increased from 16.75 to 19.77 (per 100,000) over 18 years. The incidence is the highest for Black, followed by White, Hispanic, and Asian women at 27.14, 19.86, 14.15, and 11.98 (per 100,000) in 2018, respectively. The annual increase is highest in Asian, followed by Black, White, and Hispanic women at 2.28%, 1.44%, 1.17%, and 0.87% ($P < 0.001$), respectively. On intersection analysis, postmenopausal Asian women living in the Northeast have the highest annual rise at 2.54% ($P = 0.004$). BRFSS data revealed that the proportion of women non-compliant with screening mammograms decreased from 36.03% in 2000 to 20.93% in 2018. In 2018, Asian women were the most non-compliant followed by Hispanic, Black, and White women at 40.99%, 40.06%, 21.67%, and 18.17%, respectively. Over time, White, Black, and Hispanic women improved on compliance by 3.43%, 3.32%, and 1.24% ($p < 0.05$) on screening rates biennially; however, Asian women have not made any improvement (ABPC 0.80%, $p = 0.410$). On intersectional analysis, the most non-compliant group in 2018 were Asian women in the Midwest at 54.48%. We then evaluated upstream social determinants of breast cancer, such as obesity. While the baseline incidence of obesity in Asian Americans is low compared to other racial groups, it has increased from 9.22 in 2001 to 13.67 (per 100,000) in 2016. Specifically, the incidence of obesity increased the most in postmenopausal Asian 65 to 74-year-olds at 3% compared to White, Hispanic, and Black Americans of the same age group at 2.5%, 2.2%, and 1.1% ($p < 0.05$), respectively. **Conclusions:** Although the incidence of breast cancer has decreased in the United States since 2001, the rate of distant stage breast cancer continues to rise. Postmenopausal Asian women with distant stage breast cancer are increasing at the highest rate compared to other racial groups. Further, Asian women are more non-compliant with screening mammograms and have an increased rate of obesity. Tailored interventions are warranted to enhance primary and secondary prevention and decrease distant stage cancer in this high-risk group. Research Sponsor: None.

10538 **Poster Session**

Awareness of the link between HPV, cervical cancer, and HPV vaccination: An online survey among Polish women. *First Author: Artur Kotowski, Polish Association for Good Clinical Practice GCPpl, Warsaw, Poland*

Background: In 2019 cervical cancer (CC) was the 7th most common malignant neoplasm in Polish women. Its incidence has been declining over the years, nonetheless the 5-year survival rate is still significantly lower than the EU average. Vaccination against human papillomavirus (HPV) is not included in the mandatory immunization schedule in Poland and is not reimbursed yet. The aim of the study was to assess women's awareness of the risk factors of CC (including the role of HPV) and the possibility of cancer prevention through HPV vaccination. **Methods:** The questionnaire prepared by the study team was aimed at women and conducted online using social network sites. The single/multiple-choice questions included knowledge about CC, HPV and HPV vaccination. Statistical analyses were performed using MS Excel 2016 and Medistica pvalue.io 2021 software in general population and age- dependent subgroups. **Results:** The total number of 3262 women participated in the study. The age subgroups were: aged ≤ 18 years (group 1): 1090 (33.4%), aged 19-25 years (group 2): 1615 (49.5%) and > 25 years (group 3): 557 (17.1%). Overall 81.4% of the respondents correctly associated HPV as the key factor of CC, 85.0% believed that CC could be prevented and 80.0% had heard of HPV vaccination before. In the last two parameters a statistically significant difference in age subgroups was observed ($p < 0.001$). Only 21.2% of the total number of respondents were vaccinated (26.2%, 22.0% and 9.2% in age groups 1, 2 and 3 respectively, $p < 0.001$). In all studied populations the following factors had the greatest influence on the decision to get vaccinated: parents' advice – 54.8%, pediatrician recommendation – 15.7%, possibility of free vaccination offered by municipality – 11.6%, teachers' advice - 9.7%, gynecologist recommendation - 8.2%. The main reasons behind not getting vaccinated were: high price (63.0%) and disbelief in efficacy (41.5%); only 12.2% respondents were afraid of possible side effects. 65.0% of the unvaccinated respondents declared willingness to get vaccinated in the future (71.5%, 66.1% and 52.0% in age groups 1, 2 and 3 respectively $p < 0.001$), 28.5% of the respondents were not confident of their decision at the time of submitting answers. **Conclusions:** As oncogenic types of human papillomavirus play a vital role in pathogenesis of CC, the HPV vaccination and cytological screening together with awareness-raising campaigns should be considered the best strategy for the prevention of CC, its early detection and increase in survival rates. Vaccine willingness remains at high level especially among young women, however the effectiveness of vaccination should be emphasized and the HPV free vaccination programs should be introduced by the state. The educational role of gynecologists needs to be enhanced. Research Sponsor: None.

10539 **Poster Session**

At-risk patient and healthcare provider perspectives on clinical trial participation for ductal carcinoma in situ. *First Author: Elizabeth J. Adams, Northwestern University Feinberg School of Medicine, Chicago, IL*

Background: Significant challenges exist in recruiting newly diagnosed ductal carcinoma in situ (DCIS) patients to participate in presurgical intervention trials. Perceived motivators and barriers to participation have not been formally studied from the patient or healthcare provider (HCP) perspective. Based on our experience in the Promise Study (NCT02694809), we hypothesized that delaying surgery and concern for side effects are barriers to trial participation and that access to new treatments and financial benefits are motivators. To improve recruitment, we conducted focus groups to better understand barriers and motivators for trial participation in our patient population. **Methods:** Three focus groups with post-menopausal women (PMW) without history of DCIS, one focus group with patients previously treated for DCIS, and two HCP focus groups were conducted. Due to COVID-19, the focus groups took place online via videoconferencing and included participants from across the United States. A third-party facilitator generated discussion on predetermined topics including knowledge of DCIS, clinical trial recruitment materials, hormone replacement therapy, healthcare delivery and clinical trials during COVID-19, and perceived motivators and barriers to trial participation in general and specifically for women with DCIS. Here, we focus on comparing perceived influential factors for patient participation in DCIS clinical trials in PMW and HCP focus groups. Qualitative thematic analysis was completed on focus group transcripts in NVivo. **Results:** PMW had no knowledge of DCIS prior to the focus groups and believed DCIS should be removed promptly. PMW believed barriers to DCIS clinical trial participation included the potential for the study drug to cause harm, distrust of medicine, and the fact that DCIS is not life-threatening. PMW identified helping future DCIS patients, accessing better treatment, and easing anxiety as motivators for DCIS trial participation. HCPs believed patients were motivated by increased monitoring by the medical team, financial incentive, and access to newer treatment. HCPs believed that delays in DCIS surgery, the potential for the intervention to be harmful or ineffective, and the trial causing patient anxiety were barriers. Neither group emphasized time commitment as a barrier to DCIS trial participation. PMW were not motivated by financial incentives. **Conclusions:** Knowledge about DCIS is lacking in PMW. PMW and HCPs agreed that the risk of harm caused by study interventions is a deterrent to trial participation and that access to superior treatment is a motivator. However, PMW and HCPs did not agree on other motivators and barriers which could lead to missed recruitment opportunities. Providing educational materials on DCIS and addressing motivators and barriers to clinical trial participation may increase recruitment to presurgical DCIS trials. Clinical trial information: NCT02694809. Research Sponsor: U.S. National Institutes of Health.

10540 **Poster Session**

Cross-ancestry polygenic risk score for breast cancer risk assessment. *First Author: Placede Tshiaba, MyOme, Inc, Menlo Park, CA*

Background: Breast cancer (BC) risk is influenced by many common variants with small effects. Polygenic risk scores (PRS) weight these variants based on genome-wide association studies (GWAS) and aggregate them into a single measure. PRS has primarily shown benefit in Caucasian women. We established a cross-ancestry polygenic model (caPRS) which assesses risk of breast cancer across multiple ancestries. **Methods**: Performance of multiple BC polygenic models, both published and developed in-house, were evaluated for each of five ancestry groups: European, African, South Asian, East Asian, and Admixed American. To account for ancestry-specific mean and variance, we computed principal components (PCs) for all women by projecting their genotypes onto PCs calculated on individuals in the 1000 Genomes Project (1KGP). We next centered each ancestry-specific PRS by subtracting the PRS predicted from a linear regression of PRS against the first four PCs in unaffected individuals. Each centered PRS was then divided by the SD of the corresponding 1KGP population. We defined a cross-ancestry polygenic model as a linear combination of the best performing PRS model for each ancestry group weighted by fractional ancestry. Association of the caPRS with breast cancer risk was tested in a validation cohort of >130,000 women consisting of multiple independent cohorts (the Women's Health Initiative, the Multiethnic Cohort, the ROOT cohort and the UK Biobank) using a multivariate logistic regression model that included caPRS, age, self-reported ancestry, personal history of ovarian cancer (when available) and first-degree family history of BC. Discrimination was assessed by the odds ratio (OR) per SD and the area under the receiver-operator curve (AUC). **Results**: This study included women with African/Black, East Asian, Caucasian/White, Hispanic/Latino, South Asian and 'Other' self-reported ancestry. The ancestry-specific models included in the caPRS ranged in size from 173 to >800,000 variants. The caPRS was associated with BC risk for women in each self-reported ancestry (Table). The caPRS offered a modest increase in performance over a commonly implemented 313-SNP PRS in non-European ancestries, most significantly in African/Black women where the OR per SD increased from 1.24 (1.08 - 1.43), p-value 2.3x10-3. **Conclusions**: The caPRS performed well for women of any ancestry and allows flexibility to update ancestry-specific models. These results suggest the caPRS has the potential to improve the clinical utility of existing clinical risk predictors. Research Sponsor: None.

Self-reported ancestry	Ntotal	Ncases	AUC	OR per SD (95% CI)	p-value
Caucasian/White	104,312	7,133	0.70	1.66 (1.62-1.70)	<10-324
African/Black	7,883	233	0.63	1.30 (1.14 - 1.48)	1.3 x 10-4
Hispanic/Latino	1,051	519	0.63	1.59 (1.39 - 1.82)	4.7 x 10-13
East Asian	1,690	879	0.61	1.44 (1.31 - 1.59)	6.9 x 10-14
South Asian	1,251	46	0.70	1.49 (1.10 - 2.02)	0.010

10541 **Poster Session**

Multiomic approach to examining gut microbiome sampling methods in breast cancer and control subjects. *First Author: Christina Ann Nowicki, Rush University, Chicago, IL*

Background: It is well known that estrogen exposure is a major risk factor for breast cancer (BC). Estrogen levels can be affected by the gut microbiome through enterohepatic circulation. No studies regarding gut microbiome changes in BC have examined the colonic mucosal microbiome; and there is no data on which types of gut microbiome studies would be most relevant to the study of the microbiome in BC. **Methods**: We examined differences in the gut microbiome composition in BC and control subjects using the following sample types: Home-collected stool, endoscopically collected stool, and colonic biopsy samples (for all groups, n=48 total, n=24 BC, n=24 controls). Here, we used both operational taxonomic unit (OTU) and amplicon sequence variant (ASV) based approaches in QIIME2 for 16S rDNA sequencing analysis. Alpha diversity metrics (Chao1, Pielou's Evenness, Faith PD, Shannon, and Simpson) and beta diversity metrics (Bray-Curtis, Weighted and Unweighted Unifrac) were calculated. LefSe was used to analyze differences in the abundance of various taxa between sample types. **Results:** Alpha and beta diversity metrics were different between the three sample types when using both OTU or ASV-based analysis, however there were some minor differences between analysis types in these samples. Comparing the 3 sample types, Actinobacteria and Firmicutes (Log10 LDA score >4) were the predominant phyla in home stool samples, while Bacteroidetes and Proteobacteria (Log10 LDA score >4) were higher in abundance in the colonic biopsy samples. **Conclusions:** Our data shows that alpha and beta diversity metrics differ between sampling methods (home-collected stool, endoscopically collected stool, and colonic biopsies) when looking at the composition of the gut microbiome in BC. Results remained the same regardless of ASV or OTU-based analysis. Research Sponsor: U.S. National Institutes of Health.

Alpha and beta diversity metric p-values for home-collected stool, endoscopically-collected stool, and colonic biopsies using ASV and OTU-clustering approaches.

Beta Diversity	ASV (DADA2)	OTU (De novo 99%)	OTU (De novo 97%)	OTU (Open Reference 99%)	OTU (Open Reference 97%)	OTU (Normalized Open Reference 97%)
Bray-Curtis	1.00e-5	1.00e-5	1.00e-5	1.00e-5	1.00e-5	1.00e-5
Unweighted Unifrac	1.00e-5	1.00e-5	1.00e-5	1.00e-5	1.00e-5	1.00e-5
Weighted Unifrac	1.00e-5	1.00e-5	1.00e-5	1.00e-5	1.00e-5	1.00e-5
Alpha Diversity						
Chao1	1.32e-14	2.7e-18	4.17e-19	5.24e-18	1.82e-18	3.36e-9
Evenness	1.08e-4	0.016581	0.380071	0.000821	4.98e-5	3.23e-15
Faith PD	1.61e-19	0.012464	0.000436	0.000189	0.000165	1.66e-18
Shannon	6.75e-5	0.000159	0.003327	2.35e-5	3.85e-6	8.45e-19
Simpson	0.001587	0.005427	0.015369	0.000843	0.000200	2.57e-7

10542 **Poster Session**

A novel NGS kit solution for multi-cancer early detection using circulating cell free DNA based methylation analysis. *First Author: Grace Q. Zhao, AccuraGen, Menlo Park, CA*

Background: Cancer patient survival can be greatly improved by early detection. Cell-free DNA (cfDNA)-based cancer detection using targeted methylation sequencing (TMS) holds great promise. Here, we report the performance of the first cfDNA TMS kit for early cancer detection. **Methods:** We developed a comprehensive multi-cancer TMS panel, named "Omni1" (900kb) containing ~3000 cancer specific hypermethylation markers for the detection of the 16 most prevalent solid tumor cancer types in the US. These selected biomarkers all have high signals in cancer, low signals in normal tissue and close to zero background in plasma. The TMS analysis is empowered by Point-n-Seq DNA enrichment and soft bisulfite sequencing technology. Across the different cancer types, the Point-n-Seq Methylation Index (PMI) derived from the Omni1 panel showed over 10 times the difference in the genomic DNA of tumor compared to normal tissues. 8 to 32 early-stage plasma samples from each of the 7 most prevalent cancer types were used for assay testing. cfDNA extracted from each donor was subjected to our Point-n-Seq TMS analysis with the Omni1 panel. The TMS workflow took around five hours, from cfDNA to a sequencing ready library. 6M reads were assigned to each sample resulting in ~1400X average raw coverage across the target regions. **Results:** A computational model to calculate the methylation index and the thresholds were established on independent training data sets for each cancer type. For the testing, specificity was set at 89% (CI = 0.81, 0.97, n = 55 self-claimed healthy individuals). The detection rate for stage I (n = 55) and stage II (n = 56) of all 7 cancer types combined is 65% (CI = 0.53,0.78) and 75% (CI = 0.64, 0.86) respectively. Even within this small sample size, it was clear that the detection sensitivity varied among different cancer types, and it increased from stage I to II: colorectal (65%, n = 20; 75%, n = 12), lung (75% n = 8; 92%, n = 12), pancreas (80%, n = 10; 100%, n = 10), ovary (60%, n = 5; 80%, n = 5), breast (40%, n = 7; 100%, n = 3), and prostate cancer (0%, n = 2; 22% n = 9) for stage I and II respectively. A decrease in sensitivity from stage I to II in liver (100%, n = 3; 60%, n = 5) is possibly due to variability from the small sample size. For the cases of CRC, the detection rates obtained from Omni1 are comparable to the stand-alone CRC560 panel (170 kb). **Conclusions:** In this study we demonstrated that by leveraging an economy-size panel, a robust methylation sequencing kit, and a straightforward analysis methodology, early cancer detection for multiple cancer types can be done with just 1ml plasma. The kit strategy provides an easy-to-use and distributable solution, without the complications of developing a lab-specific test that uses a large methylation panel and a high sequencing cost. Research Sponsor: Avida Biomed seed fund.

10543 **Poster Session**

Trends in the incidence of early-onset invasive colorectal cancer between 1990 and 2018, stratified by race/ethnicity, gender, and anatomic sub-sites among Pennsylvania residents. *First Author: Inimfon Jackson, Albert Einstein Medical Center, Philadelphia, PA*

Background: Recent data report a rising incidence of colorectal cancer in the younger population and epidemiological evidence is useful to enable clinicians understand evolving trends and better counsel patients on the potential risks/benefits of early screening. We explored the trends in incidence of early-onset invasive colorectal cancer by race/ethnicity, gender, and anatomic sub-sites. **Methods:** Repeated cross-sectional analyses were conducted among adults < 50 years diagnosed with invasive colorectal cancer between 1990-2018 in Pennsylvania using data from the Pennsylvania Department of Health Cancer Registry. Temporal trends in invasive cancer with age adjusted incidence rates according to race/ethnicity, gender, and anatomical sub-sites were assessed using the Enterprise Data Dissemination Informatics Exchange (EDDIE). **Results:** 16,154 cases of early-onset invasive colorectal cancer were diagnosed between 1990 and 2018. There was an increased incidence of invasive colorectal cancer in the general population especially when stratified by gender, race/ethnicity and among those < 40 years of age. While rates among Whites nearly doubled from 5.4 per 100,000 (95% Confidence Interval (CI): 4.9–6.0 per 100,000) population to 9.0 per 100,000 (95% CI: 8.2– 9.7 per 100,000) population, the rates in the Black population have been decreasing in recent years from a peak of 10.4 per 100,000 (95% CI: 8.4–12.7 per 100,000) population in 2011 to 7.3 per 100,000 (95% CI: 5.7–9.3 per 100,000) population in 2018. However, the Hispanic rates have remained stable. Across anatomical subsites, the rectum, rectosigmoid and sigmoid colon were found to have rising trends in incidence rates over time. **Conclusions:** There is increased awareness on the need for early diagnosis of colorectal cancer in the young Black population. However, we found trends toward increasing incidence rates among Whites while rates in the Black population are now decreasing. These findings accentuate the need for quality provider-patient communication during primary care visits with a goal to improve adherence to the new colorectal cancer screening guidelines regardless of race/ethnicity. Research Sponsor: None.

10544 **Poster Session**

Clinical validation of a multicancer detection blood test by circulating cell-free DNA (cfDNA) methylation sequencing: The THUNDER study. *First Author: Qiang Gao, Liver Cancer Institute and Zhongshan Hospital, Fudan University, Shanghai, China*

Background: The development of ultra-sensitive genomic and epigenomic assays enables the early detection of multiple cancers in parallel. However, large-scale prospective clinical validation data are rare. Here, we report clinical validation data from the THUNDER (The Unintrusive Detection of EaRly-stage cancers, NCT04820868) study, which evaluates the performance of ELSA-seq among 6 cancer types in lung, colorectum, liver, esophagus, pancreas and ovary, which account for 50% of cancer morbidity and 62% of cancer mortality. **Methods:** This prospective case-control study consists of four stages: marker discovery, model training, validation, and independent validation. A customized panel covering 161,984 CpG sites was established using public data and in-house data. Cancer patients were pre-specified into the training and validation sets, and healthy controls (HC) were age-matched. Two multi-cancer detection blood test (MCDBT-1 and MCDBT-2) models with different cut-offs were established from the retrospectively collected training set and tested in the validation set. An independent validation set was enrolled prospectively, matched by age, and tested with the locked MCDBT-1/2 models. An interception model was then applied based on the model performance and China cancer incidence data to infer potential positive predictive value (PPV) and clinical utility in real-world practice. **Results:** In total, the training set consisted of 399 cases and 626 HC; the validation set consisted of 301 cases and 123 HC; and the independent validation set consisted of 505 cases and 505 HC. In the training set, the specificities were 98.9% (95% confidence interval [CI], 97.7%–99.5%) and 99.7% (98.8%–100.0%) for MCDBT-1/2 models, respectively. In the independent validation set (n = 856, the rest to be sequenced and reported), MCDBT-1 and MCDBT-2 yielded sensitivity of 76.2% (72.0%–80.0%) and 70.2% (65.8%–74.4%) in 6 cancers with specificity of 96.3% (93.9%–97.9%) and 99.3% (97.8%–99.8%), respectively. Stage I–III sensitivity was 68.5% (63.1%–73.5%) and 60.8% (55.3%–66.2%) for MCDBT-1/2 models, respectively. The prediction accuracy of top predicted origin was 79.1% (74.5%–83.2%) and 83.0% (78.4%–87.0%) for MCDBT-1/2, respectively. The interception model projected an estimated PPV of 3.1% and 12.4% for MCDBT-1/2 models, respectively. MCDBT-1 could reduce 5-year cancer mortality by 20.3%–24.6% and reduce late-stage incidence by 51.7%–61.7%, and MCDBT-2 could reduce 5-year cancer mortality by 15.9%–19.9% and reduce late-stage incidence by 40.9%–49.2%. **Conclusions:** cfDNA methylation-based MCDBT-1/2 models can effectively identify multiple cancers simultaneously at early stages with promising sensitivity, specificity, and accuracy of predicted origin. Their performances are to be further validated in a prospective interventional study (NCT05227534). Research Sponsor: Guangzhou Burning Rock Dx Co., Ltd.

10545 **Poster Session**

Adapting an evidence-based cancer survivor lifestyle program for cancer prevention and control in African American and Hispanic/Latino communities. *First Author: Jamila L. Kwarteng, Medical College of Wisconsin, Milwaukee, WI*

Background: Cancer is the second leading cause of death in Wisconsin with higher mortality rates observed for Black/African American (B/AA) and Hispanic/Latino(a) (Hisp/Lat) communities. Affordable lifestyle interventions targeting healthy nutrition and physical activity patterns tailored to the needs/interests of these communities are critically needed to prevent and control cancer. In this project, we adapted the evidence-based Moving Forward lifestyle program for B/AA breast cancer survivors, which included a program workbook, in-person education/supervised exercise classes, and text messages. We sought to address cancer prevention among B/AA and Hisp/Lat community members in the general population by implementing the program within an urban public recreation system for sustainability. **Methods:** To help guide the adaptation process, project partners included an academic cancer center, an urban public recreation system, the state department of public health, and a community advisory board. Our approach comprised of focus groups with B/AA and Hisp/Lat residents, surveys collected at community events, and an After-Action Review of a 4-week program pilot. **Results:** One-hundred community members (58 B/AA and 42 Hisp/Lat) participated in the adaptation phase through eight focus groups (N = 27), 48 surveys, and 25 pilot participants. Seven key program content adaptations were targeted: 1) integrate information on basic cancer biology; 2) explain the association between cancer, nutrition and physical activity; 3) address other diseases besides cancer (heart disease, diabetes); 4) provide cooking demonstrations with culturally relevant tips to facilitate dietary changes; 5) update workbook images and content to reflect race/ethnicity of targeted populations; 6) add information on cancer screening; 7) provide information on local healthy eating and exercise resources. Key adaptations related to conducting the program within a public recreation system included: 1) dividing the program into two 8-week sessions to meet the public recreation system program calendar; 2) eliminating the text message component; 3) providing the program workbook/classes in English and Spanish; and 4) integrating different exercise approaches to meet needs/interests of different age groups, genders, and different fitness levels. **Conclusions:** Community-academic partnerships and ongoing community engagement led to meaningful adaptations to a cancer prevention and lifestyle program to address cancer disparities in the B/AA and Hisp/Lat communities. Research Sponsor: U.S. Department of Health and Human Services Office of Minority Health.

10546 **Poster Session**

Interception versus prevention in cancer screening in a Medicare population: Results from the CRC-MAPS model. *First Author: Girish Putcha, Freenome, South San Francisco, CA*

Background: This study examines the impact of detecting cancer (interception) versus adenomas and cancer (prevention + interception) on clinical outcomes in a screen-naive Medicare cohort for a hypothetical colorectal cancer (CRC) screening test or a multicancer early detection (MCED) test that includes CRC. **Methods:** CRC-MAPS, a validated microsimulation model of the adenoma-carcinoma pathway that reproduced incidence reduction (IR) and mortality reduction (MR) consistent with CISNET models and a randomized controlled trial, was used to simulate perfect adherence to a hypothetical annual screening test among previously unscreened individuals free of diagnosed CRC. Four scenarios were examined: two cancer interception and two cancer prevention + interception. Individuals were screened from age 65 to 75. CRC IR and MR outcomes compared to no screening were aggregated from age 65 until death. Threshold analysis (#5) identified the ≥10mm adenoma sensitivity needed for a base-case cancer interception test (#1) to yield CRC MR equivalent to a near-perfect cancer interception test (#2). **Results:** The base-case interception scenario (#1) resulted in 5.6% CRC IR and 21.7% MR compared to 5.2% CRC IR and 25.9% MR for the near-perfect interception scenario (#2). The threshold analysis demonstrates that when the base-case interception scenario's ≥10mm adenoma sensitivity is increased from 1% to just 2.43% (#5), the resulting MR is equivalent to a near-perfect interception test. Accordingly, the cancer prevention + interception scenarios (#3, #4) resulted in CRC IR and MR outcomes 9.7-12.9x and 2.5-3.4x (respectively) as favorable as either cancer interception scenario due to adenoma detection. **Conclusions:** This analysis highlights that even small improvements in the detection of precancerous lesions for certain cancers (e.g., adenomas for CRC), which enable cancer prevention, can yield clinical benefits that meaningfully exceed those from tests that primarily detect cancer. Future studies will explore both benefits and burdens of different screening tests. Moreover, this approach will be applied to better understand the clinical utility of MCED tests. Research Sponsor: Freenome Holdings, Inc.

Scenario	Specificity	Adenoma Sensitivity	CRC Sensitivity	CRC IR	CRC MR
1. Cancer Interception (base-case)	99%	1-5mm: 1% 6-9mm: 1% ≥10mm: 1%	60%	5.6%	21.7%
2. Cancer Interception (near-perfect)	99%	1-5mm: 1% 6-9mm: 1% ≥10mm: 1%	99%	5.2%	25.9%
3. Cancer Prevention (with FIT-like adenoma sensitivity) + Interception	99%	1-5mm: 5% 6-9mm: 10% ≥10mm: 20%	60%	54.4%	63.6%
4. Cancer Prevention (with improved FIT-like adenoma sensitivity) + Interception	99%	1-5mm:10% 6-9mm: 20% ≥10mm: 30%	60%	67.0%	73.8%
5. Threshold analysis	99%	1-5mm: 1% 6-9mm: 1% **≥10mm: 2.43%**	60%	10.3%	25.9%

10547 **Poster Session**

Socioeconomic status for predicting COVID-19-related changes in cancer prevention behaviors. *First Author: Mohamed I Elsaid, The Ohio State University College of Medicine, Columbus, OH*

Background: Disruptions of daily life activities during the CVOID-19 pandemic have adversely affected cancer-prevention behaviors. Socioeconomic status (SES) impacts on changes in cancer prevention behaviors have not been fully investigated. To tackle this gap, we examined the effects of SES on COVID-19 related changes in cancer prevention behaviors. **Methods:** We invited participants from previous studies conducted at the Ohio State University Comprehensive Cancer Center who agreed to be re-contacted to participate in a survey assessing the impact of COVID-19 on various behaviors between June and November 2020. Participants reported current cancer prevention behaviors, including physical activity, daily fruit and vegetable intake, alcohol consumption, and tobacco use. In addition, participants reported qualitative changes in current behaviors relative to pre-COVID levels. We combined current behaviors with COVID-related changes to construct a 24-point cancer prevention score. Participants were classified into low, middle, or high SES based on household income, education, and employment status. Adjusted multinomial logistic regression was used to examine the association between SES and COVID-19 related changes in cancer prevention behaviors. **Results:** The study sample included 6136 eligible participants. The average age was 57 years, 67% were female, 89% were non-Hispanic White, and 33% lived in non-metro counties. The proportion of participants in the lowest cancer prevention behavior quartile decreased significantly with higher SES [low SES vs. high SES; 32% vs. 28%; P-value < .001]. Relative to pre-COVID-19 levels, higher SES was significantly associated with increases in post-COVID-19 prevalence of more physical activity [low SES vs. high SES; 12% vs. 28%; P-value < .001], higher fruit and vegetable intake [low SES vs. high SES; 12% vs. 14%; P-value < .001], and more alcohol consumption [low SES vs. high SES; 15% vs. 22%; P-value < .001]. Higher SES was associated with lower tobacco use prevalence [low SES vs. high SES; 5% vs. 2%; P-value < .001]. Relative to the highest prevention score quartile, the adjusted odds of scoring in the lowest prevention score quartile were: adjusted odds ratio (aOR) 1.55 (95% CI: 1.27 - 1.89) and aOR 1.40 (95% CI: 1.19 - 1.66), respectively higher for low and middle SES. Low SES was significantly associated with higher odds of less frequent physical activity (aOR = 1.87; 95% CI: 1.49 - 2.35) and less fruit and vegetable consumption (aOR = 1.56; 95% CI: 1.15 - 2.12). Middle SES relative to high SES was associated with lower odds of more alcohol consumption (aOR = 0.64; 95% CI: 0.49 - 0.85) and higher odds of binge drinking (aOR = 1.32; 95% CI: 1.09 - 1.59). **Conclusions:** The adverse impacts of COVID-19 on cancer prevention behaviors were seen most in those with lower SES. Public health efforts are currently needed to promote cancer prevention behaviors, especially amongst lower SES adults. Research Sponsor: From the National Institutes of Health, the National Cancer Institute, P30 CA016058 and the National Center for Advancing Translational Sciences, UL1TR001070..

10548 **Poster Session**

Increasing primary care utilization prior to cancer diagnosis in association with cancer mortality. *First Author: Edmund Men Qiao, Department of Radiation Medicine and Applied Sciences, University of California San Diego, La Jolla, CA*

Background: Primary care physicians (PCPs) are significant contributors of early cancer detection yet few studies have investigated whether consistent primary care translates to improved downstream outcomes. We evaluated the impact of prior PCP utilization on metastatic disease at diagnosis and cancer-specific mortality (CSM) for a general cancer cohort and 12 tumor subtypes. **Methods:** We identified cancer patients ≥40 years, diagnosed from 2004-2017 within the Veterans Health Administration. For our 5-year pre-diagnostic period, we binned PCP visits into *none* (0 visits), *some* (1-4), and *annual* (5). Multivariable logistic regression assessed the effect of PCP utilization on metastatic disease at diagnosis and Fine-Gray regression with non-cancer death as a competing event evaluated their effect on cancer-specific mortality (CSM). These were repeated for each subtype. **Results:** Among 245,425 patients, mean age was 66 years with 5.7-year median follow-up. Compared with 0 visits, *some* PCP utilization was associated with 26% reduced odds of metastatic disease at diagnosis (odds ratio (OR), 95% confidence interval (CI): 0.74 [0.71-0.76] P<0.01) and 12% lower risk of CSM (hazard ratio (HR), 95% CI: 0.88 [0.86-0.89] P<0.01). *Annual* PCP utilization was associated with 39% reduced odds of metastatic disease (OR, 95% CI: 0.61 [0.59-0.63] P<0.01) and 21% lower risk of CSM (HR, 95% CI: 0.79 [0.77-0.81] P<0.01). Among subtypes, prostate cancer had the largest effect size for PCP utilization on metastatic disease at diagnosis (OR_{annual}, 95% CI: 0.32 [0.30-0.35] P<0.01) and CSM (HR_{annual}, 95% CI: 0.51 [0.48-0.55] P<0.01). Pancreas cancer had the lowest effect size on metastatic disease at diagnosis (OR_{annual}, 95% CI: 0.87 [0.73-1.04] P: 0.12) and CSM (HR_{annual}, 95% CI: 0.89 [0.82-0.97] P<0.01). The table displays additional subtypes. **Conclusions:** Increased PCP utilization prior to cancer diagnosis is associated with a significant decrease in metastatic disease at diagnosis and CSM, with annual utilization associated with the greatest decrease. These results are consistent when stratifying by tumor subtype. Consistent primary care must be emphasized for patients at risk of cancer. Research Sponsor: None.

Additional regression results.

Subtype	Metastatic disease OR 95% [CI]	Cancer-specific mortality HR 95% [CI]
Melanoma	0.36 [0.29-0.45]*	0.51 [0.44-0.59]*
Breast	0.55 [0.35-0.86]*	0.61 [0.46-0.82]*
Bladder	0.55 [0.43-0.69]*	0.73 [0.64-0.83]*
Kidney	0.61 [0.52-0.73]*	0.71 [0.62-0.82]*
Head and Neck	0.63 [0.51-0.77]*	0.80 [0.73-0.88]*
Gastric	0.64 [0.50-0.82]*	0.78 [0.52-0.73]*
Esophagus	0.69 [0.58-0.83]*	0.77 [0.71-0.85]*
Liver	0.70 [0.58-0.84]*	0.86 [0.80-0.94]*
Lung	0.75 [0.70-0.80]*	0.87 [0.84-0.90]*
Colorectal	0.79 [0.72-0.87]*	0.89 [0.82-0.96]*

Each odds ratio (OR) or hazard ratio (HR) reflects estimated effect of *annual* primary care utilization on our endpoints. CI: confidence interval; *: *P*<0.01

10549 **Poster Session**

Project BRA: Breast cancer risk assessment. *First Author: Lauren Elizabeth Nye, University of Kansas Cancer Center, Westwood, KS*

Background: In Kansas, breast cancer (BC) incidence is similar in Black and white women, yet Black women are 42% more likely to die from the disease. In models where screening is equal, there is no difference in survival from early-stage BC. Barriers to BC early detection in Black women include provider lack of knowledge in cancer risk, performing risk assessments and providing culturally sensitive education to patients. Our team developed a didactic and case-based learning intervention using Project ECHO (Extension for Community Health Outcomes) to improve provider knowledge on performing BC risk assessment and enhance risk stratified screening in Community Health Clinics (CHCs). A Community Advisory Board (CAB) was established to address barriers to early detection. **Methods:** CHCs participated in five 1-hour ECHO sessions June thru August 2021. Session topics focused on calculating BC risk, community resources, and cultural sensitivity and were led by experts in breast oncology, risk, genetics, screening, and health care equity. Pre/post surveys administered to participants assessed knowledge and satisfaction and continuing education credits were offered. A CAB member survey gained insight into organizational characteristics and community reach. Asset mapping identified barriers, resources, and opportunities to promote BC screening. Descriptive statistical analyses and the RE-AIM framework were used to assess reach and scalability of the ECHO. **Results:** Seventy-seven individuals from 16 CHCs registered to participate with a mean of 26 attendees at each session and 34% attending two or more. Participants were physicians (19%), advanced practice providers (18%), nurses (29%), and allied health professionals (34%). Sixty-three (82%) completed the baseline survey and 10 (13%) completed the post-ECHO survey. At baseline, 32% of participants reported lack of training and time as barriers to performing risk assessment. While post-ECHO survey responses were low, 60% reported their knowledge greatly or moderately improved across all topics. Participants reported clinical practice change in assessing personal history of cancer and collecting family history beyond first degree relatives. CAB members reported a broad range of expertise in community engagement and development (44%), direct patient care (15%), healthcare access (15%) and patient advocacy (26%). CAB education and collaboration led to support for tomosynthesis for women screened in our state funded BC screening program, Early Detection Works (EDW). Ongoing asset mapping identified gaps in access for Black women to the EDW program. **Conclusions:** Project BRA demonstrated successful participation in a limited series Project ECHO and achieved perceived changes in knowledge on performing BC risk assessment. Next steps include incorporating CAB informed opportunities to expand risk-based screening across Kansas and advocate for improved access to risk stratified screening. Research Sponsor: Komen Kansas and Western Missouri Community Grant.

10550 **Poster Session**

Human papillomavirus (HPV) vaccine hesitancy trends in the United States. *First Author: Eric Adjei Boakye, Henry Ford Health System, Detroit, MI*

Background: Despite the human papillomavirus (HPV) vaccine being safe and effective at preventing HPV-associated cancers, vaccine update is low. Several factors have been identified as barriers to getting the HPV vaccine. However, it is unclear if these factors have changed since vaccine licensure. Thus, we assessed trends in the top five reasons for vaccine hesitancy in the last decade in the US. **Methods:** We analyzed the 2010–2019 National Immunization Survey–Teen data, a national survey representative of the US adolescent population. We identified adolescents (n = 16,383) who had received zero dose of the HPV vaccine (unvaccinated adolescents). Parents of unvaccinated adolescents were asked how likely they will vaccinate their child in the next 12 months. Parents who responded with "not too likely", "not likely at all" or "not sure/don't know" (vaccine hesitant) were asked what the reasons are for their hesitancy. The top five most cited reasons for vaccine hesitancy: "not necessary", "safety concerns", "lack of recommendation", "lack of knowledge", and "not sexually active" were included in the study. Joinpoint regression estimated yearly increases/decreases in these reasons using annual percent changes. **Results:** The proportion of unvaccinated adolescents whose parents cited "safety concerns"' as a reason for HPV vaccine hesitancy decreased from 2010 to 2012 but increased significantly from 2012 to 2019 at an average of 8.6% annually. The proportion of unvaccinated adolescents whose parents cited "not sexually active" as a reason for HPV vaccine hesitancy decreased on average by 33.1% from 2010-2012 and then at an average of 11.5% in the remaining years. The proportion of unvaccinated adolescents whose parents cited "not necessary" as a reason for HPV vaccine hesitancy decreased from 2010-2012 but significantly decreased by an average of 11.0% yearly from 2012-2019. The proportion of unvaccinated adolescents whose parents cited "lack of recommendation" and "lack of knowledge" as reasons for HPV vaccine hesitancy decreased over the 10-year period though not statistically significant. **Conclusions:** There was a decrease in most of the reasons cited by parents for vaccine hesitancy except vaccine safety which has been increasing from 2012 to 2019. These findings suggest an urgent need to combat the rising sentiment of safety concerns among parents of unvaccinated children to increase HPV vaccine confidence. Research Sponsor: None.

10551 **Poster Session**

Validation of the *PREDICT* breast cancer tool in a multiethnic population of U.S. women after a second primary breast cancer. *First Author: Zhengyi Deng, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD*

Background: *PREDICT* is a widely used clinical tool to estimate prognosis based on treatment after a diagnosis of early-stage breast cancer (BC). However, it has not been validated for use in women diagnosed with a second primary BC. **Methods:** Women diagnosed with one or two BCs between 2000-2013 were identified from the US Surveillance, Epidemiology, and End Results (SEER) program. Validation analyses were conducted separately among women with one and two BCs. For each group, absolute and relative differences in predicted (P) and observed (O) 5-year BC-specific mortality were estimated stratified by estrogen receptor (ER) status. For women with two BCs, mortality prediction was based on demographic and tumor characteristics of their second BCs. Model discrimination was evaluated by receiver-operator curve (ROC) and area under the curve (AUC). **Results:** 6,729 women diagnosed with a second BC and 357,204 women with only one BC were included. Among women with one ER-positive BC, the predicted (P) and observed (O) BC mortality were comparable [absolute difference (P-O): -0.22%, 95%CI: -0.29%, -0.15%]. For women diagnosed with a second ER-positive disease, the model largely underestimated the BC mortality (P-O: -6.24%, 95%CI: -6.96%, -5.49%). An underestimation of 3%-15% in absolute BC mortality was observed in subgroup analyses based on age, race/ethnicity [P-O for Non-Hispanic (NH) White, NH Black, and Hispanic were -5.63%, -9,3%, and -9.24%], chemotherapy (P-O: -9.06, 95%CI: -10.79, -7.4), radiation therapy (P-O: -5.06, 95%CI: -6.29, -3.93) and tumor characteristics. *PREDICT* overestimated BC mortality for women diagnosed with one ER-negative BC (P-O: 4.54%, 95%CI: 4.27%, 4.86%) but it performed well for women diagnosed with a second ER-negative BC (P-O: -1.69%, -3.99%, 0.16%). However, in subgroup analyses among women with two BCs the tool underestimated mortality for women with a second ER-negative disease if their first cancer was diagnosed before age 50 years (P-O: -3.27, 95%CI: -6.48, -0.06), was poorly differentiated (P-O: -4.08, 95%CI: -7.09, -1.2), or ER-negative (P-O: -4.68, 95%CI: -7.62, -1.39). The overall AUCs for first and second ER-positive and ER-negative BCs ranged between 0.73 and 0.82. **Conclusions:** The *PREDICT* tool largely underestimated the 5-year BC-specific mortality in women diagnosed with a second ER-positive breast cancer and in many subgroups of women diagnosed with a second ER-negative cancer. Novel prognostic tools are needed for women diagnosed with a second breast cancer. Research Sponsor: Breast Cancer Research Foundation.

10552 **Poster Session**

Dietary influence on physical functioning in the Women's Health Initiative (WHI) randomized Dietary Modification (DM) trial. *First Author: Rowan T. Chlebowski, Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center, Torrance,, Duarte, CA*

Background: In the WHI DM randomized trial, randomization to the dietary intervention group was associated with a 21% lower breast cancer mortality (P = 0.02) (JCO 2020), and while not an intervention target, with higher physical activity as well. Therefore, we examined whether these lifestyle changes attenuate age-related physical functioning decline. **Methods:** From 1993-1998, 48,835 postmenopausal women, aged 50-79 years, were randomized to dietary intervention or usual diet comparison groups through 8 years intervention and 19 years cumulative follow-up. Breast cancer findings, as primary outcome, have been reported. Physical functioning was assessed using the RAND 36-Item Short Form Health Survey (SF-36), which assessed limitations of 10 hierarchical physical activities, scored from 0 to 100, with a higher score indicating less limited physical function. The trajectory of longitudinal physical functioning was the primary study outcome, assessed by comparing findings in the two randomization groups, overall, and by baseline physical activity and age decade. Additionally, findings were reported against a disability threshold (when assistance in daily activities is required). **Results:** Physical functioning was assessed nearly half a million times during the study (n = 495,317) with 11.0 (median) assessments per participant. Physical functioning score was significantly better in the intervention versus comparison groups during the 8-year intervention and extended follow-up through 12 years (median) (P = 0.001), representing a reduction in age-related functional decline. The intervention effect subsequently lost significance at 19 years and both randomization groups crossed the disability threshold at similar times. Differences between randomization groups in physical functioning emerged after stratification by physical activity and age decade (P-interaction = 0.007). Among all participants physically active at entry, the intervention initially had a statistically significant, favorable influence on physical functioning which attenuated post-intervention. In contrast, among younger, physically inactive women 50-59 years of age, the intervention had a persistent, statistically significant, favorable influence on physical functioning with associated delay in crossing the disability threshold. **Conclusions:** In the primary prevention setting of the WHI DM randomized trial, with long-term follow-up, a dietary intervention which has been shown to reduce breast cancer mortality also significantly reduced age-related functional decline through 12 years. Among all participants, the intervention effect was attenuated with longer follow-up. However, reduction in age-related functional decline was sustained in younger women in the intervention group who were inactive at entry, a potential target population for future behavior interventions. Clinical trial information: NCT00000611. Research Sponsor: U.S. National Institutes of Health.

10553 **Poster Session**

An ultrasensitive approach for cancer screening and tissue of origin prediction based on targeted methylation sequencing of cell-free DNA. *First Author: Tiancheng Han, Genecast Biotechnology Co., Ltd., Wuxi, China*

Background: Cancer-specific therapy requires the identification of the tumor origin. Detecting cancer and identifying the tumor origin in early stage can improve the survival and prognosis of cancer patients. However, early diagnosis of cancer is challenging as the early symptoms of cancer are mild or even absent. In order to improve the diagnostic efficacy and the patient compliance, we developed a two-stage model for cancer diagnosis and tissue of origin (TOO) classification, using DNA methylation profile evaluated through non-invasive blood-based testing as biomarker. **Methods:** cfDNA samples from 302 healthy and 598 cancer patients of 8 cancer types (colorectal, lung, liver, pancreatic, gastric, esophagus, breast and ovarian) were sequenced by our in-house-designed DNA methylation panel and randomly split into a training dataset (213:426) and a testing dataset (89:172). The testing dataset was reserved to evaluate the performance of models and would not be used during the feature selection and model development process. Methylation levels of cfDNA samples were measured by the methylated fragment ratios (MFRs) in methylated-correlated blocks (MCBs). We first selected pan-cancer markers by comparing the MFR values of MCBs between the healthy and the diseased individuals and developed a binary classifier (hyper-methylation score). Sample correctly predicted by the hyper-methylation score in the cancer group were then used for TOO marker selection and model fitting. TOO biomarkers were obtained by a series of pairwise comparisons of MFR values between any two cancer types. A deconvolution model was built to estimate the composition of ctDNA, which implied the tumor origin. **Results:** The hyper-methylation score model based on 135 MCB biomarkers achieved an area under the curve (AUC) of 0.89 in the training dataset and 0.85 in the testing dataset. Under a specificity of 94.8%, sensitivity was 66.2% in the training dataset. Using the 282 cases successfully being predicted, 583 TOO markers were selected to build the deconvolution model. In the testing dataset, the specificity was 95.5%, and the overall sensitivity was 66.3%. With increasing stage, sensitivity increased in all cancer types: 34.6%, 57.1%, 62.5% and 84.8% in stage I, II, III and IV respectively. In stage I-III, sensitivity was 52.3%. TOO classes were predicted in the 114 true positives from the hyper-methylation score model, producing a top 1 accuracy (true class matched the most probable class) of 75.4% and a top 2 accuracy (true class matched the first or the second most probable class) of 84.2%. Top 1 accuracy was 71.1% in stage I-III, vs. 84.0% in stage IV. Top 2 accuracy was 82.2% in stage I-III, vs. 90.0% in stage IV. **Conclusions:** Our cfDNA-based epigenetic method achieved outstanding performance either in pan-cancer detection or in TOO classification, and is a promising tool for early-stage cancer diagnosis. Research Sponsor: None.

10554 **Poster Session**

Predictors of use of prevention strategies among women at high-risk for breast cancer. *First Author: Kara Landry, University of Vermont, Burlington, VT*

Background: Uptake of chemoprevention and prophylactic surgery among women at high risk for breast cancer is low, despite proven efficacy. We evaluated breast cancer risk factors as predictors of uptake of prevention treatment (PT) to better understand potential associations with these decisions. **Methods:** An IRB approved registry established in 2003 at the University of Vermont of high-risk women was used to evaluate the association between both modifiable (obesity, sedentary lifestyle and alcohol use) and non-modifiable (age, history of benign breast disease [BDD], genetic predisposition) risk factors and uptake of PT. Women were eligible for inclusion in this analysis if they had one of the following risk factors (BDD, strong family history, > 20% lifetime modeled risk or genetic predisposition) and completed questionnaires regarding diet and physical activity. Alcohol use was assessed using a health questionnaire and physical activity was assessed using a 7-Day Physical Activity Recall questionnaire. We used logistic regression to estimate odds ratios (OR). **Results:** 504 women were included and had been followed for median of 13 years. Mean age was 44.5 years (range 19 – 75), 98% were Caucasian, and mean BMI was 26.9 (range 17-57). 78% had a family history of breast cancer, 60% had >20% lifetime modeled risk, 14% had a history of benign breast disease (BBD), and 9% of women had confirmed genetic risk in high or moderate risk genes. Women may have had more than one risk factor. 55% were physically active and 55%. 4.2% were sedentary and 12.3% consumed > 1 alcoholic beverage daily. 20.8% of the cohort participated in PT (8.1% took chemoprevention, 2.0% underwent prophylactic bilateral total mastectomy and 10.7% underwent risk reducing salpingo-oophorectomy). Among non-modifiable risk factors, age, genetic predisposition (OR_{adj} 8.66, 95% CI 2.30–32.33, p < 0.0001), and history of benign breast disease (OR_{adj} 4.09, 95% CI 1.89–8.86, p < 0.001) were associated with uptake of PT. Increasing age was associated with increasing uptake (ptrend was > 0.0001) and highest among women aged 60-69 years (OR_{adj}8.19, 95% CI 2.87-23.37 relative to women aged < 40). Women with a strong family history were significantly less likely to take up PT (p = 0.04). BMI, physical activity status and alcohol use were not associated with uptake of PT. **Conclusions:** Like other studies, we found a low uptake of PT among women at high risk for developing breast cancer. We found that modifiable risk factors were not associated with uptake of PT, which might suggest that high-risk women with modifiable risk factors could be targeted for interventions designed to modify risk (i.e. chemoprevention, weight reduction, etc). Interestingly, women with a strong family history may be less likely to take up PT, and studies to further examine this relationship may identify opportunities for interventions to improve uptake. Research Sponsor: None.

10555 **Poster Session**

Higher obesity and lower screening rates in Hispanic women and associated increased breast cancer in the United States. *First Author: Michelle Ann P. Caesar, California Pacific Medical Center Research Institute, San Francisco, CA*

Background: To evaluate trends in postmenopausal breast cancer and mammogram utilization in Hispanic and White women in the United States. **Methods:** Data on postmenopausal breast cancer was obtained from the United States Cancer Statistics Public Use Database between 2001 and 2018. Rates of mammogram screening for women ages 18 and older were evaluated using the Behavioral Risk Factor Surveillance System (BRFSS) from 2000 and 2018. Obesity rates for women ages 18 and older were extracted from BRFSS between 2001 and 2016. SEER*Stat 8.3.8 and Joinpoint regression program 4.8.0.1 were used to calculate incidence trends. Breast cancer and obesity incidence and trends were described using average annual percent change (AAPC). Mammogram screening trends were described using average biennial percent change (ABPC). Age groups were divided into five-year or ten-year intervals. **Results:** Over the past eighteen years, early-stage breast cancer in Hispanic women has increased annually by 1.06% (p = 0.000) and advanced-stage has also increased annually by 0.81% (p = 0.000). In contrast, there was no increase in early-stage cancer in White women, however, advanced stage increased by 1.06% annually (p = 0.000). Compared to White woomen, Hispanic women are more likely to be unscreened with mammograms (18.17% vs. 40.06%). Over time, the unscreened population is decreasing at 3.43% for White women compared to only 1.24% in Hispanic women (p = 0.000, p = 0.001). Overall in the U.S., the never-screened population has decreased biennially by 2.88% (p = 0.000). In 2016, 33.16% of Hispanic women and 28.13% of White women were considered obese, and this obesity rate has been increasing at 2.6% and 2.4%, respectively (p = 0.000). **Conclusions:** Our data showed that early- and advanced-stage breast cancer has been increasing in Hispanic women in the United States. Hispanic women were also more likely to be obese and less likely to undergo screening compared to White women. Research Sponsor: None.

10556 **Poster Session**

LVEF decline in relation to body composition among women treated for breast cancer: WF-97415. *First Author: Kerryn Reding, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: Despite an improvement in survival from breast cancer (BC), many women experience cardiotoxicity. Left ventricular ejection fraction (LVEF) is reduced by an average of 9.7% in women receiving anthracyclines. Obesity and central adiposity at BC diagnosis may influence risk of LVEF decline. We sought to examine associations between body composition and LVEF decline in the UPBEAT (Understanding and Predicting Fatigue, Cardiovascular Decline, and Events After Breast Cancer: WF-97415) study, which was conducted in collaboration with NCI Community Oncology Research Program. **Methods:** The analytic cohort was comprised of 167 women treated for stage I-III BC with chemotherapy and/or radiation in the UPBEAT prospective study, in whom LVEF was obtained at baseline (pre-treatment) and 3 months. Linear regression was used to examine LVEF decline in relation to 1) waist circumference (WC) and body mass index (BMI) at baseline and 2) changes in WC and BMI during BC treatment. All models were adjusted for age and race. **Results:** In this cohort (mean [SD] age: 55.7 [10.8] yrs; in whom 75% were white; 19% were Black), the mean (SD) LVEF at baseline was 60.7 (6.7)% with a mean decline of 2.7 (7.2)% from baseline to 3-months. Both WC and BMI at BC diagnosis were associated with LVEF decline during follow-up (Table). For each additional inch in WC, EF decreased by 0.25% points at 3 months (P=0.024); for each additional kg/m^2 in BMI, EF decreased by 0.2% points at 3 months (P=0.007). Reduced BMI during treatment was associated with LVEF decline, whereas a change in WC was not. Each kg/m^2 reduction in BMI was associated with a 0.4% point decrease in LVEF (p=0.037). Anthracycline use was associated with a 1.89% point decline in LVEF at 3 months versus non-users (p=0.049). After additional adjustment for anthracycline use, baseline WC remained statistically significantly associated with LVEF decline to the same degree. **Conclusions:** These data show that central adiposity at BC diagnosis is associated with LVEF decline during treatment, even after controlling for anthracyclines. Loss of central adiposity was not associated with LVEF decline, whereas BMI loss during treatment was. This suggests that shifts in body composition during BC treatment, potentially via loss of muscle mass, are important to monitor in patients. Future work should examine how changes in body composition, particularly changes in skeletal muscle and adipose tissue depots, influence cardiac dysfunction in BC patients during treatment. Funding: 2UG1CA189824, R01CA199167, 2UG1CA189828. Research Sponsor: U.S. National Institutes of Health.

	Mean (SD)	Median [Min, Max]
LVEF at baseline	60.7 (6.7)	60.6 [40.9, 84.0]
LVEF change*	2.7 (7.2)	1.6 [-21.7, 36.9]
		β Estimate** (95% CI)
BMI at baseline, kg/m^2	29.5 (6.4)	0.19 (0.05, 0.32)
BMI change*	0.2 (2.6)	0.38 (0.02, 0.75)
WC at baseline, inches	38.3 (5.5)	0.25 (0.01, 0.46)
WC change*	-0.1 (2.0)	0.37 (-0.47, 1.22)

*Baseline – 3 months. **Age- and race-adjusted association with LVEF change.

10557 **Poster Session**

Early mortality in real-life nationwide epidemiological study on lung cancer in non-academic French public hospitals. *First Author: Didier Debieuvre, Groupe Hospitalier de la région Mulhouse Sud Alsace, Mulhouse, France*

Background: Each decade since 2000, the French College of General Hospital Pulmonologists (CPHG) conducts a real-life nationwide prospective epidemiological, observational, multicenter study on lung cancer (LC). In 2020, the CPHG constituted the third cohort, KBP-2020-CPHG. We reported here the data on one-month and three-month mortality among general population of this cohort and compared them with 2010 cohort. **Methods:** Collection of all consecutive LC histologically or cytologically confirmed between 01/01 and 12/31/2020 in non-academic public hospital pulmonology or oncology units in France. A Scientific Committee controlled inclusion exhaustivity and quality in each center. **Results:** 82 centers collected 8,999 patients in 2020. One-month mortality was 8.8% (734/8,999) and 9.7% (680/7,051) in 2010. Three-month mortality was 21.5% (1,771/8,999) in 2020 and 23.3% (1,624/7,051) in 2010 (Table 1). According to sex, mortality at one and three months mainly affected men (525/734; 71.5% and 1,259/1,771; 71.1% respectively). Mean age at diagnosis was older than in the cohort population (67.8 y-o); respectively 69.9 and 69.8 at one and three months. At diagnosis, patients were in poorer ECOG mainly grade 2 (211/697; 30.3%) or 3 (194/697; 27.8%) for one-month and mainly grade 1 (549/1,703; 32.2%) or 2 (547/1,703; 32.1%) for three-month mortality. Among ECOG grade 3 and 4, 34.8% (194/557) and 57.1% (93/163) were dead at one month respectively; 63.5% (350/551) and 83.4% (136/163) respectively were dead at three months. According to histology, adenocarcinoma was the most common (308/734; 42%), followed by small cell lung cancer (170/734; 23.2%) at one-month; adenocarcinoma was also the most common (822/1,771; 46.4%), followed by squamous cell carcinoma (380/1771; 21.5%) at three-month mortality. Most patients who died early were stage 4, metastatic/disseminated (respectively 625/702; 89% and 1,488/1,715; 86.8% for one- and three-month mortality). In patients with COVID19 infection (n=547), mortality at one and three months was respectively 36.4% (174/478) and 46.7% (228/488). **Conclusions:** Early mortality has not improved over the two decades and remains high. KBP-2020-CPHG study was performed during COVID-19 pandemic, which may have generated delays in diagnosis and limited access to care and hospital. Early mortality at one and three months concerned mostly men, mean age nearly 70 y-o, adenocarcinoma, metastatic disease and frail patients. This confirms the potential value of LC screening program in a targeted population. Research Sponsor: AstraZeneca, BMS, MSD, Janssen, Bayer, Boehringer Ingelhei, Lilly, Takeda, Sanofi, Roche, Chugai, Pfizer.

Vital status.

		KBP-2010 N = 7,051	KBP-2020 N = 8,999
At one month	Alive	6,301 (90.3%)	7,611 (91.2%)
	Dead	680 (9.7%)	734 (8.8%)
	Missing data	70 (1.0%)	654 (7.3%)
At three months	Alive	5,357 (76.6%)	6,477 (78.5%)
	Dead	1,624 (23.3%)	1,771 (21.5%)
	Missing data	70 (1.0%)	751 (8.3%)

1 month: 30 days; 3 months: 91 days; missing data: update 02/07/2022.

10558 **Poster Session**

Racial and ethnic disparities in lifestyle changes during the COVID-19 pandemic: Exploring the socioeconomic and psychosocial mechanisms. *First Author: Ming Wen, University of Utah, Salt Lake City*

Background: Obesity, physical inactivity, excessive alcohol consumption, and poor diet are all modifiable risk factors for cancer. These unhealthy behaviors are disproportionally concentrated in racial and ethnic minorities and these disparities may have been exacerbated during the COVID-19 pandemic. This study examined racial and ethnic disparities in weight gain and other undesirable lifestyle changes during the COVID-19 pandemic and explored mechanisms underlying these lifestyle disparities. **Methods:** We used data from the 2020 *Health, Ethnicity and Pandemic Study*, a national survey representative of US households conducted in October 2020. Racial and ethnic minorities were oversampled. Participants were asked to report lifestyle behaviors before and during the COVID-19 pandemic. We examined two outcomes in this study: weight gain and experiencing any undesirable lifestyle changes (i.e., reduced exercise time, increased alcohol drinking, or increased fast-food meal consumption). The primary exposure was race-ethnicity (non-Hispanic (NH) white, NH black, Hispanic, NH Asian, NH other race). Four sets of mediators were examined: socioeconomic status (education, household income, and undesirable job changes), family and friend social relationship change, perceived and experienced racism, and psychological distress. Weighted multivariable logistic regression models were performed. Mediation effects were examined with variance decomposition method. **Results:** A total of 2,709 participants were included in our sample. Compared with white respondents, black (OR = 1.71; $p < 0.001$) and Hispanic respondents (OR = 2.17; $p < 0.001$) were more likely to experience weight gain, controlling for age and sex. Among the hypothesized mediators, undesirable job changes during the pandemic, experiencing worse family relationship, and higher levels of psychological distress were all linked to higher odds of weight gain, but none of these variables played a salient role in mediating the black-white and Hispanic-white disparities in weight gain during the pandemic. As to the odds of experiencing undesirable lifestyle changes, black (OR = 1.76; $p < 0.001$), Hispanic (OR = 2.12; $p < 0.001$), and Asian respondents (OR = 1.42; $p < 0.01$) all exhibited disadvantages relative to white respondent. These disadvantages were largely attributable to perceived racism toward one's own group and psychological distress for all three minority groups. **Conclusions:** Racial and ethnic minorities were more likely to experience unhealthy lifestyle changes relative to white individuals during the pandemic in the United States, which can be partly attributable to higher levels of perceived racism and psychological distress. The long-term effects of racial/ethnic disparities of lifestyle change during the pandemic on cancer prevention warrant further research. Research Sponsor: The Health, Ethnicity, and Pandemic (HEAP) study was funded by the Center for Reducing Health Disparities at University of Nebraska Medical Center, The Chinese Economists Society, and Calvin J. Li Memorial Foundation.

10559 **Poster Session**

Impact of the COVID-19 pandemic on stage at diagnosis of patients with breast cancer: An analysis of 11,752 patients from Oncoclínicas. *First Author: Cristiano Augusto Andrade de Resende, Grupo Oncoclinicas, São Paulo, Brazil*

Background: As a reaction to the COVID-19 pandemic, a nation-wide lockdown was enforced in Brazil in March 2020, cancer care was impacted, and cancer screening reduced. Therefore, an increase in cancer diagnoses at more advanced stages was expected. In this study, we extracted data from our nationwide real-world database to evaluate the impact of the COVID-19 pandemic on the stage at diagnosis of breast cancer (BC) cases. **Methods:** We explored curated electronic medical record data of female patients, over 18 years of age, diagnosed with BC and with established disease stage based on the AJCC 8th edition, who started treatment or follow-up in the Oncoclínicas (OC) between Jan 1, 2018, and Dec 31, 2021. The primary objective was to compare stage distribution at first visit during COVID-19 pandemic (2020-2021) with a historical control cohort from a period prior to the pandemic (2018-2019). We investigated stage distribution according to age at diagnosis and tumor ER/HER2 subtype in univariate models. Associations were considered significant if they had a minimum significance ($P < 0.1$ in Chi-square test). The historical numbers of patients with BC at OC make it possible to identify differences in the prevalence of stages in the order of 5% comparing pre and post pandemic periods with a statistical power greater than 80%. **Results:** We collected data for 11,752 patients with initial diagnosis of BC, with 6,492 patients belonging to the pandemic (2020-2021) and 5,260 patients to the pre-pandemic period (2018-2019). For both ER+/ HER2- and HER2+ tumors, there was a lower percentage of patients with early-stage (defined as stage I-II) in the years 2020-2021 vs 2018-2019 and a considerable increase in advanced-stage disease (defined as stage IV). For triple negative BC (TNBC), there was a significant higher percentage of patients with advanced-stage disease in the pandemic vs pre-pandemic period (table 1). Age over 50 years was associated with a greater risk of advanced stage at diagnosis after the onset of the pandemic, with an absolute increase of 7% (P two-sided <0.01) **Conclusions:** We observed a substantial increase in cases of advanced-stage BC in OC institutions as a result of delays in BC diagnoses due to the COVID-19 pandemic. The impact appeared greater in older adults, potentially because of stricter confinement in this group. Research Sponsor: None.

SUBTYPE	STAGE	2018-2019	2020-2021	P two-sided
ER+ HER2-	Stage I-II	69%	67%	0.061
	Stage III	18%	18%	-
	Stage IV	13%	15%	0.026
HER2+	Stage I-II	68%	58%	<0.01
	Stage III	20%	22%	-
	Stage IV	13%	20%	<0.01
TNBC	Stage I-II	65%	62%	0.324
	Stage III	24%	21%	-
	Stage IV	11%	17%	<0.01

10560 **Poster Session**

Trends in oncological disease burden: A comparative study between higher and lower-middle-income countries. *First Author: Georgina Hanbury, Imperial College Healthcare NHS Trust, London, United Kingdom*

Background: Cancer is a major cause of morbidity and mortality worldwide. Ten million cancer-related deaths were recorded in 2020, a rise of 66% over the preceding two decades. Malignancies of the breast, lung, prostate and colon account for over 40% of new cancer diagnoses worldwide. This study observes trends in oncological disease burden among higher (HIC's) and lower-middle-income countries (LMIC's) between 2000 and 2019. **Methods:** Mortality to incidence ratios (MIR) were calculated using the Global Burden of Disease database by extracting age standardized mortality and incidence rates per 100 000 for breast, lung, prostate and colorectal cancer for the years 2000-2019. The European Union (EU) 15+ countries were taken to represent HIC's. 8 of the LMIC's in the World Bank group were included as their data quality rating was 3/5 or higher. This cohort comprised Egypt, Sri Lanka, Ukraine, El Salvador, Republic of Moldova, Philippines, Kyrgyzstan and Nicaragua. Breast, lung, colorectal and prostate cancer were included as the tumor types with highest global incidence. Median MIR (with interquartile range) were computed for each LMIC and EU15+ groups for males and females for each of the four tumor types. **Results:** Between 2000 and 2019 median MIR for the LMIC group was higher than for EU15+ group for all four cancer types in males and females. Wilcoxon rank sum of the 2019 data showed a statistically significant difference (p <0.001) in MIR between HIC's and LMIC's (table 1). For breast, prostate and colorectal cancer the difference in median MIR between LMIC group and EU15+ decreased over the observation period, for lung cancer the difference increased. **Conclusions:** Globally there are wide geographical variations in MIR. Cancer outcomes appear consistently worse in LMIC's compared to HIC's. Availability of cancer screening, access to treatment and risk-factor prevalence may contribute to the above trends. Identifying these regional disparities provides an opportunity to target resource allocation to regions that would derive the greatest benefit. Research Sponsor: None.

Median MIR values in 2019 in each tumor type.

	Breast	Lung		Colorectal		Prostate
	Female	Male	Female	Male	Female	Male
HIC's	0.224	0.879	0.800	0.418	0.404	0.286
LMIC's	0.423	1.022	1.012	0.655	0.669	0.513
Difference	0.290	0.143	0.212	0.238	0.265	0.227

10561 **Poster Session**

Patient-reported disruptions to cancer care in the U.S. during the COVID-19 pandemic: A national cross-sectional study. *First Author: Sharanya Iyer, Case Western Reserve University, Cleveland Heights, OH*

Background: Disruptions to cancer care during the COVID-19 pandemic due to disease mitigation efforts, supply-chain issues, and fear of COVID-19 have all been reported, but study of their extent has been limited. The purpose of this study is to evaluate the extent and associations with patient reported disruptions to cancer treatment and other care during the COVID-19 pandemic using nationally representative data. **Methods:** This cross-sectional study uses data from the 2020 National Health Interview Survey (NHIS), an annual, cross-sectional survey of US adults. Adults who reported requiring current cancer treatment or other care related to their cancer in the second half of 2020 were included. Rates of patients with self-reported changes, delays, or cancellations to cancer treatment or other cancer-related care due to the COVID-19 pandemic were calculated and their associations with demographic and other variables were analyzed. All data were adjusted using sample weights and specific variables to account for stratification and other survey characteristics using the Stata svy command. Chi-square testing was used to compare proportions across variable groups. Univariable logistic regression analysis was utilized to assess variable associations with change, delay, or cancellations to cancer care during the COVID-19 pandemic. Multivariable logistic regression analysis was used to create a model adjusted for select demographic variables. **Results:** A sample-weighted 2,867,326 adults (n=574) reported requiring cancer treatment and/or other cancer care since the start of the COVID-19 pandemic. Of these, 189 (32.1%) reported any change, delay, or cancellation due to the pandemic. On univariable analysis, patients who were younger, female, had comorbidities, and uninsured were significantly more likely to report care disruptions. On adjusted analysis, younger age and female sex remained significant predictors. In a sample-weighted subset of 1,600,587 patients (n=331), 291 (87.9%) reported virtual appointment use. There was no association with disruptions across breast, prostate, lung, and colorectal cancer groups. **Conclusions:** Approximately 1/3 of patients experienced disruptions to cancer care during the COVID-19 pandemic. Patients with younger age or female sex were more likely to have disruptions in care, which may reflect risk stratification strategies in the early stages of the pandemic. The longitudinal impact of these disruptions on outcomes merits further study. Research Sponsor: None.

Significant variables from multivariable logistic regression analysis for any change to cancer treatment or other care during the COVID-19 pandemic adjusted for race, urban-rural classification, household income, insurance status, and number of comorbidities.

Characteristic		OR (95% CI)	P-Value
Age	< 65	Ref	
	65-74	0.75 (0.43, 1.30)	0.30
	75	0.43 (0.22, 0.83)	0.013*
Sex	M	Ref	
	F	1.63 (1.02, 2.60)	0.039*

10562 **Poster Session**

Factors associated with the occurrence of myocardial infarction in patients treated for melanoma. *First Author: Xianying Pan, Department of Pharmacoepidemiology, Bristol Myers Squibb, Princeton, NJ*

Background: Treatments for melanoma increasingly involve the use of immune checkpoint inhibitors (ICIs), which are associated with cardiac toxicities. Our study aims to examine predictors of myocardial infarction (MI) in melanoma patients receiving treatment. **Methods**: The United Healthcare (Optum Clinformatics) Closed Claims + Lab Results Database (01/2007 – 03/2021) was used to examine factors potentially associated with the occurrence of hospitalized MI in melanoma patients. Adult patients were included if they: 1) had ≥12 months of continuous insurance coverage at baseline; 2) had ≥2 outpatient or ≥1 inpatient claims with an International Classification of Diseases (ICD) code indicative of melanoma; 3) received ≥1 type of cancer treatment (surgery, chemotherapy, radiotherapy, ICI, or targeted therapy); 4) had a claim with a melanoma ICD code within 5 days before the first cancer treatment; and 5) had no history of MI at baseline. Baseline was defined as the year prior to the first date of treatment; MI occurrence was identified from inpatient claims. We conducted a time-to-event (MI) analysis using a multivariate Cox proportional hazards regression model, with backward selection and death as a competing risk. **Results**: A total of 42,101 patients (58.8% male; median age of 68 yrs at baseline) were included in the study. Of these, 954 patients (2.3%) experienced a MI, and 5,578 (13.2%) died before having a MI. Compared with patients who underwent surgery only, those who received multiple treatments with an ICI were more likely to have a MI (hazard ratio [HR] = 1.25, 95% confidence interval [CI]: 1.01-1.55; Table). Men had a higher risk than women (HR = 1.47, 95% CI: 1.27-1.71), as did older people (compared with 65-74-yr-olds, HRs were 0.24, 0.49, 1.41, and 2.06 for <55-, 55-64-, 75-84-, and ≥85-yr-olds, respectively; all $P<.05$). Being Asian and having certain comorbidities at baseline were also associated with a higher MI risk (Table). **Conclusions**: In this retrospective cohort analysis of patients with melanoma, we observed an increased risk of MI among patients who received multiple treatments with ICIs, compared with surgery only. More research is needed to further elucidate predictors of MI events related to cancer treatment. Research Sponsor: Bristol Myers Squibb.

Patient characteristics and treatment types associated with hospitalized MI.

Factor of interest	Comparator	Hazard ratio*	95% Confidence interval*	*P*-value
Treatment (vs surgery only)	Multiple treatments with ICIs	1.25	1.01-1.55	.04
	Multiple treatments without ICIs	1.08	0.94-1.24	.29
Race (vs White)	Asian	1.89	1.14-3.14	.01
	Black	1.08	0.79-1.47	.62
	Hispanic	0.94	0.63-1.38	.73
Comorbidity (yes vs no)	Diabetes	1.48	1.28-1.72	<.001
	Hypertension	1.32	1.14-1.53	<.001
	Chronic kidney disease	1.55	1.29-1.85	<.001
	Peripheral vascular disease	1.37	1.06-1.78	.02

*The Cox model included all covariates in the table, as well as age, sex, and geographic region (death was the competing risk).

10563 **Poster Session**

The increasing incidence of alcohol-related cancers in young adults in the United States: Who is most at risk? *First Author: Atharva Rohatgi, Palo Alto Medical Foundation Research Institute, Palo Alto, CA*

Background: To evaluate incidences and trends of alcohol-associated cancers in United States adults over the last 18 years. **Methods:** Data was extracted from the United States Cancer Statistics database from 2001 to 2018. SEER*Stat Joinpoint Regression program 4.8.1 was used to calculate incidences and trends. Average annual percentage change (AAPC) was used to describe trends. Based on the ICD-O-3 criteria, liver, colon, oral cavity, esophagus, and pharynx cancers were classified as alcohol-related cancers. **Results:** Over the last 18 years, the incidence of alcohol-associated cancers decreased overall in males and females by 0.9% every year ($p < 0.001$). Alcohol-associated cancers increased significantly in younger patients under the age of 39 years old ($p < 0.001$). Based on race, Black men and women had the highest incidence at 135.17/100,000 followed by 132.50 in White individuals, 105.84 in Hispanic individuals, and 104.28 in Asian individuals. By region, the incidence was found to be the highest in the Midwest at 132.89/100,000 and lowest in the West at 120.33. Based on cancer types, the most common alcohol related cancer was colorectal cancer with an incidence at 36.49/100,000 in 2018, followed by oral cavity cancers at 11.69, liver cancer at 6.76, esophagus cancer at 4.51, and larynx cancer at 2.92. Of all these types of cancers, liver cancer had the highest annual increase at 2.43% ($p < 0.001$). Using a projection model, we found that liver cancer is estimated to surpass colorectal cancer by the year 2035. On intersectionality analysis, White men and women in the Northeast between the ages of 75-79 had the highest incidence of alcohol-associated cancers at 584.10/100,000 in 2018. However, over the last 18 years, White men and women in the South between the ages of 20-24 had the highest annual increase at 4.08% ($p < 0.001$). **Conclusions:** Over the last 18 years, alcohol-related cancers increased in the younger patients, particularly those residing in the South. Liver cancer is increasing at the highest rate. Research Sponsor: None.

10564 **Poster Session**

A five-year epidemiological profile of patients with cancer managed by a Haitian cancer program. *First Author: Joseph Bernard, Innovating Health International, Port-Au-Prince, Haiti*

Background: Cancer epidemiology in Haiti is poorly understood. The national cancer registry is not functional, and data reported by GLOBOCAN are estimations that do not totally reflect the reality of cancers in Haiti. The aim of this study was to present the five-year epidemiology of malignancies managed by one of the main cancer programs in Haiti. **Methods:** A retrospective study was conducted on patients aged 15 years old and above with pathological and/or clinical diagnosis of cancer managed from January 2016 to December 2020 at Innovating Health International (IHI), a cancer center located in Port-au-Prince, Haiti. The chart review collected variables such as age, gender, date of admission and cancer type in order to present this epidemiological profile of cancers. **Results:** Overall, 3060 patients with cancer were managed during the study period. 84.4% of the patients were female and 15.6% male. The mean and median ages of the study population were respectively 52.5 [range: 15 –92] and 53.0 years. Adolescents and young adults (15-39 years old) represented 18.9 % of this cohort and geriatric cases (≥ 65 years old) were 21.0%. Breast cancer was the most common type (n = 1391, 45.5%%), followed by gynecological cancers (n = 746, 24.4%) with cervical cancer representing 77.5 % of these cases (n = 578); gastrointestinal cancers (n = 252, 8.2%) dominated by colorectal (n = 92, 36.5%) and gastric cancer (n = 58, 23.0%); head and neck cancers (n = 129, 4.2%); hematological malignancies (n = 128, 4.2%) with lymphomas representing 60.9% of the cases (n = 78); sarcomas (n = 114, 3.7%), urological cancers (n = 73, 2.4%) with prostate cancer representing 56.1% of the cases; skin cancers including melanoma (n = 60, 1.9%); lung cancer (n = 24, 0.8%); thyroid cancer (n = 13, 0.4%) and central nervous system (CNS) cancers (n = 6, 0.2%). 4.1% of the patients (n = 124) had a cancer of unknown primary (CUP). Breast (53.5%), cervical (28.9%) and gastrointestinal (5.0%) cancers were the most common types among women, while gastrointestinal (25.8%), hematological (16.1%), head and neck (14.7%) and urological (12.6%) cancers were the most diagnosed among men. **Conclusions:** Cancer mainly affects Haiti's young, active and female population. Breast and cervical cancers were the most prevalent in this retrospective cohort regardless of the age group. The under-representation of prostate and other urological malignancies, lung cancer, acute leukemias and CNS cancers was likely due to underdiagnosis, misdiagnosis, under-referral or early mortality. An active cancer registry is needed to better evaluate the real cancer burden in Haiti. Research Sponsor: None.

10565 **Poster Session**

An update on the overall epidemiology, clinical characteristics, and outcomes from the COVID-19 and Cancer Consortium (CCC19). *First Author: Dimpy P Shah, University of Texas Health Science Center San Antonio, San Antonio, TX*

Background: Despite mitigation and treatment strategies, COVID-19 continues to negatively impact patients (pts) with cancer. Identifying factors that remain consistently associated with morbidity and mortality is critical for risk identification and care delivery. **Methods:** Using CCC19 registry data through 12/31/2021 we report clinical outcomes (30-day case fatality rate [CFR], mechanical ventilation use (MV), intensive care unit admission (ICU), and hospitalization) in adult pts with cancer and laboratory confirmed SARS-CoV-2, stratified by patient, cancer, and treatment-related factors. **Results:** In this cohort of 11,417 pts (with 4% reported vaccination prior to COVID-19), 55% required hospitalization, 15% ICU, 9% MV, and 12% died. Overall outcome rates remained similar for 2020 and 2021 (Table). Hydroxychloroquine was utilized in 11% and other anti-COVID-19 drugs (remdesivir, tocilizumab, convalescent plasma, and/or steroids) in 30%. Higher CFRs were observed in older age, males, Black race, smoking (14%), comorbidities (pulmonary [17%], diabetes mellitus [16%], cardiovascular [19%], renal [21%]), ECOG performance status 2+ (31%), co-infection (25%), especially fungal (35%), and initial presentation with severe COVID-19 (48%). Pts with hematologic malignancy, active/progressing cancer status, or receiving systemic anti-cancer therapy within 1-3 months prior to COVID-19 also had worse CFRs. CFRs were similar across anti-cancer modalities. Other outcomes (ICU, MV, hospitalization) followed similar distributions by pt characteristics. **Conclusions:** Unfavorable outcome rates continue to remain high over 2 years, despite fewer case reports in 2021 owing to multiple factors (e.g., pandemic dynamics, respondent fatigue, overwhelmed healthcare systems). Pts with specific socio-demographics, performance status, comorbidities, type and status of cancer, immunosuppressive therapies, and COVID-19 severity at presentation experienced worse COVID-19 severity; and these factors should be further examined through multivariable modeling. Understanding epidemiological features, patient and cancer-related factors, and impact of anti-COVID-19 interventions can help inform risk stratification and interpretation of results from clinical trials. Research Sponsor: American Cancer Society and Hope Foundation for Cancer Research, U.S. National Institutes of Health.

	Hospitalization (55%)	ICU (15%)	MV (9%)	30-d CFR (12%)
Age (median, IQR)	69 (58-78)	69 (59-76)	68 (59-74)	73 (64-81)
Male sex	3195 (60%)	990 (19%)	623 (12%)	753 (14%)
Black race	1273 (64%)	375 (19%)	257 (13%)	288 (14%)
Solid tumor	4046 (51%)	1025 (13%)	616 (8%)	853 (11%)
Hematologic malignancy	1302 (63%)	449 (22%)	282 (14%)	278 (13%)
Active and progressing cancer status	1113 (70%)	307 (20%)	183 (12%)	418 (26%)
Systemic anti-cancer therapy within 1-3 months prior to COVID-19 diagnosis	560 (58%)	157 (16%)	99 (10%)	168 (17%)
Y2020	5083 (55%)	1422 (16%)	902 (10%)	1130 (12%)
Y2021	1129 (55%)	294 (15%)	139 (7%)	223 (11%)

10566 **Poster Session**

Development of key performance indicator (KPI) for real-time monitoring of treatment of early breast cancer to control socioeconomic and indigenous systemic bias. *First Author: Euan Thomas Walpole, Cancer Alliance Queensland, Woolloongabba, Australia*

Background: Disparity in outcome for different cancer groups exist particularly for indigenous and poor socioeconomic background. Patient and treatment data on a population basis was examined. **Methods:** Population data for the state of Queensland, Australia (population 5.2M) collected by Cancer Alliance Queensland as part of government cancer registry roles plus additional linked data available as a gazetted quality assurance committee was examined to find patients with early breast cancer treated with surgery, chemotherapy (CT) and radiotherapy (RT) between 2005-2015. **Results:** A cohort of 8279 women received treatment with 89.3% having the surgery, CT, RT sequence. Time to completement threshold was 37 weeks using empirical cutpoint estimation in Stata. Overall survival (OS) was 94% at 5 years if < 37 weeks versus 88.5% if not. ($p < 0.001$). Multivariate analysis of socioeconomic and clinical characteristics for survival was also significant for increasing age, indigenous status, socioeconomic disadvantage, multiple co morbidities and advancing disease stage. Private hospital cases had a better outcome. When delay is analysed between treatments, only time to CT from surgery > 9.5 weeks was significant for OS (HR 1.42 $p < 0.001$). Indigenous status, socioeconomic status and private facility no longer were significant. Multiple co morbidities and advanced stage were still significantly associated with poorer survival. Funnel plots of treatment centre show the association with public hospital treatment and lower volume centre with delay. **Conclusions:** This data is retrospective so can inform local service evaluation but implementation of a KPI for delay to adjuvant chemotherapy of 9.5 weeks can provide real time targets for patient care. We measured delay in the recent 5 years (before survival available) which shows consistent delays and it will included as a reporting function of MDT management software. Whilst the increased use of neoadjuvant CT will assist, systematic reporting of this KPI has potential to remove treatment biases for indigenous and lower socioeconomic patients. More recent data will be available for presentation. Research Sponsor: Queensland State Government, Australia.

10567 **Poster Session**

Exploring "the healthy immigrant effect" among elderly Asian patients with cancer: A nationwide population-based assessment. *First Author: Manan Nayak, Dana-Farber Cancer Institute, Boston, MA*

Background: Asian Americans are the fastest-growing immigrant group in the U.S. As the oldest immigrant group on average, they are at heightened risk for cancer and other diseases. This study explored whether the risk is mitigated by the healthy immigrant effect (HIE), an epidemiological phenomenon that has been well documented among Latino immigrants. Evidence of a healthy immigrant effect among Asians as a whole or in specific Asian subgroups is limited, and almost none focus on the elderly with a cancer diagnosis. This original research study examines the evidence for an HIE in a large ethnically diverse sample of elderly persons with a cancer diagnosis. **Methods:** This is a retrospective observational study utilizing data collected across 14 regions of the U.S. SEER-Medicare Health Outcomes Survey (SEER-MHOS), a linked dataset sponsored by the NCI and the Center for Medicare & Medicaid Services. Logistic regression analyses were conducted to examine HIE among Asians in the aggregate and subgroups of Asians for smoking and body mass index (BMI), using survey language and ethnic concentration as proxies for nativity. **Results:** Asians, in the aggregate, had comparable social backgrounds and had better health behaviors (i.e., lower smoking and BMI) than non-Hispanic Whites. When Asians were disaggregated, Hawaiians and Japanese had higher smoking and obesity rates than Chinese. A protective effect was observed among Asians in the aggregate living in an ethnic enclave with lower smoking prevalence and lower BMI. Chinese respondents opting to complete surveys in their native language or living in ethnic enclaves were less likely to be overweight, but no significant associations were found in relation to their smoking. **Conclusions:** Support for a healthy immigrant effect was largely consistent for Asians in the aggregate with respect to both language and ethnic concentration, but support was mixed among subgroups of Chinese patients. The presence of the HIE suggests that the health status and needs of recent Asian immigrants seeking oncologic care may be different than Asians who have been in the U.S. longer. These findings suggest a need for community-based efforts to encourage preservation of a healthier living style observed among first-generation immigrants. Research Sponsor: None.

10568 **Poster Session**

Analysis of genomic alterations in pan-cancer from a large real-world Chinese population. *First Author: Zhouhuan Dong, Department of Pathology, The Chinese PLA General Hospital, Beijing, China*

Background: Effective targeted therapy sorely depends on comprehensive and precise genomic profiling. Besides, single nucleotide variations (SNVs) and InDels, gene fusions, as drivers and therapeutic targets of great importance, are not yet well characterized in Chinese patients. **Methods:** Formalin-fixed, paraffin-embedded (FFPE) tumor tissues from 1,384 pan-cancer patients were collected and sequenced using next-generation sequencing (NGS) targeting 40 cancer genes including SNV, fusion and assessing copy number variation (CNV) (AmoyDx HANDLE Classic Panel). qPCR and fluorescence in situ hybridization (FISH) were further applied to verify NGS detected fusion genes. **Results:** 1,384 patients were recruited including 890 lung cancers, 272 colorectal cancers, 174 gastric cancers, and 48 endometrial cancers. The prevalence of fusion genes (5.49%), including *ALK*-fusion (2.67%), *ROS1*-fusion (0.94%), *RET*-fusion (0.72%), *NRG1*-fusion (0.29%), and *NTRK*-fusion (0.07%), was nearly double the frequency of previously reported data from East Asians. Prevalence of fusion genes varied in different types of cancers. For instance, *ALK* (3.7%), *ROS1* (1.5%), *RET* (1.0%) and *NRG1* (0.2%) fusions were largely found in patients with non-small cell lung cancer (NSCLC), and were rarely detected in other cancer types. Further analysis of genomic alterations in fusion-positive patients revealed that, *TP53* (21%) was the most frequently co-occurred mutated gene with *ALK* fusion, while *RET* fusions and *ROS1* fusions were rarely accompanied by other mutated genes. In addition, two patients with *RBPMS-NRG1* fusion were accompanied by *BRAF* and *RB1* mutations, whereas no co-occurred mutation was found in patients with other partners of *NRG1*. Patients with inconsistent results of RNA-based NGS and FISH validation fusions are still being followed for treatment and survival, updated data will be available at the time of the presentation. **Conclusions:** Genomic alterations in real-world Chinese populations have specific characteristics, especially fusion genes. Further characterization of these variants is essential for clinics to guide appropriate targeted therapies. Research Sponsor: None.

10569 **Poster Session**

Prevalence of incidental pathogenic germline variants detected in cfDNA in patients with oncogene-driven non-small cell lung cancer. *First Author: Laura Mezquita, Hospital Clinic-DIBAPS, Barcelona, Spain*

Background: Preliminary data has highlighted inherited predisposition to lung cancer (LC) related to certain pathogenic germline variant (PGV) in cancer predisposing genes, including patients (pts) with tumors harboring somatic driver oncogene alterations (alt); however, the frequency of PGV in LC is unknown. Liquid biopsy assays may be able to identify incidental PGV (iPGV) in pts with solid tumors at scale. Here, we report the prevalence of iPGV in genes predisposing to cancer in pts with advanced non-small cell LC (aNSCLC) relative to driver alt status. **Methods:** Genomic results were retrospectively queried from 31126 pts with aNSCLC who had Guardant360 testing as part of routine clinical care from 10/2020-12/2021. iPGVs were defined as being non-synonymous, non-VUS alt in selected genes known to increase lifetime cancer risk (Table) with variant allele frequency (VAF) >30% and pathogenicity defined by a proprietary bioinformatics pipeline. Clinical factors such as age, gender, histology, and diagnosis status (new/progressing) were extracted from test requisition forms. The driver group included guideline-recommended and emerging somatic mutations (m) in *EGFR/KRAS/BRAF/MET/HER2*, fusions (f) in *ALK/ROS1/RET/NTRK1-3* and amplifications (a) in *HER2/MET*. **Results:** Out of 31126, 720 (2.3%) of pts had predicted iPGV, of whom 54% were female, with a median age of 64 (22-100); most pts were newly diagnosed (66%). Among them, 92% of pts had iPGVs identified in the homologous recombination and repair (HRR) pathway, 3% in mismatch repair (MMR) pathway and 5% *EGFR* iPGVs. A total of 335 (47%) pts with iPGVs had somatic driver alt (Table**):** 20% of pts with iPGV had *KRAS*m (n=144/720; 67 *G12C*), 12% *EGFR*m (n=87; 28 *ex19del*, 35 *ex21(L858R)*), 2.5% *BRAF*m (n=18), 2.5% *MET*m ex14 skip (n=18), 0.1% *HER2*m (n=1), 0.8% *ALK*f (n=6), 0.1% *ROS1*f (n=1), 0.1% *RET*f (n=1), 0.1% *HER2*a (n=1), and 0.4% *MET*a (n=3). *ATM* iPGVs were enriched in pts with driver alt. (45% driver vs 27% non-driver, p<0.0001) while *BRCA1* iPGVs were more frequently observed in pts without driver alt. (17% vs 8%, p<0.0001). Distribution of other iPGVs was similar across driver/non-driver groups. **Conclusions:** In this large cohort, 2.3% of pts with aNSCLC were iPGV-carriers; 47% of pts had oncogene-driven tumors, particularly with *KRAS, EGFR, BRAF* and *MET* alt. iPGV and lung carcinogenesis need further evaluation to define the role of genetic predisposition in LC risk and to determine the highest risk individuals to explore screening and therapeutic strategies, such as in pts with other solid tumors. Research Sponsor: None.

Landscape/prevalence of driver alt in pts with aNSCLC and iPGV.

	Total	*KRAS*m (N=144)	*EGFR*m (N=87)	*Fusions* (N=9)	*MET*ex14 (N=18)	*MET*a (N=3)	*BRAF*m (N=18)	*ERBB2* m/a (N=3)
ATM	126	84	28	2 *ALK* 1 *ROS1*	1		7	3
BRCA1	25	13	7	1 *ALK*	1		3	
BRCA2	76	23	31	1 *RET*	14	2	5	
CHEK2	6	4			1		1	
FANCA	14	8	2	2 *ALK*	1	1		
PALB2	6	4		1 *ALK*			1	
RAD51D	1	1						
MLH1 MSH6 PMS2	1						1	
	5	5						
	1	1						
EGFR	18		18					

10571 **Poster Session**

Sociodemographic trends in COVID-19 mortality in patients with cancer: A nationwide analysis. *First Author: Sree Jambunathan, University of Toledo College of Medicine and Life Sciences, Toledo, OH*

Background: The COVID-19 pandemic has caused unprecedented disruptions in medical care, especially in those with cancer. Prior studies have demonstrated a higher risk of mortality in patients with cancer and COVID-19, which could be due to factors such as immunosuppression and higher burden of co-morbidities. However, there are limited studies examining the impact of sociodemographic factors including race, gender, rurality, and region on mortality in patients with COVID-19 and cancer. This study aims to characterize and analyze sociodemographic trends in COVID-19 mortality in patients with cancer. **Methods:** Data on patients with COVID-19 and cancer listed on death certificates from the Multiple Cause of Death Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER) database were extracted. Age-adjusted mortality rates (AAMR) were calculated and compared across sociodemographic groups. **Results:** A total of 18,467 total deaths occurred in patients with COVID-19 and cancer listed on multiple cause of death certificates in 2020, with overall AAMR of 4.4 (95% CI: 4.4-4.5). AAMR for patients with COVID-19 and cancer was significantly higher in Non-Hispanic (NH) Black or African American (7, 95% CI: 6.8-7.3), NH American Indian or Alaska Native (6.4, 95% CI: 5.4-7.3), and Hispanic or Latino (5.4, 95% CI: 5.2-5.7) groups than NH White (4, 95% CI: 3.9-4.1) and NH Asian or Pacific Islander (2.5, 95% CI: 2.3-2.7). AAMR was also higher in males (5.9, 95% CI: 5.8-6.1) and those in Northeast (5.6, 95% CI: 5.4-5.8) and Midwest (5.3, 95% CI: 5.2-5.5) census regions. Those in medium metro counties had significantly lower AAMR (3.8, 95% CI: 3.7-4) compared to other locations based on the NCHS Urban-Rural Classification Scheme for Counties. **Conclusions:** AAMR in patients with any cancer and COVID-19 was significantly higher in NH Black or African American, NH American Indian or Alaskan, and Hispanic or Latino race/ethnicity groups, as well as in males. Regional and rurality disparities also exist. This study highlights persistent disparities in COVID-19 and cancer outcomes and identifies groups at higher risk of mortality. Future studies examining sociodemographic trends in COVID-19 mortality in patients with specific cancers are necessary. Research Sponsor: None.

AAMR of patients with COVID-19 and cancer listed on multiple cause of death certificate.

Race	Age Adjusted Mortality Rate (95% CI)
NH Asian or Pacific Islander	2.5 (2.3-2.7)
NH White	4 (3.9-4.1)
Hispanic or Latino	5.4 (5.2-5.7)
NH American Indian or Alaska Native	6.4 (5.4-7.3)
NH Black or African American	7 (6.8-7.3)

10572 **Poster Session**

Characteristics of patients with neuroendocrine tumors in the United States: A study of 392,412 patients. *First Author: Ravali A. Reddy, Department of Obstetrics and Gynecology, Stanford University School of Medicine, Palo Alto, CA*

Background: To evaluate the characteristics and trends amongst patients with neuroendocrine tumors in the United States. **Methods:** Data was obtained from the United States Cancer Statistics database from 2001 to 2018. SEER*Stat 8.3.9.2 and Joinpoint regression program 4.9.0.0 were used to calculate characteristics and trends of these cancers per 100,000. The age-adjusted incidences were determined based on the standard population in the United States from 2000. **Results:** Of 392,412 patients with neuroendocrine tumors, 53.1% were identified in women and 46.9% in men. White, Black, Hispanic, Asian/Pacific Islander and unknown race comprised 73.6%, 14.1%, 7.8%, 2.7%, and 1.7% of the patient population respectively. The majority (64.7%) of tumors originated from the digestive system, followed by 24.5% from the respiratory system. In 2018, the incidence of all neuroendocrine tumors was higher in older (70-79 years) patients as compared to younger (< 50 years) ones at 30.17 vs. 2.79/100,000, in women as compared to men at 8.36 vs. 7.77/100,000, and in White patients as compared to Black, Hispanic, and Asian/Pacific Islander patients (10.82, 10.15, 5.08 and 4.80/100,000 respectively). Amongst different types of neuroendocrine tumors, those originating from the digestive system had the highest incidence at 6.72/100,000 in the year 2018 with colon tumors being the most common subtype. On trend analysis, the groups with the highest annual percent increase included: younger (< 50 years) patients increasing at 5.06%, Hispanic patients rising at 6.44%, and appendiceal tumors increasing at 12.89% per year. On intersection analysis, Black patients between the ages of 70-79 had the highest incidence at 33.39/100,000, while younger (< 50 years) Hispanic patients had the largest increase at 6.22% per year. **Conclusions:** The incidence of neuroendocrine tumors has increased over our study period. The highest incidence was found in older Non-Hispanic Black patients, with younger Hispanic patients having the highest annual percent increase. Further studies are warranted to better characterize the reasons for these trends and disparities amongst minority patients affected by these tumors. Research Sponsor: None.

10573 **Poster Session**

Genetic ancestry correlates of the cancer somatic mutational landscape from tumor profiling data of 50,000 patients with cancer. *First Author: Francisco De La Vega, Tempus Labs, Inc., Chicago, IL*

Background: The incidence and mortality of cancer vary widely across race and ethnicity. This is attributed to an interplay of socioeconomic factors, environmental exposures, and genetic background. Cancer genomic studies have underrepresented minorities and individuals of non-European descent, thus limiting a comprehensive understanding of disparities in the diagnosis, prognosis, and treatment of cancer among these populations. Furthermore, the social constructs of race and ethnicity are far from precise categories to understand the biological underpinnings of such differences. In this study, we use a large real-world data (RWD) patient cohort to examine associations of genetic ancestry with somatic alterations in known cancer driver genes. **Methods:** We inferred genetic ancestry from approximately 50,000 de-identified records from cancer patients of diverse histology who underwent tumor genomic profiling with the Tempus xT next-generation sequencing (NGS) assay. Our cohort includes patients with brain, breast, colorectal, hematopoietic, lung, and ovarian cancers, among others. We used 654 ancestry informative markers selected to overlap the target regions of the 648-gene Tempus xT NGS assay to infer global ancestry proportions at the continental level: Africa (AFR), America (AMR), Europe (EUR), East Asia (EAS), and South Asia (SAS). We imputed race/ethnicity categories using ancestry proportions on subjects lacking such metadata. **Results:** Most patients were of European descent (72%), however, continental genetic ancestry inference identified 4.7 and 3.8-fold more patients with substantial (> 50%) AFR and AMR ancestry, correspondingly, compared with TCGA. We observed higher percentages of AFR ancestry patients with prostate, breast, and colorectal cancer (1.8-3.1%) and AMR ancestry patients with colorectal cancer (2.4%) compared to the overall cohort-level distributions ($p < 0.05$). Using imputation, we identified 60% and 121% more patients as likely Black and Hispanic/Latino, respectively. We observed several associations between genetic ancestry with tumor mutation burden (TMB), e.g., a reduction in median TMB in Asian breast cancer patients (Asian TMB mean = 2.3 m/Mb vs 4.4 for Black, 3.3 for Hispanic, and 4.2 for White; $p < 0.0001$), in paired tumor/normal sequencing data. Furthermore, we found associations between ancestry and nonsynonymous somatic mutations in cancer genes, e.g. in *CTNNB1* with EAS ancestry (OR = 1.18) and *EGFR* with EAS (OR = 1.24), AMR (OR = 1.30), and EUR (OR = 0.89) ancestries (all $p < 0.001$) in lung cancer patients. **Conclusions:** Our results support the use of genetic ancestry inference on RWD to improve upon the social constructs of race and ethnicity, allowing us to better understand the impact of shared germline genetic or exposure backgrounds into cancer mutational processes that influence incidence, progression, and outcomes. Research Sponsor: Tamous Labs, Inc.

10574 **Poster Session**

Human papillomavirus-associated cancers in Taiwan over the last 18 years: The potential impact of screening, vaccination, and smoking. *First Author: Cheng-I Liao, Department of Obstetrics and Gynecology, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan*

Background: Human papillomavirus (HPV) is a causative agent of many human cancers. This study aims to determine the incidences and trends of HPV-associated cancers in the Republic of China. **Methods:** HPV-associated cancers included: cervical carcinoma, oropharyngeal squamous cell carcinoma (SCC), anal/rectal, vulvo-vaginal, and penile SCC. Deidentified data were obtained from Taiwan's National Health Insurance Research Database from 2001 to 2018. SEER*Prep 2.6.0, SEER*Stat 8.3.9.2, and Joinpoint regression program 4.9.0.0 were used to calculate incidences and trends of HPV-associated cancers per 100,000. The age-adjusted incidence was adjusted by the WHO 2000 standard population. **Results:** A total of 55,248 HPV-associated cancers were identified. Of these, 34,730 (62.9%) were identified in women and 20,518 (37.1%) in men. The majority (60.0%) were cervical followed by oropharyngeal at 37.6%, and other HPV-associated cancers comprised 2.4%. Over the 18-year study, the overall age-adjusted incidence of HPV-associated cancers decreased from 13.41 to 8.92 (per/100,000) with an annual decrease of 2.02% ($P< 0.001$). More specifically, cervical cancer incidence decreased from 20.42 to 7.70 per 100,000 with an annual decrease of 5.6% ($P< 0.001$). Other cancers, such as vaginal and vulvar, decreased 2.34% ($P< 0.001$) and 1.82% ($P< 0.001$), respectively. With respect to oropharyngeal SCC, the incidence was over 12-fold higher in men compared to women (8.37 vs. 0.67/100,000) with both sexes increasing at 3.61% ($P< 0.001$) and 3.59% ($P< 0.001$) annually. Anal/rectal SCC increased at 3.55% ($P< 0.001$) whereas penile cancer decreased at 2.52% ($P< 0.001$). Of note, all HPV-associated cancers among non-smokers decreased 2.02% ($P< 0.001$) annually, whereas they increased in smokers at 1.00% ($P> 0.05$) per year. This increase in incidence was particularly evident in oropharyngeal SCC and cervical carcinomas. **Conclusions:** Women comprised over 60% of HPV related cancers, with cervical cancer being most common followed by oropharyngeal cancer. Over the last 18 years, cervical and vulvovaginal cancers decreased, but the rates of oropharyngeal cancers in men was 12-fold higher than women and continues to increase. Public awareness and education of these trends are needed toward prevention and screening. Research Sponsor: None.

10575 **Poster Session**

The disproportionate burden of cancer associated with social behaviors in young women in the United States. *First Author: Caitlin Ruth Johnson, California Pacific Medical Center Research Institute, San Francisco, CA*

Background: To evaluate the incidences and trends of social determinant risk factor-associated cancers in the United States from 2001 to 2018. **Methods:** Social determinant risk factor-associated cancers, as classified by the CDC, were included: obesity, alcohol, tobacco, physical inactivity, and human papillomavirus (HPV). Data was obtained from the United States Cancer Statistics program from 2001-2018. SEER*Stat 8.3.9.2 and Joinpoint regression program 4.9.0.0 were used to calculate incidences and trends of cancers per 100,000. The age-adjusted incidence (AAI) was adjusted by the US 2000 standard population. **Results:** Over the 17-year study period, a total of 28,175,859 cancers were identified. Of these, 51.4% developed in men and 48.6% in women. Over 65.8% were risk factor-associated cancers and 34.2% were unrelated to these factors. Of note, over 60.1% of risk factor-related cancers developed in women compared to 39.9% in men. Although the incidence of risk factor associated cancers did not significantly change at 413.2/100,000 in women, this incidence decreased by 1.15% annually ($P< 0.001$). The age-specific incidences decreased in older (> 50 years) men and women. Of the younger (20-45 years) group, these risk factor-associated cancers increased from 91.5 to 97.3/100,000 with an annual increase of 0.4% ($P< 0.001$) in younger women; there was no change for younger men on trend analyses over the study period. **Conclusions:** Over 65% of cancers in the US were associated with social determinants of health. There is a disproportionate burden of risk factor-associated cancers in women with increasing rates in younger age groups. Further research is needed to better understand the rationale of these important trends. Research Sponsor: None.

10576 **Poster Session**

Impact of germline mutations on surgical decision-making in women with DCIS. *First Author: Rachel E Ellsworth, Murtha Cancer Center Research Program, Uniformed Services University of the Health Sciences,, Windber, PA*

Background: Ductal carcinoma in situ (DCIS) is both a malignant, yet pre-invasive disease of the breast. While the majority of DCIS have a low risk of recurrence, a subset of women with germline pathogenic variants (PV) in cancer predisposition genes are at increased risk for breast cancer recurrence. Uptake of genetic testing and treatment with risk-reducing surgeries (RRS), including bilateral mastectomy (BM), in women with DCIS, has not been well-studied. The aim of this study was to determine the prevalence of PVs in women with DCIS and the impact on surgical decision making. **Methods:** All women diagnosed with unilateral DCIS 2001-2020 enrolled in the Clinical Breast Care Project were identified. Demographic, genetic test results and surgical procedures were extracted from the database. Test-eligibility was assigned using National Comprehensive Cancer Network (NCCN) criteria. Panel genetic testing was performed in the research setting using DNA from 465 women. Statistical analyses were performed using Fisher's exact tests and Chi-square analyses with $p < 0.05$ defining significance. **Results:** The overall PV frequency in women with DCIS was 8.1%. Within the test-eligible group, 35.1% pursued clinical genetic testing, including 13.2% who pursued testing only after a second cancer event. Of the 39 women with PV, 20 (51.3%) were detected only in the research setting, with 11 (28.2%) of these women not eligible for genetic testing based on NCCN criteria. In the 419 women who did not undergo BM at diagnosis, recurrence was significantly higher ($p = 0.001$) in women with PV (33.3%) compared to those without PV (11.6%). **Conclusions:** Genetic testing is suboptimal in women with a primary diagnosis of DCIS. Twenty percent of women with PV, who may have benefited from BM, did not undergo genetic testing at the time of diagnosis and recurred. These data suggest that genetic testing at the time of diagnosis should be standard for all women with DCIS. Research Sponsor: Uniformed Services University of the Health Sciences.

10577 **Poster Session**

Mainstreamed genetic testing of patients with breast cancer: Experience from a single surgeon's practice in a large U.S. academic center. *First Author: Kanhua Yin, Massachusetts General Hospital, Boston, MA*

Background: Germline genetic testing for cancer susceptibility has proven to be a powerful tool in cancer risk assessment, screening, and prevention but a huge gap exists between the number of germline genetic testing candidates and the number of patients actually tested. This study aimed to evaluate the impact of mainstreamed genetic testing (MGT) model into a single academic breast surgeon's practice on genetic test completion. **Methods:** Before September 2019 (pre-MGT phase), a breast surgery practice at Massachusetts General Hospital followed a traditional model of pre-test consultation with a genetic professional. After September 2019 (post-MGT phase), the same practice offered eligible patients with immediate testing in the same visit. We evaluated the appointment completion in the pre-MGT phase and compared the test uptake and test results between the two phases. **Results:** We identified 204 patients in the pre-MGT phase and 202 patients in the post-MGT phase. In the pre-MGT phase, the median waiting time for genetic counseling was seven days for patients with a newly diagnosed cancer, 211 days for patients with a remote personal history of cancer, and 224 days for non-cancer patients who had a family history. A total of 105 (51.5%) patients completed a genetic counseling appointment (Table). In the post-MGT phase, a significantly higher proportion of patients (88.1%, $p < 0.001$) consented to genetic testing, while the proportion of patients who tested positive was lower (pathogenic variant: 11.9% vs. 20.0%; variant of uncertain significance: 19.9% vs. 28.0%; $p = 0.047$). **Conclusions:** Implementing MGT can reduce the number of clinical visits, significantly shorten patients' wait time to test initiation, and increase the completion of genetic testing. Research Sponsor: None.

Patient referral and uptake of genetic counseling appointment in the pre-MGT phase.

Variable	Total (n = 204)	Newly diagnosed cancer (n = 23)	Personal hx of cancer (n = 8)	No cancer (n = 173)
Seen by GC, n (%)				
Had referral in EMR	73 (35.8)	13 (56.5)	3 (37.5)	57 (33.0)
Did not have referral in EMR	32 (15.7)	10 (43.5)	1 (12.5)	21 (12.1)
Total number of patients seen by GC	105 (51.5)	23 (100)	4 (50.0)	78 (45.1)
Not Seen by GC, n (%)				
Did not have referral in EMR	51 (25.0)	0	1 (12.5)	50 (28.9)
Had referral in EMR but couldn't contact patient to schedule appointment	29 (14.2)	0	3 (37.5)	26 (15.0)
Had referral in EMR but patient did not show or cancelled appointment	14 (6.9)	0	0	14 (8.1)
Had referral in EMR but patient declined appointment	3 (1.5)	0	0	3 (1.7)
Had referral in EMR but not seen	1 (0.5)	0	0	1 (0.6)
Had referral in EMR and has GC appointment scheduled	1 (0.5)	0	0	1 (0.6)

Notes: Values reported as n (%). Abbreviations: EMR, electronic medical record; GC, genetic counselor; Hx, history; MGT, mainstreamed genetic testing.

10578 **Poster Session**

Prevalence and spectrum analysis of germline *DICER1* variants of solid tumors: Decoding the mysterious signals of the genome. *First Author: Pibao Li, Shandong Provincial Third Hospital, Jinan, China*

Background: DICER1 syndrome is a rare genetic condition predisposing to multiple cancer types and causes by germline *DICER1* variants. Deleterious mutations identified were mostly located in the RNase III domain. VUSs found in other domains may be also crucial in the inheritance of high-risk neoplasms although there is insufficient evidence. Our study aimed at describing the spectrum of *DICER1* variants detected in solid tumors to improve the identification of potentially high-risk *DICER1* variants. **Methods:** Germline mutations including SNV, small INDEL in 448 patients with solid tumors were analyzed by next-generation sequencing (NGS) panel. The pathogenicity of germline mutations was categorized based on American College of Medical Genetics and Genomics (ACMG) guidelines. **Results:** In total, 3 (0.67%) patients (diagnosed as bladder cancer, schwannoma, and medulloblastoma) were identified harboring truncating pathogenic (P)/likely pathogenic (LP) germline mutations in the RNase III domain. The remaining 445 (99.33%) patients carried 447 uncertain significance (VUS) mutations, of which 416 (92%) were missense mutations lied in different domains and 52% (234/450) located in exon 20-23. The median age was 60 years old with an age range from 0 to 90. The higher frequency cancer type contained lung cancer (35.9%), glioma (10.0%), liver cancer (8.4%). In addition, the two highest frequencies of *DICER1* missense variants were c.3334A > G (p. Asn1112Asp, n = 58) and c.3227G > A (p. Ser1076Asn, n = 53), which lied in unknown functional domain of the protein and had been reported in Clinvar. Their clinical significance and pathogenicity remain further study. **Conclusions:** In our study, *DICER1* germline mutations mostly occurred in exon 20-23 and 92% were missense mutations. We reported 3 new cases of tumors associated with *DICER1* syndrome, which expanded the DICER1-related tumor spectrum. Understanding the clinical significance of germline *DICER1* VUS could improve the identification of potentially high-risk variants. Reclassifying these variants could make them useful for predictive, prognostic, and preventive purposes in clinical practice. Research Sponsor: None.

10579 **Poster Session**

Co-occurrence of germline pathogenic variants in Chinese patients with solid tumors. *First Author: Yan Zhang, The Sixth Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China*

Background: Germline mutations play an important role in cancer risk and susceptibility. With the growing implementation of next generation sequence of multiple gene panel, an increasing number of cases that carry two or more inherited cancer-predisposing alleles in the same individual are being described. However, understanding the impact of these combined mutations on the patient's phenotype can be particularly challenging. To further understand these combined mutations, we analyze the genetic susceptibility mutations of Chinese solid tumor patients to explore the characteristics of multiple germline variants. **Methods:** Genetic mutations were reviewed in cancer patients who underwent hybridization capture based next-generation sequencing (NGS). The pathogenicity of germline mutations was categorized based on American College of Medical Genetics and Genomics (ACMG) guidelines, and only pathogenic and likely pathogenic variants were included in this study. **Results:** Germline variants were identified in 1267 individuals, including 1244 patients harbored one germline mutations and 23 patients carried ≥2 germline mutations, and there was no age difference in the two groups (57 vs 55, $p = 0.62$). In the ≥2 germline mutations group, genes most frequently involved were *BRCA1/2* (12/47, 25.5%), *CHEK2* (4/47, 5,1%), *TP53*(4/47, 5,1%) and *MUTYH* (4/47, 5,1%). Most of these variants affected DNA damage repair pathways [57% homologous recombination repair (HR), 15% mismatch repair (MMR)]. Besides, double variants in HR and HR pathway were found in 8 patients, HR and MMR pathway were found in 5 patients. Surprisingly, the 50-year-old man with colorectal cancer with three pathogenic variants of the [*FH -BRCA2- FANCD2*] genes showed a high aggregation of tumors associated with leiomyomatosis and renal cell cancer and HBOC. **Conclusions:** We found over 56.5% patients with multiple pathogenic variants in DNA damage repair pathways, which may have important implications for the treatment strategy for these patients. Next-generation sequencing technologies now provide the opportunity to perform simultaneous parallel testing of large numbers of inherited cancer genes, which could guide the clinician as to what the effect of each combination of mutations might be. Research Sponsor: None.

10580 **Poster Session**

Implementation of universal, pan-cancer germline genetic testing in patients with cancer in Jordan. *First Author: Hikmat Abdel-Razeq, King Hussein Cancer Center, Amman, Jordan*

Background: Detection of pathogenic germline variants (PGVs) has a significant and growing impact on the management of patients with many types of cancer. Most research to date evaluated individuals of European background, which can result in skewed genetic testing criteria and variant interpretation. Additional data are needed from diverse populations. This study aimed to investigate a universal germline testing strategy and the pattern and frequency of PGVs among all newly diagnosed cancer patients at a single center in Jordan. **Methods:** In this prospective, observational study, consecutive patients newly diagnosed with cancer were classified as meeting or not meeting National Comprehensive Cancer Network (NCCN) germline genetic testing criteria. All patients underwent an 84-gene panel test, independent of age, stage or family history. Demographics and clinical history were collected and analyzed from information provided by the clinicians on the test requisition form. Descriptive statistics were employed, and statistical significance was determined by two-tailed Fisher's exact test and unpaired t test. **Results:** In total, 1377 cancer patients of Arabic background were enrolled, of which 831 (60.3%) met NCCN criteria (Table). PGVs were identified in 210 (15.3%). Excluding the 29 patients who were carriers for autosomal recessive conditions, 192 PGVs were identified in 181 (13.1%) patients. PGVs were most commonly identified in *APC* (p.I1307K variant, 55, 28.6%), *BRCA2* (35, 18.2%), *BRCA1* (21, 10.9%), and *TP53* (12, 6.3%). While patients who met NCCN testing criteria were more likely to have a PGV (p<0.0001), 44 (24.30%) patients with PGVs did not meet criteria. Among those with PGVs, 177 (97.8%) were potentially eligible for increased screening per NCCN/expert opinion guidelines, 69 (38.1%) targeted therapies, and 89 (49.2%) clinical trials; this included 41 (22.7%), 6 (3.3%), and 14 (7.7%) patients, respectively, that did not meet NCCN testing criteria. 1445 variants of uncertain significance (VUS) were identified in 833 (57.7%) patients, but no difference in VUS rate was observed between those meeting and not meeting criteria (p=0.7354). **Conclusions:** Overall PGV rate among cancer patients from one center in Jordan was similar to that reported in the literature. While the VUS rate was high, similar rates were observed in those meeting and not meeting criteria. Testing restricted to guidelines could have missed approximately a quarter of patients with PGVs, >95% of whom might qualify for increased screening, targeted therapies, and/or clinical trials. Research Sponsor: Invitae.

	In criteria (n=831)	Out of criteria (n=546)	Total (N=1377)
Mean age at genetic testing ± SD (years)	49.2 ± 12.4	59.2 ± 11.3	53.1 ± 12.9
Female	683	326	1009
Male	148	220	368
Cancer type:	546	223	769
Breast	105	87	192
Colorectal	58	15	73
Prostate	64	3	67
Ovarian	3	57	60
Lung	14	22	36
Uterine/endometrial	41	139	180
Other			

10581 **Poster Session**

Constitutional MLH1 promotor hypermethylation: Clinical characteristics and testing frequency of a poorly recognized mechanism for Lynch-associated malignancies. *First Author: Rakesh Biswas, Inova Schar Cancer Institute, FAIRFAX, VA*

Background: MSI-H colorectal cancer is most often a result of deleterious mutations in mismatch repair genes, but can also occur through repressed gene transcription due to hypermethylation of the MLH1 promoter, often associated with BRAF V600E mutations. However, there is a subset of patients who have a "constitutional epimutation", resulting in hypermethylation of MLH1 throughout normal tissue. We observed a young patient develop a second primary Lynch associated malignancy (see Table 1) who was found to have a constitutional epimutation in MLH1 that prompted us to review the frequency with which the test was ordered and the positivity rate, as well as outline the clinical history in the positive cases. **Methods:** We reviewed all of the testing ordered for MLH1 hypermethylation of peripheral blood (MLHPB) at the Mayo Clinic Laboratory between 09/01/2020 and 09/01/2021. To the best of our knowledge, this is the only clinically available testing lab in the United States. We reviewed positive casesfor characteristics including the number of malignancies, age of diagnosis, and family history. **Results:** 33 MLHPB total tests were ordered in the United States at the Mayo Clinic laboratories between 09/01/2020 and 09/01/2021. Three of the tests were positive, including the single test ordered by our institution, and one of the two additional positive tests was available for detailed review. Our institution's positive test case was a 41 year old women who developed T4N2M0 colorectal cancer 5 years after being treated for endometrial cancer. She had endometrial cancer with absence of MLH1 and PMS2 staining and had a negative germline cancer risk panel at age 36. Five years later, she developed a T4N2 colorectal cancer after which repeat germline testing with RNA sequencing was negative and she was found to have constitutional MLH1 promoter hypermethylation. We were able to obtain clinical information about two of the three individuals with positive tests (See Table). **Conclusions:** Recognition of constitutional MLH1 hypermethylation may allow for earlier recognition of Lynch related malignancies in affected patients and families. Testing appears infrequent and this condition often goes unrecognized. Specific consensus guidelines may improve recognition and cancer screening in this population. Research Sponsor: None.

	Patient 1	Patient 2
Age at cancer diagnosis	36	27
Types of cancer(s)	Endometrial cancer, Colon adenocarcinoma (cecal)	Colon adenocarcinoma (cecal)
Family History of Lynch Associated Cancer	None	None

10582 **Poster Session**

Pathogenic *TP53* variant allele frequency across different somatic tissues in two patients with mosaic Li-Fraumeni. *First Author: Tin-Yun Tang, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The integration of germline genetic testing, frequently from blood, into routine oncological care has increased the frequency at which pathogenic *TP53* mutations are found in a variant allele frequency (VAF) range suggestive of either mosaic Li-Fraumeni Syndrome or clonal hematopoiesis of indeterminate potential (CHIP). Mosaic LFS is a rare and poorly described phenomenon wherein a pathogenic *TP53* mutation is dispersed in low levels through multiple somatic tissues after stochastically developing during early embryogenesis. In comparison, CHIP is restricted to the bone marrow niche. Germline mosaicism in Li-Fraumeni Syndrome (LFS) is inferred when genomic DNA from a second source recapitulates the exact same *TP53* mutation. Given the challenges with sample acquisition, mosaicism has not been previously described in depth in the medical literature. **Methods:** Two pediatric patients with LFS-associated cancers (glioblastoma, osteosarcoma & ALL respectively) underwent clinical genetics evaluation and were found to have pathogenic *TP53* mutations. Initial genetic testing was performed in a CLIA/CAP environment through a send out test or internally. A broad array of somatic tissues was collected at autopsy with subsequent DNA isolation and amplicon sequencing in triplicate to determine the mean VAF of the pathogenic *TP53* allele. **Results:** For both patients, the initial germline test suggesting mosaic LFS had a VAF between 20-30%. Confirmatory intent fibroblast culture in Patient 1 was reported as negative by an external clinical lab and Patient 2's VAF was much lower. The VAFs for the rest of the somatic tissues as well as in their corresponding cancers are reported below (Table) as means and standard error of the triplicate. Despite the negative fibroblast culture, Patient 1 did demonstrate mutant *TP53* in other tissues, confirming mosaicism. **Conclusions:** The proportion of pathogenic alleles is highly heterogeneous amongst different somatic tissues in mosaic LFS patients. Although CHIP exclusion through germline testing of cultured skin fibroblasts is common, our patients' skin samples were amongst the tissues with the lowest VAFs. Mosaicism should be highly suspected when tumor sequencing demonstrates an identical mutation to the putative germline mosaic one even with equivocal fibroblast culture results. Research Sponsor: Clinical Translational Science Collaborative of Cleveland, UL1TR002548.

Mean VAF percentage in tissue samples with standard error.

DNA Source	Patient 1 *TP53* c.901_902dupCC	Patient 2 *TP53* c.635_636delTT
Blood or Bone Marrow	20-30%[1]	25.70%[2]
Fibroblast Culture	Undetected[1]	8.91 ± 0.24%
Skin	1.62 ± 0.07%	1.66 ± 0.09%
Glioblastoma or ALL	98.82 ± 0.66%	56.59 ± 0.21%
Cerebellum	0.10 ± 0.00%	2.32 ± 0.06%
Colon	7.67 ± 0.64%	8.57 ± 0.35%
Liver	4.90 ± 0.36%	17.62 ± 0.18%
Lung	9.00 ± 0.65%	13.49 ± 0.38%
Muscle	2.91 ± 0.23%	2.18 ± 0.08%
Pancreas	1.10 ± 0.24%	15.93 ± 0.59%

[1]External clinical sequencing reports can only report a VAF range.
[2]In-house CLIA/CAP sequencing.

10583 **Poster Session**

Trends in and determinants of germline *BRCA1/2* testing in patients with breast and ovarian cancer. *First Author: Kelsey S. Lau-Min, Division of Hematology/Oncology, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA*

Background: Germline *BRCA1/2* testing (GT) is instrumental in identifying patients with breast and ovarian cancer who may be eligible for biomarker-driven poly ADP ribose polymerase inhibitor (PARPi) therapy. Little is known about recent trends and determinants of GT since PARPi were approved for these patients. **Methods:** We performed a retrospective cohort study of patients with breast and ovarian cancer who were eligible for GT (diagnosed with breast cancer under age 45, triple negative breast cancer under age 60, male breast cancer or ovarian cancer) between 1/2011 and 3/2020 in the nationwide Flatiron Health EHR-derived deidentified database. Duration of follow-up was at least one year for each patient. Spline regressions estimated the annual prevalence of GT within one year of diagnosis. Multivariable log binomial regressions estimated adjusted relative risks (RR) of GT by patient and tumor characteristics. Multiple imputation with chained equations was conducted for missing data. **Results:** Among 2,982 eligible patients with breast cancer, 1,682 (56%) underwent GT within one year of diagnosis with a median time of 42 days. GT increased from 37% in 2011 to 68% in 2020, with a significantly higher RR after PARPi were approved for breast cancer in 1/2018 (RR 1.35, 95% CI 1.20-1.51). In multivariable analyses, there were no appreciable differences by sex, race or ethnicity, but there was a negative linear relationship between GT and age (RR 0.93, 95% CI 0.90-0.96 for every 5 years). After adjusting for age, the 87 breast cancer patients with Medicare were also less likely to undergo GT despite being eligible (RR 0.67, 95% CI 0.48-0.95 vs commercial insurance). Among 5,563 eligible patients with ovarian cancer, 1,968 (35%) underwent GT within one year of diagnosis with a median time of 101 days. GT increased from 23% in 2011 to 53% in 2020, with a significantly higher RR after PARPi were approved for ovarian cancer in 12/2014 (RR 2.25, 95% CI 2.01-2.52). Although insurance status was not a significant determinant of GT in patients with ovarian cancer, older age (RR 0.95, 95% CI 0.93-0.97 for every 5 years) and Black race (RR 0.80, 95% CI 0.66-0.98 vs white race) were associated with a lower likelihood of GT in multivariable analyses. All results remained similar in pre-planned sensitivity analyses restricted to the post-PARPi approval period, limiting to patients who remained alive one year after diagnosis and using the non-imputed dataset. **Conclusions:** GT remains underutilized in patients with breast and ovarian cancer. Although GT has increased since PARPi were approved for this population, significant disparities by age, race and insurance status persist but differ by tumor type. This study is limited by potential misclassification due to missing GT performed outside the Flatiron Health network. Multifaceted patient-, clinician- and system-level strategies are needed to ensure that all eligible patients receive GT. Research Sponsor: None.

10584 **Poster Session**

Retrospective analysis of non-BRCA gene pathogenicity variation in Chinese patients with ovarian cancer. *First Author: Li yuan Guo, Harbin Medical University Cancer Hospital, Harbin, China*

Background: Ovarian cancer (OC) is the most lethal gynecologic cancer. Pathogenic (harmful) variants (PV) in *BRCA1* and *BRCA2* are the strongest hereditary risk factors for the development of ovarian cancer. To date, there is little information regarding the frequency of non-*BRCA* gene PV in Chinese women with OC that undergo genetic cancer risk assessment. In this study we analyzed wild-type *BRCA1/2* OC patients (pts) registered in our database. **Methods:** Peripheral blood of 766 women, diagnosed with ovarian cancer, were taken from the recruited cases with the consent of performing germline genetic testing. Germline mutations including SNV, small INDEL were analyzed by next-generation sequencing (NGS). The pathogenicity of germline mutations was categorized based on American College of Medical Genetics and Genomics (ACMG) guidelines. **Results:** Of 766 OC pts, 460 pts (60%) underwent *BRCA1/2* testing only, while 306 pts (40%) consented in multigene panel testing (MGPT). *BRCA1/2* detection rate was 16.8% (129/766), while the detection rate for non-*BRCA* genes was 7.5% (23/306). There was a significant statistical difference in average age that the non-*BRCA* gene pathogenicity variation group was higher than the *BRCA* gene pathogenicity variation group (62 vs. 57, p=0.018). Wild-type B*RCA1/2* OC pathogenic variants (PV), were diagnosed in *BLM* (n=4, 17.4%), *ERCC5* (n=2, 8.7%), *MUTYH* (n=2, 8.7%), *RAD51C* (n=2, 8.7%), *RAD51D* (n=2, 8.7%), *ATM* (n=1, 4.4%), *BRIP1* (n=1, 4.4%), *CDH1* (n=1, 4.4%), *CHEK2* (n=1, 4.4%), *ERCC4* (n=1, 4.4%), *LZTR1* (n=1, 4.4%), *MSH3* (n=1, 4.4%), *PALB2* (n=1, 4.4%), *PMS2* (n=1, 4.4%), *RAD50* (n=1, 4.4%) and *SLX4* (n=1, 4.4%) genes. Of all the 23 non-*BRAC* gene pathogenicity variations, 57% (13/23) lay in the Homologous Recombination Repair (HRR) pathways. Moreover, a 48-year-old woman with ovarian cancer with two pathogenic variants of the [*BRCA2- MUTYH*] genes was detected in the retrospective cohort study. **Conclusions:** *BLM*, *ERCC5*, *MUTYH, RAD51C* and *RAD51D* genes are the main contributors to hereditary wild-type *BRCA1/2* OC in our cohort. The average age of non-*BRCA* gene pathogenicity variation group was higher than the *BRCA* gene pathogenicity variation group. Therefore, multi-gene PANEL detection is recommended for ovarian cancer patients, especially for older patients. Research Sponsor: None.

10585 **Poster Session**

NGS analysis of germline mutation profile of patients with hepatocellular carcinoma in China. *First Author: Xiaobing Wu, Eastern Hepatobiliary Surgery Hospital, Shanghai, China*

Background: Hepatocellular carcinoma (HCC) is the fourth most common cause of cancer-related death worldwide with very poor prognosis. Many studies have focused on oncogene characteristics, however, the germline landscape of Chinese HCC patients has not been fully clarified. The purpose of this study is to assess the inherited genetic factors regarding germline mutations in Chinese HCC patients. **Methods:** Genetic mutations were reviewed in 1670 Chinese HCC patients who underwent hybridization capture based next-generation sequencing (NGS). The pathogenicity of germline mutations was categorized based on American College of Medical Genetics and Genomics (ACMG) guidelines. **Results:** Of 1670 patients with HCC, 110 (6.7%) patients were identified to carry 111 pathogenic variants(P) or likely pathogenic variants(LP) in 112-cancer predisposition gene panel, and there was no age difference between P/LP group and non-P/LP group (average age: 57 vs 56, p = 0.64). The most frequently germline mutated genes were *BRCA1/2* (11.7%), followed by *ATM*(4.5%), *BLM*(4.5%), *ERCC2*(4.5%), *ERCC3*(4.5%) and *BRIP1*(3.6%), *ERCC4*(3.6%), *FANCD2*(3.6%), *MUTYH*(3.6%), *RAD50*(3.6%). Of all the 111 germline mutations, 47% (n = 52) lay in the Homologous Recombination Repair (HRR) pathways. Both in P/LP group and non-P/LP group, the most frequently somatic mutated genes were *TP53*, *TERT* and *MUC16*. 7/110(6.4%)of patients in P/LP group were high TMB(≥10 mutations/megabase) and 131/1560(8.5%) in non-P/LP group. There was no statistical difference in TMB between P/LP and non-P/LP group. **Conclusions:** Taken together, we have presented the spectrum of pathogenic germline mutations in Chinese HCC patients. P/LP germline variants in cancer predisposition genes were detected in 6.7% of those patients, and predisposition genes associated with HCC risk needs further investigation. Inherited genetics should not be overlooked in HCC as there are important implications for precision treatment, future risk of cancers, and familial cancer risk. Research Sponsor: None.

10586 **Poster Session**

Genetic counselling and testing for breast and ovarian cancer in Asia: A multinational survey of unmet needs. *First Author: Ava Kwong, Surgery Centre & Cancer Genetics Centre, Hong Kong Sanatorium & Hospital, Hong Kong, Hong Kong*

Background: Enabling equitable access to healthcare services among women remains a challenge in Asia. Differences in the presentation and treatment stage contribute to disparities in cancer outcomes. Genetic testing provides accurate risk assessment to help guide personalised preventative and treatment options. However, there is a critical need for research to further our understanding of barriers in leveraging optimal benefits of genetic testing and counselling (GT&C) to address cancer among women. **Methods:** A team of multinational experts was assembled to form the Asian Consensus and Recommendations on Genetic Testing and Counselling (ACROSS) Consortium to assess the challenges in adoption of GT&C for patients with breast and ovarian cancer in Asia. Critical publications were identified, and a pre-meeting questionnaire was developed. The questionnaire was refined to align with the objectives over iterations, and final approval was obtained from the steering committee. Survey responses were gathered from oncologists from ten countries across Asia. The expert committee discussed the survey results to highlight (1) current knowledge, attitude, and practices; (2) unmet needs and gaps; and (3) recommendations for addressing critical obstacles. **Results:** Adoption of GT&C for cancer is low in Asia. Lack of time, resources, and access to genetic counsellors are major difficulties faced. In most cases, the practising oncologists provide pre-test genetic counselling and communicate test results. For breast cancer (BC), most experts preferred germline testing only, with few opting for somatic testing if germline testing was negative. The agreement was lower among the ovarian cancer (OC) experts, with advocates for either germline or somatic testing or both. There was a lack of consensus on clinical criteria for selecting suitable candidates for genetic testing and the use of multiple gene panel germline testing. The need for government-aided subsidies and training programmes was highlighted. **Conclusions:** Recommendations from the expert panel included (1) development of guidelines and criteria to identify candidates suitable for GT&C; (2) training healthcare professionals with required competencies; (3) improving accessibility and affordability; (4) increased patient education and awareness; and (5) adoption of GT&C into the national healthcare system. The consortium agreed that a multifaceted plan of action combining the expertise of clinicians, scientists, and policymakers is required to facilitate uptake of GT&C in Asia. Research Sponsor: AstraZeneca.

Key survey findings.

Topic	BC (%)	OC (%)
Routine GT&C	65	52
Limited access to genetic counsellors	56	63
Practical constraints	88	85
Pre-test counselling (self)	56	56
Germline testing only	76	19
Multigene panel (all major genes)	50	67
Results communicated (self)	65	78
Aware of regional/national training programmes	47	63
Aware of government-aided subsidies	24	15

10587 **Poster Session**

DNA damage repair (DDR) germline mutations (GMs) in pancreatic ductal adenocarcinoma (PDAC): A mono-institutional retrospective study. *First Author: Maria Bensi, Oncologia Medica, Comprehensive Cancer Center, Fondazione Policlinico Universitario Agostino Gemelli–IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy*

Background: GMs in DDR genes, in particular BRCA1/2, are associated with increased risk of cancer, including PDAC. Their identification is crucial for the clinical relevance, the best treatment choice, and the family implications in cancer prevention. However, there are few data regarding the epidemiology and the prognostic role of DDR GMs in PDAC patients (pts). The aim of our study is to determine the prevalence of DDR GMs, their correlation with clinicopathological features and their prognostic role. **Methods:** Unselected PDCA pts, assessed by BRCA1/2 GM analysis or multigenic panel at our Institution, were retrospectively analyzed. We divided the overall population into three groups based on GMs: pts with pathogenic variants (PVs), pts with variants of uncertain significance (VUS) and pts with no alterations. Clinicopathologic characteristics and treatment data were collected. The incidence of DDR GMs variants and their association with overall survival (OS) were evaluated. Univariate and multivariate analyses for OS were performed. **Results:** From September 2019 to August 2021, 200 PDAC pts were tested for DDR GMs: all pts were evaluated for BRCA 1/2; 140 pts were tested for further DDR GMs by a multigenic panel. Twenty-five pts (12.5%) had PVs, 45 (22.5%) pts had VUS and 130 (65%) pts had no GMs. BRCA 1-2 PVs were found in 10 pts (5%). Out of 91 pts with metastatic disease, the rate of PVs BRCA1/2 was 8.8%. Among 140 pts tested with multigenic panel, further PVs included: 7 (5%) ATM, 5 (3.6%) MUTYH, 1 (0.7%) TP53, 1 (0.7%) BARD1, and 1 (0.7%) MSH6. The most frequent VUS were: CHECK2 (5%), APC (3.6%), ATM (3.6%) and BRCA2 (3.6%). Regarding cancer family history, a statistically significant difference was reported between the 3 group (76% in PV pts, 82% in VUS pts and 60% in pts with no GMs; p 0.01). No difference was found concerning age (p 0.69), stage at diagnosis (p 0.31) and platinum-exposure (p 0.27). Out of 189 evaluable pts, median OS was 23 months. A significant difference in OS was observed in the 3 groups (30 months in PVs pts, 14 months in VUS pts and 24 months in pts with no GMs, p 0.0006). No factor, including the presence or the type of GMs, age, stage and family history, was significantly associated with OS at the multivariate analysis. **Conclusions:** In our study, we observed a high incidence of DDR GMs PV (12.5%), beyond BRCA 1/2, regardless of age, stage and family history. Despite retrospective nature of our analysis, small population, and single-institution evaluation, our findings confirm the importance of genetic testing for BRCA1/2 and, where available, of a multigenic test in all PDAC pts, due to the therapeutic implications and cancer risk prevention in patients relatives. The prognostic role of DDR GMs and the impact of VUS remain unclear. Research Sponsor: None.

10588 **Poster Session**

Universal genetic testing versus guideline-directed testing for hereditary cancer syndromes among traditionally underrepresented patients in a community oncology program. *First Author: Jeremy Clifton Jones, Mayo Clinic, Jacksonville, FL*

Background: Detection of pathogenic germline variants (PGVs) has implications for cancer screening, prognostication, treatment selection, clinical trial enrollment and family testing. Published guidelines provide indications for PGV testing, determined by clinical and demographic factors, but these leave a significant number of cases missed by guideline-directed testing (incremental PGV). We have previously shown that 50% of patients with PVGs would not have been detected with guideline-based testing alone. In this project, we aimed to determine the feasibility and generalizability of this approach within a more racially/ethnically diverse cohort from a community cancer practice. **Methods:** We completed a prospective study of proactive germline genetic sequencing among patients with solid tumor malignancies at a community-based oncology practice in downtown Jacksonville, FL between June 2020, and September 2021. The patients were unselected for cancer type, stage, family history, race/ethnicity, and age. PGVs identified using an 84-gene NGS platform were stratified by penetrance. National Comprehensive Cancer Networks (NCCN) guidelines were used to determine incremental PGV rates. **Results:** 221 patients were enrolled, median age 63.0 years, 21.7% male. 56.6% of patients were white (non-Hispanic), 32.6% were black/African American, 5.4% were Hispanic. 39.8% of patients were commercially insured, 52.4% insured by Medicare/Medicaid and 2.7% uninsured. The cohort was comprised predominantly of breast cancer (61.5%), lung cancer (10.4%) and colon cancer (7.2%) patients. A total of 27 PGVs were identified in 23 patients. We found no significant difference in the rate of PGVs based on race/ethnicity. The overall rate of variants of uncertain significance (VUS) was numerically higher in black/African American patients (61.1%) compared with other ancestry (45%). 13 of 23 (56.5%) patients with detected PGVs did not meet NCCN guidelines for germline genetic screening (incremental PGVs). **Conclusions:** This prospective study found that universal multi-gene panel testing among patients from a racially/ethnically diverse cohort from a community cancer practice was associated with an increased detection of heritable variants with treatment implications over the predicted yield of targeted testing based on guidelines. This study is the first to evaluate this approach in an exclusively community-based practice. Clinical trial information: NCT04456140. Research Sponsor: Mayo Clinic Center for Individualized Medicine.

10589 **Poster Session**

Integrated germline and somatic cancer testing provides opportunity to identify cancer risk and resolve variant origins. *First Author: Kingshuk Das, Invitae, San Francisco, CA*

Background: Germline and somatic genetic testing are established tools for the management of cancer patients. Somatic testing is primarily used to inform therapy and germline testing is used to diagnose hereditary cancer predisposition syndromes. While somatic testing can detect germline variants, the interpretation and reporting algorithms are optimized to predict therapeutic efficacy. As a result, germline variants may be missed or only interpreted in context of their potential to act as a therapeutic target. We retrospectively reviewed a series of patients who received both germline and somatic testing to examine the opportunities for concurrent germline testing to improve somatic reporting. **Methods:** Our study reviewed data from 43 patients with solid cancer diagnoses who were otherwise unselected and underwent testing with a 435-gene somatic genetic test and an 83-gene germline test. The most frequent cancers were pancreatic (18), ovarian (8), and prostate (7). **Results:** Out of the 43 patients, 7 (16%) harbored a pathogenic or likely pathogenic germline variant (PGV) in a cancer susceptibility gene. PGVs were identified in *MLH1, MSH6, CHEK2, PALB2, CDKN2A, NBN,* and *MUTYH*. Notably, 3 of these genes (*CHEK2, PALB2, MUTYH*) were not considered therapeutic targets, and therefore were only included as ancillary findings near the end of the preliminary somatic test reports (generated prior to integration of germline test results). In addition, 40 of 43 (93%) patients had at least one variant detected by somatic testing in at least one of the germline panel genes (mean number variant genes = 4.1, maximum = 10); all of these variants were within the reportable range of the germline assay, and therefore germline test results were able to resolve their germline versus somatic origins. The genes that most frequently had somatic variants identified were *TP53* (79% of patients), *CDKN2A* (37%), *SMAD4* (30%), and *FLCN* (21%). **Conclusions:** Due to the size of commonly ordered somatic gene panels, there is a high probability of detecting variants in hereditary cancer predisposition genes (> 90% of patients in this study) that can provide either therapy or cancer risk information or both. Given that a significant proportion (16% in this study) of cancer patients harbor PGVs (which can further inform treatment, disease surveillance, preventive measures, and risk assessment for family members), it is crucial to resolve the somatic versus germline origin of these variants. Since interpretation and reporting algorithms for somatic testing are optimized for therapy prediction, and variables such as specimen tumor purity, tumor ploidy, and variant allele fraction render estimates of variant origin unreliable for diagnostic purposes, it is important to take advantage of germline testing concurrently in patients receiving somatic testing to glean this critical information. Research Sponsor: None.

10590 **Poster Session**

Germline screening rates and patterns for patients with pancreatic cancer at an academic medical center. *First Author: DeJuana Coleman, University of Virginia Cancer Center, Charlottesville, VA*

Background: Current National Comprehensive Cancer Network guidelines recommend germline genetic testing for all pancreatic cancer patients irrespective of family history. Germline testing provides insight on inherited pathogenic variants that may influence care. Approximately 10% of pancreatic adenocarcinoma (PDAC) patients have pathogenic mutations which may have treatment implications and warrant the introduction of targeted therapy approaches. Patients with germline BRCA1/2 or PALB2 mutations have increased sensitivity to platinum chemotherapy and PARP-inhibitor therapies. Germline testing results may have important implications for patients' family members for earlier targeted screening. A better understanding of the current state of testing is needed to develop systems to improve screening rates. We conducted a retrospective review of clinical practice patterns at an academic cancer center to assess the current uptake. **Methods:** Patients with pancreatic adenocarcinoma seen at the University of Virginia Health System within the 2021 calendar year were identified. Retrospective review of genetic counseling referral and germline genomic screening for individual patients was performed. **Results:** 210 patients with pancreatic adenocarcinoma were identified. 39 (19%) PDAC patients had a referral to genetic counseling placed in the electronic medical record and 44 (21%) completed germline screening. Of the patients referred to genetics, 17/39 patients (44%) met with a genetic counselor which led to germline screening, 3/39 (8%) patients were referred and saw genetics after receiving germline testing results. Among patients who completed germline screening, 27/44 (61%) had testing initially ordered by their oncologist with referral to genetic counseling based on testing results 3/27 (11%). **Conclusions:** Despite guideline recommendations, germline testing rates are low among this PDAC population. Genetic counselors are essential members of a multidisciplinary team and guide patient discussions and decision making with regards to germline testing. Typical practice has involved referral to meet with a genetics counselor prior to testing; however many patients elect not to schedule a visit and consequently do not obtain germline screening. Barriers may include costs associated with genetic counseling/testing, time constraints, and patient understanding of the relevance of testing for their cancer care. We observed that offering germline testing to PDAC patients with referral to genetic counseling based on results and patient preference is a viable practice pattern. Upfront clinician driven germline testing may offer an opportunity to improve access to germline screening. Prospective clinical trials are needed to increase rates of germline testing and genetic counseling for PDAC patients. Research Sponsor: None.

10591 **Poster Session**

Oncologist knowledge of cost of genetic testing. *First Author: Shayna Weiner, University of Michigan, Ann Arbor, MI*

Background: Genetic testing allows patients and their families to identify hereditary cancer syndromes. Financial barriers to genetic testing are a major concern for patients offered genetic risk assessment. The cost of germline genetic testing has decreased substantially over the last several years. It is not clear, however, that oncologists are knowledgeable about the cost of genetic testing. The purpose of this study was to investigate oncologists' knowledge of genetic testing costs. **Methods:** We deployed a survey to all oncologists who are members of the Michigan Oncology Quality Consortium, a physician-led quality improvement collaborative whose members represent 95% of the oncologists in Michigan. The modified Dillman method was used to achieve the maximum response rate. Responses were collected from December 2020 through May 2021. The responses to the question, "If a patient were to ask you how much it would cost for them to have clinical genetic testing for hereditary cancer syndromes, what would you tell them?" were independently coded by three investigators into one of three categories – correct and helpful, correct and not helpful, or incorrect and not helpful. We investigated associations between the number of years in practice and how important was cost as a barrier to genetic risk assessment. **Results:** The response rate to the survey was 61.2% (194/317). Only 25% of respondents provided an answer that was deemed to be both correct and helpful to a patient, for example "approximately $250 if out of pocket." Nearly 40% of respondents gave an answer that was correct but was non-specific and would not help a patient decide about pursuing genetic testing. This category included responses such as deferring to a genetic counselor or that cost varies based on insurance. About 28% gave an incorrect response, such as "several thousand dollars" or responded, "I don't know." No associations were found between cost response category, number of years in practice, or reported responses that financial barriers play a role in referral patterns. **Conclusions:** The majority of oncologists in our statewide sample do not have an accurate understanding of the cost of germline genetic testing. Lack of precise information about the costs of testing may lead patients to believe that genetic testing is either not important or not within reach. Furthermore, providing incorrect information can have a downstream effect and prevent patients and their families from pursuing genetic counseling. Improving oncologists' knowledge about the cost of testing may decrease barriers to uptake of genetic risk assessment. Research Sponsor: U.S. National Institutes of Health, PI funded.

Physician Response	Count (%)
Correct and Helpful	48 (24.7)
Correct and Not Helpful	76 (39.2)
Incorrect and Not Helpful	54 (27.8)
Missing	16 (8.2)
Total	194

10592 **Poster Session**

Relative disclosure of information on hereditary cancer syndromes: A systematic review and meta-analysis. *First Author: Muhammad Danyal Ahsan, Weill Cornell Medicine, New York, NY*

Background: Evidence-based guidelines recommend that patients (probands) diagnosed with a hereditary cancer syndrome share the information with blood relatives as relatives can have 50% risk for harboring the same pathogenic mutation. This information offers the opportunity for relatives to undergo genetic counseling, genetic testing, early detection, and prevention of cancer. Limited literature on this topic suggests underutilization of recommended family member disclosure. We sought to evaluate rates of familial disclosure of hereditary cancer syndrome information in the first meta-analysis on this topic. **Methods:** We conducted a systematic review and meta-analysis in accordance with PRISMA guidelines (PROSPERO no.: CRD42020134276). We searched key electronic databases to identify studies evaluating hereditary cancer cascade relative disclosure. Eligible trials were subjected to meta-analysis. **Results:** Thirty studies met inclusion criteria. This review included 3,779 probands and 12,751 at-risk relatives. Among 12,751 included relatives, 72% (CI 64-79%) received information about the hereditary cancer syndrome identified in their family and 28% (CI 19-37%) underwent genetic testing. On meta-analysis, there was a higher rate of disclosure among female vs male relatives (79% [73% - 84%] vs 67% [57% - 75%]) and a higher rate among first-degree vs. second degree relatives (83% [77% - 88%] vs 58% [45 – 69%]). The data regarding the contribution of race/ethnicity to disclosure were limited and inconsistent, with two studies demonstrating non-White vs. White relatives being less likely to have results disclosure and two studies finding no correlation; however, both studies finding no difference were limited by small sample sizes. Finally, one study found that higher proband annual income was associated with improved familial disclosure. **Conclusions:** Despite a growing understanding of the importance of cascade genetic counseling and testing, probands do not disclosure information on hereditary cancer syndromes to most at-risk relatives. Very few relatives complete genetic testing, representing a critical missed opportunity for precision cancer prevention. Future studies are needed to elucidate barriers to hereditary cancer syndrome disclosure and create innovative strategies to facilitate this essential process. Research Sponsor: None.

10593 **Poster Session**

Determining concordance of LFSPRO *TP53* germline carrier risk predictions to standard genetic counseling practice. *First Author: Elissa B. Dodd-Eaton, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Li-Fraumeni Syndrome (LFS) is a hereditary cancer syndrome associated with a germline mutation in the *TP53* tumor suppressor gene and an increased risk of developing a spectrum of cancers throughout a carrier's lifetime. Early cancer detection in patients with *TP53* mutations can dramatically improve cancer survival rates. However, it can be difficult to identify patients at risk of LFS due to the overlap of the multiple cancer types with other inherited cancer syndromes. Risk prediction modeling has been widely accepted by the clinical community, however, currently there is not an available tool to assist in risk prediction of LFS during genetic counseling sessions. LFSPRO is a statistical model that has previously been validated on large research cohorts in predicting the likelihood of a proband having LFS based off detailed patient and family history information. To improve the clinical utility of LFSPRO, a user-friendly interface is still needed. Additionally, we aim to evaluate concordance between LFSPRO's abilities in predicting the likelihood of a proband having LFS and currently established clinical testing criteria. **Methods:** We developed a Shiny App to create a user-friendly interface for genetic counselors (GCs) to run LFSPRO. Determining concordance of LFSPRO to standard germline testing criteria and the clinical utility of the LFSPRO Shiny App is underway by GCs within the Department of Clinical Cancer Genetics at MD Anderson Cancer Center through prospective data collection and completion of user surveys. Following a standard genetic counseling session, individuals identified as concerning for a potential germline *TP53* mutation are evaluated with LFSPRO to compare performance of the model to established *TP53* testing guidelines. Concordance is then evaluated in prediction of *TP53* mutation carrier status from LFSPRO, current clinical criteria and clinical judgment. Data collection began 12/21/2021 and is currently ongoing. **Results:** Close collaboration with GCs and clinicians on the development of the LFSPRO Shiny App has achieved automated de-identified input data, clear pedigree drawing, important demographic data, interpretable risk results and risk visualizations to be used at the GC's discretion. To date, 29 individual's family data have been run through LFSPRO. Of these, 11 have not currently completed *TP53* testing and concordance cannot be determined. Of the 18 remaining, 14 individuals' LFSPRO results were concordant with current clinical criteria. Further data collection is needed to appropriately analyze concordance. **Conclusions:** The LFSPRO Shiny App aims to provide an additional tool for GCs and clinical providers to assess patient risk for LFS. This ongoing study will help establish the clinical utility of LFSPRO in a single institution's genetic counseling practice with the potential to be applied to other patient care settings in the future. Research Sponsor: Cancer Prevention & Research Institute of Texas.

10594 **Poster Session**

Genetic epidemiology of breast cancer (BC) risk genes from a diverse real-world oncology practice in Brazil. *First Author: Bernardo Garicochea, Grupo Oncoclinicas, São Paulo, Brazil*

Background: As germline testing in BC is becoming more accessible, a large body of evidence from distinct populations is revealing different prevalence of affected genes or recurrent and founder mutations. We evaluated a series of Brazilian BC patients from diverse regions of the country that were studied in a single laboratory facility for likely pathogenic/pathogenic variants (PV) and variants of unknown significance (VUS) in BRCA1/2 and other BC susceptibility genes (ATM, BARD1, CDH1, CHEK2, PALB2, RAD51C, RAD51D and TP53). **Methods:** We used multi-gene NGS panels covering from 35 to 105 genes, including copy number alterations, to perform sequencing in patients with diagnosis of BC from 2016 to 2021. With patient consent, we extracted clinical and pathological data from curated Real-World Database of Oncoclínicas Group to classify tumors according to hormone receptor (HR) and HER2 status and assess family history of cancer. Primary endpoint was prevalence of PV and VUS in BRCA1/2 and other breast cancer risk genes. **Results:** In total, 1,520 patients with BC were included in the analysis, 99% were female, median age at genetic testing was 46 years and 84% had family history of cancer. BC subtype was available in 717 cases (43% HR+/HER2-, 26% HER2+, 31% triple negative). Median age at genetic testing in HR+/HER2- population was 49 years and 44 years in HER2+ and triple-negative cases. Overall, 11.7% (CI95% 10.1-13.4) of the population had at least one PV in any BC risk gene: 50 in BRCA1, 49 in BRCA2, 22 in TP53 (17 had Brazilian founder p.R337H haplotype), 19 in PALB2, 18 in CHEK2, 15 in ATM, 7 in other genes (BARD1, CDH1, RAD51C, RAD51D) and 4 patients had co-existing PV in 2 BC risk genes. BRCA1/2 PVs were found in 7% of BC patients and BRCA1/2 VUS in 3%, being higher in triple-negative cases (11% PVs) than HR+/HER2- (5% PVs) and HER2+ (3%). For other BC risk genes, 5% of the patients had a PV, without differences according to BC subtype, and the prevalence of VUS was 14%. The prevalence of TP53 Brazilian founder mutation in BC was 1.2%. Median age of genetic testing was younger in population with BRCA1 PV (43 years) than BRCA2 PV (47 years) and other genes PV (46 years). **Conclusions:** In this real-world cohort of BC patients enriched for high-risk features such as young age at diagnosis, positive family history and triple-negative disease, the prevalence of BRCA1 and BRCA2 PV was very similar and represented only 56% of all PV detected. Different from other studies, TP53 mutations are the third most common germline alteration in the Brazilian population, with close to 80% of the cases presenting the founder mutation p.R337H. BC with epidemiologic high-risk features should be offered a germline test in Brazilian patients due to the considerable chance of a PV detection. Research Sponsor: None.

10595 **Poster Session**

Patient-reported outcomes among males undergoing prostate cancer germline testing: Interim results from the Prostate Cancer Genetic Risk, Experience, and Support Study (PROGRESS) Registry. *First Author: Veda N. Giri, Departments of Medical Oncology, Cancer Biology, and Urology, Cancer Risk Assessment and Clinical Cancer Genetics Program, Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA*

Background: Indications for prostate cancer (PCA) germline testing (GT) have greatly expanded, necessitating thousands of men to seek genetic evaluation through traditional genetic counseling and alternate delivery approaches. Therefore, there is an important need for patient-reported outcomes among men undergoing genetic testing which has been understudied. PROGRESS (Prostate Cancer Genetic Risk, Experience, and Support Study) was therefore developed to garner men's experience with PCA germline testing. Here we provide an interim update on recruitment and results from registry participants. **Methods:** PROGRESS is a patient-driven registry of clinical, genetic, and patient-experience information among men undergoing PCA genetic testing. Survey covers demographic information, PCA history, mode of genetic counseling, satisfaction, decisional conflict, intention to share genetic results with family and physicians, attitude towards genetic testing, knowledge of cancer genetics, medical literacy, and numeracy. Descriptive statistics summarized results with counts and percentages for categorical variables and mean and standard deviation for continuous variables. All analyses were performed with SAS 9.4 (Cary, NC). **Results:** Current enrollment is 217 participants. Among 140 men with complete demographics, 93.57% are White, 98.6% non-Hispanic/Latino, 85% with bachelor's degree or higher. Among 143 respondents, 60% reported a diagnosis of PCA. Among 85 men who reported on Gleason score, 24.7% had Gleason > = 8. Regarding family history, 23.5% reported a $1^{st}/2^{nd}$ degree relative with PCA and 58.1% reported a $1^{st}/2^{nd}$ degree relative with any cancer. Among 150 men who reported genetic results, 40.7% had a genetic mutation, 18% reported having a VUS, and 10.7% reported not knowing their results. Among 185 men who reported on mode of genetic evaluation, 58.4% met with a genetics professional and 21.7% reported their doctor had discussed genetic testing. Satisfaction was high (n = 121) (highest score 30; mean score 27.92 + 2.73) and decisional conflict was low (n = 138) (mean score 26.07 + 10.18; range 16-80). Majority of 140 respondents discussed their results with their family (93.6%). Knowledge of cancer genetics was modest, with correct responses among 140 respondents of 50.1% + 28.1. **Conclusions:** Current participants of the PROGRESS Registry report high satisfaction with their genetic evaluation process. However, resources are needed to increase knowledge and understanding of genetic results. Greater engagement of African American males is critically needed to garner diverse perspectives and develop resources for men and their families applicable across populations. Target goal of the registry is 500 males; men can be referred to participate in the PROGRESS Registry at www.progressregistry.com. Research Sponsor: Department of Defense 2019 Idea Development Award (W81XWH2010310).

10596 **Poster Session**

Germline mutations in ATM, CHEK2, and other known/potential breast cancer susceptibility genes among BRCA-negative Uruguayan patients with breast cancer. *First Author: Lucia Beatriz Delgado, Hospital de Clínicas, Montevideo, Uruguay*

Background: Breast cancer (BC) is the most frequent and the leading cause of death from cancer in Uruguayan women. In a previous study, we found BRCA1/2 germline mutations in less than 25% of the Uruguayan breast/ovarian cancer families studied. Due the impact and relevance of genetic testing in BC prevention and with the commitment to assure a wide accessibility, we developed genetic testing facilities at the University Hospital with the aim of analyzing and characterizing germline mutations in non BRCA known susceptibility and likely susceptibility genes. **Methods:** We studied 104 families who met the National Comprehensive Cancer Network (NCCN) criteria of hereditary BC. Analysis by next generation sequencing of BRCA1/2 genes revealed that 23 out of 104 cases studied (22%) carried pathogenic variants. Germline DNA from 42 cases BRCA negative was sequenced and analyzed for nine additional susceptibility genes (ATM, BARD1, CDH1, CHEK2, NBN, PALB2, PTEN, STK11 y TP53) included in a genetic panel. Also, in 24 cases negative for this panel we analyzed large deletions in BRCA1/2 by multiplex ligation-dependent probe amplification (MLPA) testing. In addition, to identify novel non-canonical causative genes, we extended our analysis to a complete exome sequencing of cases tested negative in genetic panels and MLPA analysis. **Results:** Among the 42 cases BRCA negative the sequencing of the extended genetic panel revealed 12 (28.8%) variants, 8 of uncertain significance (VUS) and 4 pathogenic, 2 novel (one in the ATM gene: NM_000051: c.614T > G and other in p53: NM_000546: c.245insT) and 2 previously reported (one in PALB2: NM_024675: c.2186insA and one in PALB2/1: NM_024675c.G7T genes). Regarding the VUS, it is worth highlighting the one found in exon 12 of CHEK2 (NM_007194: c.1333T > C) which was unusually frequent (16.7%) in our cohort when compared with public databases. Analysis of large deletions in BRCA1/2 in 24 cases without mutations in the genetic panel were negative for MLPA testing. Otherwise, complete exome sequencing of germline DNA from 22 cases negative for BRCA1/2 and for the genetic panel, revealed 18 variants, 16 that generate stop codons and 2 that generate loss of the termination codon (stoploss), suggesting a high potential for pathogenicity. Some striking examples are represented by the PSG2, CEP 135 y CEP 162, ZNF17 and ZNF260 genes. **Conclusions:** Of the 42 BRCA-negative cases, 4 (9.5%) carried a PV in a cancer susceptibility gene. The negative results obtained with MLPA in cases negative for BRCA and the extended genetic panel suggest that large deletions of BRCA are not a relevant cause of cancer susceptibility in this cohort. Otherwise, whole exome sequencing of 22 cases negatives for the previous genetic test showed pathogenic or probably PV in genes with no current evidence of association with breast and ovarian cancer. Research Sponsor: ANII and CSIC of the University of Uruguay.

10597 **Poster Session**

Evaluation of Lynch syndrome risk models in a multicenter diverse population. *First Author: Jenny Lu, Harvard University, Cambridge, MA*

Background: Lynch syndrome (LS) is the most common cause of hereditary colorectal cancer (CRC) with an increased CRC lifetime risk of 70-80%. LS affects 1:250 individuals and is caused by pathogenic variants in the mismatch repair (MMR) genes. Statistical prediction models such as MMRpro and PREMM5 are widely used to identify LS carriers. However, these models are trained and validated in mostly white populations, and there remains a gap in understanding their performance in Hispanic populations. The purpose of this study was to evaluate the performance of MMRpro and PREMM5 on a large Hispanic cohort from the Clinical Cancer Genomics Community Research Network (CCGCRN). **Methods:** We validated MMRpro and PREMM5 on 3,490 CCGCRN families, of which 1,122 are Hispanic and 2,062 Non-Hispanic. The two models were evaluated for discrimination using the C-statistic, calibration using the observed to expected ratio (O/E), and overall performance using the root Brier score and negative and positive predictive value (NPV/PPV) at the 5% carrier probability threshold. Evaluations were stratified by ethnicity, and 95% confidence intervals were obtained via bootstrapping for all measures. **Results:** The C-statistic is 0.90 for both MMRpro (95% CI: 0.88, 0.92) and PREMM5 (95% CI: 0.87, 0.92). When stratified by ethnicity, the C-statistics are 0.96 (95% CI: 0.94, 0.97) and 0.86 (95% CI: 0.83, 0.89) for Hispanics and Non-Hispanics, respectively, in MMRpro, and 0.96 (95% CI: 0.94, 0.97) and 0.84 (95% CI: 0.79, 0.88) in PREMM5. Both models underpredict mutation probabilities, with O/E ratios ranging from 1.79 to 1.96. At a 5% threshold, variations in PPV between Hispanics and Non-Hispanics are observed in both models: 0.72 (95% CI: 0.63, 0.80) and 0.43 (95% CI: 0.37, 0.50) in Hispanic and Non-Hispanic groups in MMRpro; 0.50 (95% CI: 0.43, 0.57) and 0.25 (95% CI: 0.20, 0.30) in PREMM5. We observe less variation and higher values in NPVs in both models. **Conclusions:** Overall, MMRpro and PREMM5 perform well in this cohort in predicting the probability of having a pathogenic variant in an MMR gene, with modest underprediction. While these results offer reassurance for the clinical use of MMRpro and PREMM5 in Hispanic populations, further validation studies in underrepresented racial and ethnic populations are crucial. Research Sponsor: None.

10598 **Poster Session**

Scenery of multilocus inherited neoplasia alleles syndrome (MINAS) in a single Brazilian institution. *First Author: Andre Marcio Murad, Personal. Oncologia de Precisao e Personalizada, Belo Horizonte, Brazil*

Background: Genetic testing of hereditary cancer using comprehensive gene panels can identify patients with more than one pathogenic mutation in high and/or moderate-risk-associated cancer genes. This phenomenon is known as multilocus inherited neoplasia alleles syndrome (MINAS), which has been potentially linked to more severe clinical manifestations.To determine the prevalence and clinical features of MINAS in a large cohort of adult patients with hereditary cancer homogeneously tested with the same gene panel. **Methods:** A cohort of 1,234 unrelated patients with suspicion of hereditary cancer was screened using a validated NGS panel including 20 genes associated with hereditary cancer. **Results:** One hundred and forty two (8.7%) patients harbouring probably pathogenic or pathogenic mutatations and 9 harbouring two pathogenic mutations in dominant cancer-predisposing genes were identified, representing 6.3% (9/142) of patients with pathogenic mutations. All (9/9) of these cases presented clinical manifestations associated with only one of the mutations identified. One case showed mutations in MEN1 and MLH1 and developed tumours associated with both cancer syndromes. Interestingly, three of the double mutants had a young age of onset or severe breast cancer phenotype and carried mutations in moderate to low-risk DNA damage repair-associated genes; two of them presented biallelic inactivation of CHEK2. We included these two patients for the sake of their clinical interest although we are aware that they do not exactly fulfil the definition of MINAS since both mutations are in the same gene. **Conclusions:** Genetic analysis of a broad cancer gene panel identified the largest series of patients with MINAS described in a single study. Overall, our data do not support the existence of more severe manifestations in double mutants at the time of diagnosis although they do confirm previous evidence of severe phenotype in biallelic CHEK2 and other DNA repair cancer-predisposing genes. Research Sponsor: None.

10599 **Poster Session**

Variants of unknown significance (VUS) in patients with hereditary CRC without a known pathogenic variant. *First Author: Marija Stojovska, Center for Biomolecular Pharmaceutical Analyses, UKIM-Faculty of Pharmacy, Skopje, Macedonia*

Background: Nearly 5-10% of all newly diagnosed colorectal cancer (CRC) cases develop due to the presence of a highly penetrant pathogenic variant in one of the hereditary colorectal cancer (hCRC) associated genes. NGS technology raised the opportunity for fast and efficient detection of these variants, but still in ~20-30% of patients with hCRC the genetic defect remains unknown. Recent data shows that 6-8% of these cases harbor pathogenic/VUS variant in low/moderate penetrance genes not directly associated with hCRC. **Methods:** A total of 109 patients with hCRC (43 with polyposis and 66 with non-polyposis syndromes) were analyzed by NGS covering coding and exon/intron sequences of 109 genes, of which 25 associated with known hCRC syndromes and 83 other cancer predisposition genes. **Results:** Pathogenic variants were detected in 63/109 (57.7%) of analyzed patients; 54/63 (85.7%) of these had a pathogenic variant in one of the genes associated with hCRC (APC, MMR genes, MUTYH, NTHL1, BMPR1A) and 9/63 (14.3%) had a pathogenic variant detected in genes not directly related to hCRC (CHEK2, FANCL, FANCM, ERCC2, BRIP1, FLCN, BLM). In 26/109 (23.8%) patients a rare VUS variant was detected, of which 14/26 (53.8%) in double strand repair (DRG) genes (BLM, CHEK2, PALB2, ATM, MRE11A, BRIP1, FANCM, FANCL and ERCC2), 8/26 (30.8%) in one of the known hCRC genes (APC, MSH6, PMS2 and POLE) and 4/26 (15.4%) in other cancer predisposition genes (KIT, NSD1, CDH1, EZH1 and FH). VUS variants in DRG genes were more common in patients with MSI- HNPCC (9/15, 60%), compared to patients with polyposis syndromes (6/15, 40%). The VUS variants in other cancer predisposition genes were dominantly present in patients with oligopolyposis. Most (21/26, 80.8%) VUS variants were detected as single variants, while only five patients (5/26, 19.2%) had two different variants in two different genes. In 20/109 (18.3%) patients who presented primarily with MSI- HNPCC or oligopolyposis phenotypes, no pathogenic and/or VUS variants were detected in the 109 analyzed genes. **Conclusions:** Genetic basis of hereditary CRC was not clearly defined in a large proportion (42.3%) of patients in our cohort. Although a VUS variant was detected in a significant portion (23.8%), a major fraction (18.3%) of patients had no known genetic variant detected. The presence of a high frequency of VUS variants in DRG genes indicates that this pathway plays an important role in CRC carcinogenesis. Although we cannot exclude the presence of deep intronic and/or regulatory region pathogenic variants in the analyzed genes, it appears that the current list of identified cancer predisposition genes responsible for the hereditary CRC is far from being complete. The influence of environmental factors in conjunction with polygenic inheritance might also play a key role in a fraction of hCRC in our population. Research Sponsor: Center for biomolecular pharmaceutical analysis.

10600 **Poster Session**

***TP53* pathogenic variants with low allele fraction in germline genetic testing.** *First Author: Yanqing Wu, Department of Interventional Oncology, The First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China*

Background: Blood or saliva DNA generally considered to be representative of germline genome in genetic cancer risk assessment. However white blood cells from these samples may also include somatic origin DNA due to post-zygotic variation or, most commonly, clonal hematopoiesis (CH). Low variant allele fraction (VAF) found in germline genetic testing suggest the possibility of somatic variant and may lead to misinterpretation of genetic risk. *TP53*, of which germline pathogenic variants are associated with Li-Fraumeni syndrome (LFS), is frequently mutated in CH. This analysis investigated characteristics of *TP53* pathogenic variants with low VAF. **Methods:** We reviewed the prevalence and distribution of *TP53* pathogenic variants(PVs) detected in 11,277 advanced cancer patients who underwent clinical testing with a clinical NGS pan-cancer panel. Potential somatic PVs were defined as variants with low VAF from 10% to 35%. The VAF were evaluated in matched tumor tissue samples if available. **Results:** *TP53* pathogenic variants were detected in 36 (0.32%) patients from blood or saliva samples, VAF between 10% and 35% were identified in 8(22.22%) patients and 7 of them were performed NGS sequencing in matched tumor tissue samples. The average VAF of tissue samples were 9.31times lower than blood or saliva samples(21.69% vs 3.88%). **Conclusions:** *TP53* pathogenic variants with low allele fraction in blood or saliva samples indicate the possibility of somatic variant, a reduced VAF in matched tumor tissue samples may contribute to confirmation for suspicion of somatic origin. Research Sponsor: None.

10601 **Poster Session**

Effects of healthcare provider recommendation for genetic testing. *First Author: Emerson Delacroix, University of Michigan, Ann Arbor, MI*

Background: This pilot study was conducted to elucidate the barriers and drivers for genetic testing by combining validated measures to inform the content of a clinical trial aimed at increasing uptake of clinically appropriate genetic testing amongst individuals with a personal history of cancer. Previous research shows that the rate of recommendation of genetic testing varies among Healthcare Providers (HCPs) despite national guidelines. Here we evaluate the rate and effect of HCP recommendation on the uptake of clinical cancer genetic testing. **Methods:** Data for these analyses were obtained from a cross-sectional survey completed by 794 adults (> 18 years) who were diagnosed with cancer in the past 10 years and were seen at an academic medical center within the past two years. Statistical analysis includes logistic regression and crosstabulation with SPSS and R statistical software. **Results:** Provider recommendation of genetic testing was found to be a very strong indicator of receiving genetic testing across all cancer types (OR = 146.4, p = < .001). HCPs more frequently recommended genetic testing to females (OR = 12.5, p = < .001), younger patients (OR = 1.05, p = < .001). While females are more likely to receive a recommendation, there were no significant differences on genetic testing uptake when a HCP recommended it for any gender. **Conclusions:** Without the recommendation of their provider, patients were significantly less likely to receive genetic testing that could affect their cancer treatment, surveillance, or family members. More aggressive patient health education is needed in cancer affected patients to decrease knowledge deficits and increase motivation for cancer genetic testing uptake. Education to providers regarding genetic testing recommendation guidelines could increase motivation to refer patients for genetic testing and counseling. Research Sponsor: U.S. National Institutes of Health.

10602 **Poster Session**

A pilot study to increase cascade genetic testing in families with hereditary cancer syndromes. *First Author: Steven J. Katz, University of Michigan, Ann Arbor, MI*

Background: There is great need to build and evaluate tools and strategies to improve cascade genetic risk evaluation in families at high risk for hereditary cancer. The Genetic Information and Family Testing (GIFT) Trial (CA254822) is a population-based intervention that examines features of a virtual platform that provides genetic risk education (GRE) and low-cost genetic testing (GT) to relatives of adult patients diagnosed with cancer in 2018-19 in Georgia and California and tested positive for a clinically relevant germline pathogenic variant (PV). We present findings of a pilot study intended to inform the GIFT Trial protocol and platform features. **Methods:** We surveyed 277 women diagnosed with breast cancer in 2017, reported to the Georgia SEER registry, and received genetic testing (95% of whom had a clinically relevant PV). We then invited respondent patients to enroll in the intervention phase which provided online GRE, human pretest genetic navigator support, and an offer of low-cost GT through Color Health, Inc. to all untested 1st or 2nd degree relatives. Respondent patients were eligible for the intervention if they reported a PV on genetic testing and had at least one relative who had not received GT. Enrolled patients invited relatives through the platform by providing email addresses. Family clusters were block randomized to free vs $50 test costs at the time of the initial patient invitation. **Results:** At study midpoint, 117 of 277 patients (42%) had returned surveys: median age was 51 and 22% were African American. The most frequent PVs reported by the patients were *BRCA1/2* (41%), *CHEK2* (21%), and *PALB2* (8%). Half (54%) had previously encouraged all of their brothers to get GT and 71% had encouraged all of their sisters to get GT. Three-quarters (78%) strongly agreed it was important for relatives to understand their genetic risk for cancer, and half (54%) strongly agreed they would like to make it easier for relatives to get genetic testing. The median number of patient-reported untested relatives in a family was 8.5 (25th-75th percentile: 4-14). Most respondent patients were eligible for the intervention phase (N = 108, 93%). About one-quarter had enrolled in the intervention at midpoint (16 of 53 in no-cost arm vs 16 of 55 in $50 arm). Patients in the no-cost arm invited 21 relatives, 10 of whom had enrolled with 8 ordering GT (38% of invited relatives). Patients in the $50 arm invited 38 relatives, 18 of whom had enrolled with 17 ordering GT (45% of invited relatives). Overall, about half of enrolled relatives (46%) were men . **Conclusions:** Breast cancer patients with PVs make substantial efforts to communicate with family members about genetic risk; but they strongly endorse the need for additional support to facilitate this complex communication. Interim pilot findings suggest that a low-cost online navigator-supported intervention can directly engage relatives with little difference in GT uptake by test cost arms. Research Sponsor: None.

10603 **Poster Session**

Outcomes of the BRCA quality improvement dissemination program in three health systems. *First Author: Erica M. Bednar, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The BRCA Quality Improvement Dissemination Program (BQIDP) was disseminated to 3 community-based health systems' oncology clinics in 2017. The BQIDP occurred over 3 years and aimed to increase rates of guideline-recommended referral (ref), genetic counseling (GC), and germline genetic testing (GT) for patients diagnosed with invasive epithelial ovarian, fallopian tube, and primary peritoneal cancer (OC) and triple-negative breast cancer diagnosed at age 60 or younger (TNBC). The BQIDP applied virtual implementation facilitation to support sites' development, implementation, and tracking of quality improvement (QI) interventions. Interventions were adapted from prior QI initiatives and published interventions. **Methods:** Baseline metrics (patients diagnosed 1/1/2015 to site's BQIDP launch date Autumn 2017) were compared to metrics of patients diagnosed during BQIDP implementation (site launch dates Autumn 2017 to Autumn 2020). Two-sample test of proportions was used to assess for statistically significant change in rates pre and post BQIDP implementation at each site. QI interventions targeted provider and patient education, retrospective and prospective case finding with alerts to providers and patients, case finding by review of somatic test results and genetic counselor tumor board attendance, streamlined ref and scheduling processes, and infusion-suite based GC. **Results:** All clinics increased rates compared to baseline (Table). Statistically significant improvement was noted for patients with OC in receipt of GC at Site A, ref and receipt of GC at site B, and receipt of GC at site C. Statistically significant improvement was noted for patients with TNBC in ref and GT at sites A and B. **Conclusions:** Improved rates of ref, GC and GT for patients with OC and TNBC were observed at all 3 sites compared to baseline. Baseline ref, GC, and GT metrics for patients with TNBC were higher than for patients with OC at all sites. Tailored and facilitated QI efforts can promote patients' receipt of guideline-recommended cancer genetics services in health system oncology clinics. Research Sponsor: MD Anderson Moon Shots Funding.

	Site A			Site B			Site C		
Metrics	Pre	Post	p-value	Pre	Post	p-value	Pre	Post	p-value
	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
OC Ref	85/122 (69.7)	129/165 (78.2)	0.102	37/56 (66.1)	88/96 (91.7)	***<0.001***	125/193 (64.8)	128/174 (73.6)	*0.069*
OC GC	40/122 (32.8)	103/165 (62.4)	***<0.001***	25/56 (44.6)	60/96 (62.5)	***0.032***	92/193 (47.7)	102/174 (58.6)	***0.036***
OC GT	72/122 (59)	104/165 (63)	0.490	35/56 (62.5)	69/96 (71.9)	0.230	95/193 (49.2)	98/174 (56.3)	*0.174*
TNBC Ref	138/174 (79.3)	153/173 (88.4)	***0.021***	131/141 (92.9)	115/117 (98.3)	***0.041***	121/131 (92.4)	124/136 (91.2)	*0.724*
TNBC GC	95/174 (54.6)	107/173 (61.8)	0.171	103/141 (73)	90/117 (76.9)	0.476	97/131 (74)	108/136 (79.4)	*0.299*
TNBC GT	127/174 (73)	142/173 (82.1)	***0.042***	119/141 (84.4)	112/117 (95.7)	***0.003***	99/131 (75.6)	109/136 (80.1)	*0.368*

10604 **Poster Session**

Hereditary cancer screening at an urban safety net hospital. *First Author: Sydney Brehany, University of Colorado School of Medicine, Aurora, CO*

Background: Individuals with hereditary cancer syndromes (HCS) have a high lifetime risk of developing cancer. However, the rate at which at-risk individuals undergo genetic evaluation is low, particularly for individuals that belong to populations that are historically underserved. We sought to characterize the demographic factors that may be associated with receipt of recommended HCS evaluation and follow-up. **Methods:** All patients with pathologically confirmed breast, ovarian, or fallopian tube cancers and qualifying for hereditary breast and ovarian cancer (HBOC) testing based on NCCN guidelines from 2016 to 2021 at an urban safety-net hospital were included in this analysis. Institutional review board approval was obtained. Demographic and oncologic data, as well as HBOC genetic testing outcomes were collected through retrospective chart review using a standardized data collection tool. Univariate logistic regression models were constructed to test the association of variables with receiving hereditary cancer genetic testing. **Results:** A total of 312 patients were included in the analysis, 90% of which had breast cancer. Forty percent were non-English speaking, 31% were non-White, and 25% were uninsured. Overall, 70% of patients were referred for genetic counseling and 65% underwent testing. Our analysis showed higher association of genetic testing uptake with Spanish language [odds ratio (95% confidence interval)] [1.74 (1.04, 2.93)], stage II disease [2.15 (1.11, 4.16)], and having a referral to genetic counseling [9.21 (5.32, 15.96)]. A lower rate of genetic testing was associated with patients identifying as Black [0.36 (1.87, 0.70)], having Medicare insurance [0.29 (0.14, 0.61)], a higher Charlson Comorbidity Index [0.31 (0.13, 0.73)], and older age [0.94 (0.92, 0.96)]. Uninsured patients had a similar association with genetic testing uptake as patients with Medicaid. Variables seeming to have no association with genetic testing uptake include family history of cancer, type of cancer, performance status, substance use, and Latinx ethnicity. A pathologic variant was found in 13% of our population. A variant of unknown significance (VUS) was found in 33% of Hispanic or Latinx patients and in 46% of non-Hispanic or Latinx patients who received testing, for a combined VUS prevalence of 39%. **Conclusions:** Our analysis shows that genetic testing rates for patients meeting HBOC syndrome criteria at an urban, safety-net institution were higher than expected, particularly for Spanish speaking patients and those with Medicaid or no insurance. We hypothesize this may be due to the emphasis our institution places on the care of uninsured patients through programs to make services accessible, as well as strong engagement with the Spanish speaking community. These results can help guide future interventions to target patient groups with lower rates of genetic testing, as well as maintain the successes seen among our diverse population. Research Sponsor: None.

10605 **Poster Session**

Genetic risk assessment in primary care settings: An evaluation of NCCN guidelines. *First Author: Kara J. Milliron, University of Michigan, Ann Arbor, MI*

Background: Lynch syndrome (LS) and hereditary breast and ovarian cancer (HBOC) have a population prevalence of 1/279[1] and 1/400[2], respectively. Despite this, >80% of patients referred for cancer genetic counseling report personal or family history of breast cancer[3]. This disparity may be due to increased media attention for HBOC, lower levels of provider awareness of LS, and less discussion of colorectal cancer within families compared to breast cancer[4]. However, potential biases in National Comprehensive Cancer Network (NCCN) criteria for genetics evaluation (GE) have not been studied. This project examined the performance of NCCN guidelines for identifying individuals meeting criteria for GE ascertained through primary care (PC) settings. **Methods:** Individuals scheduled for routine PC appointments at three Michigan Medicine affiliated practices from 10/24/18 through 1/24/22 were emailed a link to complete an online personal and family history (P/FHx) risk assessment module (INHERET) collecting information about cancer diagnoses (age/cancer type) in 1st, 2nd, and 3rd degree relatives. The module was written at a 4th grade reading level and could be accessed on any internet-connected device. NCCN guidelines were applied to determine if patients met criteria for GE of HBOC and/or LS. **Results:** A total of 465 individuals completed the module; nearly one in three (30.6%, 142/465) met NCCN criteria for GE of HBOC or LS. Of those meeting criteria, 132 (92.9%) had no personal history of cancer. The most common indication for GE was HBOC (29.5%, 137/465) and 30 patients (6.5%) met HBOC referral criteria solely based on Ashkenazi Jewish ancestry. Only 17/465 (3.7%) individuals met NCCN criteria for GE of LS. Interestingly, 12/17 (70.6%) who met criteria for GE of LS also met criteria for GE of HBOC. The completion rate was not 100% and cannot be determined; it is not known how many patients were offered the option of completing the module. This limits the study, as ascertainment bias cannot be assessed. **Conclusions:** Nearly one-third of PC patients who completed the P/FHx module met NCCN criteria for genetic evaluation of HBOC and/or LS. Referrals for HBOC outnumber those for LS, even though LS is just as common[1, 2, 3]. Further evaluation of NCCN criteria is needed to evaluate whether patients may be over-referred for HBOC and/or under-referred for LS. Unfortunately, we were not able to confirm receipt of email invitations or accurately calculate completion rate of the P/FHX risk assessment module, which limited our ability to assess for ascertainment/response bias. Research Sponsor: U.S. National Institutes of Health.

Demographics of patients meeting NCCN guidelines for GE of HBOC and/or LS.

	Demographic n	NCCN criteria met
All patients	465	30.6% n = 142
Male	130	22.3% n = 29
Female	335	33.7% n = 113
Age <50	385	31.9% n = 123
Age ≥50	80	23.8% n = 19
European ancestry	286	36.4% n = 111
Black/African American ancestry	15	33.3% n = 5
Asian ancestry	105	11.4% n = 12
Multiracial or Other ancestry	55	38.2% n = 21

10606 **Poster Session**

Risk-stratified FIT for urgent colonoscopy in Lynch syndrome: A clinical service throughout the COVID-19 pandemic. *First Author: Anne G Lincoln, King's College London, London, United Kingdom*

Background: Lynch syndrome (LS) is an inherited disorder characterized by pathogenic variants within mismatch repair genes resulting in an increased risk of colorectal cancer (CRC). In England, the fecal immunochemical test for Haemoglobin (FIT) is currently used in non-LS symptomatic and screening populations to guide subsequent colonoscopy. Herein, we report results from a national emergency clinical service implemented during the COVID-19 pandemic which used FIT to prioritize colonoscopy in LS patients while endoscopy services were limited. **Methods:** Regional genetic and endoscopy services across England were invited to participate. Patient eligibility was determined by 1) Diagnosis of Lynch Syndrome 2) Planned colonoscopic surveillance between 1 March 2020 and 31 March 2021. Requests for FIT testing from participating NHS Trusts were sent to the NHS Bowel Cancer Screening South of England Hub's Research Laboratory in Surrey. The Hub sent patients a FIT kit (OC-Sensor™ (Eiken, Japan)), instructions for use, a questionnaire, and a pre-paid return envelope. Lab reports with feecal haemoglobin (f-Hb) results were returned electronically for clinical action. LS patients were risk-stratified for colonoscopy based upon the following f-Hb thresholds: (1) f-Hb ≥10μg of Haemoglobin (Hb)/g (μg/g) faeces: triaged for colonoscopy via an urgent two-week wait (2WW) pathway, (2) f-Hb ≤10μg/g: schedule patients for colonoscopy within 6-12 weeks, where local endoscopy service availability permits. **Results:** Fifteen centers across England participated in the clinical service from 9th June 2020 to 31st March 2021. An uptake rate of 64% was observed from this cohort (375/588 invites), though 21 cases were removed from analysis due to repeat FITs, insufficient sample, missing clinical data, or FIT completed after colonoscopy. Of the remaining 354 patients analyzed, 269 patients (76%) had a f-Hb of <6μg/g. 6% (n=23) of patients had a f-Hb that was at or between greater than the limit of detection of the assay (≥6μg/g) yet below 10μg/g.18% (n=62) had FIT results of ≥10μg/g and met criteria for urgent colonoscopy triage via the 2WW pathway. Of the 62 urgently triaged patients, 22 had detectable adenomas, 6 had advanced adenomas (AAs), and 4 were diagnosed with CRC (table). **Conclusions:** The utility of FIT during the pandemic has demonstrated clinical value for LS patients requiring CRC surveillance. Further longitudinal investigation on the efficacy of FIT in people with LS is warranted and will be examined as part of the multi-center prospective research study "FIT for Lynch Syndrome" (ISRCTN15740250) which is presently recruiting patients in the UK. Research Sponsor: 40tude Curing Colon Cancer Charity.

Summary of findings by varying f-Hb cut-offs where ≥10μg/g is FIT +.

Cut-off (μg/g)	Adenomas	Advanced Adenomas	CRC	No Abnormalities Detected (NAD)	Pending or missing colonoscopy	Total (%)
<6	60	15	2	85	107	269(76)
6-9.9	4	1	0	10	8	23(6)
≥10	22	6	4	24	6	62(18)

10607 **Poster Session**

Fertility preferences, concerns, and preservation among young women with breast cancer who carry germline genetic pathogenic variants compared with non-carriers. *First Author: Rebecca M. Lewinsohn, Harvard Medical School, Boston, MA*

Background: Young women with breast cancer who carry germline genetic pathogenic variants predisposing to breast and other cancers, including *BRCA1* or *BRCA2*, may face unique challenges when making fertility decisions. Limited data exist on differences in fertility preferences, concerns, and preservation strategies between carriers and non-carriers. **Methods:** Participants in the Young Women's Breast Cancer Study, a prospective cohort of women diagnosed with breast cancer at ≤ 40 yrs, who completed a baseline survey with a modified Fertility Issues Survey were included in this analysis. Genetic variant status was determined by medical record review complemented by survey self-report. We excluded carriers whose test date was after baseline survey completion or unknown. Fisher exact and Wilcoxon signed-rank tests were used to compare categorical and continuous variables, respectively, between carriers and non-carriers. **Results:** Of 1052 eligible women, 118 (11%) tested positive for a pathogenic variant (59% *BRCA1*, 32% *BRCA2*, 4% *TP53*, and 5% other unique pathogenic mutations) and 934 (89%) tested negative or were not tested. Carriers' median age was 36 yrs (range 23-40) vs 37 (range 17-40, p = 0.01) in non-carriers. Similar proportions (p = 0.67) of carriers (38%, [45/118]) and non-carriers (37%, [343/934]) desired more biologic children before diagnosis. Desire declined after diagnosis similarly in both groups (carriers, 25% [29/118] vs non-carriers, 26% [242/934], p = 0.46). Among these women (n = 271), concern about passing on cancer risk to offspring was common and, although numerically higher among carriers, this difference was not statistically significant (carriers, 55% [16/29] vs non-carriers, 40% [96/242], p = 0.12). In contrast, among those not interested in or unsure about future fertility (n = 738), concern about cancer risk heritability was infrequently reported as affecting fertility decisions (carriers, 11% [9/83] vs non-carriers, 9% [56/655], p = 0.54). The same proportions (p = 0.89) of carriers (36% [43/118]) and non-carriers (36% [339/934]) were somewhat or very concerned about becoming infertile after cancer treatment, and fertility preservation strategy utilization was similar between groups (carriers, 11% [13/118] vs non-carriers, 12% [111/934], p = 0.21). **Conclusions:** Young women with breast cancer who carry germline pathogenic variants are similarly concerned about future fertility and as likely to pursue fertility preservation as non-carriers. Concern about cancer risk heritability was common among both carriers and non-carriers desiring future fertility, suggesting a gap between perceived and actual risk. Genetic counseling should be included in fertility discussions for all young women with breast cancer, with tailored, risk-mitigating recommendations for those who carry genetic variants. Research Sponsor: Susan G. Komen Foundation and Breast Cancer Research (BCRF).

10609 **Poster Session**

Building a multidisciplinary consortium in Iowa to advance genetic counseling and testing in patients with cancer. *First Author: Sandra Megally, Association of Community Cancer Centers, Rockville, MD*

Background: As cancer clinicians develop increasingly complex treatment plans, the results from somatic and/or germline tests are guiding personalized treatment decisions. Many patients with cancer do not get optimal genetic counseling/testing when indicated. To ensure that cancer clinicians are following the latest clinical recommendations around genetic counseling/testing, the Iowa Oncology Society (IOS), working in collaboration with the Association of Community Cancer Centers (ACCC), developed a multiphase initiative to inform quality improvement (QI) opportunities. **Methods:** In 2021, IOS launched a multidisciplinary consortium to advance genetic counseling and testing in oncology. Engaging a diverse group of stakeholders, IOS held a focus group to explore the current landscape, conducted three educational lunch and learn sessions, produced a podcast, and hosted a working group meeting. These meetings and activities were designed to explore ways to overcome common barriers in care delivery and identify effective practices to coordinate cancer genetic counseling and testing in clinical practice. **Results:** Through this initiative, IOS identified several key improvement opportunities for cancer clinicians treating patients in Iowa. Since 43 percent of Iowa's population is rural, this initiative also identified practical strategies for oncology practices in low-resource areas. The following insights and suggestions were generated from this initiative: 1) Cancer programs may implement creative ways to collect patient history and screen patients for hereditary cancer syndromes. 2) Clinicians may use more effective education materials when referring patients for genetic counseling. 3) Clinicians may clarify language/communication to reduce confusion about somatic vs. germline test results. 4) Cancer programs may form partnerships with local genetic counselors and/or organizations that offer telehealth services. IOS summarized these ideas and disseminated education and resources to guide cancer clinicians in assessing and improving their own practices. **Conclusions:** This multiphase initiative represents a framework for a state oncology society to engage other stakeholders and lead interdisciplinary efforts to improve care for patients with cancer. As the landscape of genetic counseling evolves, IOS supports legislative efforts aimed at having Medicare recognize certified genetic counselors (CGCs) as healthcare providers. IOS plans to build on this initial work to advance cancer genetic counseling and testing throughout the state by developing additional programming in 2022. Research Sponsor: self-funded by Iowa Oncology Society.

10610 **Poster Session**

Clinical characteristics of patients with *PMS2* mutations. *First Author: Samiksha Pandey, William Beaumont Hospital, Royal Oak, MI*

Background: Lynch syndrome is a hereditary cancer predisposition syndrome caused by mutations in mismatch repair genes, *MLH1, MSH2, MSH6*, and *PMS2.* The cancer risks and clinical presentation of *PMS2* associated Lynch syndrome is not well defined. This study outlines the characteristics of patients with *PMS2* mutations identified in a large academic center. **Methods:** Patients with a pathogenic or likely pathogenic *PMS2* variant identified between June 1, 2009 and Dec 31, 2021 were selected from a database at the Nancy and James Grosfeld Cancer Genetics Center at Beaumont Health. Data on demographics, cancer type and molecular testing were retrospectively analyzed. **Results:** A total of 92 patients from 61 families were found to carry a pathogenic or likely pathogenic variant in *PMS2.* The mean age at testing was 54 (19 to 95). A majority (50) of the family were Caucasian, while the rest were African American (2), Middle Eastern (2), Multiracial (8). The most common variant was c.137G > T (p.Ser46Ile), seen in twelve of 61 families. Forty-two patients (45.6%) had a personal history of cancer, with a mean age at diagnosis of 63. Of these forty-two patients, four had multiple malignancies, including one patient with six separate cancers. The most common malignancies were breast (16), colon (12), followed by uterine cancer (8), pancreatic (4), prostate (3) and other cancers. The mean age of diagnosis of breast cancer was 56 (41 to 78), colon cancers was 57 (32 to 75), uterine cancer 59 (50 to 72). Tumor *IHC* was performed in thirteen cases and 11 demonstrated loss of *PMS2* protein expression. *MSI* was performed in 8 cases and 5 were unstable and 3 were stable. **Conclusions:** This study reveals the the clinical spectrum of cancers in *PMS2* related Lynch syndrome. The most common cancers were breast, colon and uterine cancer, with older age of diagnosis. There was evidence of a more severe phenotype, exemplified by a patient with six cancers, suggesting higher penetrance. Further research is needed to better characterize the clinical presentation of *PMS2* related Lynch syndrome. Research Sponsor: None.

10611 **Poster Session**

Hysterectomy as a risk-reducing procedure in *BRCA1* and *BRCA2* women. *First Author: Ana Teresa Pina, IPO Lisboa EPE, Lisboa, Portugal*

Background: *BRCA1/2* pathogenic variants (PV) are associated with an increased lifetime risk of developing several malignancies, particularly breast (BC) and ovarian (OC) cancers. The association between *BRCA1/2* and endometrial cancer (EC) is controversial. Therefore, adding hysterectomy (HT) to risk-reducing (RR) bilateral salpingo-oophorectomy (BSO) is of uncertain benefit. In our multidisciplinary group this decision is personalized and takes in account other gynaecological pathologies or, for BC survivors, tamoxifen treatment. Objectives of this study are to assess the risk of EC on *BRCA1/2* families registered in our program and to discuss the role of prophylactic HT in *BRCA1/2* carriers. **Methods:** Pathologic confirmed EC cases were extracted from the prospective follow up cohort of 949 women diagnosed with a *BRCA1/2* PV through the hereditary breast, ovarian and prostate program at our centre. Data was collected from the medical records. **Results:** Of the 949 women, 345 (36.3%) were diagnosed with a *BRCA1* PV, 603 (63.5%) with a *BRCA2* PV and 1 (0.1%) with PV in both genes. Of all women, 648 (68.3%) had a previous cancer diagnosis while 291 (30.7%) were in primary risk management. Excluding non-melanoma skin cancer, EC was the fourth most frequent neoplasia: BC (553, 85.3%), ovarian, fallopian and peritoneal cancer (117, 18.1%), thyroid cancer (15, 2.3%) and EC (8, 1.2%). BSO with HT was performed in 372 (39.1%) women: RR in 259 (69.6%; *BRCA1* 36.7%, *BRCA2* 63.3%, history of cancer 75.7%, no history of cancer 24.3%) and therapeutic in 113 (30.4%; ovarian/fallopian cancer 92.0%, uterine cancer 8.0%). BSO alone was performed in 174 (18.3%), being RR in 170 (97.7%; *BRCA1* 34.7%, *BRCA2* 65.3%, history of cancer 72.9%, no history of cancer 27.1%). HT alone was performed in 3 (benign disease). Regarding family phenotype, we found another 2 cases of EC in possible *BRCA* carriers. For these 10 cases of EC, median age of diagnosis was 58.5 years (42-75), 7 in *BRCA1* and 3 in *BRCA2* patients (pts). Pathology: endometrioid (5), serous (1), mixed (2, 1 endometrioid and serous and 1 endometrioid, squamous cell and seromucous) and carcinosarcoma (2). Six (out of 10) pts had previous BC: 4 *BRCA1* (2 triple negative, 2 luminal-like) and 2 *BRCA2* (2 luminal-like), 4 of them had previous tamoxifen use (2 *BRCA1*, 2 *BRCA2*). In 1 case the diagnosis of EC occurred after RR BSO (*BRCA1*, no tamoxifen use) and another during the RR surgery (*BRCA2*, tamoxifen use). There was no significant association of EC with *BRCA1* or *BRCA2* (two-sided $p = 0.149$). EC was the cause of dead in 5 pts (50%), all *BRCA1*. **Conclusions:** EC was the fourth most frequently cancer registered in our cohort of *BRCA1/2* women. *BRCA1* women, representing around 1/3 of all cohort, had 70% of all EC diagnoses. This apparent excess of *BRCA1* EC diagnoses was not statistically significant. Tamoxifen may be a confounding factor. While an association was not confirmed at this time, our data also reinforces the need to discuss HT with our *BRCA1/2* pts. Research Sponsor: None.

10612 **Poster Session**

Questioning a Li-Fraumeni Syndrome diagnosis: Characterization of a commonly observed germline *TP53* variant, p.Arg156His. *First Author: Bita Nehoray, City of Hope, Duarte, CA*

Background: Germline pathogenic variants (PV) in the *TP53* gene are associated with Li-Fraumeni syndrome (LFS). Increased use of multi-gene panel testing has identified *TP53* variants suspected to have reduced penetrance, a departure from the significantly increased cancer risks expected with LFS, posing challenges in variant classification and clinical management. *TP53* c.467G>A (p.Arg156His), R156H, is a variant with over 250 observations across multiple laboratories with prior discordant classification. R156H was recently downgraded by laboratories from likely pathogenic (VLP) to variant of uncertain significance (VUS). Characterization of R156H to clarify clinical significance has the potential to impact care for many. **Methods:** R156H carriers were identified through the Li-Fraumeni & TP53: Understanding & Progress (LiFT UP) study (https://liftupstudy.org) from 2019-2022. Clinical data were collected and reviewed for phenotypic characterization and to determine whether LFS Classic and/or Chompret criteria were met, and to assign Li-Fraumeni spectrum classification (Kratz et al.). **Results:** Proband/family characteristics are in the Table. Twenty R156H carriers were identified in 11 families. Seventeen carriers had a personal history of cancer; 8 had a LFS core cancer. All core cancers were breast except for an astrocytoma and a pediatric sarcoma. Two breast cancer cases also carried a *BRCA2* PV. The average age at first cancer diagnosis was 40.5 years (range 6-71). No families met Classic LFS criteria. One proband met Chompret criteria due to breast cancer <31 years (who also carried a *BRCA2* PV). Ten families were classified as attenuated LFS per Kratz et al. **Conclusions:** Most families in our case series did not meet LFS criteria, raising the question of appropriate clinical management and the willingness to de-escalate LFS surveillance. Our series supports the downgrade to VUS, but the presence of a few non-breast LFS core cancers warrants work to determine if R156H is a reduced penetrance PV. Recruitment of these families is ongoing through the LiFT UP study to perform segregation analyses and cancer risk estimations. This work may guide evaluation of other variants presenting similar challenges. Research Sponsor: U.S. National Institutes of Health.

Family	1	2	3	4	5	6	7	8	9	10	11
Cancer history (age)	BR (30)	ASTRO (22)	MNG (36), CML (47)	CX (23), PNET (35), OMEL (59), BR (58)	PAN (71), RCC (71)	N/A	PAN (59)	N/A	OV (32), RCC (67)	SARC (6)	BR (38)
Family history (+=R156H)	BR	BR (+), THY (+), RCC, PR	PR (+), PAN, BR, LG	GB, PR, OMEL, BR	CO, THY	BR (+), LK	N/A (adopted)	BR, OV (+), CO, LYM, HD, UT	BR, CX, CLL, LG, PR	N/A	N/A
Co-occurring PV	*BRCA2*			*BRCA2*		*APC* I1307K					

ASTRO Astrocytoma, BR Breast, CO Colon, CX Cervix, GB Gall Bladder, HD Hodgkin's Disease, LG Lung, LK Leukemia, LYM Lymphoma, MNG Meningioma OMEL Ocular Melanoma, OV Ovary, PAN Pancreas, PNET Primitive Neuroectodermal Tumor, PR Prostate, RCC Renal, SARC Sarcoma, THY Thyroid, UT Uterine.

10613 **Poster Session**

Impact of COVID-19 on individuals with paraganglioma/pheochromocytoma history and/or hereditary risk. *First Author: Samantha Greenberg, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT*

Background: Patients with paraganglioma/pheochromocytoma (PPGL) or hereditary predisposition to PPGL often need screening with biochemical labs, imaging and physical exam. Given the rarity of PPGL and hereditary PPGL, care is often provided through specialty centers. Subsequently, patients may have experienced restrictions on travel and delayed scheduling of non-elective procedures due to COVID-19. This study aimed to analyze the impact of COVID-19 on seeking PPGL management. **Methods:** Patients with a personal history of PPGL or hereditary PPGL risk from the University of Michigan, Brigham Women's Hospital, and Huntsman Cancer Institute were sent a survey in 2021. The survey included questions regarding tumor history (Y/N), gene status, demographics, and experience with COVID. The survey assessed whether they missed any exams related to PPGL diagnosis or screening. Comparative analyses utilized regression and chi-square tests. Patient factors measured in analyses evaluated COVID surveillance (labs, imaging, doctor visit) as the primary outcome and age, institution, gene status, sex, and PPGL history as predicting variables. **Results:** In total, 241 respondents across three institutions completed the survey. The cohort was primarily female (n = 158, 65.6%). A majority of the cohort identified as White (n = 222, 92%) and non-Hispanic (n = 226, 93.8%). PPGL history was reported in 158 patients (65.6%), 43 of which were pheochromocytoma and 113 were paraganglioma, primarily in the head and neck (n = 78). At time of survey completion, 209 (87%) respondents answered COVID-related questions. Thirty-nine respondents (19.2%) reported missing doctor visits, while 31 (15.3%) report missing HPPGL imaging and 33 (16.3%) report missing lab tests. There were no differences by institution ($p > 0.05$) on patient reported missed visits. Logistic regression analysis showed no difference in missing visits based on having a hereditary PPGL predisposition gene or sex of respondent (all p-values > 0.05). There was no difference based on PPGL history, though it is unknown if patients missed PGL follow-up or screening. Individuals who missed imaging (Y/N) were more likely to report missing their lab tests (OR = 1.8, $p < 0.01$) and doctor visit (OR = 1.25, $p < 0.01$). Age was a significant predictor for missing doctor visits ($p = 0.02$) with an odds ratio of 1.002 per 1 year increase in age. **Conclusions:** Though institutions had different COVID-19 restrictions and guidelines by state, there was no difference on missing surveillance or screening. Over 15% of respondents reported missing at least one aspect of PPGL care, indicating a need to re-engage those with PPGL and hereditary PPGL to return to typical screening and surveillance. Patients who miss one aspect of surveillance are likely to have missed other aspects of surveillance and will require evaluation of all aspects of screening to return up to date on needed visits and procedures. Research Sponsor: None.

TPS10614 **Poster Session**

Adjusting the TMIST study design to accommodate slower than expected accrual: ECOG-ACRIN EA1151. *First Author: Etta Pisano, American College of Radiology, Philadelphia, PA*

Background: The ECOG-ACRIN Tomosynthesis Mammographic Imaging Screening Trial (TMIST), which opened in 2017, is a randomized trial designed to assess whether Tomosynthesis Mammography (TM) should replace Digital Mammography (DM) for breast cancer screening. It is hypothesized that women assigned to TM for 3-5 screening rounds will have fewer advanced breast cancers than the women assigned to DM. Advanced cancers are those that have distant metastases or positive nodes, are invasive tumors greater than or equal to 2.0 cm in size, or are invasive tumors greater than 1.0 cm in size that are triple negative or HER 2+. The initially planned enrollment of 164,946 women was due to be completed by the end of 2020, with follow-up concluded by 2025. There were substantial challenges in meeting this timeline, including the organizational and funding structure of the NCI National Clinical Trials Network which is dependent upon sites using their existing staffing resources (not always readily available at the time of study activation). This led to longer than anticipated start of enrollment for most interested sites and lower than anticipated annual enrollment per participating site based ultimately on the staffing support that could be allocated to manage TMIST. In addition, research staffing shortages and periodic research operations closures due to COVID-19 have also impacted enrolling TMIST sites, though unevenly, since the start of the pandemic. Enrollment plateaued at approximately 2,100 subjects per month by the end of 2020. With that accrual rate expected, the trial design was modified to reduce the sample size so that the study could be completed by 2027. **Methods:** With the approval of the NCI CIRB, we changed how the primary endpoint measure for TMIST is assessed from the number of advanced cancers that occur by 4.5 years after randomization to the time from randomization to occurrence of advanced cancers. All advanced cancers occurring within 7 years of randomization are now included and all participants followed for at least three years. In addition, the power of the study of the study was modified from 0.9 to 0.85, while the originally assumed effect size at 4.5 years was retained These changes allowed a reduction of sample size to 128,905, with subject recruitment projected to end in 2024. As of February 14, 2022, there are 125 sites open, 114 in the U.S. and 11 in other countries, with an additional 31 sites planning to open. As of February 14, 2022, a total of 63,845 women have been enrolled in the trial worldwide at 115 sites, with 20% of US participants self-identifying as belonging to minority racial and ethnic groups and 70% consenting to optional blood and/or buccal cell collection. Clinical trial information: NCT03233191. Research Sponsor: U.S. National Institutes of Health.

TPS10615 **Poster Session**

NRG-CC008: A nonrandomized prospective clinical trial comparing the non-inferiority of salpingectomy to salpingo-oophorectomy to reduce the risk of ovarian cancer among BRCA1 carriers [SOROCk]. *First Author: Warner King Huh, Department of Obstetrics and Gynecology, University of Alabama at Birmingham, Birmingham, AL*

Background: Studies of ovarian cancer screening in the general population have not demonstrated a reduction in ovarian cancer mortality. High-grade pelvic serous carcinomas (HGSCs) have traditionally been thought to originate from the ovarian surface epithelium. However, more recent data strongly suggests that most HGSCs originate from precursor lesions found in the distal fallopian tube. Serous tubal intra-epithelial carcinoma (STIC) lesions are found in association with HGSCs in 50-60% of cases and other early serous precursor lesions can be identified in an additional 25% of cases. The Society of Gynecologic Oncology has recently issued recommendations that salpingectomy can be considered at the completion of childbearing in indiviuals at increased genetic risk of ovarian cancer who do not agree to salpingo-oophorectomy. They also indicated that approximately 30% of *BRCA1* mutation carriers choose not to remove their ovaries, and the mean age at RRSO for those who do is in the late 40s, much later than recommended age per guidelines. The purpose of this study is to compare risk-reducing approaches in high-risk women with deleterious germline *BRCA1*mutations; specifically, to demonstrate the non-inferiority of bilateral salpingectomy compared to bilateral salpingo-oophorectomy to reduce the incidence of ovarian cancer among deleterious germline *BRCA1*mutation carriers. **Methods:** This is a non-randomized prospective trial to determine if bilateral salpingectomy is non-inferior to bilateral salpingo-oophorectomy in terms ovarian, primary peritoneal, and fallopian tube cancer risk among gBRCA1m carriers between 35 and 50 years old. Individuals choose the treatment they want to receive in collaboration with their physician(s). The primary endpoint is the time to development of incident HGSC, specifically ovarian, primary peritoneal, or fallopian tube cancers. Secondary endpoints include measurement of health-related quality of life, estrogen deprivation symptoms, sexual function, menopausal symptoms, cancer distress, Medical Decision Making, and adverse events. **Results:** As of 1/31/2022, 116 individuals have been enrolled into this trial. A recent amendment was put forward to allow the following individuals to also participate in this trial: 1) Individuals who are receiving hormonal therapy for maintenance therapy (eg, tamoxifen, AIs, etc), 2) Individuals with a history of any prior cancer and have completed chemotherapy, at least 30 days ago, and 3) Individuals who are considering Assisted Reproductive Technologies (eg, IVF). Furthermore, there is ongoing consideration of allowing general Ob/Gyn providers to recruit patients to this trial and perform procedures, with proper pathology training and sign off at their hospitals. NCI grant UG1CA189867. Clinical trial information: NCT04251052. Research Sponsor: U.S. National Institutes of Health.

TPS10616 **Poster Session**

A phase 3 study to determine the breast cancer risk reducing effect of denosumab in women carrying a germline *BRCA1* mutation (BRCA-P Study). *First Author: Nizar Bhulani, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*

Background: Women with *BRCA1* mutations have a 50-70% lifetime risk of developing breast cancer. Currently, prophylactic mastectomy is the only strategy that significantly reduces breast cancer risk. Recent evidence suggests that the RANK/RANKL signaling pathway plays a pivotal role in the development of *BRCA1*-mutated tumors. Targeting the RANK pathway has been shown to attenuate breast epithelial proliferation *in vitro* and *in vivo,* and to profoundly reduce mammary tumor formation in mouse models. The RANKL inhibitor, denosumab, an FDA approved drug for the treatment of osteoporosis, is potentially an ideal chemopreventive agent for women with a germline *BRCA1* mutation because it: (a) could potentially reduce breast cancer risk, and (b) concomitantly protect bone health in women who have already undergone bilateral salpingo-oophorectomy or in naturally postmenopausal women. The BRCA-P study will evaluate the reduction in the risk of any breast cancer (invasive or DCIS) in women with a germline *BRCA1* mutation who are treated with denosumab compared to placebo. Sub-studies include measurement of bone turnover markers; epigenetic profiling of tumor tissues; measuring denosumab's effect on bone and breast density; measurement of serum RANK, RANKL, OPG, progesterone, LH and FSH; and measurement of quality of life. **Methods:** This is a randomized, double-blind, placebo-controlled, multi-center international phase 3 study to determine the breast cancer risk reducing effect of denosumab in women carrying a germline *BRCA1* mutation. Eligibility: Women with a confirmed *BRCA1* germline mutation; ages $\geq$ 25 years and $\leq$ 55 years; no evidence of breast or ovarian cancer; no preventive breast surgery planned at randomization; ECOG performance status 0-1. Eligible participants will be randomized 1:1 to receive 120 mg of subcutaneous denosumab or placebo every 6 months for 5 years. Thereafter, all participants will be followed up for 5 years. Primary endpoints: Time to the occurrence of any breast cancer (invasive or DCIS). Secondary endpoints: Time to invasive triple negative breast cancer; time to other *BRCA1* mutation associated malignancies, time to clinical fractures. Statistically, a 35% reduction in breast cancer risk would be detected with an 80% power and a two-sided significance level of 5% if 167 breast cancer cases are observed. We expect to observe the number of events needed if 1459 subjects per group (2918 in total) are randomized. The study is currently enrolling participants in Austria, Australia, Israel and Spain. The study will shortly begin accrual in Germany, United Kingdom, and at more than 30 sites across the United States. Globally, the trial is coordinated by the Austrian Breast & Colorectal Cancer Study Group and by the Alliance for Clinical Trial in Oncology in the US. EudraCT: 2017-02505-35. Clinical trial information: NCT04711109. Research Sponsor: U.S. Department of Defense; The National Cancer Institute, Pharmaceutical/Biotech Company.

TPS10617 **Poster Session**

A randomized phase III study assessing the efficacy of liquid biopsy in early diagnosis of recurrence and second malignancies in lung cancer survivors. *First Author: Sana Raoof, Memorial Sloan Kettering, New York, NY*

Background: Lung cancer survivors are highly enriched for extensive smoking histories and have an increased risk of subsequent primary cancers, including those of the larynx, mouth and throat, esophagus, pancreas, bladder, thyroid, stomach, small intestine, colon, rectum, and kidney. Guideline-concordant surveillance after definitive treatment for lung cancer consists of periodic chest CT scans, which do not visualize the majority of second malignancies that this population ultimately develops. Disadvantaged and minority patients are diagnosed with recurrence and second primary cancers at later stages due to reduced compliance with survivorship surveillance. To address these issues, we propose utilizing multi-cancer early detection (MCED) liquid biopsies. MCED liquid biopsies are part of a rapidly growing field of research that assesses parallel cancer screening for multiple cancer types with point of care blood, urine, or saliva sampling. We selected a methylation-based screening liquid biopsy for multiple reasons: 1) it has the highest PPV and specificity of any test clinically validated in the multi-cancer detection setting thus far, 2) it produces a tissue of origin, allowing for targeted workup of positive findings, and 3) it requires only a single test, which we believe will minimize attrition among vulnerable populations with decreased access to healthcare. We designed a 9,000-patient prospective, multi-institutional randomized clinical trial to assess the efficacy of liquid biopsy in early diagnosis of recurrence and second malignancies in lung cancer survivors. To ensure over 25% of participants are of minority status, we have recruited multiple community hospitals to the study in partnership with Memorial Sloan Kettering Cancer Center. Patients included in this study are survivors of non-metastatic non- small cell lung cancer, status-post definitive treatment (surgery or radiation) with no evidence of disease for at least one year. Participants will be randomized 1:1 to standard surveillance or standard surveillance plus six-monthly methylation-based liquid biopsy tests over a two-year study period, and strict guidelines on follow-up of positive liquid biopsy testing will be provided to reduce harms from false positives or over-diagnosis. **Methods:** The primary endpoint of this study is the incidence of late stage cancer (distant recurrence or new primary cancer of stage III/IV). Secondary endpoints include cancer-specific mortality, eligibility for definitive interventions once cancer is diagnosed, and utilization of liquid biopsy versus standard of care scans. This is the first randomized controlled trial of screening liquid biopsy in a survivorship population and the first trial utilizing liquid biopsy in a large minority population. Research Sponsor: GRAIL.

TPS10618 **Poster Session**

Longitudinal immunological responses of COVID-19 vaccination in patients with solid tumors on active treatment: A pilot study. *First Author: Lifen Cao, University Hospitals at Cleveland Medical Center, Cleveland, OH*

Background: Coronavirus disease 2019 (COVID-19), caused by betacoronavirus SARS-CoV-2, is associated with an increased risk of severe infection or death in cancer patients compared to the general population. The CANVAX trial recently demonstrated that short term immune responses to SARS-CoV-2 vaccines are modestly impaired in patients with cancer— particularly those who receive myelosuppressive chemotherapy. Because little is known regarding longitudinal antibody or T-cell responses in cancer patients who receive cytotoxic chemotherapy or non-myelosuppressive targeted systemic therapy, the aim of this longitudinal study is to assess immune B and T cell responses to SARS-CoV-2 over a 12-month period in solid tumor patients who receive chemotherapy or non-immunosuppressive therapy compared to healthy individuals without cancer. **Methods:** This is an ongoing prospective non-interventional clinical trial (NCT05238467). Approximately 100 patients will be enrolled into three different arms. Accrual began in May 2021 and 37 patients have been enrolled. Eligible patients must not have prior COVID-19 infection < 6 months from study enrollment and have a diagnosis of a solid tumor (breast, genitourinary, or gastrointestinal cancers), who either: received myelosuppressive chemotherapy within 60 days prior to initial or booster COVID vaccination, or who started on chemotherapy within 30 to 60 days after the initial or booster COVID vaccination (Arm A); or received non-immunosuppressive treatments (Arm B); or have no history of cancer or prior history of cancer but beyond 12 months from completion of curative cancer treatment (Arm C, control cohort). Whole blood will be collected in accordance with standard operating procedures. Blood samples analyzed for the presence of antibodies against the major antigenic components of SARS-CoV-2 including the spike glycoprotein (S), receptor binding domain (R) and nucleocapsid phosphoprotein (N). Antibody levels will be quantified utilizing quantitative ELISA. T-cell responses will also be quantified. The primary endpoint is seroprotection rate with an antibody titer protective (1:40) at any point: baseline, 2, 6, and 12 months. The secondary endpoint is to evaluate differences in longitudinal immunological responses to SARS-CoV-2 over a 12-month period. The difference of the seroprotection rate among 3 cohorts of participants will be examined using chi-square test. Moreover, the effect of treatment (chemotherapy, endocrine, TKIs) on seroprotection will be estimated using multivariable logistic regression controlling the effects of confounders, such as age, gender and cancer type. COVID antibody titers measured over time (baseline, 8 weeks, 6, 9, 12 months after the second vaccination) will be analyzed using mixed-effect models. Clinical trial information: NCT05238467. Research Sponsor: Institutional Fund.

11000 **Clinical Science Symposium**

Development and assessment of the effectiveness of an LGBT cultural sensitivity training for oncologists: The COLORS training. *First Author: Matthew B. Schabath, Moffitt Cancer Center, Tampa, FL*

Background: Published studies report oncologists have limited knowledge about LGBT health and cancer needs but also report high interest in receiving education regarding the unique health needs of LGBT patients with cancer. As such, our group developed the Curriculum for Oncologists on LGBT populations to Optimize Relevance and Skills (COLORS), an interactive web-based LGBT cultural sensitivity training for oncologists that focused on focused on improving knowledge and communication skill-building. We report here on the results from two single-arm feasibility/acceptability trials and one randomized pragmatic trial (RPT) demonstrating effectiveness of the COLORS training. **Methods:** The first single-arm trial included 44 oncologists from three cancer centers in Florida and the second single-arm trial included 50 oncology fellows recruited through ASCO. The RPT included 225 oncologists randomly selected for equal distribution across the U.S., and participants were randomly assigned to either the COLORS training or a publicly available, web-based LGBT comparison training. Each of these studies included pre- and post-training assessments of LGBT-related knowledge, attitudes, and affirming practices. The RCT included a 3-month follow-up assessment to gauge retention of LGBT-affirming knowledge, attitudes, and practices over time. **Results**: Both single arm trials demonstrated that the COLORS training was feasible, acceptable, and results from the pre- and post-training assessments suggested the training improved knowledge, attitudes, and affirming practice behaviors. In the RPT, those randomized to COLORS demonstrated significant improvements in LGBT-related attitudes pre- to post-training ($p < 0.01$), and no significant changes in attitudes were observed among those randomized to the comparison training ($p = 0.98$). Both trainings yielded significant ($p < 0.01$) increases from pre- to post-training in LGBT-affirming practice behaviors. Likewise, both trainings yielded significant ($p < 0.01$) improvements in knowledge from pre- to post-training. Similar significant findings were observed when we analyzed the 3-month follow-up assessment. **Conclusions:** Results from the prior single-arm trials and the current RCT demonstrate that the COLORS training is effective in improving oncologist knowledge, attitudes, and affirming clinical practices related to the care of LGBT patients with cancer. Part of this work was funded by the Bristol Myers Squibb (BMS) Foundation and BMS Company. Research Sponsor: Bristol Myers Squibb Foundation (BMSF), Florida Academic Cancer Center Alliance (FACCA).

11001 **Clinical Science Symposium**

Challenges faced by female oncologists in sub-Saharan Africa. *First Author: Miriam Claire Mutebi, Aga Khan University Hospital, Nairobi, Kenya*

Background: Recent articles by ASCO and ESMO have identified challenges facing female oncologists in western contexts. The challenges female oncologists face in sub-Saharan Africa (SSA) have yet to be explored. This study was launched by the AORTIC Education and Training Committee to determine the most common and substantial challenges faced by female oncologists in SSA and identify potential solutions. **Methods:** A diverse panel of 32 female oncologists from 20 countries in SSA was recruited through professional and personal networks. Following an initial meeting to review terminology, a modified three-round Delphi process took place. Participants iteratively reviewed a list of previously identified challenges facing women in oncology in SSA and identified new challenges. The survey was conducted via REDCap, a secure-web-based software platform. Participants reflected on personal experiences or those of colleagues, and were asked to indicate their agreement with each listed challenge, as well as propose solutions. Descriptive statistics identified the most common challenges. Following the third survey, a focus group was held to enrich study data. A thematic analysis is being conducted on the focus group transcript to identify key themes, and a subsequent modified Delphi process is being executed to build consensus around potential solutions to identified challenges. **Results:** Response rates for the 3 modified Delphi rounds were 66%, 66%, and 53%. The challenge with the greatest agreement was, "pressure to maintain a work-family life balance and meet social obligations". These were felt to be unique to women in SSA due to an extended family network with several responsibilities beyond the nuclear family. The next two top-scored challenges were "lack of female support and networks", and "micro-aggressions" (Table). **Conclusions:** Female oncologists in SSA experience many of the challenges that have been previously identified by similar studies in other regions, with different degrees of perceived importance. Some challenges have a different lived experience for female oncologists in SSA. The second part of this study will include thematic analysis of the recent focus group and explore potential solutions to mitigate these challenges, which will add insight and potential paths forward to optimizing a diverse workforce in SSA. Research Sponsor: None.

Top 10 challenges facing female oncologists in Africa: Delphi study results

Challenge	Total Score
Pressure to maintain a work-family balance and meet social obligations	74
Lack of female support and networks	73
Micro-aggression	71
Delivered by women, led by men (skewed work distribution at level of leadership)	70
Lack of mentors	69
Lack of support (e.g., financial, research)	68
Lack of access to support, including staff, infrastructure, operating times, leadership/management support	67
Being perceived as less competent than male counterparts	67
Dysfunctional and leaky pipeline	67
Glass ceiling	66

11002 **Clinical Science Symposium**

Examination of speakership gender disparity at an international oncology conference. *First Author: Jessica Caro, Perlmutter Cancer Center, NYU Langone Health, New York, NY*

Background: Gender disparity is an important issue in medicine, as women occupy a minority of academic leadership positions despite increased representation in the physician workforce. One important aspect is the gender gap of speakers at academic meetings, which limits opportunities for career advancement and mentorship. This underrepresentation of women is largely anecdotal in oncology. We hypothesized that original research is less frequently presented by women at the annual ASCO meeting. We sought to examine presentation patterns from recently featured ASCO speakers, categorized by presentation type and gender. **Methods:** We conducted a retrospective, observational review of data from the 2018-2021 ASCO annual meetings. Mixed-gender coders extracted data from the ASCO Annual Meeting library and institutional public websites. Speaker-identified gender was unavailable; binary gender was determined by presenter name, pronouns, and video files. For original research, we collected data on last authors as well as these roles are also considered meritorious. Cochran–Mantel–Haenszel tests were used to investigate the association of gender and roles adjusted for each stratification variable individually. Common odds ratios (ORs) were estimated for each association. Breslow-Day Tests were used to test the homogeneity of these ORs among the different levels of each stratification variable. No adjustments for multiple testing were used. **Results:** We reviewed 4267 unique presentations, including those which highlighted original research (Poster Discussion, Oral Abstract, Clinical Science Symposium, Plenary) vs. education (Case-Based Panel, Education Sessions, Highlights of the Day). For original research, women were significantly more likely to have an ASCO-appointed role (discussant, speaker, or chair) than a first or last author role (48% vs. 32.7% of presentations, $p < 0.0001$), even after adjusting for conference year (OR 0.53, 95% CI: 0.45-0.61), session type (0.52, 0.45-0.61), degree (0.50, 0.43-0.58), academic rank (0.55, 0.47-0.64), and geographic region (0.58, 0.50-0.68). There was no difference between in-person and virtual conferences ($p = 0.584$). For education sessions, women comprised 46.1% ($n = 626$), nearly half, of these speaking roles (all ASCO-appointed) compared with men. 38% of the data was independently re-reviewed to confirm accuracy; 96.4% concordance was observed in presenter gender. **Conclusions:** Women are less likely to present highlighted original research and are more likely to have an appointed educational role at ASCO annual meetings. This likely reflects broader gender disparity within academia. Future analyses could be improved by examining speaker-identified gender. As high-profile original research can elevate careers, examining factors contributing to this observed disparity may reveal important approaches to address gender leadership gaps in oncology. Research Sponsor: None.

11003 **Poster Discussion Session**

Medical student clinical cultural awareness in cancer care of sexual and gender minorities. *First Author: Cherry Au, Rush University Medical Center, Chicago, IL*

Background: Health disparities in lesbian, gay, bisexual, transgender, and queer/questioning (LGBTQ+), or sexual and gender minorities (SGMs), patients are a known in health care. SGMs have higher cancer risk but lower rates of screenings, resulting in a higher likelihood of late-stage disease. Relevant gaps in medical school curricula regarding SGMs must be addressed to prevent these disparities. The purpose of this study is to evaluate medical students' (MS) clinical cultural awareness in cancer care of SGM patients. **Methods:** This study was a cross-sectional survey distributed to medical degree students actively enrolled at a large urban academic center. This survey was adapted from a study by Schabath et. Al. The survey had 38 questions on demographics, attitudes, and knowledge of SGM topics. Questions were scored on a Likert scale from 'strongly disagree' to 'strongly agree' with 'don't know' and 'prefer not to answer' as options. Results are reported using descriptive statistics. **Results:** There were 238 responses. Most respondents were white (63.9%), cis-gender female (57.6%), and heterosexual (78.6%). Distribution according to year are as follows: MS1 36.6%, MS2 14.7%, MS3 27.3%, and MS4 19.3%. Attitudes are listed in the table below. Four of the seven questions on knowledge had "Don't Know" as the most common response. Notably, 47.1% of respondents did not know if screening gay/bisexual men with anal pap is associated with increased life expectancy. Students were interested in learning guidelines regarding SGM cancer screening and considerations for patients who are on hormone therapy. **Conclusions:** While most medical students are comfortable treating LGBTQ+ patients, most are not confident in their knowledge. This difference is most profound in knowledge of transgender patients. Schools must consider longitudinal education in SGM topics to improve student knowledge to produce confident and competent providers. Participants Responses to Attitude Items. Research Sponsor: None.

Question	Strongly Agree, n (%)	Agree, n (%)	Neutral, n (%)	Disagree, n (%)	Strongly Disagree, n (%)	Don't know, n (%)	Prefer not to answer, n (%)
I am comfortable treating LGB patients	132 (55.5)	85 (35.7)	11 (4.6)	4 (1.7)	0 (0.0)	4 (1.7)	0 (0.0)
I am confident in my knowledge of the health needs of LGB patients	31 (13.0)	95 (39.9)	54 (22.7)	42 (17.6)	10 (4.2)	4 (1.7)	0 (0.0)
I am comfortable treating transgender patients.	86 (36.1)	102 (42.9)	24 (10.1)	15 (6.3)	3 (1.3)	5 (2.1)	1 (0.4)
I am confident in my knowledge of health needs of transgender patients.	8 (3.4)	60 (25.2)	70 (29.4)	77 (32.4)	16 (6.7)	4 (1.7)	1 (0.4)
I would be interested in education regarding the unique health needs of LGBTQ patients	159 (66.8)	58 (24.4)	11 (4.6)	4 (1.7)	3 (1.3)	0 (0.0)	1 (0.4)
I would be willing to be listed as an LGBTQ-friendly provider	165 (69.3)	50 (21.0)	15 (6.3)	1 (0.4)	0 (0.0)	5 (2.1)	0 (0.0)

11004 **Poster Discussion Session**

Seeking racial equity in hematology and oncology: A fellow-led educational series to promote reflection and action. *First Author: Jacob Newton Stein, UNC Hospitals Hematology/Oncology, Chapel Hill, NC*

Background: With the murder of George Floyd and health disparities laid bare by the COVID pandemic, the US is reckoning with racial injustice. Across medicine and oncology, institutions are grappling with how to address systemic racism and improve care for patients of color. At the University of North Carolina (UNC), trainees developed an educational curriculum to raise awareness of implicit bias and introduce methods to address racial inequities. We present our findings on feasibility and acceptability of a fellow-led course on racism in medicine at a major academic medical center. **Methods:** UNC oncology fellows adapted a curriculum on implicit bias and racism in medicine in spring 2021. Our aims were 1) to improve knowledge and awareness about implicit bias and systemic racism and 2) introduce methods to address racial inequities. We used lived experiences and collated materials from scientific literature and lay media to illustrate key points. Sessions were: 1) Introduction and Implicit Bias, 2) Implicit Bias in Action: A Case Study, 3) Race-Based Metrics: Journal Club, 4) Career Perspective on Equity in Oncology. Videos, journal articles, and group discussion were employed to appeal to many learning styles. **Results:** Four sessions were held virtually for the Divisions of Oncology and Hematology. Attendance ranged from 28 to 35 per session. A post curriculum survey assessed perception of racial inequality in medicine and the series' effects using a Likert scale. Twenty-nine participants completed the survey, 12 of whom were fellows. Of all participants, 71% reported that the course improved knowledge or awareness of racial inequities "some" or "a great deal" and 61% reported that it improved their comfort level addressing racial inequities "some" or "a great deal." All participants endorsed at least "some" racial inequity in medicine. Notably, over 75% of participants indicated interest in further sessions. **Conclusions:** Formulation of an educational curriculum by fellows and delivered in a division wide setting was feasible and well received by participants with robust discussion and interest in further work. Fundamental to this series' effectiveness was creating a space for discussion and reflection among colleagues. The goals of improving knowledge and introducing methods to address racial inequities were met. Importantly, our course was integrated alongside institutional efforts on DEI. We were limited by a lack of pre-course survey results due to a technical error. Given the current groundswell of interest and focus in improving racial equity in our society, we encourage other institutions to take similar steps to highlight issues of systemic racism and continue to move our field in the right direction. Research Sponsor: None.

11005 **Poster Discussion Session**

The parent penalty: Parental leave and return to work in trainees and early-career faculty in oncology. *First Author: Sindhu Janarthanam Malapati, University of Arkansas for Medical Sciences, Little Rock, AR*

Background: Prime childbearing years occur during medical training and early career, leaving physicians with tough choices between family planning and career growth. Restrictive parental leave (PL) policies can affect physician well-being and limit decisions about reproduction. We evaluated Medical and Radiation Oncology trainees and early career faculty to assess policies and practices regarding PL and return to work. **Methods:** An anonymous 48 question cross-sectional survey developed by researchers with expertise in gender equity was distributed via email and social media channels between May and June 2021 to oncology trainees and physicians within 5 years of terminal training. Descriptive statistics were used to compare study groups. **Results:** 255 physicians completed the survey-54% female, 65% Medical Oncology and 35% Radiation Oncology, 71% trainees and 29% early career faculty. 46% (117) had no formal PL policy during training. PL impacted selection of first job for 37% (94) participants. Of all responders, 114 used PL, either in early career (18%), as a trainee (69%) or both (13%). Duration of PL during training was ≤4 weeks in 37%, 4-6 weeks in 19%, 6-8 weeks in 12% and ≥8 weeks in 24%. 27% of those who took PL as a trainee had to extend training to allow for this. Only 27%(31) of those who took PL had resources available at workplace to assist with transitioning back to work, primarily from informal mentoring by faculty/colleagues (65%, 20). Other important findings are summarized in the Table. **Conclusions:** In this study evaluating parental leave in oncology trainees and early faculty, almost half of the participants had no formal parental leave policy during training and majority of those who took parental leave during training had parental leave only for 6 weeks or less. Most participants experienced a parental leave penalty: guilt when seeking help and feeling overwhelmed at return to work. Policies and practices around parental leave need to be restructured to meet the needs of the evolving oncology workforce. Research Sponsor: Centennial Scholar, University of Wisconsin.

Feelings endorsed by those who took Parental leave	N=114
Felt pressured to work while on PL (including research/ administrative)	50% (57)
Option for part time/ lighter rotations at return to work	19% (22)
Extra call/ clinic/ hospital service/ presentations after PL	32% (36)
Felt that accommodations they required for PL/ lactation placed extra demands on co-workers	48% (55)
Felt guilty asking co-workers for help	60% (68)
Overwhelmed with demands of work and home	79% (90)
Negative feeling regarding returning to work	35% (40)

11006 **Poster Discussion Session**

Global oncology and cancer disparities education. *First Author: Victoria Forbes, UConn Health Center, Farmington, CT*

Background: Comprehensive patient care requires an understanding of medical guidelines and the intersectional context of the patient's identity and experiences. Hematology/Oncology programs must explicitly teach topics addressing various disparities of care to prepare trainees for informed care. We have developed a Global Oncology and Disparities of Cancer Program to address this gap. **Methods:** The telementoring program was piloted in 2019 at Dartmouth and has evolved to include didactics, discussion, and evaluations. Participants from across the globe include medical students, residents, Hematology/Oncology Fellows, Faculty, Global Health Scholars, and cancer clinicians. US Hematology/Oncology trainees from Dartmouth and the University of Connecticut consistently participate in the international program. Monthly sessions from September 2021-June 2022 include: Esophageal and GI Cancers in Rwanda, HCC and Cholangiocarcinomas, Gastric Cancer, ASCO International, Global Med ED in Haiti, Breast Cancer in Kosovo, Breast Cancer Risk Factor Prediction Tools Research, Shared Decision Making in Breast Cancer, Hemoglobinopathies, and Health Disparities and Capacity-Building in Rwanda. A pre-course survey was sent to identify participant's demographics, barriers, and expectations. We will administer a post-course survey. **Results:** We have preliminary data for our ongoing project. However, we anticipate complete data collection and analysis before the ASCO Meeting. 24 participants were enrolled. 12 (52%) of the participants were located outside of the US in locations such as Haiti, Kosovo, and France. Using a 5-point Likert scale, 11 (46%) participants were "not at all" or only "slightly" aware of obstacles faced by Oncology patients and caregivers in seeking access to healthcare in the US. 7 (29%) participants answered similarly regarding those in low- and middle-income countries. Meanwhile, participants rated ''gaining different perspectives'' as their most important reason for attending with 19 (79%) rating this as "very important" or above. For anticipated improvement from the course, understanding risk factors and cancer biology internationally and recognizing disparities in healthcare between domestic and international settings were the highest rated with 18 (75%) expecting an improvement to a "large degree" or higher. **Conclusions:** We developed a virtual educational experience to enhance participants' ability to address disparities of care through challenging Global Oncology topics. Our course is ongoing however initial surveys show a need and desire for this content from participants. We intend to analyze the course surveys to shape future courses. This program can serve as a model for Hematology-Oncology programs to address unmet needs in the curriculum and prepare trainees to provide more complete care to improve cancer outcomes. Research Sponsor: None.

11007 **Poster Discussion Session**

A collaborative model for continuing medical education: Impact of a distance learning curriculum for existing radiation oncology centers in Africa and Latin America. *First Author: Meridith Leigh Balbach, Vanderbilt University School of Medicine, Nashville, TN*

Background: We aimed to evaluate the outcomes and generalizability of a distance learning curriculum on intensity modulated radiotherapy (IMRT), a course developed for radiotherapy clinics across Africa and Latin America (LATAM) at no cost, as measured by a knowledge-based multiple-choice exam, learner self-evaluation, and open-ended feedback. **Methods:** Following needs identification studies, a curriculum entitled "IMRT 2.0" was created for an audience that included medical physicists, radiation oncologists, radiation therapists, and trainees. Volunteer educators delivered 27 hour-long sessions 1-2 times weekly for four months using video conferencing to African and LATAM programs in English and Spanish, respectively. Recordings and educational materials were shared following each session. Pre- and post-course multiple choice examinations were administered to LATAM participants, and pre- and post-course Likert scale self-evaluation and open-ended feedback were collected for both programs. Paired sample t-tests and chi-squared tests were performed for all available paired quantitative and categorical data, respectively. Pearson correlation coefficient, multivariate linear regression, and spline regression models were used to explore impact of course attendance on outcomes. **Results:** 25 centers across Africa (12 + 1 sister institution in Pakistan) and LATAM (12) were recruited, the majority (92%) of which were recently transitioning or planning to transition to IMRT, yielding a total of 332 enrolled participants. 27 sessions were delivered with a mean of 44 (std dev 22.5) and 85 (std dev 25.4) participants per session for the African and LATAM programs, respectively. Paired pre- and post-course data demonstrated significant improvement in both knowledge ($n = 51$, $p < .001$) and overall self-confidence ($n = 85$, $p < .001$). Synchronous participation did not predict greater score improvement or increase in self-confidence. Thematic analysis suggests that participants found great value in this course and look forward to future learning. **Conclusions:** A volunteer-driven course on IMRT is generalizable across regions in different languages and serves as an effective hub to arm participating centers with the knowledge and confidence they need to enhance patient care at their institutions. This benefit may propagate as participants become the next generation of trainers. Other fields and specialties aiming to reduce global health care disparities through training efforts could consider adopting this approach. Research Sponsor: Elekta Corporate Giving Committee.

11008 **Poster Discussion Session**

Mapping global oncology priorities: A survey of the directors of the NCI-designated cancer centers. *First Author: Laura Prakash, Clinical Monitoring Research Program Directorate, Frederick National Laboratory for Cancer Research, Frederick, MD*

Background: By 2040, an estimated 69% of all cancer deaths globally will occur in LMICs. Recognizing this, ASCO formed the Academic Global Oncology Task Force in 2017 to help formalize the global oncology (GO) field. Their recommendations included: better engagement with the National Cancer Institute (NCI) Center for Global Health (CGH), increased funding, and development of forums to highlight global cancer research and control activities. To further clarify how GO programs are defined and to better understand the perspectives and needs of cancer research leaders, CGH conducted a survey of the 71 Directors at the NCI-Designated Cancer Centers (NDCC). **Methods:** A 19-question survey was designed using Microsoft Forms and sent to the NDCC Directors via email. Responses were collected from July to September 2021. Two coders reviewed the qualitative responses to categorize the data into thematic areas. Analyses were conducted in Microsoft Excel. **Results:** Seventy of 71 (99%) NDCC Directors responded to the survey. 41 NDCCs (59%) reported dedicated GO programs or plans to create such a program within 5 years. Additionally, 16 Directors reported GO activities without a dedicated program, while 13 reported no GO activities. The Directors described GO as having high/extremely high (39%) or moderate (50%) importance relative to other priorities, across all types of NDCCs (basic, clinical, or comprehensive). Eight NDCCs (11%) described GO as a low priority or non-priority. 31 NDCCs (44%) reported dedicated funding for GO activities. Directors estimated interest in GO to be higher among junior faculty and trainees than senior and mid-career faculty. Future goals for established or developing GO programs included: recruitment of leadership, formalizing a strategic vision, establishing partnerships, and increasing the number of activities with international collaborations. Barriers noted were limited funding, limited capacity and expertise, and prioritizing the needs in domestic NDCC catchment areas. **Conclusions:** Despite variation across NDCCs, GO interest is strong as expressed by Center Directors. Strategic planning, increased funding, and improved collaboration within and between NDCCs were reported as necessary to strengthen GO at NDCCs. Continued leadership from ASCO, the NCI, and other international organizations can help facilitate dialogue and increase the prioritization of GO activities at NDCCs. Research Sponsor: U.S. National Institutes of Health, Funded by the NCI Contract No. 75N91019D00024.

11009 **Poster Discussion Session**

Assessing the landscape in medical oncology medical education scholarship: A scoping study. *First Author: Ruijia Jin, University of British Columbia, Vancouver, BC, Canada*

Background: Medical oncology and medical education have both expanded exponentially over the past 50 years; as such, it is important to understand the current status of postgraduate medical oncology education and develop ways to advance this field. This study undertakes a scoping review of medical education literature in medical oncology to inform future scholarship in this area. **Methods:** MEDLINE (Ovid), Embase (Ovid), ERIC (EBSCO), and Web of Science (UBC Core Collection) were searched to find peer-reviewed English language articles on Postgraduate Medical Education in Medical Oncology published between 2009 and 2020. The review was designed in accordance with updated methodological guidance for the conduct of scoping review. Articles were classified by learning specialty, learner training level, region of authorship, single or multi-institution, year of publication, whether the journal was an education journal, quantitative vs qualitative design, study methodology, and category or topic. A modified Kerns framework for curriculum development was used to assess the type of curriculum intervention, Boyer's definition of scholarship was used to classify the type of scholarship, and the CanMEDS Framework was used to map the domains of physician competency each study aims to address. Results were interpreted using descriptive statistics and collated and summarized utilizing predetermined conceptual frameworks. **Results:** 2959 references were initially found across the 4 databases. After title and abstract screening, 305 articles remained; after full text review, a total of 144 articles were included in our final analysis. These data showed that postgraduate medical oncology graduate medical education scholarship is increasing and most commonly observed in the United States. Quantitative studies were most common with surveys used as the most popular study approach. In terms of CanMEDS framework, Professional and Medical Expert comprised the large majority of education focuses, while very few articles addressed Leader or Health Advocate. Curriculum development, professional development, and attitudinal skills (communication skills, ethics) were the dominant research themes, while no articles discussed teacher training. **Conclusions**: By investigating the body of current literature, this research identifies areas of highest priority in postgraduate medical oncology graduate medical education and opportunities for growth. Whereas areas like professionalism and attitudinal skills are well-studied, research is lacking in leadership, health advocacy and teaching training. This study provides guidance for future medical education scholarship in medical oncology and establishes a benchmark to examine changes in medical oncology educational scholarship over time. Research Sponsor: None.

11010 **Poster Discussion Session**

Online scaffolds: A constructivist approach to oncology fellow learning. *First Author: Sam Brondfield, University of California-San Francisco, San Francisco, CA*

Background: Oncology is a vast and fast-paced field. Fellows must expend significant effort to learn and stay updated. Up-to-date learning tools covering core oncology content in a digestible manner are lacking. Additionally, passive lectures are common in oncology, while constructivist approaches that may improve learning are rare. Therefore, we piloted updatable online modules ("scaffolds") as a learning tool for oncology fellows. **Methods:** Author SB, a University of California, San Francisco (UCSF) solid-tumor oncologist, designed 12 scaffolds (breast, non-small cell lung, small cell lung, head/neck, salivary/thyroid, upper gastrointestinal, lower gastrointestinal, germ cell, bladder/renal/adrenal, prostate, melanoma, and sarcoma) using Google Slides between 12/2018 and 6/2019. The scaffolds included bullet points and tables/figures synthesized from the ASCO self-evaluation program textbook's solid tumor chapters and the National Comprehensive Cancer Network (NCCN) guidelines. We emailed scaffold links to all UCSF and Stanford oncology fellows in 2019-2020, including instructions for fellows to update the scaffolds without exceeding 20 slides per scaffold, 5 lines per slide, or 7 words per line. The scaffolds were reintroduced to new fellows at the beginning of each academic year. SB audited to ensure no erroneous information was added. In December 2021 we reviewed updates tracked in Google Slides and conducted one UCSF and one Stanford focus group with four 1st-3rd year fellows each. **Results:** Between 7/2019 and 12/2021, fellows made 60 updates to the scaffolds, with a mean of 5 updates per scaffold ranging from new trials to changes in management. During the same period, the auditor made 9 updates and found no erroneous fellow updates. Fellow updates occasionally exceeded specified limits, requiring correction. Content analysis revealed that fellows considered the scaffolds to be accessible and succinct learning tools that 1) addressed a dearth of similar resources, 2) served as effective preparation for clinical work and examinations, 3) provided structured information for rapid review, and 4) made subsequent interactions with complex resources such as NCCN guidelines easier. Barriers to fellows updating the scaffolds included lack of ownership and low confidence in judgment regarding appropriate updates. **Conclusions:** In this two-institution pilot, oncology fellows used and subsequently updated online scaffolds in a constructivist fashion. This model has the potential to fill a crucial gap in available learning resources and can be applied to other specialties. Assigning scaffolds to fellows with faculty mentorship may facilitate ownership and bolster fellow confidence in updating these tools. Individual institutions may update their own versions of the scaffolds to align with institution-specific needs. Research Sponsor: UCSF Education Innovations Funding Grant.

11011 **Poster Discussion Session**

Implementation and efficacy of a fellow-led, case-based noon lecture series. *First Author: James Dickerson, Stanford Hospital & Clinics, Stanford, CA*

Background: For new fellows, learning clinical oncology represents an enormous challenge. Few data support specific didactic approaches. The senior author (TPJ) developed a novel curriculum, emphasizing deliberate practice as part of a design grounded in Ericsson's "expert performance approach". These noon conferences are case based with a focus on key clinical trials and NCCN guidelines. In comparison to didactics given directly by faculty, these conferences are primarily presented by a senior teaching fellow with an invited faculty member adding additional commentary as an "expert discussant". We surveyed fellows to assess perception of efficacy and also created a board style test to evaluate knowledge gains. **Methods:** The curriculum began in 2020. After one year, we surveyed fellows with a five-point likert scale survey to quantify their perception of the curriculum. In 2022, we created a pair of 18-question lung cancer specific board style tests for the five teaching sessions on lung cancer. Prior to the first conference, the pre-test was sent to fellows electronically; after the final lecture the other 18-question test was sent out. Differences in the overall cohort's test score were examined via a paired student t-test. **Results:** On the 2021 survey, 59% of fellows responded (17 of 29). Of the respondents, 83% attended at least half of the lectures (14 of 17). When asked to compare this conference series to traditional lecture-based series, 59% (10 of 17) agreed with the statement that "this series is one of the very best I've encountered" and all said it was at least "better than average." 94% of respondents (16 of 17) said the series equipped them for clinical practice to either a "significant" or "remarkable" degree. 94% of respondents (16 of 17) agreed the conferences helped them learn to "think like oncologists." For the five session lung cancer block, fellows reported attending an average of 3.6 ± 1.4 sessions (n = 13). On the 18-question pre-test (n = 19), the average score ± one standard deviation was 73% ± 15%. For the post-test (n = 13), the average was 68% ± 17% (p = 0.48). **Conclusions:** We developed a novel curriculum to replace traditional didactics. Fellows perceived the curriculum to be exceptionally strong as compared to traditional lecture series, felt it prepared them well for practice, and said it taught them to think like oncologists. Pre/post knowledge assessments did not show an improvement in knowledge. Distribution to larger numbers of fellows–especially early learners–may better power a study to detect improvements in learning. Research Sponsor: None.

11012 **Poster Discussion Session**

Coupling gamified continuing education with confidence-based assessment to address knowledge gaps and assess attitudes towards liquid biopsy for cancer screening among primary care providers. *First Author: Jillian L Scavone, Vindico Medical Education, Thorofare, NJ*

Background: Blood-based liquid biopsy assays offer a simplified approach to detect cancer early, guide clinical decision making, and predict treatment success. Given their novelty, primary care providers need education to improve knowledge and confidence regarding their use. The use of gamification in continuing medical education (CME) has been shown to increase engagement and knowledge transfer, and confidence-based learning can improve the educational experience by identified areas in which learners lack comfort. **Methods:** We provided a gamified CME activity based on the principles of confidence-based learning designed to educate primary care providers (PCPs) on the latest advances regarding the use of liquid biopsy for cancer screening. The game coupled knowledge questions with self-assessment of confidence to gage awareness of these topics. Pre- and post-test was used to quantify the impact of the education. The CE activity was available for credit from March 31, 2021 to March 31, 2022. **Results:** As of January 2022, 389 PCPs have participated. Overall, participants scored an average 76% on gaming questions related to the rationale behind the use of cell free DNA (cfDNA) for cancer screening and the benefits of liquid biopsy over tissue biopsy, demonstrating relatively high baseline knowledge on these topics. Self-reported confidence among those who answered correctly, however, was only 3.4 out of 5.0, suggesting a lack of comfort with the concepts despite answering correctly. On topics related to specific studies that demonstrated the clinical utility of liquid biopsy, participants scored only 59% and confidence scored averaged 3.17 out of 5.0, demonstrating a lack of knowledge and comfort on these topics. Across all topics, providers scored a 61% on a pre-test. Post-learning, providers scored 89%, highlighting the impact of the education on knowledge gaps. Moreover, while 52% of participants had never ordered a liquid biopsy for cancer screening prior to the education, 69% report being likely or extremely likely to do so because of the education provided. **Conclusions:** Integration of gamified and confidence-based learning into CE activities is an impactful way to identify and address knowledge gaps while also informing the need for future education. In this study, while self-report of confidence generally correlated with knowledge scores, confidence scores were only average even among those who answered correctly, demonstrating the need for skills-based learning that may improve comfort with liquid biopsy in the clinical setting. Research Sponsor: This activity is supported by an educational grant from GRAIL, Inc.

11013 **Poster Discussion Session**

Impact of social media on the emotional health and burnout of pediatric and adult oncology professionals: A SWOG and COG survey. *First Author: Scott Moerdler, Department of Pediatrics, Rutgers Cancer Institute of New Jersey, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ*

Background: Social media (SoMe) engagement is common in oncology, especially for patients and support groups, allowing for education and support. However the impact on oncology professionals remains unknown. The purpose of this study was to evaluate professional SoMe use and its potential associations with wellbeing and burnout. **Methods:** An electronic survey was developed and piloted by pediatric and adult oncologists. Questions included demographics, details of SoMe use, and emotional health assessments including a 2-item burnout questionnaire. The survey was distributed to all members of SWOG Cancer Research Network and Children's Oncology Group via Qualtrics. Data was analyzed as of 2/6/2022. **Results:** The initial survey demographic and emotional health questions were completed by 1558 individuals. Of these, 1069 (68%) reported not using SoMe professionally, while 489 (31%) did. SoMe engagers were primarily female, born 1976–1984, attendings, from academic institutions, and balanced across adult and pediatrics (Table). Among those who use SoMe professionally, 54% (267/489) reported burnout, compared to 66% (701/1069) in the non-SoMe group ($p = 0.0001$). Remaining emotional health outcomes were similar between groups: choosing this job/career again, time for personal/family life, and career satisfaction ($p > 0.1$ for all). An additional section on the impact of SoMe on emotional health was completed by 473 SoMe engagers. While 49% (233/473) reported that SoMe has no impact on burnout, 18% (86/473) felt that SoMe helps alleviate burnout. SoMe use was reported to have somewhat/extremely positive impact on wellness (defined as physical, mental, emotional, spiritual wellness) by 28% (131/473). Networking and recognized shared experiences were the top areas of SoMe that improved wellness. Close to half (208/473, 44%) responded that SoMe does not negatively impact wellness. Professional anxiety, amount of time spent online, and keeping up to maintain an online presence were the most frequently noted aspects that negatively impact wellness. Nearly half (232/473, 49%) somewhat/strongly agree that SoMe provides a sense of community. One limitation includes distribution to engaged cooperative group members which may impact results. **Conclusions:** This analysis suggests that social media engagement might help provide a positive impact on the wellness and reduce burnout among oncology professionals. We hope to further explore themes with qualitative interviews to better understand the impact of SoMe on our emotional health. Our goal is to develop educational interventions based on these salient positive and negative factors. Research Sponsor: None.

	No SoMe (n = 1069)	Yes SoMe (%) n = 489
Female (%)	78%	72%
Born 1976 – 1984 (%)	27%	50%
Role: Attending Physician (%)	35%	45%
Practice Type: Academic Institution (%)	74%	75%
Field: Adult Oncology (%)	33%	41%
Pediatric Oncology (%)	54%	41%
Other (%)	13%	17%

11014 **Poster Discussion Session**

Factors associated with altmetric attention scores for randomized phase III cancer clinical trials. *First Author: Michael Kevin Rooney, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The rise of the internet and social media has created new opportunities for the rapid sharing of scientific findings among professional and public communities. Altmetric Attention Scores (Altmetrics) are real-time measures of scientific impact and attention through various public outlets, including news, blogs, and social media. Distributions and patterns of Almetrics for high-impact clinical cancer research remain under-reported. Our goal was to describe the relationship between Altmetrics and other characteristics of published trials. **Methods:** We identified all two-arm superiority phase III cancer randomized controlled trials (RCTs) with a publication date between 2015-2020 from HemOnc.org. For included trials, we tabulated the followed the data: Altmetric score as of February 11, 2022; positive study (yes/no); FDA registration trial (yes/no); primary endpoint (categorized as overall survival (OS), progression-free survival (PFS), event-free/disease-free survival (EFS/DFS), or other); journal tier (defined as tier 1: *NEJM, Lancet, JAMA*; tier 2: *JCO, Blood, Lancet Oncology, JAMA Oncology, Annals of Oncology* or Tier 3: other). Univariable testing was performed with Pearson correlation, Wilcoxon rank sum, and Kruskal-Wallis testing to identify associations between predictor variables and Altmetrics. For factors with significant univariable associations, we generated a multiple linear regression model to identify clinical trial factors predictive of Altmetric attention scores, with alpha = 0.05 defining statistical significance. **Results:** Of 673 publications identified per inclusion/exclusion criteria, Altmetric scores were found for 638 (95%). The median score was 38.9 (IQR 12.4-126.7) – well above the 95th percentile for all Altmetric scores. On univariable testing, positive studies ($P < 0.001$), registration trials ($P < 0.001$), those published in tier 1 journals ($P < 0.001$), and trials with primary endpoint of OS ($P = 0.002$) were associated with increased Altmetric scores. On multivariable testing, positive studies ($P = 0.006$), registration trials ($P < 0.001$), studies published tier 1 journals ($P < 0.001$), and those reporting on OS ($P = 0.03$) persisted as significantly associated with increased engagement as measured by Altmetric scores. **Conclusions:** Social media and other online platforms represent an increasingly important avenue for the sharing of scientific and medical research. In this cross-sectional observational study, we found that certain characteristics of cancer clinical trials and publications are predictive of impact as measured by Altmetric scores. Specifically, positive registration trials published in traditionally defined high-impact journals and those reporting on OS as a primary endpoint tend to have the greatest Altmetric attention scores. The significance and consequences of these relationships warrant further investigation. Research Sponsor: None.

11015 **Poster Session**

Burnout among early-career medical oncologists: A single-institution experience. *First Author: Anmol Singh, MD Anderson Hematology/Oncology Fellowship, Houston, TX*

Background: Burnout is a psychological syndrome defined by the Maslach Burnout Inventory (MBI) as emotional exhaustion, depersonalization, and a low sense of personal accomplishment. Risk of job-related burnout for early-career medical oncologists can significantly impact career longevity and health outcomes for providers and patients alike. Because little is known about burnout specific to early-career academic oncologists, we sought to characterize the prevalence of burnout and associated factors among Assistant Professors at MD Anderson Cancer Center (MDACC). **Methods:** For this IRB-approved retrospective study, an electronic survey was developed for Assistant Professors in medical oncology at MDACC. Participants were all involved directly in patient care with at least some clinical effort. Our survey included nine questions validated in the MBI addressing equally the 3 aforementioned domains of burnout. An additional 31 questions were formulated to assess personal and professional factors that may contribute to burnout at our institution (clinical workload, research expectations, communication, COVID, and home-life). Each question was scored on a scale of 1 to 5, with higher scores correlating to higher levels of burnout. Descriptive statistics were used to describe the prevalence of burnout, and logistic regression analyses were performed to identify characteristics associated with burnout. **Results:** Among 70 (of 86 total) Assistant Professors who responded, mean duration on faculty was 3.1 years (standard deviation +/-1.8). Mean clinical effort was 67% (range, 19-95). Gender identifications were 44% female, 54% male, and 2% non-binary. 54% of respondents reported symptoms of burnout already, including 21% endorsing severe burnout. Severe burnout was more common for solid tumor providers than liquid tumor providers (55% vs 13%, $p = .03$). Using the MBI, severe emotional exhaustion (25%) was more prevalent ($p < .0001$) than depersonalization (6%) or lack of personal accomplishment (17%). Sentiments of being "emotionally drained" (20%), fatigue to face another day on the job" (37%), and "becoming more callous" (30%) were especially concerning among early-career faculty. Emotional exhaustion was associated with a feeling of less autonomy over personal decision making ($p = .03$) and female gender ($p = .04$). **Conclusions:** Burnout exists with high prevalence among early-career medical oncologists in this single-institution analysis. Emotional exhaustion was the specific manifestation of burnout in this population. Further validation of these data nationwide is anticipated. Interventions focusing on reducing emotional exhaustion are under development to reduce medical oncology-specific burnout in an academic setting for faculty retention and for deliverance of optimal care to patients with cancer. Research Sponsor: None.

11016 **Poster Session**

Feasibility of virtual stress management and resiliency training (SMART) for oncology fellows during the COVID-19 pandemic. *First Author: Colt Williams, Mayo Clinic, Rochester, MN*

Background: Stress Management and Resiliency Training (SMART) is a validated resilience training program designed to reduce stress, improve emotional resilience, and decrease burnout. The prevalence of burnout among practicing oncologists is as high as 40%, but unknown among oncology trainees. We implemented a virtual format of the SMART program to the Hematology/Oncology fellowship at Mayo Clinic to assess the feasibility of such a delivery, measure baseline rates of burnout in this group, and to investigate if a virtual method of delivery is as effective as in-person delivery as described in the literature. **Methods:** The SMART project was a mixed-methods, prospective, single arm clinical trial. Hematology/Oncology Fellows at Mayo Clinic were invited to participate. Four one-hour training sessions were conducted virtually. Fellows were given access to SMART online video modules and a book which supported the content covered during virtual training, a companion resilience mobile app, and a paperback mindfulness journal. Stress, burnout, and emotional resilience were measured at baseline and three months post-intervention using the Perceived Stress Scale (PSS), Maslach Burnout Inventory (MBI), and Connor-Davidson Resilience Scale (CD-RISC2). Changes in mean scores on the PSS, MBI, and CD-RISC2 were assessed using the Wilcoxon signed-rank test. Program feedback and feasibility data were obtained during a virtual focus group. Audio transcripts from the focus group were codified for thematic analysis and verified by intercoder triangulation. A 6-month assessment will be due in March 2022. **Results:** 26 of 50 fellows invited participated in our study. At baseline, 24% of participants had measurable burnout and 92% had moderate to high stress. At 3-months, the number of participants with moderate to high stress decreased to 71%, while rates of burnout remained unchanged. The PSS demonstrated a decrease in mean stress (-10.9%, $p = 0.005$), while the MBI demonstrated decreased emotional exhaustion (MBI-EE -6.01%, $p = 0.04$), an improved sense of personal achievement (MBI-PA 28.1%, $p < 0.001$), but slightly worse feelings of depersonalization (MBI-DP 16.46%, $p = 0.05$). The CD-RISC2 suggested no change in global emotional resilience (-0.71%, $p = 0.82$). Thematic analysis of the focus group data revealed that participants overwhelmingly found the program beneficial (83% of all responses), 20% indicated improved stress, and 15% indicated improved work performance. **Conclusions:** Oncology fellows in this study had lower rates of burnout compared to practicing oncologists. Virtual implementation of the SMART program is feasible and resulted in improvements in stress and prevented worsened burnout. Outcomes were comparable to previously published studies conducted in-person. Focus group participants found the training beneficial, reported lower stress, and improved work performance. Research Sponsor: None.

11017 **Poster Session**

A systemic look at professional burnout and well-being within an urban cancer center as a roadmap to recovery. *First Author: Alyson B. Moadel, Albert Einstein College of Medicine, Bronx, NY*

Background: As the U.S. health care system's vulnerabilities have been laid bare by an unremitting pandemic, it behooves us to build in resiliency as we look towards recovery. The "burnout epidemic" facing oncology clinicians has been well documented prior to the pandemic. From a systemic perspective, however, data across the cancer service line is scant. In an effort to identify the stress points and strengths of an oncology service line, we present cross-sectional data from 2018 examining burnout, physical and emotional well-being, and self-care needs across all primary cancer center roles within a major urban cancer center in NYC. **Methods:** An anonymous online survey was completed by 310 of 646 (48%) cancer service providers comprised of physicians, nurses, clinical support staff, managers, and clerical staff. The abbreviated Maslach Burnout Inventory (MBI-9), the Mental Health Inventory (MHI), and the brief COPE were included. **Results:** Respondents ranged from nurses (15%) to clinical support staff (29%), with 79% identifying as female. In a snapshot view, 25% of the sample endorsed feeling burned out from work. Rates of emotional exhaustion were highest among nurses (41%) and lowest among physicians (14%), $p < 0.06$. Depersonalization rates ranged from 1% for physicians to 11% for nurses and clerical staff ($p < 0.003$). A breakdown of those who would not choose the same career over again: clerical (36%), management (28%), nurses/clinical support staff (23%) and physicians (11%), $p < 0.053$). Clinical levels of distress ranged from 20% (clerical staff) to 30% (nurses). Self-reported health (1-5) was lower among clerical staff and nurses (3.1) compared to physicians (3.9), $p < 0.001$. The majority of staff utilized adaptive coping strategies including positive reframing and planning, with religion and humor often endorsed. Interest in counseling and communication skills training ranged from 56%/57% among physicians to 84%/88% among clerical staff, respectively. **Conclusions:** This panoramic view of one cancer service line just prior to the pandemic points to particular systemic stresses in areas of emotional exhaustion, career choice questioning, and psychological and physical health. While levels of burnout fall within and below rates reported in the literature, it also points to fault lines affecting key service line positions, particularly nurses and clerical staff. At the same time, it highlights an underlying resiliency in coping and receptivity to self-care and development. In response to this internal needs assessment, our cancer center is working towards building a stronger foundation in which staff will not only survive the expected and unexpected stresses of working in health care but find meaning and joy in work. While we cannot predict the future, we can learn from the past. In this vein, a Well-Being Committee that includes representatives across the cancer service line was launched in 2022. Research Sponsor: Montefiore Einstein Cancer Center internal funds.

11018 **Poster Session**

Impact of structured debriefing sessions on residents rotating on inpatient oncology. *First Author: Hina Dalal, Loyola University Medical Center, Maywood, IL*

Background: Participating in end-of-life (EOL) care may lead to physician distress and burnout. Residents rotating on inpatient oncology services often care for patients and families nearing the EOL. There is no standardized resident training for EOL care nor are there standardized methods to assist with resultant emotional distress. Studies have demonstrated that residents on hematology/oncology rotations experience acute empathy decline, which can lead to cynicism and depersonalization, contributing to burnout (McFarland, 2016). Our objective was to prospectively evaluate the impact of a structured debriefing session during a 4-week inpatient oncology rotation on residents' concerns about death and rotation satisfaction. **Methods:** During week 1, residents completed a 10-item Concerns about Dying (CAD) instrument (Mozer, 2004). During week 3, residents participated in a structured 60-minute debriefing session with a clinical psychologist or licensed social worker specializing in hematology-oncology. During week 4, residents completed the CAD and an end-of-rotation self-assessment. **Results:** 58 individual residents rotated through inpatient oncology at Loyola University Medical Center from 7/2020 – 1/2022. 15 residents were excluded as they did not complete both the pre and post surveys. Trainees had a lower CAD score at the end of their oncology rotation, indicating a more positive attitude towards death and dying. PGY1s had the greatest decrease in CAD score over 4 weeks. Anxiety (70%), relief (70%), satisfaction/pride (63%) and sadness (58%) were the most common emotions residents felt while providing EOL care. 42/43 (98%) residents were comfortable discussing EOL topics with a licensed counselor and 40/43 (93%) felt the debriefing had a positive impact on their rotation. 38/43 residents (88%) believed the debriefing reduced sentiments of cynicism and dissatisfaction caused by emotional distress related to EOL care. **Conclusions:** Resident concerns about death decreased during a 4-week inpatient oncology rotation in which a structured debriefing program occurred during week 3. Although the study protocol does not provide causation, it suggests the debriefing allowed residents to reflect on EOL care and enhance their ability to cope with distress. The favorable feedback from this pilot led to a permanent curricular change for the inpatient oncology rotation. Strategies to assess and manage emotional strain among residents providing EOL care remain limited and warrant further investigation. Research Sponsor: None.

CAD* scores during week 1 and 4.

Training Year	Number of residents (n)	Week 1	Week 4	Difference
PGY-1	28	4.0	2.6	-1.4
PGY-2	6	3.6	2.8	-1.0
PGY-3	9	3.3	2.6	-0.7
Overall	43	3.8 ($M = 3.8$, $SD = 0.3$)	2.6 ($M = 2.6$, $SD = 0.07$)	-1.1 Paired t-test analysis: $t(42) = 24$, $p < 0.001$

*Responses based on Likert Scale, '1' = disagree completely and '5' =agree completely, higher number indicates a more negative attitude toward death and dying.

11019 **Poster Session**

ASCO oral presenters five years later: Leaks in the pipeline? *First Author: Forrest Kwong, Oregon Health & Science University, Portland, OR*

Background: There is growing awareness of the challenges of retaining oncologists engaged in research, and this leaky academic pipeline is most notable for women in medicine. Studying academic oncologists is challenging due to their many affiliations, but with an estimated attendance of over 30,000 oncologists, the ASCO annual meeting is a highly sought-after stage for presenting new research. To better understand the continued research engagement of oncologists active in research, we used public data from ASCO annual meetings to follow a cohort of oral abstract presenters over 5 years. **Methods:** To define our initial cohort of oncologists engaged in research, we used the 2016 ASCO Annual Meeting Digital Program to identify first author oral abstract presenters. We tracked if each presenter was subsequently listed as an author of any research type (oral abstract session, poster session, education session, etc.) at the 2017, 2018, 2019, 2020 and 2021 ASCO conferences. We then filtered out researchers who were not listed as authors at ASCO in consecutive years to look at only those researchers who continued to have active ASCO involvement. To evaluate by gender, each presenter's name was referenced with the publicly available Wiki-Gendersort tool for an unbiased assignment. **Results:** 209 first author oral abstract presenters were identified at the 2016 ASCO conference. We found that 67.9% of the initial 209 researchers were listed as authors at ASCO in 2017, 55.5% continued to be authors in 2018, 46.9% in 2019, 42.6% in 2020, and only 38.3% were still listed as authors 5 years later in 2021. When looking at sustained first authorship, 8.1% of the initial 209 research cohort continued to be listed as first authors for 5 consecutive years through 2021. We also looked at the breakdown of other types of ASCO presentations and found that 122 of the initial 209 research cohort presented posters in 2016. Of these 122 researchers, 60 (49.2%) remained authors of posters throughout the consecutive 5 years. This is significantly higher than the number of researchers who continued to author oral abstracts in 2021 49.2% vs. 3.8% ($P < 0.0001$). When evaluating the differences between gender, there were approximately twice as many men presenters as women (122 men vs 65 women; 22 names were unisex or unknown). The rate of retention was similar for men (47 of the initial 122 males, 38.5%) and women (25 of the initial 65 females, 38.5%) at 5 years ($P = 1$). **Conclusions:** We conducted a descriptive study evaluating the rate of sustained activity in academic oncology over 5 years. Our research suggests that about one-third of ASCO presenters will continue to have sustained yearly authorship at 5 years post-oral abstract presentation. Compared to men, the leaky academic pipeline is comparable for women in the 5 years following an oral abstract presentation at ASCO. Research Sponsor: None.

11020 **Poster Session**

Preventing healthcare professional burnout in oncology: How creative patient encouragement can go both ways. *First Author: Grace Lee, Northwestern University Feinberg School of Medicine, Chicago, IL*

Background: Cancer treatment is a difficult process that not only affects the patients themselves, but also their caregivers and healthcare professionals (HCPs). A cancer diagnosis is often a life-changing experience for both patients and caregivers, who may feel vulnerable and stressed in the face of such a complex disease. HCPs in oncology, who are constantly present on the frontline between life and death, often experience emotional and physical exhaustion. Such burnout of HCPs can lead to adverse effects on patient care. Therefore, it becomes important to prevent and manage HCPs' fatigue to not only improve patient care, but also HCPs' quality of life. **Methods:** This study qualitatively examined the experiences of HCPs who collaboratively interacted with patients and caregivers in the clinical setting. The Pacemakers initiative was developed and piloted in a large urban academic medical center with the aim to promote creative encouragement and companionship among HCPs and patients/caregivers. HCPs held ceremonies with personal awards for patients/caregivers during their treatment course, and their experience with the ceremonies was evaluated qualitatively with a survey. A thematic analysis was subsequently performed on the HCPs' reflective essays ($N = 22$) to identify recurring themes (italicized) in their experiences. **Results:** In general, we found that the HCPs felt that they were *benefiting* from taking part in the creative patient encouragement ceremonies. Many described the experience as *motivating* or *inspiring* ($n = 15$), highlighting how such collaboration renews optimism and prevents burnout. The HCPs also reported *feeling acknowledged* for their behind-the-scenes work and support ($n = 5$) and grateful to be given the *opportunity to acknowledge their patients and caregivers* ($n = 13$), as well. Another common theme was that the HCPs felt that they were able to *connect emotionally* ($n = 14$) with the patients and caregivers, describing moments of shared laughter and tears. Lastly, the HCPs reported feeling a sense of *togetherness* with patients and caregivers ($n = 13$), often describing the relationship as akin to a team or family, and many stated that they were able to develop a *more personal connection* ($n = 15$) with patients and caregivers through the ceremonies. **Conclusions:** Overall, we find that the benefits of encouraging patients and caregivers extend to HCPs. The positive impact of identifying and celebrating small but meaningful joys in the clinical setting is considerable especially upon HCPs, who find such experiences to be rewarding and refreshing. HCP burnout is common in oncology, and the findings of this analysis suggest that inspiring mutual encouragement and fostering collaboration between HCPs, patients, and caregivers are critical in reducing and preventing such fatigue. Research Sponsor: None.

11021 **Poster Session**

Alleviating the click fatigue on clinicians to improve referrals for colorectal cancer screening. *First Author: Robby Amin, Horizons: South Georgia's Cancer Coalition, Albany, GA*

Background: The impact of clinician burnout on patient care is pervasive across medical delivery systems. The effects are also felt in preventive care where cancer screening efforts rely on clinician referrals through the electronic medical records (EMRs). Though designed to support healthcare, EMRs are a significant source of clinician burnout given the number of clicks or navigation time needed to refer a patient. This is a barrier to Patient Navigation (PN) when ordered tests do not materialize into screenings or when clinicians order labs/imaging and the pending orders are not created. This causes frustration for all clinical staff involved, delays the workflow processes, and leads to missed opportunities for PN. We implemented an 'order set' intervention to reduce the click burden linked to colorectal cancer (CRC) screening referral among clinicians in South Georgia. **Methods:** The 'order set' intervention was developed to facilitate PN for a Colorectal Cancer Control Program (CRCCP) aimed at implementing Evidence-Based Interventions to increase CRC screening rates in Georgia. The 'order set' was designed to address workflow issues by consolidating steps associated with CRC screening. This reduced typing input and the need to click between multiple windows within the EMR while making a referral to PN. The intervention was piloted in the Albany Area Primary Health Care (AAPHC) system after modifications were made to the EMR and clinician workflows. The monthly CRC screening rates continue to be generated and tracked post-implementation. **Results:** The use of the 'order set' reduced the click burden from 78 to 7 inputs and clinician EMR interaction time from 110 seconds to 29 seconds. Providers from 4/7 clinics have adopted the 'order sets' when making referrals for CRC screening. Two clinics provided post-implementation screening data. The pre-implementation screening rates for one clinic were comparable (August = 59.3%, September = 57.6%) to post-implementation (October = 56.3%, November = 56.6%, December = 57.2%), while the second clinic showed some increase (August = 58.6%, September = 60%) vs. (October = 61%, November = 62.1%, December = 62.8%). **Conclusions:** The 'order sets' intervention reduced the time clinicians spent creating referrals for CRC screening, including fecal immunochemical tests (FIT) and colonoscopies. Additional follow-up and rollout to clinics participating in the program is underway to evaluate further the impact of the order sets on CRC screening outcome and process measures, including qualitative interviews with clinicians. There is significant potential in the application of order sets to various workflow processes to aid in preventative health efforts. Challenges linked to the COVID-19 pandemic and staff turnover affected acquisition of patient referral data. Research Sponsor: Center for Disease Control.

11022 **Poster Session**

Piloting virtual mentorship: Evaluating acceptability and influence on wellness and professional identity in medical oncology (MO). *First Author: Andrea S. Fung, Cancer Centre of Southeastern Ontario, Kingston, ON, Canada*

Background: Despite extensive literature on the value of mentorship in academic medicine, little evidence exists to inform mentorship practices in MO. In 2021, the Canadian Association of Medical Oncologists (CAMO) piloted a national, 6-month virtual mentorship program consisting of 2 group mentoring events and additional 1-on-1 mentoring activities, to better support the needs of MO trainees. Feedback was obtained from participants to gain insight into how virtual mentorship might impact physician wellness and formation of professional identity, and to inform future iterations of CAMO's virtual mentorship strategy. **Methods:** All Canadian MO residents/fellows were invited to participate in the program. Electronic surveys were completed by participants at baseline, after each group event, and at program completion. Surveys evaluated the program content and format, and used validated questionnaires for evaluating physician wellness/burnout (Stanford Professional Fulfillment Index [SPFI]), and professional identity (Macleod Clark Professional Identity Scale [MCPIS]). Cohort characteristics and survey responses were summarized using descriptive statistics. Procedures for survey data collection and analysis were ethics approved. **Results:** At baseline, respondents (n = 38) were predominantly female (63%), and < 35 years (76%). 50% were married. On average, 78% of respondents ranked the virtual group mentoring events as meeting expectations. Program strengths identified by participants included meeting mentors outside of their own centre, meeting other trainees from across the country, and learning more about work-life balance/physician wellness. The main critique was insufficient time for interaction. Of the 34 MCPIS respondents, 94% were pleased to belong to the profession of MO, 91% identified positively with members of their profession and 77% felt like a member of the profession themselves. The average score on the SPFI scale was 2.73±0.71 (n = 34). Although 85% of respondents found their work meaningful, 71% satisfying, and 50% felt they were contributing professionally in valued ways, only 38% met criteria for professional fulfilment (score ≥3.00). 27% met criteria for burnout (score ≥1.33), 15% found their work physically exhausting and 9% found their work emotionally exhausting. **Conclusions:** CAMO's pilot virtual mentorship program highlights that technology can be successfully leveraged to facilitate mentoring. The majority of MO trainees identified positively with their profession, yet only 38% reached the threshold for professional fulfillment and nearly a third met criteria for burnout. Longitudinal follow-up among mentored trainees is needed to provide insight into whether mentorship may influence physician wellness and professional identity over time. Research Sponsor: None.

11023 **Poster Session**

Effect of transition from inpatient oncology service to oncology consult service on fellow burn out and training. *First Author: Anosha Tariq, Jinnah Sindh Medical University, Karachi, Pakistan*

Background: The hematology-oncology inpatient service at the University of Louisville underwent a major change in July 2021 from a medical oncology service run by hematology/oncology fellows and attendings to a hospitalist-run service with hematology/oncology fellows and attendings sharing patient care responsibility as a consulting service. We planned this study because, to date, no published work has studied the effect of transitioning from an inpatient to consult service on fellow burnout, education, and training. **Methods:** A survey was distributed in July 2021, and a follow-up survey was sent in January 2022. The survey had 38 questions regarding the impact of the workload on time for study, research, personal and professional life, which were scored from 1 to 5. Two tail paired t-test was used to compare the difference in means. The survey also contained questions from the Mayo Clinic Resident Well-Being Index (RSWBI). This index has been validated to identify distress among fellows and allows for the comparison of local results with national data from RSWBI. In RSWBI, scores range from 0-7, with 0 being the lowest risk and 7 being the highest risk of burnout. A cut-off of a score ≥ 5 identifies individuals with a high degree of distress, is associated with an increased risk of error, suicidal ideation, and burnout, and has been validated in more than 1700 residents/fellows. **Results:** We distributed the survey to 2nd and 3rd-year fellows. 5/6 fellows completed the survey. 3 of them were male and 2 females. Change in inpatient service structure did not impact time for study, research, patient encounter, or ability to handle the volume of work. Improvement in adequate time preparing for clinic was statistically significant (P=0.03), and other improvements were also noted in concentration, time for family, and better personal and professional relationships (Table). RSWBI median score before the transition was 3.6, which improved to 2.0 after the transition to consulting service, which was similar to the national average where the median score was 2.0 among 8237 residents/fellows. 2 fellows (40%) were at high risk of distress before the transition. 1 fellow (20%) was at high risk of distress after the transition, which was comparable to the national average where 19.4% resident/fellows scored ≥5. **Conclusions:** These results show increased levels of distress in fellows that improved to the national average following transition from a primary inpatient medical oncology service to a consult service. Research Sponsor: None.

Outcome	Mean Jul 2021	Mean Jan 2022
Time for study/research	2.8	3.0
Time for patient encounter	3.6	3.8
Time preparing for clinic	3.0	4.0*
Handle work on call	3.6	3.8
Time for family	2.6	3.8
Compassion for coworkers/patients	3.4	3.8
Personal/professional relationships	2.6	3.8
Concentration	3.2	4.0
Use of alcohol or drugs	1.6	1.4

Comparison of means. *p=0.03.

11024 **Poster Session**

A needs assessment survey to inform a general practitioner in oncology (GPO) training program in Nepal. *First Author: Bishal Gyawali, Brigham and Women's Hospital, Boston, MA*

Background: Nepal is a low-income country with a population of over 30 million that faces a significant burden of cancer, with approximately 60,000 patients receiving a cancer diagnosis per year. However, a lack of cancer care providers is recognized as a major barrier to cancer care in Nepal. To address this gap, a national GPO training program may be an effective task-shifting strategy to increase the oncology workforce. A needs assessment survey was conducted to determine baseline oncology training for Nepalese General Practitioners (GPs) and the feasibility and desirability of establishing a GPO training program in Nepal. **Methods:** A survey was distributed to 171 GPs in Nepal. The survey was distributed via the REDCap electronic database, a secure-web-based software platform based at Queen's University in Kingston, Ontario, Canada. Reminders were sent out via social media accounts. The survey results were recorded anonymously from February to July 2021. **Results:** Data was collected from 71 GPs in Nepal. Data revealed significant gaps in oncology training, with only 6% of respondents reporting undergoing a mandatory oncology rotation during their training, and 15% indicating their training adequately prepared them to care for patients with cancer. Although respondents reported seeing an average of 1-5 cancer patients per day, only 9% reported providing chemotherapy treatment, and 36% indicated regular provision of follow-up cancer care. Only 1 in 5 general practitioners reported having radiation oncology services available at their institution or an institution within the same zone. 96% of GPs surveyed agreed that there is a need for a GPO program, and 71% reported they would be very interested in participating in this type of training. A majority of respondents indicated a preference for self-directed and small-group learning as the preferred modes of content delivery in a GPO training program. **Conclusions:** Our findings indicate a need and high level of desirability for a national GPO training program in Nepal. Further, the needs assessment provides insight into practitioner perspectives on information needs and content delivery. This data will be used to guide future curriculum development for the Nepal GPO program. Research Sponsor: ASCO Young Investigators Award.

Demographics and needs assessment of survey respondents.

Variable	Frequency	Percentage
Total	**71**	**100.0**
Gender		
Man	62	87.3
Woman	9	12.7
Others	0	0.0
Age		
< 25	0	0.0
25-34	19	26.8
35-44	44	62.0
45-54	6	8.5
55-64	2	2.8
≥ 65	0	0.0
Years in practice		
1-5	40	56.3
6-10	20	28.2
11-15	4	5.6
16-20	2	2.8
>20	5	7
Location of current practice		
Metropolitan city	33	46.5
Sub-metropolitan city	5	7
Municipality	31	43.7
Village Development Committee (VDC)	2	2.8
Perceived need for a GPO training program in Nepal?		
Yes	68	95.8
No	1	1.4
Unsure	2	2.8
Willingness to participate in a GPO training program in Nepal if available		
Very interested	50	71.4
Somewhat interested	16	22.9
Neutral	2	2.9
Somewhat not interested	0	0.0
Not interested	2	2.9

11025 **Poster Session**

Characterization of industry relationships in oncology. *First Author: Rebecca A. Harrison, BC Cancer, The University of British Columbia, Vancouver, BC, Canada*

Background: Collaborative relationships between academic oncology and the pharmaceutical industry are essential for therapeutic development in oncology. Despite this, formal training and mentorship in developing productive industry collaborations are not routinely included in oncology training. Since little research has been done to characterize and optimize the efficiency of these relationships, we sought to better understand the nature of such collaborations in order to identify areas for optimization. **Methods:** An electronic survey was administered to 1000 randomly selected ASCO members. The survey included 23 questions eliciting demographic and practice information, and 26 questions eliciting respondents' views around oncology-industry collaborations. Survey results were analyzed using descriptive statistics. **Results:** There were 225 survey respondents. Most were from the United States (70%), worked at an academic institution (60.1%), worked in medical oncology (81.2%), and had an active relationship with industry (85.8%). 26.7 % of respondents reported difficulty establishing a relationship with industry collaborators. Many relied on federal (39.5%) or departmental (30.2%) funding to supplement their research ventures. Partnerships were initiated by the respondents themselves (34.6%) or industry partners (31.9%) with similar frequency, whereas institutional affiliations (15.7%) and collaborative groups (5.8%) were reported as less common means for establishing collaborations. The majority (85.3%) of respondents stated these collaborations were of importance to their career. Inclusion in industry sponsored trials (71.1%) and commitment to research funding (66.3%) were considered early signs of a productive relationship, whereas lack of effective communication (86.1%) or little engagement by senior industry leadership (63.1%) were early red flags. Most respondents (75%) did not report having had mentorship in developing these relationships. Scientific integrity was generally thought to be preserved (92%) and there was little concern over the quality of the collaborative product (95%). Many shared concern over potential conflict of interest if a compensated relationship promoted an industry product for clinical care/research (60%), yet also stated these relationships did not shape their interactions with patients (67%). **Conclusions:** This study provides novel data characterizing the nature of collaborative industry-academia relationships in oncology. While respondents considered these collaborations an important part of clinical and academic oncology, formal education or mentorship around these relationships is rare. Further study exploring the structure of effective industry collaborations, optimizing methods to provide education in this area at all career stages, navigating conflict of interest issues in these relationships, and understanding industry perspectives is warranted. Research Sponsor: None.

11026 **Poster Session**

Gaps in adolescent and young adult oncology education during medical and pediatric hematology/oncology fellowship training. *First Author: Adam Duvall, University of Chicago Medicine, Chicago, IL*

Background: There are limited data on the extent of adolescent and young adult (AYA) education in pediatric and medical oncology fellowship programs. The purpose of this study was to assess the prevalence and content of AYA-focused training during pediatric and medical oncology fellowship and identify knowledge gaps for targeted educational curricular development. **Methods:** An anonymous, web-based survey for educators and trainees was developed, piloted and optimized by a study team comprising pediatric and adult oncologists. The survey contained questions on respondent demographics, AYA curriculum, provider comfort in managing specific AYA care domains, and priorities for future AYA educational content. In October 2021, email invitations containing the survey link were sent to program directors (PDs) and associate program directors (APDs) at 251 hematology/oncology fellowship programs (with 119 pediatric and 178 adult PDs/APDs) identified through the American Medical Association's Fellowship and Residency Electronic Interactive Database Access. PDs were asked to participate and also distribute the survey to current fellows. The survey remained open for 3 months. Fisher's exact test was used to assess for associations between discrete variables including amount of current education vs level of importance and demographic groups. **Results:** Respondents represented 69 programs (27%). There were 130 respondents who completed curriculum and demographic questions and 112 who completed detailed topic questions. Respondents comprised 51 PDs/APDs (32 pediatric and 19 adult) and 58 fellows (33 pediatric and 25 adult). 85% of PDs (44/51) do not have a formal AYA curriculum. Of these, 80% (35/44) offer some topic-specific lectures, while 20% (9/44) provide little/no education in any topics. For nearly all topics, at least 45% of respondents reported little/no education. Although onco-fertility and survivorship are the most frequently taught topics, 36% and 42% of respondents, respectively, reported little/no education in these areas. Substance abuse is least commonly taught. Both PDs and fellows believe that AYA topics are more important for inclusion in future curricula despite how infrequently they are currently taught (very/extremely important for inclusion vs moderate/great deal of current amount of education, $p = 0.0001$ for all topics). Overall, respondents indicated the most important topics for inclusion in fellowship curriculum were onco-fertility (82%), survivorship (78%), and communication (77%). **Conclusions:** These data highlight the large gap in hematology/oncology fellowship education in AYA topics and a paucity of formal educational curricula. Efforts are needed to provide both medical and pediatric oncology fellows with the knowledge and skills required to provide optimal care for AYAs. Research Sponsor: None.

11027 **Poster Session**

Efficacy of a novel journal club series at an academic hematology/oncology fellowship program. *First Author: Vivek Patel, Vanderbilt University Medical Center, Nashville, TN*

Background: Journal club (JC) is an essential tool in hematology/oncology fellowship to develop critical appraisal skills. The traditional JC format of reviewing an article followed by group discussion may not provide optimal education in appraising literature. We applied a novel JC curriculum and measured impact on fellow comfort with trial design, statistics, and endpoint interpretation. **Methods:** A novel JC curriculum was implemented for hematology/oncology fellows at Vanderbilt in the 2021-2022 academic year. JC for the prior year utilized the traditional format. We developed five focused learning objectives (LO's) for each JC and emphasized the goal was to not place the paper in clinical context but to focus on developing the foundational tools for critical appraisal skills. The sessions involved (1) 15 minute introductory lecture from a biostatistician to cover foundations of the LO's; (2) group discussion led by an upper year fellow to describe the paper in the context of the LO's; (3) question and answer session from the fellows to both the statistician and a clinical trial expert. We developed anonymous pre and post surveys to understand the impact of the novel JC curriculum on a 5-point Likert scale. Two sample unpaired t-test was used to compare mean differences. **Results:** A total of 15/22 fellows (68%) completed the pre-survey and 12/22 fellows (55%) completed the post survey. There was an even distribution of fellows by year in the pre survey and 33% first years, 41% second years, and 25% third years in the post survey. There was a statistically significant improvement in pre and post mean fellow comfort in understanding differences in trial types (2.9 vs. 4, $p < 0.001$), randomization strategy (2.6 vs. 4.25, $p < 0.001$), endpoints (3 vs. 4.1, $p < 0.001$), and interpretation of the statistical methodology of represented data (3 vs. 4.3, $p < 0.001$) on a 1-5 Likert scale (5 being entirely comfortable). In a subset analysis, we did a direct comparison of fellows who had previously participated in both JC formats ($n = 9$); the new format was rated as a more useful tool for learning data interpretation than prior with a mean of 4.8/5. When comparing fellow perception in the utility of traditional compared to the novel JC, there was a statistically significant mean improvement in utility of JC to prepare fellows to understand differences in trial types (1.9 vs. 4.1, $p < 0.001$), randomization strategy (1.4 vs. 4.5, $p < 0.001$), endpoints (2.7 vs. 4.5, $p < 0.001$), and interpretation of the statistical methodology of represented data (2.33 vs. 4.6, $p < 0.001$) favoring the novel JC. **Conclusions:** Fellows' comfort with trial design and content significantly improved with our novel JC. To our knowledge, this is the first time such a curriculum has been used in hematology/oncology training. Our successfully piloted novel JC model can be adapted to other fellowships to improve foundational skills in the critical appraisal of clinical trials. Research Sponsor: None.

11028 **Poster Session**

Applying cognitive integration to oncology: A novel asynchronous foundational science curriculum for medical students during clerkships. *First Author: Sam Brondfield, University of California, San Francisco, San Francisco, CA*

Background: Cognitive integration (CI) connects foundational science (FS) to medical practice and improves clinical reasoning. While evidence supports CI in medical training, the clinical relevance of FS is often obscure to medical students, particularly in oncology, and few learning materials exist to support CI during clerkships. Providing effective and engaging tools to promote CI may enhance understanding of FS relevance to clinical medicine. We therefore aimed to create an online module to integrate FS into clerkships. **Methods:** Previous student feedback at our institution advocated for clinically relevant FS content. Applying Cognitive Theory of Multimedia Learning principles, we (an oncologist, a biochemist, and an instructional designer) created a cancer module grounded in the hallmarks of cancer (HoC), a key FS principle. To emphasize clinical relevance, we recorded patient interviews incorporating FS. The module, composed in Qualtrics, includes an introduction and four cases, each starting with a brief patient interview, followed by clinical text, images, questions, and explanations. Content co-created by the oncologist and biochemist combined clinical and FS perspectives and referenced the HoC throughout. We piloted a draft with a focus group of four students. The evaluation plan includes written learner feedback, a case-based pre/post-test, and review of clerkship assessments for evidence of CI. **Results:** We produced an FS oncology module with an estimated engagement time of two hours, which students may complete over multiple sittings. The development team met monthly over the course of one year. Filming and editing cost $100/hour. Overall, the project required approximately 60 faculty person-hours and 12 instructional designer person-hours. The patients interviewed for the module expressed gratitude for sharing their stories with students. The student focus group yielded unanimously positive feedback about the content, the multimedia format, the level of FS covered, and the use of authentic patient videos to enhance clinical relevance. Students strongly preferred this module compared to prior online learning activities. **Conclusions:** This novel interactive module can serve as a model for development of clerkship curricula promoting CI. Module creation based on real patients resulted in authentic story-telling and enhanced FS relevance. Content development involving a clinician and a basic scientist aligned with CI goals. Limitations include the need for funding and instructional design assistance. A randomized controlled trial comparing a series of novel FS modules to older recorded lectures may demonstrate improved outcomes. Involving learners in curriculum development may decrease faculty burden and increase student interest in FS. Research Sponsor: None.

11029 **Poster Session**

Adapting a medical school cancer research education program to the virtual environment. *First Author: Omar Vayani, The University of Chicago Pritzker School of Medicine, Chicago, IL*

Background: As the number of patients with a cancer diagnosis grows in the United States, there is an increasing need for physician scientists with oncology-related research training to develop new approaches to screening, diagnosis, therapy, and survivorship. A single US medical school developed the National Cancer Institute-funded Scholars in Oncology-Associated Research (SOAR) cancer research education program. Due to the COVID-19 pandemic, SOAR transitioned from fully in-person in 2019 to virtual in 2020 and hybrid in 2021. This study examines whether the in-person, virtual, or hybrid formats provide better educational experiences as rated by participants. **Methods:** SOAR includes a seminar series, an 11-week full-time cancer research experience, weekly research cluster group meetings, and tumor board and interprofessional shadowing experiences. In 2019 all program activities were in-person. In 2020 all activities were virtual with the shadowing suspended. In 2021, seminars and tumor boards were virtual, shadowing was in-person, and all other activities were hybrid. Pre- and post-surveys were collected from all participants to assess understanding of oncology and associated medical specialties. How participant understanding of oncology and related specialties changed within each year's program was analyzed with a Wilcoxon rank-sum test. The Kruskal-Wallis test was used to examine change in understanding between the cohorts. **Results:** 37 students participated in SOAR (2019 n = 11, 2020 n = 14, 2021 n = 12). Self-reported understanding of oncology as a clinical ($p < 0.01$ for all) and research discipline ($p < 0.01$ for all) improved within all three cohorts. There was no significant difference between each cohort's improvement in research understanding ($p = 0.6158$). However, there was a trend towards more of an improvement in the in-person cohort ($p = 0.0796$) for clinical understanding. There was no significant difference between each cohort's improvement in understanding of oncology-related disciplines such as medical oncology, radiation oncology, pediatric oncology, surgical oncology, and survivorship as both clinical and research disciplines ($p > 0.1$ for all). **Conclusions:** A virtual cancer research education program can be as effective as an in-person or hybrid program for research education although it may be suboptimal for learning about clinical oncology. Given the ongoing challenges presented by the COVID-19 pandemic, flexibility is needed in delivering cancer research education programs such as SOAR. With modern research methodology and communications technology, cancer research is becoming increasingly diverse and flexible in terms of research environment. If program leaders are steadfast in their adaptation of research education programs to a virtual or hybrid environment, participant understanding of oncology as a clinical and research discipline remains robust. Research Sponsor: None.

11030 **Poster Session**

Medical student readiness to treat LGBTQ patients. *First Author: Matthew B. Schabath, Moffitt Cancer Center, Tampa, FL*

Background: The lesbian, gay, bisexual, transgender and queer (LGBTQ) community experiences cancer health disparities. It is thus imperative that medical trainees receive training in the care of LGBTQ populations. Identifying gaps in trainees' knowledge and comfort in providing care for this population is important in preparing future physicians. **Methods:** A Likert-scale survey of US medical students at three institutions assessed attitudes, comfort and knowledge in providing care for LGBTQ patients. Results were quantified with descriptive and stratified analyses. Exploratory factor analysis found four factors in which attitude summary measure (ASM) scores were calculated; lower values indicate more agreeability with given attitude items. Total knowledge scores were calculated with higher values indicating greater knowledge. **Results**: Of 300 medical students who completed the survey, the majority were female (55.7%), white (54.7%), and heterosexual (64.3%). The majority of students felt comfortable (strongly agree/agree) participating in the care of patients who identify as lesbian (94.3%), gay (96.0%), and bisexual (96.3%); this percentage dropped to 82.3% for non-binary and 71.3% for transgender patients. Only 27.0% of students reported confidence in their knowledge of health needs of transgender patients. LGBTQ self-identification, percent of core rotations completed, and having LGBTQ friends/family were significantly associated with various ASM subscales (Table 1). Knowledge questions had high percentages of "neutral" responses, and students who identified as LGBTQ had significantly higher total knowledge scores. **Conclusions**: Overall, medical students feel comfortable and willing to provide care for LGBTQ patients. However, as in our prior study in oncologists, there is limited knowledge about specific LGBTQ health and cancer needs. More education and training in the needs of transgender and non-binary patients is indicated. Research Sponsor: None.

Stratified analysis for attitude summary measures and total knowledge scores.

Characteristic	Attitude Summary Measures				Knowledge Total Score
	Discuss Health Needs	Comfort in Treating	Education	Comfort of Inquiry	
LGBTQ Friends/Family–No	3.2 (2.8)	2.1 (2.7)	2.3 (2.9)	2.0 (1.0)	4.5 (1.0)
LGBTQ Friends/Family–Yes	2.4 (1.6)	1.2 (1.0)	1.5 (0.8)	1.8 (1.0)	5.0 (0.9)
No Completed Core Rotations	2.4 (1.9)	1.2 (1.0)	1.5 (0.7)	2.0 (1.0)	4.8 (0.8)
50% or Fewer Completed Core Rotations	2.5 (1.3)	1.7 (1.4)	1.8 (1.0)	2.0 (0.5)	4.9 (0.8)
Over 50% Completed Core Rotations	2.4 (1.2)	1.4 (1.0)	1.5 (0.9)	1.8 (1.0)	5.1 (0.8)
LGBTQ Self-Identification–No	2.7 (1.5)	1.4 (1.0)	1.7 (0.8	2.0 (0.8)	4.8 (0.8)
LGBTQ Self-Identification–Yes	2.1 (1.5)	1.2 (0.6)	1.3 (0.5)	1.8 (1.3)	5.2 (0.8)

NOTE: Measures are reported as median (interquartile range). Bold indicates significant difference at $p<0.05$. Medians were compared between groups unless distributions of scores were dissimilar, in which case mean ranks were compared.

11031 **Poster Session**

Transdisciplinary research in energetics and cancer (TREC) training program for early career investigators. *First Author: Melinda L. Irwin, Yale School of Public Health, New Haven, CT*

Background: Given the rising prevalence of obesity, poor diet and physical inactivity, known in combination as "energy balance" or "energetics", as well as their associations with cancer incidence and mortality, innovative research, clinical care and training of scientists are needed to lower the prevalence of these risk factors and in turn, lower cancer incidence and mortality rates. **Methods:** With NCI support (R25CA203650) from 2016-2021, we developed and offered an annual one-week, in-residence Transdisciplinary Research in Energetics and Cancer (TREC) Training workshop, followed by a yearlong mentoring program, that focused on energy balance and cancer research across the cancer control continuum. **Results:** We recruited, educated, trained and mentored 123 early career investigators (TREC Fellows) from 64 different institutions and from diverse academic backgrounds (i.e., 20% basic, 33% clinical and 47% population sciences) in transdisciplinary research in energetics and cancer. Fellows accepted to the TREC Training Program worked with more than 20 expert international TREC Faculty on developing grant applications and original research toward key gaps in energy balance and cancer research. TREC Fellows have published over 270 manuscripts in peer-reviewed journals, with at least 62 published manuscripts including the TREC Fellow as first or senior author and including a TREC Faculty and/or Fellow as co-author. Since completing the Program, TREC Fellows have received at least 31 extramural grants, as principal investigator. Building upon the strengths of the previous five years, we were awarded a competitive renewal to continue the TREC Training Program through 2026. TREC Training program goals are: (1) to continue to offer a TREC Training Program for ~100 academically diverse early career investigators including a 5-day in-residence workshop focused on the Fellows research, networking, mentoring and professional development; (2) to evaluate the TREC Training Program and track TREC Fellows career development; and (3) to disseminate the TREC Training sessions, webinars and newsletter to the broader community of investigators. **Conclusions:** To our knowledge, no other in-residence training program exists that focuses on energetics and cancer research. Our vision is to continue the TREC mission of training scientists and clinicians to develop a cadre of well-trained, diverse researchers. The overall impact of this transdisciplinary training course will be defined by the degree to which TREC Fellows produce innovative research approaches and discoveries, thereby accelerating the dissemination and implementation of evidence-based approaches into everyday practice and patient care and improving the health of the population at risk for cancer as well as cancer survivors. Research Sponsor: U.S. National Institutes of Health.

11032 **Poster Session**

Impact of learning program on treatment recommendations by molecular tumor boards and an artificial intelligence-based annotation system: A prospective study. *First Author: Kuniko Sunami, Department of Laboratory Medicine, National Cancer Center Hospital, Tokyo, Japan*

Background: Treatment recommendations (TRs) by molecular tumor boards (MTBs) based on comprehensive genomic profiling tests are crucial for enrolling cancer patients in genotype-matched trials. Our previous study of Japanese designated 'Core' hospitals using simulated cases showed that TRs for biomarkers with high evidence levels (ELs) were highly concordant between central consensus and MTBs, whereas those with low ELs showed low concordance, indicating that a learning program (LP) about obtaining information on matched trials, particularly for those with low ELs, is needed to improve the quality of TRs by MTBs (Kage H. ESMO 2021). Therefore, we conducted a nationwide prospective study to investigate the clinical utility of an LP for MTBs in designated 'Hub' hospitals and explore the efficacy of an artificial intelligence (AI)-based annotation system. **Methods:** Fifty simulated cases were randomly divided into 2 groups (pre- and post-tests) by the central statistician, stratified by high vs. low ELs. Each MTB at 'Hub' hospitals (group), treating physicians at 'Core' hospitals (individual), and an AI company were eligible. Each participant made TRs for the first 25 cases, then participated in the LP, and made TRs for the second 25 cases. The online LP shared the methodology of making the optimal TRs and showed central consensus TRs for simulated cases. The primary endpoint was the proportion of MTBs that met prespecified 'accreditation' criteria for the second 25 cases: > 90% concordance for high ELs and > 40% for low ELs. Expected and threshold proportions of 'accreditation' MTBs were 50% and 20%, respectively, and the planned sample size was 24 MTBs. The improvements in concordance rates in TRs on post-tests were key secondary endpoints. The concordance rate of TRs with the AI system was an exploratory endpoint. **Results:** From May to December 2021, 47 participants applied, and 42 (27 MTBs, 14 individuals, and an AI company) were eligible. The primary 'accreditation' rate of MTBs was 55.6% (95% CI, 35.3-74.5%, $p < 0.001$), and the 'accreditation' rate of individuals was 35.7% (95% CI, 12.8-64.9%, $p = 0.17$). TR concordance rates improved significantly, from 57.5% (95% CI, 51.7-63.1%) to 65.7% (95% CI, 59.2-71.6%) [odds ratio (OR): 1.23, $p = 0.04$]. A prespecified subgroup analysis showed an improved concordance rate for biomarkers with low ELs for MTBs (OR, 1.32: 95% CI, 1.00-1.73), but not for individuals (OR, 1.11: 95% CI, 0.75-1.63). TR concordance rates with the AI system were 80% (95% CI, 60.0-91.4%) and 84% (95% CI, 64.3-93.9%) for pre- and post-tests, respectively. **Conclusions:** This LP significantly improved the quality of TRs by MTBs, potentially leading to providing more matched trials to cancer patients. TRs by the AI system showed higher concordance with central consensus TRs than MTBs, suggesting the clinical utility of AI-based TRs over those by MTBs. Research Sponsor: Japanese Ministry of Health, Labour and Welfare.

11033 **Poster Session**

A longitudinal study assessing the impact of ongoing COVID-19 pandemic among hematology-oncology trainees. *First Author: Sufana Shikdar, University of Oklahoma Health Science Center, Oklahoma City, OK*

Background: Hematology-Oncology (HO) trainees faced significant challenges due to the COVID-19 pandemic highlighted by a previous survey (Durani, Urshila, et al. "Impact of COVID-19 on Hematology-Oncology Trainees: A Quantitative and Qualitative Assessment." *JCO Oncology Practice* (2021): OP-21). Despite the positive impact of effective vaccines, the pandemic is still ongoing; thus, the challenges remain. Our aim is to evaluate how well the trainees have adapted to changes in their clinical training environment after the early phase of the COVID-19 pandemic. **Methods:** A cross-sectional internet-based survey (Shih, Grace, et al. "The impact of the COVID-19 pandemic on the education and wellness of US Pediatric Anesthesiology Fellows." *Pediatric Anesthesia* 31.3 (2021): 268-274) from December 10, 2021, to January 10, 2022, was obtained from the trainees enrolled in Accreditation Council for Graduate Medical Education (ACGME)-accredited HO fellowship programs in the United States in their fourth (PGY4), fifth (PGY5), and sixth (PGY6) postgraduate year. **Results:** The survey was completed by 102 trainees. Demographics of the participants are reported in Table . Interestingly, 51% reported an impact of COVD-19 on their employment plans, primarily due to the inability to interview in person (24%, n=23). Trainees experienced several stressors due to the pandemic, including fear of getting sick from a patient (71%) or a coworker (66%). Approximately 27% (n=26) experienced mental health issues requiring additional care. Less than one-third of the trainees were concerned about clinical expertise and procedural skills. Trainees also felt that the change of conference to virtual format impacted their learning activities compared to in-person education (66%, n=64). Most trainees (52%, n=53) reported limited involvement in COVID-related research and journal club education. Most had access to socialization (59%, n=60), virtual office hours (70%, n=72), and telehealth visits (83%, n=85). Female trainees (18%) were more likely to seek mental health care than the male trainees (7.8%) (P=.02). Female trainees (33%) also reported facing more challenges in their employment plans compared to males (16%) (P=.003). **Conclusions:** Our study highlights the challenges experienced by hematology-oncology trainees with the ongoing COVID-19 pandemic and reveals the gender gap related to employment plans and seeking mental health care. Research Sponsor: None.

Survey respondent characteristics.

Characteristics	N = 102	%
Age, y, mean	32.7 (SD 2.4)	
Gender		
Male	49	48
Female	53	52
Postgraduate year (PGY)		
PGY4	29	28
PGY5	31	30
PGY6	42	41
Quarantined due to work-related COVID-19 exposure		
Yes	21	20
Training extension		
No	99	97

11034 **Poster Session**

Professional development in a Twitter hematology/oncology network for trainees. *First Author: Muhammad Salman Faisal, Roswell Park Cancer Institute, Buffalo, NY*

Background: While resources exist to address the needs of graduate medical trainees, online resources to assist trainees with specialty-specific professional development have not been fully developed or described in the past. The Hem-Onc Fellows Network (@HemOncFellows) is an online community for hematology-oncology trainees in all stages of training, including medical students, residents, fellows, and doctoral students. The network's goals are to provide professional development in hematology-oncology, create a community and safe space for hematology-oncology trainees, and amplify the voices and needs of trainees. **Methods:** The @HemOncFellows Twitter account was created in February of 2021. The hashtag #HOFellows was registered and certified with healthcare Symplur. The network hosts Twitter Spaces (TS) with guests every two weeks and distributes a newsletter. Fifteen TS were held between July 2021 and February 2022. For each TS, a specific topic of professional development was discussed. At least one content expert was invited to each TS to provide additional commentary. Demographics of TS participants and newsletter subscribers were gathered and qualitative and quantitative analysis was performed. **Results:** Since its inception, the Hem-Onc Fellows Network has grown to more than 2200 followers. Symplur has over 500 #HOFellows tweets from November of 2021 to early February of 2022. The network organized 15 TS: 14 in professional development topics and one meet-and-greet for new matched fellows in December. TS had an average of 41 participants per event. Most participants were United States-based but there were participants from 21 countries worldwide. Forty-eight participants attended three or more spaces, including 15 hem-onc fellows and 17 internal medicine residents. The newsletter has 48 subscribers. **Conclusions:** We demonstrate that implementing a trainee network on Twitter attracted participation and engagement from a diverse pool of trainees worldwide. TS represents a novel educational tool for engaging trainees and facilitating professional development. Research Sponsor: None.

11035 **Poster Session**

The future of the oncology workforce: Presenters at an international trainee oncology conference. *First Author: Andrea Anampa-Guzmán, Universidad Nacional Mayor de San Marcos, Lima, Peru*

Background: In 2017, ASCO established the ASCO medical student and resident Abstract Forum. This study aimed to describe the characteristics of the ASCO medical student and resident abstract forum participants. **Methods:** We conducted a retrospective, observational study of Abstract Forum participants from 2017 to 2021. Descriptive statistics were used to summarize the participants' demographics by gender, stage of training, and institution location. We reported the publication rates and career paths of presenters. **Results:** The number of participants has more than tripled in the five years since the program's inception. Female participants are almost half of the total. In 2017, there was only one international participant. Over the subsequent five years, international members have steadily increased and represented nearly one-third of all participants in 2021. In the inaugural year, most forum participants were from institutions with ASCO Sponsored Oncology Student Interest Groups (OSIG), but in 2021 almost half were from institutions without OSIGs. The majority of participants were medical students, followed by internal medicine residents. Of a total of 179 abstracts presented between 2017 and 2021, 35 (19.55%) were subsequently published as full-text peer-reviewed manuscripts. Studies presented orally and studies presented by participants from the United States were significantly more frequently published as articles. 58.49% of medical student presenters that started residency chose Internal Medicine or Radiation Oncology. 50% of the student presenters that graduated internal medicine residency went to Hematology-Oncology fellowship. Most of the resident presenters that completed residency went to pursue careers in Hematology-Oncology (72.73%). **Conclusions:** The steady increase in participants since the program's creation demonstrates interest in the medical student and internal medicine resident community in these types of initiatives. The increase in international participants over the years highlights opportunities for ASCO to expand its global reach and efforts, particularly in low-income countries where trainees have the highest need for mentoring and organized support. Our study provides critical insights into the profile of participants of the Abstract Forum. Participation in this program should be encouraged, especially in countries with high cancer prevalence and mortality. Research Sponsor: None.

11036 **Poster Session**

Google search engine analytics for cancer immunotherapy: What patients are searching for on the internet and where they find answers. *First Author: Neeraj V. Suresh, University of Pennsylvania Department of Otorhinolaryngology-Head and Neck Surgery, Philadelphia, PA*

Background: Immunotherapy in the treatment of cancer has been on the rise and is on the forefront of current cancer research. As such, patients are increasingly turning to the Internet and online resources to answer their questions. For any given Google search, artificial intelligence and machine learning algorithms generate a "People Also Ask" (PAA) section which returns the most commonly associated questions to the original search query, with corresponding websites to answer those questions. Using a search engine optimization (SEO) tool, we determined the most frequently searched terms and questions regarding cancer immunotherapy online, and the websites used to answer them. **Methods:** The top Google search queries and PAA questions with associated volume metrics were extracted for the terms "immunotherapy" and "cancer immunotherapy" using an SEO tool. PAA questions and corresponding websites were categorized by specific topic and Rothwell's classification system. Websites were further quality assessed using the Journal of the American Medical Association (JAMA) benchmark criteria. **Results:** Global searches for cancer immunotherapy increased significantly each year since 2015. Countries with the most search volume were the U.S. (44%), the U.K. (12%), and India (11%). PAAs (n = 674) and the most frequently searched questions regarding cancer immunotherapy, by average monthly search volume (searches per month), were on: definitions/how it works (n = 6.6K, 21.3%), side effects (n = 4.4K, 14.2%), cost (n = 2.9K, 9.4%), immunotherapy vs. chemotherapy (n = 1.8K, 5.8%), drug options (n = 1.7K, 5.5%), signs immunotherapy is working (n = 1.2K, 3.9%), different types of immunotherapy (n = 1.1K, 3.5%), route of administration (n = 800, 2.6%), efficacy/success rate (n = 800, 2.6%), and effect on life expectancy (n = 300, 1.0%). The top cancers that patients searched immunotherapy treatments for were: lung (n = 1.9K, 23.2%), melanoma (n = 1.5K, 18.3%), pancreatic (n = 700, 8.5%), breast (n = 600, 7.3%), and bladder (n = 500, 6.1%). The most queried immunotherapy drugs were Pembrolizumab/Keytruda (n = 87K), Nivolumab/Opdivo (n = 33K), and Ipilimumab/Yervoy (n = 11.1K). Websites used to answer PAA questions were mostly those of academic institutions (n = 294, 43.6%), commercial organizations (n = 167, 24.8%), and government databases (n = 126, 18.7%). **Conclusions:** The field of cancer immunotherapy is rapidly evolving and patients often look to the Internet to answer their latest questions. Using our findings, academic institutions, commercial organizations, and physicians involved in multidisciplinary cancer care can cater their patient communications and websites to more directly align with patients' most common questions and concerns on immunotherapy. Research Sponsor: None.

11037 **Poster Session**

Evaluating the quality of clinical evidence in gastrointestinal cancers PubMed searches: How relevant are the results? *First Author: Ivy Riano, Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical Center, Lebanon, NH*

Background: Bibliographic repositories have become increasingly important as clinical evidence is more accessible on the internet. Often, oncologists rely on published literature to guide patient care. However, with the proliferation of journals and increasing number of peer reviewed papers, current search strategies have the potential to retrieve large numbers of irrelevant or misleading articles. Moreover, access to current best evidence may require paid subscriptions. Here, we assessed the quality of retrieved medical literature pertaining to treatment of gastrointestinal cancers using the PubMed database. **Methods:** We interrogated 6 focused-therapy questions in 3 categories: medical oncology (MedOnc), surgical oncology (SurgOnc), and alternative medicine (AltMed). We extracted journal metrics of the first two pages (40 results) from each search. We defined the composite outcome "relevant result" as the product of removing results from 1) predatory journals (Beall's list), 2) non-English language, and 3) no free access publications. As a sensitivity analysis, we defined 2007 as a cutoff for "relevant" publications and Impact Factor (IF) > 3 or H-index > 50. **Results:** Two hundred and forty results were retrieved (80 per search type). Forty-eight percent of the journals were European (n = 115), 40% US-based (n = 96), and 94% were in English (n = 225). Most journals (n = 170; 70.8%) had an IF between 1-10, followed by ~21% with an IF > 10 (n = 51); yet ~45% (n = 107) were in the Clarivate Analytics top quartile. Sixty percent (n = 139) of articles were free to access. The articles had a median H-index of 117 [IR 59, 168]. When modelling the multivariate association with "relevant result", year of publication after 2007 had an OR = 1.07 (95% CI = 1.01-1.14; $p< 0.02$) and availability through GOLD Open Access by Clarivate Analytics had an OR = 1.09 (95% CI = 1.03-1.15; $p< 0.0008$). MedOnc retrieved more papers published in journals with IF > 10 (n = 31; 38.8%) than SurgOnc searches (n = 12; 15%; $p< 0.001$). Only the AltMed searches included non-peer reviewed publications (n = 4; 5%) and 4 results were from "predatory journals", all in MedOnc. **Conclusions:** Articles had a 7% higher chance of being considered a "relevant result" if they were published after 2007 and a 9% higher chance if available under GOLD Open Access. Publications identified as "relevant results" with an IF or H-index above the established cutoffs, had a 6% higher chance to be in the top 40 PubMed search results. In the sensitivity analysis the results remain virtually unchanged. Importantly, nearly 40% of papers indexed in PubMed do not have free full-text articles, making them unavailable to oncologists without access to a medical library or paid subscription. These results highlight the imperative to deliver relevant, freely accessible information that can impact the care of the cancer patients. Research Sponsor: None.

11038 **Poster Session**

The need to develop the career pathway in oncology as an opportunity to improve the satisfaction of young oncologists in Spain: A national survey by the Spanish Society of Medical Oncology (SEOM) + mir section. *First Author: Pablo Jiménez Labaig, Department of Medical Oncology. Cruces University Hospital, Barakaldo, Spain*

Background: A long-term planning of the oncologists' career path is essential to approach the continuous changes in the oncology field given the need of further subspecialization after the training period. Our aim is to evaluate the current professional development of young medical oncologists in Spain and seek improvement strategies to enhance their careers in order to guarantee commitment with research and improve in patient care and outcomes. **Methods:** The SEOM +MIR Section launched a national online survey in May 2021 aimed at young medical oncology consultants (<6 years of experience) and last year medical oncology residents. Spanish professionals were invited to participate via email through the SEOM database. A descriptive analysis was performed using R software v4.1.2. **Results:** A total of 162 responses were eligible. 103 (64%) were women. 129 (80%) were consultants and 33 (20%) were residents. 92 (68%) performed standard clinical care and 11 (7%) research activity. 118 (73%) were subspecialized in a main area of interest and almost half of them, 70 (59%), chose it because it was the only option available after finishing residency. 87 (54%) had considered different employment opportunities other than standard clinical care and 38 (23%) showed an interest in enhancing their research activity. 141 (87%) showed relevant concern about their employment stability (table attached). 82 (51%) had considered working abroad: 33 (44%) outside European Union. The main reasons were: 132 (81%) believed the professional standing in Spain was worse than other countries, 41 (25%) thought it might increase their professional development and 33 (20%) argued for better salary conditions abroad. Among them, 21 (13%) had signed at least 4 contracts and 66 (41%) had ≥5 employment contracts in the last 5 years. 27% of respondents indicated that the figure of the boss had been the most contributing professional in their professional career. The mentor (20%) and the tutor (18%) also stand out as relevant figures in terms of professional development. Up to 27% of the sample refers not to have obtained any help from the figures mentioned. **Conclusions:** An absence of engagement in the long-term career paths of young medical oncologists in Spain was observed. Research is not defined in the current early professional life. Furthermore, there is a lack of contractual quality and planning for the entry into the labour market of newly trained oncologists. The lack of such a career pathway has consequences that encourage the search for employment opportunities different from clinical care and in other countries. Research Sponsor: Spanish Society of Medical Oncology (SEOM).

Level of satisfaction of young oncologists with their job stability.

Level of concern of job stability	N	Percentage (%)
1	7	4.32%
2	2	1.23%
3	6	3.70%
4	6	3.70%
5	12	7.41%
6	6	3.70%
7	17	10.49%
8	21	12.96%
9	23	14.20%
10	62	38.27%
Total:	162	100.00%

11039 **Poster Session**

The impact of mentoring on early career faculty: Assessment of a virtual mentoring program. *First Author: Akanksha Sharma, Pacific Neuroscience Institute/Saint John's Cancer Institute, Los Angeles, CA*

Background: Participation in mentorship programs for early career physicians may be crucial to developing key skills and professional networks to navigate racial, ethnic and gender leadership disparities in medicine. A 6-month virtual facilitated peer mentorship program was developed and piloted through the Society for Neuro-Oncology (SNO) Women & Diversity Committee. The evaluation of the program's feasibility to positively impact early career physicians, investigators and trainees is presented here. **Methods:** We designed and conducted a virtual mentoring program pilot open to SNO's multidisciplinary members in residency, fellowship, or early career phase, leveraging peer-mentoring sessions with mid-to late-career physician mentors. A curriculum with online resources was provided recommending groups meet for 6 sessions: 3 involving the mentor and 3 dedicated to peer-mentoring. Group assignments were based on time-zones and interests. Pre- and post-participation surveys assessed mentee experience. Descriptive statistics were used to assess participant demographics and survey results. **Results:** Our call for participation was broad; all 20 mentee applicants participated in 5 groups. Mentees were 90% women and 60% were from diverse racial and ethnic backgrounds. Most were aged 31-40 (75%) and junior faculty (50%) in neuro-oncology (65%). The 5 senior mentors (3 men and 3 of diverse race and ethnic backgrounds) practiced either neuro-oncology (3), neurosurgery (1) or radiation oncology (1). The proportion who reporting having a signature lecture increased from 15% to 62% during the pilot. A large majority reported their participation was worthwhile (85%), that they would participate again (92%) and would recommend it to others (92%). Feedback themes included positive personal growth, peer support, networking and job opportunities, access to CV reviews, lack of and desire for late career female mentors, and virtual scheduling constraints. While the pilot was limited by several variables, it was timely to connect participants in Q3 of 2020 early in the COVID-19 global pandemic. The virtual meeting environment created a venue to share and discuss topics such as work-life balance, burnout, leading through change and social connection. Despite not achieving 100% professional concordance, participants found the experience worthwhile. The tools and curriculum of topics provided was implemented differently across groups, leading to varied experiences. Finally, we did not have 100% post pilot follow up despite multiple attempts limiting our complete understanding of the pilot. **Conclusions:** This virtual mentorship pilot program proved feasible and of value in development of early career women and diverse individuals. A resource toolkit has been designed to scale and diffuse. Research Sponsor: None.

11040 **Poster Session**

Generating meaningful peer-to-peer engagement through a mentor-led, small group social learning experience on the evolving standards of care for advanced HER2+ breast cancer. *First Author: Latha Shivakumar, Association of Community Cancer Centers, Rockville, MD*

Background: Although the COVID-19 pandemic quickly created a spotlight on distance learning, identifying models that can deliver effective educational programs and best serve the needs of oncology clinicians remains a significant challenge. **Methods:** We conducted an educational program on the evolving standards of care for advanced HER2+ breast cancer hosted on a novel digital platform that offers a personalized social learning experience which prioritizes engagement, peer-to-peer learning, and mentorship within a small group setting. **Results:** 87 learners within 10 groups of professionally-connected clinicians participated. Learners progressed through foundational self-study modules, collaborated on asynchronous group challenges, and participated in synchronous live group discussions over six weeks (approximately 4 hours total). Quantitative and qualitative analysis of data extracted from these components highlights the impact of this program (Table). Notably, the learner population was more specialized and engaged than could be expected of a traditional CME program. Feedback suggests strong impact of the live group discussions on learners' intended practice changes. Additionally, analysis of group challenges and live group discussions revealed several key insights into learner thinking about treatment guidelines, including their differing opinions about the role of surgery/radiation in patient care, uncertainty about the mechanisms of action (MOAs) of discussed therapies, and their apprehension about implementing therapies that may impact the heart and lungs. **Conclusions:** The outcomes from this analysis highlight the utility of this type of social learning platform to create a safe, supportive learning environment that encourages multiple real-time and asynchronous interactions and shared experiences between clinicians who treat patients with advanced HER2+ breast cancer, as well as offering unique and convenient mentoring opportunities for clinicians interested in leading these digital small groups. Program impact. Research Sponsor: Daiichi Sankyo and AstraZeneca.

Quantitative Highlights

- **92% of participants specialized in oncology or hematology/oncology**
- **Average of 5 platform interactions per learner**
- **70% of learners completed all 5 self-study modules**
- **94% reported that they intended to make changes to their practice based on, or that their current practice had been reinforced by, the experience**

Qualitative Highlights

- **Differing opinions regarding the role of surgery and/or radiation in patient care**
- **Uncertainty about MOAs of available therapies**
- **Apprehension about certain therapies that may impact the heart and lungs**

11041 **Poster Session**

Quality and content of online cancer information: An analysis of NCI-designated cancer center YouTube videos. *First Author: Luke Kim, University of California, San Francisco School of Medicine, San Francisco, CA*

Background: The internet and social media have become a common source of medical information. Previous analyses have found that YouTube videos disseminate biased cancer related information of low to moderate quality. We analyzed online information disseminated by NCI-designated Cancer Centers (CC) through their YouTube pages. **Methods:** We searched CC websites and online search engines to identify CC-specific YouTube pages. Our sample included each CC's top 20 most-viewed videos uploaded during 2019, which were < 5 minutes long, and available in English or Spanish. We examined video content themes and speaker demographics. For patient education videos, we evaluated content understandability and quality of information using validated measures [i.e., Patient Education Materials Assessment Tool (PEMAT) and DISCERN]. Data was summarized using descriptive statistics. **Results:** A total of 31 of 64 clinical NCI-designated CC had dedicated YouTube pages. Only 6 (19%) CC had videos in languages other than English. A total of 402 videos were examined for content themes and demographic characteristics. 43% focused on patient education (n = 175), 36% research (n = 139), 24% survivorship (n = 95), and 13% clinical trials (n = 52). 32% (n = 119) of speakers were doctors and 18% (n = 65) patients. Perceived speakers' ethnicity was 57% White (n = 229), followed by Asian (15%, n = 60), Black or African American (8%, n = 32), and Latinx (4%, n = 16). Perceived gender of speakers was 49% women (n = 197) and 51% men (n = 203). Most videos were understandable (91%, n = 159), but only 21% (n = 36) provided high quality information. Videos discussing treatments lacked discussion of risks, alternate options, and effects on quality of life. **Conclusions:** Most patient education videos uploaded to NCI-designated CC YouTube pages have low to moderate quality information and limited ethnic diversity of speakers. With ongoing trends of increasing misinformation spreading through social media, CC have an opportunity to create and disseminate high-quality, reliable, and comprehensive educational videos that meet the informational needs of patients with cancer and their caregivers. Research Sponsor: None.

	No. Videos (%)
Overall Quality	
High quality of information (DISCERN 4 or 5)	36 (21%)
Understandable (PEMAT > 75%)	159 (91%)
Understandability	
Uses medical terms only when needed and defines them	141 (81%)
Organized in short sections*	98 (73%)
Provides summary of information*	98 (73%)
Reliability of information	
Sources of information used are clear	17 (10%)
Provides additional sources of support and information	47 (27%)
Quality of information on treatment choices (n = 56)	
Describes how a treatment works	44 (79%)
Describes benefits of treatment	49 (88%)
Describes risks of treatment	16 (29%)
Effect of treatment in quality of life	16 (29%)
Clearly presents there is > 1 treatment choice	23 (41%)
Supports shared decision making	22 (39%)

*N = 138; videos < 1 min excluded.

11042 **Poster Session**

Are YouTube videos a reliable information source for young women with metastatic breast cancer? *First Author: Nina Morena, McGill University, Montreal, QC, Canada*

Background: Young women with metastatic breast cancer (MBC) are an underserved population, rendering them susceptible to media sources that lack in credibility and reliability. YouTube (YT) is the most commonly used search engine following Google. This study aims to assess the quality of MBC YT videos and to identify common themes in MBC experiences. **Methods:** A systematic review of YT videos with search terms "metastatic breast cancer young" was conducted in 08/2021. Title, date uploaded, length, poster identity, number of likes, dislikes, and comments were collected. Understandability, actionability were assessed using the Patient Education Materials Assessment Tool (PEMAT) for audiovisual (A/V) materials; information reliability/quality was assessed with DISCERN. Scoring was done by 3 reviewers. Themes, presence of sponsorships, healthcare professionals' and patients' narratives were also reported. **Results:** 101 videos were identified. Of these, 78.2% were sponsored. Average video length was 14.9 minutes (SD 22.5). Majority were posted by nonprofit groups and breast cancer advocacy organizations. Mean PEMAT A/V score was 78.8% (SD 15.3) and 43.1% (SD 45.2) for understandability and actionability, respectively. Overall, videos had moderate reliability and quality levels; mean DISCERN score was 2.44/5 (SD 0.7). Patient narratives were shared in 63.3% and healthcare professionals in 57.4%. Identified themes include treatment (66.3%), family relationship (45.5%), motherhood (37.6%), terminal status (31.6%), the path to diagnosis (28.7%), and spousal relationship (24.7%). **Conclusions:** YouTube videos about MBC are highly understandable but demonstrate low to moderate rates of actionability, with low reliability and quality scores. Many have a potential commercial bias. More research is needed to evaluate their impact on patient decisions and possible interventions provided by healthcare institutions. Research Sponsor: St Mary's Hospital Foundation.

Distribution of PEMAT and DISCERN scores.

Tool	Value	Mean	SD	Min	Max	Median	Mode
PEMAT Understandability	Total points (numerator)	7.6	1.9	3.0	12.0	7.0	7.0
	Total possible points (denominator)	9.9	1.2	5.0	12.0	10.0	10.0
	Score (%)	78.8	15.3	30.0	100.0	77.8	70.0
PEMAT Actionability	Total points (numerator)	1.4	1.4	0.0	4.0	1.0	0.0
	Total possible points (denominator)	3.1	0.3	3.0	4.0	3.0	3.0
	Score (%)	43.1	45.2	0.0	100.0	33.3	0.0
DISCERN	Total points	39.0	11.1	18.0	68.0	39.0	38.0
	Average on 5	2.4	0.7	1.1	4.3	2.4	1.8

11043 **Poster Session**

Characterizing online engagement and academic impact of oncology research during the COVID-19 pandemic. *First Author: Chandrasekar Muthiah, Medical College of Wisconsin, Wauwatosa, WI*

Background: There is increasing use of social media as a platform to discuss research and educate. An article's impact can be assessed through the Altmetric Attention score (AAS), which considers the volume of social media mentions (Twitter, Facebook, Wikipedia, policy, etc), and the PlumX Impact score, which incorporates interactions on these platforms and citations. COVID-19 has encouraged novel literature in oncology, and these metrics may holistically evaluate the immediate impact of articles in addition to gradual accrual of citations. We explored the relationship between traditionally used bibliometrics (citations, impact factor) and new bibliometrics (AAS, PlumX) of the top 100 trending articles on cancer and COVID-19. **Methods:** The 100 articles with highest AAS featuring keywords "cancer" and "COVID-19" between March 1, 2019 and January 15, 2022 were identified via Altmetric explorer. AAS, journal, social media mentions, open access status and other characteristics were collected. Scopus database was utilized to identify PlumX scores and citation count. Analysis included Spearman correlation coefficients and ANOVA. **Results:** Of the 100 articles, 64% were original investigations, 18% editorials/perspectives, 6% guidelines/consensus articles and remaining article types < 6% each. Original investigations comprised of 41% retrospective cohort, 33% cross-sectional, 20% prospective cohort, and remainder < 4% each. Most articles were open access (91%), from cancer-focused journals (77%), and based in North America (36%); 25% were in Europe, 24% multi-continental, and remainder < 8% each. Most publications were in 2020 (56%) and 2021 (40%). AAS and PlumX did not correlate with number of citations or impact factor. Open access publications were associated with greater PlumX (p = 0.033) compared to closed access; this was not seen with AAS. ANOVA showed greater AAS in Australian articles (p = .004) and greater PlumX in North American articles (p = .04). Article type or publication year did not impact AAS and PlumX. **Conclusions:** In our analysis, Altmetrics and PlumX did not correlate to traditional bibliometrics (citation count, impact factor) in cancer and COVID-19 articles. This suggests that these tools may be complimentary rather than predictive of citations. However, this may change given likely insufficient time for citations to accrue for 2021 studies. There were more editorials/perspective articles compared to similar studies in other specialties, suggesting greater impact of such articles in oncology during COVID-19; this is perhaps due to reliance on expert opinion given paucity of data. Additionally, we noted that PlumX benefits from open access status. Overall, as the use of social media for research dissemination grows, researchers and journal editors may employ alternative metrics to better understand ways to increase the influence of oncology literature during the pandemic. Research Sponsor: None.

11044 **Poster Session**

Comparing online engagement and academic impact of lung cancer research: An altmetric attention score and PlumX analysis. *First Author: Arun Muthiah, Rhode Island Hospital-The Warren Alpert Medical School of Brown University, Providence, RI*

Background: Social media has proven vital in the rapid dissemination of literature to medical professionals and the public. In recent years, seminal research articles have yielded breakthrough therapies for lung cancer, including targeted drugs and unique immunotherapy-based combinations. New metrics such as the Altmetric Attention score (AAS) and PlumX Impact score capture interactions through social media and other public forums and serve as swifter counterparts to citations, which can take years to accrue. In this study, we characterize and compare AAS, PlumX and traditional bibliometrics (citation count, impact factor [IF]) of the top 100 trending articles on lung cancer. **Methods:** The 100 articles with the highest AAS featuring the keywords "lung cancer" between 01/2019 and 12/2021 were identified via Altmetric explorer. AAS, open access status, article type, topic, year and continent of publication were collected. PlumX and citation count were identified via Scopus database. Analysis included Spearman correlation coefficients and ANOVA. **Results:** A majority of the 100 articles were original investigations, of which 40% were RCTs, 22% retrospective cohort, 14% prospective, 9% basic science, 8% cross-sectional and 6% genome-wide association studies. Most articles focused on NSCLC (59%) and were conducted in North America (44%); 13% were in Europe, 36% multi-continental and the remainder < 5% each. PlumX positively correlated with both citation count ($p < .001$, $r = .765$) and IF ($p < .001$, $r = .581$). AAS did not correlate with citation or IF. Articles on guidelines ($p < .001$) and screening ($p < .001$) were associated with higher AAS in comparison to other article types and topics, respectively. Basic science articles were associated with a higher PlumX ($p < .001$) in comparison to others article topics. Year and continent of publication did not impact PlumX or AAS. Open access status did not correlate with PlumX or AAS. **Conclusions:** In our study, PlumX scores strongly correlated with citations and IF for recently published articles on lung cancer; this mirrors trends in other specialties. PlumX may be predictive in terms of academic impact, making it valuable to the research community. Though AAS did not correlate with traditional bibliometrics, its association with guidelines and screening articles suggests AAS may reflect interactions amongst a broader community (oncologic and non-oncologic clinicians). With the growing use of social media, the continued exploration of alternative metrics will play a role in understanding readership and fields of interest in lung cancer and in anticipating academic impact. Research Sponsor: None.

Article type (n)	Original	86
	Review/Meta-analyses	6
	Case studies	4
	Editorial/commentary/guideline	4
Article topic (n)	Targeted therapy	18
	Pathogenesis	13
	Immunotherapy	12
	Screening	11
	Epidemiological/Risk factors	10
	Other (diagnosis, chemo, RT, surgery, basic science, etc)	36

11045 **Poster Session**

#SurgOnc: Global discussions about surgical cancer care on Twitter during COVID-19. *First Author: Sofia Gereta, Department of Medical Education, Dell Medical School, The University of Texas at Austin, Austin, TX*

Background: Social media platforms such as Twitter are highly utilized to communicate about cancer care. Although surgery is the primary treatment for solid malignancies, little is known about public perceptions or communication behaviors regarding this treatment modality. Further, prolonged lockdowns and widespread delays of planned operations during the COVID-19 pandemic have magnified the importance of virtual communication about surgical cancer care. **Methods:** Tweets referencing cancer surgery were collected from January 2018 to January 2022 using Twitter's Application Programming Interface. Account metadata was used to predict user demographic information and to compare tweeting metrics across users. Natural language processing models were applied to tweet content to resolve common topics of conversation and to classify tweets by cancer type. **Results:** There were 442,840 original tweets about cancer surgery by 262,168 users. Individuals accounted for most users (65%) while influencers accounted for the least (1.4%). Influencers made the most median impressions (19,139). Of 240,713 tweets discussing surgery for specific cancers, breast (20%) and neurologic (17%) cancers were most mentioned. When adjusting for national rates of procedures performed, tweets about surgery for neurologic cancers were the most common (231 tweets per 1000 procedures) whereas those for urologic cancers were the least common (15 tweets per 1000 procedures). Discussions about cancer surgery research made up 31% of tweets before the pandemic but only 11% of tweets during the pandemic. During the pandemic, concern regarding COVID-19 related delays was the most tweeted topic (23%). Cancer surgery research was most cited by oncologists, as well as in tweets about hepatopancreatobiliary and colorectal cancers. The cost of surgery was commonly mentioned in tweets about breast and gynecologic cancers and contained the most negative sentiment score (-0.7). **Conclusions:** Twitter was highly utilized to discuss surgical cancer care during the COVID-19 pandemic. During the pandemic, conversations shifted focus from research to survivorship and reflected real-time events such as COVID-19-related surgical delays. We identified the financial burden of cancer care as a commonly held concern among patients discussing cancer surgery on social media. Future public health outreach about cancer surgery may be optimized by coordinating with influencers and by targeting topics of concern like cost of surgery and undermentioned content like urologic cancers. Twitter's role as a platform for research dissemination was disrupted by the COVID-19 pandemic, and further tracking is needed regarding online research discussions after the pandemic. Research Sponsor: None.

11046 **Poster Session**

Evaluation of trends in breast cancer–related content on TikTok. *First Author: Nanda Siva, West Virginia University School of Medicine, Morgantown, WV*

Background: Social media plays an important role in disseminating information to patients. It is important to investigate the healthcare content on popular platforms to understand the material consumed by patients that may influence their medical decision making. TikTok has over 1 billion monthly active subscribers and has become common ground to communicate healthcare information, including that of breast cancer. This study aims to provide an analysis of breast-cancer related information on TikTok. **Methods:** The most popular TikTok hashtag related to breast cancer was identified, and the top videos were gathered on January 23, 2022. Data was collected to reach a target of 100 videos. Exclusion criteria were non-English videos, repeated videos, or upload of movie/tv clip without educational info. The video source was characterized based on healthcare role, gender, and race. Healthcare provider was defined as an individual with a professional medical degree (MD, PA, RN, other). The videos were categorized into patient experience, educational, advertisement, and other. Specific content components, including chemotherapy, surgical intervention, mammogram, and self-breast exam, were tracked. **Results:** The hashtag "#breastcancer" was identified as the most popular, with 773.8 million views. The videos had a combined 258,886,300 views, 31,573,400 likes, 413,604 shares, and 567,520 comments. Of the 100 videos analyzed, 91 were uploaded by a layperson, 2 by a healthcare professional, and 7 by a company. The healthcare professionals consisted of one OB/GYN and one general surgeon. The racial designations of the main subjects in the videos were 87.2% White, 3.2% Black, 2.1% Hispanic, 4.3% Asian, and 3.2% undetermined. Content categorization revealed 81% patient experience, 22% educational, 6% advertisement, and 8% other. The major topics presented in the videos related to surgical treatment (39%), chemotherapy (37%), and radiation treatment (2%). **Conclusions:** An overwhelming majority of breast cancer related information on TikTok was not presented by qualified healthcare professionals and exhibited a lack of cultural diversity and inclusivity. Research Sponsor: None.

Specific components of TikTok videos analyzed (n=100).

Components	*%*
Chemo Side Effects	31
Emotional Support	29
Success with Treatment	22
Flat Closure	15
Self-breast Exam	6
Breast Reconstruction	6
General Check Breasts	3
Mammogram	2
Lymphedema	0

11047 **Poster Session**

Are we doing it right? Mentorship challenges for oncology fellows and early-career faculty from backgrounds underrepresented in medicine. *First Author: Dame Idossa, University of California-San Francisco, San Francisco, CA*

Background: Physician workforce diversity can be a driver of institutional excellence, improving innovation and reducing health disparities. The current diversity of the hematology/oncology (HO) workforce does not reflect that of the US population. The role of mentorship in increasing HO fellows' interest in pursuing careers in HO has been described previously. However, the mentorship experiences of fellows and early career faculty from backgrounds underrepresented in medicine (UIM) in HO has not been fully characterized. Therefore, we compared the mentorship experiences of UIM and non-UIM trainees and early career faculty in HO subspecialties. **Methods:** We conducted cross-sectional online survey of HO subspecialists including current fellows and faculty within 5 years of end of training. The anonymous survey was distributed via email and social media channels in April 2020. Fisher's exact test and multivariable logistic regression models were used to conduct comparisons between study groups. **Results:** Of the 306 respondents, 64 (21%) were UIM and 161 (53%) identified as male. UIM participants were less likely to have a primary mentor (66%) than non-UIM participants (80%, $p = 0.015$). Among those who had a primary mentor, UIMs were more likely to meet infrequently (greater than every 3 months, $p = 0.007$). Furthermore, UIMs were more likely to report having mentors outside their own institution (47% vs 40% non-UIM, $p = 0.002$) and making compromises to gain access to mentorship (36% vs 23% non-UIM, $p = < 0.001$). In addition, UIM participants were less likely to have an advisor (38% vs 54% non-UIM, $p = 0.017$), a coach (13% vs 20% non-UIM, $p = 0.054$), or a sponsor (19% vs 26% non-UIM, $p = 0.046$). UIMs were also less likely to apply for grants (34% vs 42% non-UIM, $p = 0.035$) and awards (28% vs 43%, non-UIM $p = 0.019$). In multivariable models, UIM individuals were more likely to make compromises to gain access to mentors (OR = 1.96, $p = 0.047$) and this remained significant for females (OR = 2.17, $p = 0.005$). Lastly, US born individuals had higher odds of having a primary mentor than non-US-born individuals (OR = 2.43, $p = 0.004$). **Conclusions:** In the largest study to date characterizing the mentorship experience of HO trainees and junior faculty, we found that UIM individuals were significantly less likely to find effective mentorship and were less likely to apply for awards and grant support. Understanding the challenges of UIM trainees can help shape training environments in academic medicine to ensure these are grounded in diversity and inclusion. Given the importance of workforce diversity, training programs in HO must consider structured programs and other innovations to improve mentoring experiences of UIM trainees and junior faculty. Research Sponsor: University of Wisconsin Carbone Cancer Center.

11048 **Poster Session**

Gender disparity in authorship of clinical trials leading to cancer drug approvals between 2008 and 2018: The glass ceiling of academic oncology. *First Author: Lynne O. Chapman, Baylor College of Medicine, Houston, TX*

Background: Authorship, expressly premier positions (first, corresponding, or senior author), in peer reviewed journals is widely acknowledged as scientific credit in academia. Yet, gender inequities and biases pervade this facet of the scientific ecosystem. We reviewed the authorship of pivotal FDA trials that established the standards of care in oncology over the past decade with the goal of defining the magnitude of gender disparity in the most influential literature of the field in recent years. **Methods:** We collected and assessed data from the primary publication of 231 trials that enabled FDA drug approvals in hematology and oncology from July 2008 to June 2018. Author gender was assigned from listed names using statistical probability and confirmed using institutional websites and online databases (genderchecker database, biographical paragraphs, and social media). Authors where gender was not clearly identified (1.23%) were excluded. To account for equal authorship contribution, we included co-authors as distinct data points, and credit was given to reports for any women in premier authorship positions (first, corresponding, or senior author) to avoid overestimating disparity. Descriptive statistics were used, and 95% confidence intervals (95%CI) were reported using modified Wald method. Proportions were compared using Fisher-exact and Chi-squared test. Unadjusted P values of < 0.05 were considered significant. **Results:** A total of 4664 (98.8%) authors were included in this analysis across 227 publications. Of these, 1287 (27.6%) were female with a median of 25.9% female authorship in total per trial. Female authorship was significantly higher for non-randomized (30.4% v 26.5% for randomized, $P = 0.007$) and phase 1/2 trials (29.9% v 26.3% for phase 3, $P = 0.009$) and varied with trial size ($P < 0.001$), with the proportion greater in trials with $\leq$100 patients versus those with $>$ 500 patients. Female authorship in fields of breast and gynecological oncology was higher (41.3%) than other cancers (26.0%, $P < 0.001$). Women were proportionally less likely to hold premier (9.2% v 18.2%, OR 0.46, 95%CI: 0.4 – 0.6, $P < 0.001$), first (3.2% v 6.3%, OR 0.49, 95%CI: 0.3 – 0.7, $P < 0.001$), senior (3.3% v 6.0%, OR 0.54, 95%CI: 0.4 – 0.8, $P = 0.002$) and corresponding (2.5% v 5.8%, OR 0.42, 95%CI 0.3 – 0.6, $P < 0.001$) authorship but not second author role (4.1% v 5.1%, OR 0.80, 95%CI 0.6 – 1.1, $P = 0.17$). **Conclusions:** The under-representation of women in premier authorship positions in pivotal clinical trials, demonstrated in our study, serves as a barometer of a biased academic infrastructure, amplifying existing calls to address barriers that limit the full inclusion of women in oncology. Research Sponsor: None.

11049 **Poster Session**

National impact of the COVID-19 pandemic on clinical trial staff attrition: Results of the SWOG Cancer Research Network Survey of Oncology Research Professionals. *First Author: Don S. Dizon, Lifespan Cancer Institute and Brown University, Providence, RI*

Background: Severe shortages in clinical trial staffing across the United States and internationally has been anecdotally noted, but data are lacking. To better assess the scope and impact of staffing shortages, SWOG conducted a Cooperative Group-wide survey of Oncology Research Professionals (ORP). **Methods:** The survey was developed by SWOG leadership and was granted an IRB exemption by Lifespan IRB (Providence, RI). The survey was disseminated by email in January 2022 to Head Clinical Research Associates (CRAs, n = 100) using an inclusive distribution list that goes to the site-identified administrative leader of each SWOG Member and National Community Oncology Research Program institution. The data were collected and managed using REDCap electronic data capture tools hosted at Lifespan. Descriptive statistics were performed and qualitative analysis conducted to identify major themes. **Results:** The response rate was 87% and 41 of 87 respondents completed the full survey (47%). The majority of respondents were female (89.6%), not Hispanic (87.8%) and White (85.1%). The proportion that identified as Hispanic or Asian was 12.8 and 6.9%, respectively. One participant identified as Black and another as American Indian/Alaskan native. The most common work setting was within an academic medical center (47.9%) and 57.8% held a management or leadership role at their institutions. The majority (79%) used an Institutional IRB for trials not overseen as part of the National Clinical Trials Network. Over 80% of respondents reported their institution is experiencing a personnel shortage due to COVID-19. Proportion who reported this negatively impacted IRB processes was 50%, financial review was 42%, and legal review was 26.9%. On a scale of 0 (none) to 6 (significant), the impact was most significant on audit activities and accrual to trials (both rated 5), transfer of data to sponsors and sponsor visits (both rated 4.5); all other aspects rated a 4, including screening procedures, regulatory activities, and data collection. Ranked reasons for attrition were desire for better pay, seeking better opportunities, and seeking more flexible working conditions. General burn out was ranked as the fourth most common cause. Important themes included increasing trial complexity, morale, lack of support (due to staff shortages), lack of opportunities for promotion, unfilled positions, and the lack of experience of new hires. **Conclusions:** Over 80% of research programs affiliated with SWOG report staffing shortages due to the COVID-19 pandemic and the impact of these shortages touch every aspect of clinical research. Initiatives to recruit, train, and retain staff are urgently needed. As in other areas of medicine (e.g. hospital nursing), the potential for post-pandemic persistence of this issue requires an immediate national response. Research Sponsor: U.S. National Institutes of Health.

11050 **Poster Session**

Race- and sex-based variation in industry research and general payments to medical oncologists in the United States. *First Author: Imraan Jan, Department of Radiation Oncology, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ*

Background: Industry partnerships offer financial incentives, prestige, and can facilitate career advancement in oncology. However, not all physicians may have equal access to these opportunities. We hypothesized that physicians who are underrepresented in the medical oncology workforce based on race, ethnicity, and gender receive less industry funding. **Methods**: All US medical oncologists (MOs) who received $\geq$1 industry research payment between 2016 and 2020 according to the Open Payments database were included in this retrospective study. Information extracted from Open Payments included MO's name, institution, research payments (i.e. funding for a research project where the physician is a Principle Investigator), and general payments (i.e. fees not associated with research, such as consulting and travel fees). Additional web searches were conducted using institutional websites, NPPES NPI registry, LinkedIn, Doximity, Scopus, and NIH RePORTER to determine each MO's race, ethnicity, sex, academic rank, degrees, h-index, institutional NIH research funding rank, and individual receipt of NIH funding. Log-linear regression was performed to identify associations of both industry and general payment data. **Results**: Of 7,542 physicians meeting inclusion criteria, 69% were male, 65% White, 29% Asian, 2% Black, and 4% Hispanic, which is comparable to the American Medical Association Physician Masterfile figures for MO. The median sum research payment and general payment was $134,857 and $11,537 per physician respectively. Significantly higher mean research payments were associated with an MS (+72%; $P = 0.003$) or PhD degree (+30%; $P = 0.009$), h-index (+3%; $P < 0.001$), top 50 institution rank by NIH funding (+44%; $P < 0.001$), and associate professor rank (+95%; $P < 0.001$). Significantly lower mean research payment were observed for Black physicians (-36%; $P = 0.022$) and those with non-academic affiliation (-47%; $P < 0.001$). No significant association was observed between sex and research payment. Significantly higher mean general payments were associated with male sex (+46%; $P < 0.001$), MS degree (+171%; $P < 0.001$), h-index (+2%; $P < 0.001$), and Asian race (+72%; $P < 0.001$). Significantly lower mean general payments were associated with an affiliation with a non-academic practice (-31%; $P = 0.012$). **Conclusions**: Black physicians received smaller sums of industry research payments compared to White physicians. Female sex was associated with decreased general payments compared to male sex. Further exploring the underlying mechanisms determining access to industry payments may help facilitate greater equity and inclusivity in oncology. Research Sponsor: None.

11051 **Poster Session**

Trainee and program director perspectives of parental leave and parenthood in oncologic specialties. *First Author: Sara Beltran Ponce, Medical College of Wisconsin, Milwaukee, WI*

Background: Delays in pregnancy exacerbate infertility. Thus, trainees are forced to make complex family planning decisions while juggling all aspects of training. In addition to a lack of parental leave and financial constraints, trainees are often concerned with the perceptions of leave and parenthood. Two single specialty surveys found that most program directors (PDs) felt parenthood negatively impacted trainee performance, disproportionately for women. We aim to understand PD and trainee perspectives of parental leave and parenthood in oncologic trainees. **Methods:** Contact information for PDs in oncologic specialties was gathered from FRIEDA. Surveys were distributed to all eligible PDs with a request to forward a parallel survey to their trainees. Social media links for both surveys were shared on Twitter. Tests of association for descriptive analyses included Fisher's exact test, Chi-square test, or the Mantel-Haenszel Chi-Square test, as appropriate. All computations were performed using SAS version 9.4. **Results:** 195 PDs and 286 trainees completed the survey with 49% and 56% female and 89% and 41% parent respondents, respectively. Per PDs, 73% of programs have a maternity leave policy, 48% have a paternity leave policy, and 5% have a fertility services policy. PDs and non-parent trainees (NPTs) rated the negative impact of parenthood on overall education ($p < 0.001$ for PDs, $p < 0.001$ for NPTs) and academic productivity ($p < 0.001$ for PDs, $p < 0.001$ for NPTs) as higher for women trainees than men trainees. PDs and NPTs also rated the burden of parental leave on co-trainees as greater for women trainees as compared to men trainees ($p < 0.001$ for PDs, $p < 0.001$ for NPTs). Among PDs, no significant differences by gender or specialty were found in advising for or against parenthood in training, but PDs in surgical specialties reported providing less support for trainees starting a family ($p < 0.001$) and trainees in surgical specialties reported being less supported ($p < 0.001$). Women trainees were more likely than men trainees to indicate that they would have started a family sooner if not in medicine ($p < 0.001$). 89% of parent trainees would choose to have children in training again, and 84% would recommend parenthood in training. **Conclusions:** Although many programs have parental leave policies, a substantial number continue to lack them. Concerns about negative perceptions of parenthood by trainees are valid, particularly for women who are significantly more likely to be seen as having their education and academic productivity impacted by parenthood. In addition, specialty choice impacts the support given to trainees as they start families. Despite these barriers, the vast majority of parent trainees would still choose to have children in training and recommend this path to fellow trainees. Additional initiatives to normalize and support family planning in medical training for interested trainees are warranted. Research Sponsor: None.

11052 **Poster Session**

Female representation in oncology leadership in Africa: Analysis of trends in the African organization for cancer research and training in cancer (AORTIC). *First Author: Miriam Claire Mutebi, Aga Khan University Hospital, Nairobi, Kenya*

Background: Board membership in oncology organizations and invitation to speak at major oncology conferences is an established indicator of gender disparities in oncology leadership. Recent studies note an upward trend in female board membership and female speakers at oncology conferences in European and American contexts. However, little is known about trends of female representation in board membership and at oncology conferences in Africa. AORTIC is the premier African cancer organization and hosts a biennial conference, during which its council members are elected for a two-year term. The conference hosts over 1000 participants and is highly regarded internationally. As the largest gathering of African oncologists, the conference presents a unique opportunity for insight into workforce disparities and trends. This study presents an analysis of female council membership and speaker participation at the 2015, 2017, 2019 and 2021 AORTIC conferences. **Methods:** AORTIC conference programmes and AORTIC elections for council membership in 2015, 2017, 2019 and 2021 were analyzed for gender representation. Speakers were divided into categories including keynote speakers, facilitators, session speakers, panelists, and oral abstract presenters. For each AORTIC session, data was collected on speaker name, gender, and affiliated country. Participants who presented multiple times were counted multiple times, as their role often varied between sessions. Personal data and country affiliation was determined through online biographies of speakers and/or visual confirmation of professional photographs. A simple descriptive analysis of the data and trends is presented here. **Results:** Since 2015, the proportion of female speakers and council members at AORTIC has increased. In 2015, females accounted for 44% of speakers, in contrast to 55% in 2021. In 2021, females made up over 50% of all speaker categories except keynote. The proportion of female council members also increased, from 42% in 2015 to 69% in 2021. Trends in geographic representation of speakers were also analyzed for gender, revealing an increase in female speakers residing in Africa. (Table) **Conclusions:** The proportion of female speakers and council members at Africa's largest cancer conference has increased significantly since 2015. Female speaker participation was higher than in North America and Europe in 2017 and surpassed 50 % in 2021. In addition, female council membership in AORTIC has surpassed 50%, up to 69% in 2021. These trends suggest a rise in female leadership in cancer research and training on the continent, indicating that strengthening local platforms in LMIC may be associated with improved gender assimilation. Research Sponsor: None.

Proportion of female speakers and council members at AORTIC.

Year	Female Speakers %	Female Council Members %
2015	44 %	42%
2017	44 %	58%
2019	51 %	56%
2021	55 %	69%

11053 **Poster Session**

Recent trends of "manels" and gender representation among panelists at the ASCO annual meeting. *First Author: Sophia C. Kamran, Massachusetts General Hospital and Harvard Medical School, Boston, MA*

Background: Gender disparities in academic medicine are a long-acknowledged concern. Efforts to recognize this imbalance and increase inclusivity continue, particularly in academic medical conferences. In June 2019, NIH Director Francis S. Collins MD, PhD publicly called for an end to all-male speaking panels ("manels"). It is unclear whether academic oncology conferences followed suit. We investigated the prevalence and longitudinal trends of manels and gender representation at the ASCO Annual Meeting during 2018-2021. **Methods:** Using ASCO online programs, 2018-2021 faculty information was obtained. Data collected included perceived or self-reported gender, medical specialty, panel role (chair vs. non-chair), type of session, and topic. Primary outcomes included percentage of manels and proportion of female panelists over time. Female representation among chairs, specialties, and topics were evaluated. Cochran-Armitage test was used to analyze time trends in the proportion of manels and female representation. Fisher's exact test was used to compare each session type, topic, or specialty to other categories combined. P-values are based on a two-sided hypothesis. **Results:** During 2018-2021, there were 670 sessions total, 81 of which (12.1%) were manels. Among 2,475 faculty members, 1,181 (47.7%) were females. Over time, there was a significant decrease in the number of manels, from 17.4% in 2018 to 9.9% in 2021 ($p = 0.030$) and a corresponding increase in proportion of female panelists from 41.6% to 54.0% ($p < 0.001$). The largest decrease in manels occurred between 2018 (17.4%) and 2019 (10.5%). Among session type and topic, the highest proportion of manels was observed for leadership/special sessions (17.1%, $p = 0.419$) and translational/pre-clinical topics (19.6%, $p = 0.024$), respectively. The chair role was majority male (53.2%) in 2018 but increased to > 50% female representation in 2019-2021 ($p = 0.157$). The lowest proportion of female panelists were in pathology/radiology/dermatology specialties (combined 26.2%, $p = 0.001$). Female panelists were underrepresented for the topics of genitourinary cancers (38.6%, $p = 0.029$) and translational/pre-clinical sciences (36.7%, $p < 0.001$). Females were overrepresented in the topic of supportive oncology (70.3%, $p < 0.001$). There was a positive trend toward improved female representation among translational/pre-clinical sciences (27.4% in 2018 to 41.8% in 2021, $p = 0.031$), but with little improvement among genitourinary cancers (41.1% in 2018 to 40.7% in 2021, $p = 0.969$). **Conclusions:** The number of female ASCO panelists increased during the study period and surpassed 50% in 2021, with a corresponding decrease in the proportion of manels. Still, there are certain topics/specialties where female representation has remained stagnant. ASCO Annual Meeting organizers should continue to strive for diverse gender representation and the elimination of manels. Research Sponsor: None.

11054 **Poster Session**

Where is your lactation room? Lactation policies and practices in oncology trainee and early career physicians. *First Author: Sindhu Janarthanam Malapati, University of Arkansas for Medical Sciences, Little Rock, AR*

Background: Training and early career years coincide with childbearing and raising young families, which places increased demands on new parents. With increasing numbers of female oncologists in the workforce, there is a need to assess and amend current workplace lactation policies. We surveyed Medical and Radiation Oncology trainees and early career faculty to assess policies and practices regarding lactation during training and early career. **Methods:** An anonymous 48 question cross-sectional survey developed by researchers with expertise in gender equity was distributed via email and social media channels between May and June 2021 to oncology trainees and physicians within 5 years of terminal training; program directors (PDs) were surveyed separately. Descriptive statistics were used. **Results:** Of the 255 complete responses, 26% (65) respondents breastfed for any length of time upon return to work. Of these, 54% (35) were trainees and 46% (30) early career faculty. 69% (45) had access to a designated lactation room; however, 57% (37) noted that duration of their pumping breaks was inadequate to access and use the lactation room. Most (60%, 39) did not feel comfortable asking for protected time to pump. Employment contracts did not specifically include pumping breaks for 66% (43), while 34% (22) were unsure about their contract policies surrounding lactation. Of all breastfeeding mothers, 77% (50) felt their colleagues to be supportive of their needs; a minority reported negative responses due to pumping breaks from faculty (11%), co-fellows/colleagues (8%) and clinic staff (15%). 51% (33) bought a wearable pump prior to return to work, of which 70% (23) found it financially burdensome. Most common reasons for buying a wearable pump were to improve efficiency during work hours (61%, 20) and lack of adequate pumping breaks (39%, 13). Among 23 PDs who responded to the survey, 65% (15) had a program policy regarding lactating trainees, 9% (2) blocked clinic appointments to allow pumping breaks, 91% (21) provided lactation rooms, 83% (19) reported the lactation rooms are easily accessible. **Conclusions:** Both infrastructure and time accommodations made for the lactating parent are inadequate. There is a disconnect between the trainee and PDs' perception of provided accommodations. Systemic changes that provide adequate time and space for lactation to busy clinicians and trainees is imperative to ensure retention of women oncologists in the workforce. Research Sponsor: Centennial Scholar, University of Wisconsin.

11055 **Poster Session**

Identifying predictors of equitable gender representation among hematology and oncology fellowship programs. *First Author: Sasirekha Pandravada, Advocate Lutheran General Hospital, Park Ridge, IL*

Background: While gender disparities have largely been bridged among hematology and oncology fellows at the national level, there exist many individual fellowship programs that still have marked gender disparity. Our study is the first to examine gender differences among fellows at an institutional level in order to model characteristics of hematology and oncology programs that lead to more equitable gender representation. **Methods:** For each of the 148 hematology or oncology fellowship programs listed in the Fellowship and Residency Electronic Interactive Database, we collected data on gender, faculty academic rank, and fellow postgraduate year as listed on individual program websites. Further, a program was identified as an academic center if it had an affiliated medical school. Zip code data was used to identify geographic region, local population density, and racial diversity of each program's surrounding neighborhood. Multiple linear regression was used to model which factors contributed to a program having a higher percentage of female fellows. **Results:** 3600 faculty and 1488 fellows were included in the analysis. While women were well represented nationally among fellows (46.4%), 52.4% of fellowship programs had fewer than 50% women, and 28.6% of programs had fewer than 35% women. An individual program was more likely to have more female fellows if it had a higher percentage of female assistant professors ($p<0.01$), associate professors ($p<0.01$), assistant professors overall ($p<0.01$), a female program director (PD) or associate program director (APD) ($p=0.02$), and a designation as an academic center ($p<0.01$). Notably, the percentage of female full professors had no significant impact ($p=0.11$) on whether a program was likely to have more female fellows. **Conclusions:** While women are well represented nationally among hematology and oncology fellows, nearly one in three fellowship programs still have significant gender disparity. Our multivariate model identified several significant factors that predict whether a program was likely to have gender parity among fellows: a higher percentage of female assistant professors, associate professors, assistant professors overall, a female PD or APD, and a designation as an academic center. Whether these factors together highlight the importance of accessible mentorship or direct female faculty role models requires further study. However, by beginning to identify these significant factors, we hope to aid fellowship programs focus efforts when trying to achieve equitable gender representation. Research Sponsor: None.

Gender representation among hematology and oncology fellows and faculty.

	Fellow (PGY4-PGY6)	Assistant Professor	Associate Professor	Full Professor	Program Director
% Female	46.4%	51.1%	44.8%	25.1%	48.6%
% Programs with <50% Female	52.4%	41.0%	58.1%	89.5%	-
% Programs with <35% Female	28.6%	18.1%	31.4%	75.2%	-

11056 **Poster Session**

Exploring perceptions of gender bias in oncology: A survey study. *First Author: Nino Balanchivadze, Department of Hematology and Oncology, Henry Ford Cancer Institute, Detroit, MI*

Background: Gender inequalities contribute to burnout and have contributed to an ongoing exodus of women from academic oncology. Our aim was to explore the perceptions and experiences of oncology professionals regarding gender bias in the workplace with the hope of providing critical information to support equity initiatives. **Methods:** An anonymous, 22-question survey was sent via Survey Monkey to 1512 physicians with oncology-related specialties from National Cancer Institute (NCI) designated cancer centers whose emails were publicly available. Likert-scale questions (never-rarely-sometimes-often-very often) were analyzed with Kruskal-Wallis and Wilcoxon rank sum tests (percentages shown as frequency of having responded "sometimes-often-very often"). Chi-square test was used for categorical variables. **Results:** A total of 274 physicians completed the survey (response rate 18%): 152 (55.5%) self-identified as female (F); 112 (42%) as male (M); 7 (2.6%) as gender non-conforming or transgender; 3 (1.1%) chose not to answer. Most were White (59.9%), followed by Asian (20.4%), Middle Eastern (5.8 %), Multiracial (5.1%), Hispanic (3.6%), and Black (1.5%). The plurality (n = 103; 37.6%) were < 40 years old. Primary fields of practice included 118 (43.1%) in adult oncology, 45 (16.4%) in combined hematology/oncology, 44 (16.1%) in radiation oncology, 44 (16.1%) in adult hematology, and 23 (8.4%) in other specialties. Female gender was associated with experiencing gender bias more often than male gender in the following areas: clinical practice (80.9% F vs 20.6% M), research activities (73.0% F vs 15.2% M), having difficulty balancing work and non-work responsibilities (95.4% F vs 78.6% M), being held to higher standards compared to physicians of other genders (73.1% F vs 14.2% M), being mistaken as a non-physician (78.9% F vs 6.3% M), and being scrutinized by others while tending to child-care needs (48.8% F vs 23.2% M) (all $p < .001$). Female gender was associated with using techniques to navigate gender challenges more often than male gender, including wearing a white coat (55% F vs 7% M; $p < .001$), ensuring that "Doctor" is written on identification (33% F vs 3% M; $p = .002$), emphasizing a professional look (53% F vs 10% M; $p = .003$) and working harder to establish expertise in the field (72% F vs 18% M; $p = .003$). When asked about strategies to address workplace gender-related bias, 63% would like policies on gender-related discrimination, (66.4% F vs 65.2% M; $p = .93$), 62% would like policies that prioritize leadership representation (74.3% F vs 51.8% M; $p < .001$), and relatively few (37%) would prefer formal lectures/instruction for staff (38.2% F vs 37.5% M; $p > .99$). **Conclusions:** Self-identified female academic oncologists at NCI Cancer Centers reported facing gender-related challenges in daily practice at much higher rates than men. There is a clear need to identify root causes and create initiatives to promote gender equity in the field of oncology. Research Sponsor: None.

11057 **Poster Session**

The impact of diversity, equity, and inclusion training in an independent community oncology practice. *First Author: Mark T. Fleming, Virginia Oncology Associates, U.S. Oncology Research, Norfolk, VA*

Background: Historically, Diversity, Equity, and Inclusion (DEI) efforts have largely been left out of private practice medical facilities – mainly present in large academic hospital centers. Virginia Oncology Associates (VOA), a member of The US Oncology Network, is an independent community oncology and hematology practice specializing in the diagnosis and treatment of cancer and blood disorders. VOA has approximately 600 total employees consisting of physicians and clinical and non-clinical staff. In August of 2020, VOA launched an initiative to foster a culture of inclusion with the creation of its Inclusion Council (IC). Sixteen employees', both clinical (3 physicians) and non-clinical, were chosen to participate. The council reports to VOA's joint policy board. **Methods:** The council partnered with an outside organization, Virginia's Center for Inclusive Communities, to launch a practice-wide DEI training program focusing on unconscious bias and microaggression. The training was initially planned to be in person, but due to the constraints of the COVID pandemic, the training was performed using a virtual platform. The members of IC attended three two-hour sessions while other staff members and physicians were mandated to participate in at least one training session. After completion of the sessions, a survey was sent to all employees and physicians to measure the impact of DEI training. All employees were also given the opportunity to provide additional, anonymous, written feedback. **Results:** Table. A total of 169 employees responded. 72% of respondents agreed or strongly agreed that the program increased awareness of unconscious bias and microaggression, 67% felt that the program helps foster a culture of inclusion in the workplace, and 66% of respondents felt that the program met expectations. **Conclusions:** DEI efforts are vital in all aspects of health care delivery and oncology settings. DEI training met staff expectations and positively fostered a culture of inclusion by bringing attention to unconscious bias and microaggression in a community oncology practice. Research Sponsor: None.

Summary of employee respondent's views on DEI training.

Training Impact N=168	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
Increased Awareness of Unconscious Bias and Microaggression	33(20%)	87(52%	29(17%)	13(8%)	5(3%)
Help Foster Culture of Inclusion in Workplace	26(15%)	87(52%)	39(23%)	9(5%)	7(4%)
Met expectations	26(15%)	85(51%)	43(26%)	9(5%)	5(3%)

11058 **Poster Session**

Self-identification of gender and race/ethnicity in hematology and oncology journal editorial boards: What is the state of diversity? *First Author: Ivy Riano, Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical Center, Lebanon, NH*

Background: Underrepresentation of women and minorities persists in many aspects of the scholarly publication process as demonstrated by our initial findings presented at ASCO21. Having a gender-balanced and diverse editorial team promotes collaborative work and decreases the publication bias against women. In our initial study, gender and race/ethnicity were determined based on publicly available data. We aimed to add to our study by asking editors to self-report their gender and race to assess the diversity of editors at leading hematology and oncology journals by self-reporting. **Methods:** We identified 60 journals in oncology, hematology, radiation oncology, and surgical oncology with the highest impact factors. Editors-In-Chief (EiC) and Second-In-Command (SiC) editors (such as deputy, senior and associated editors) were included in the analysis. A demographic survey assessing gender, race/ethnicity, age, and job characteristics was sent to 793 participants via email. Data were analyzed with R software. **Results:** A total of 66 out of 793 editorial board members responded to the survey. Gender breakdown of respondents was 36 (54.5%) men and 30 (45.8%) women. Most respondents were between the ages of 40 and 60 (69.7%). Thirty-eight (57.6%) of the editors had ≤5 years of editorial experience. Of the 66 respondents, 44 (66.7%) self-identified as non-Hispanic white, followed by 14 (21.2%) as Asian and 3 (4.5%) as Hispanic. Only 1/66 (1.5%) editors self-identified as Black or Native Hawaiian/Other Pacific Islander, and 1/66 (1.5%) did not identify themselves with a racial group. **Conclusions:** Underrepresented groups in medicine (URM) and women occupied a minority of leadership roles on editorial boards in high-impact hematology and oncology journals. Notably, this study provides new insights into editorial board diversity by using self-reporting as a primary methodology. Limitations of the cross-sectional study is that URM and women are more likely to respond to surveys on diversity, equity, and inclusion potentially skewing the results. Diversity in editorial boards not only can enhance scientific discovery by encouraging submissions from researchers with diverse backgrounds but also promotes career advancement for women and URM. Research Sponsor: None.

Self-Reported Editor's Race/Ethnicity	Editor-In-Chief Female n (%)	Editor-In-Chief Male n (%)	Second-In-Command Female n (%)	Second-In-Command Male n (%)
White	3 (100.0)	3 (75.0)	20 (74.1)	18 (56.2)
Black	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.1)
East Asia	0 (0.0)	0 (0.0)	4 (14.8)	5 (15.6)
South Asia	0 (0.0)	0 (0.0)	2 (7.4)	3 (9.4)
Middle Eastern & North Africa	0 (0.0)	1 (25.0)	0 (0.0)	1 (3.1)
Hispanic	0 (0.0)	0 (0.0)	0 (0.0)	3 (9.4)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)
Do not identify with any racial category	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.1)

11059 **Poster Session**

Experiences of researchers fulfilling VHA's "fourth mission" during the COVID-19 pandemic. *First Author: Kenneth Csehak, New York University, New York, NY*

Background: As the largest integrated healthcare system in the US, the Veterans Health Administration (VHA) is chartered "to serve as the primary backup for any health care services needed...in the event of war or national emergency" according to a 1982 Congressional Act. This mission was invoked during the COVID 19 pandemic to divert clinical and research resources, resulting in dramatic changes in the activities of investigators and research staff. This study uses established behavioral change frameworks to examine the experience of VHA cancer researchers during the pandemic. **Methods:** We conducted a mixed methods study on the effects of the pandemic on VHA researchers. We used an electronic questionnaire composed of Likert scale statements and open-ended questions, which was constructed using the 14 domains of the Theoretical Domains Framework (TDF) and the Capability, Opportunity, and Motivation (COM-B) model for behavior change. Likert scale statements were quantified and content analysis was performed on open ended responses. **Results:** The questionnaire was distributed electronically to 118 researchers participating in national VHA collaborations, with 42 responses (36%). Several significant themes and findings emerged. Only 36% of respondents did not feel that their research focus changed during the pandemic. (TDF: professional role and identity maps to COM-B Motivation). And 81% of respondents reported a diverse range of research interests (COM-B: M). Only 11 of 42 respondents (26%) reported prior experience with infectious disease research (TDF: skills maps to COM-B: C), and 31 of 42 (74%) agreed that they gained new research skills during the pandemic (COM-B: C). When asked to describe support structures helpful during the pandemic, 29% mentioned local supervisors, mentors and research staff (COM-B: C, M), 15% cited larger VHA organizations (COM-B: C) and 18% mentioned remote work abilities or telehealth (COM-B: O). Lack of timely communication from supervisors and remote work, particularly for individuals with caregiving responsibilities, were seen as limiting factors for research during the pandemic (COM-B: O). Although 83% of respondents agreed that they will be prepared to respond to future crises after COVID (COM-B: C), fewer than half (40%) of respondents felt professionally rewarded for pursuing research related to COVID, with 50% feeling neutral (COM-B: M). **Conclusions:** This study demonstrated the tremendous effects of the COVID 19 pandemic on research activities of VHA investigators. We identified perceptions of insufficient recognition and lack of professional advancement related to pandemic era research. Improving the structure of remote work and team communication represent high yield areas for improvement. It is essential to understand barriers and facilitators of crisis redeployment in the VHA, to make the transition effective and fulfilling for those carrying out the mission. Research Sponsor: VA Health Services Research and Development CDA, Other Foundation.

11060 **Poster Session**

Gender and early career faculty disparities in hematology and medical oncology board review lectures series. *First Author: Leen Mohammad Al-Kraimeen, Jordan University of Science and Technology, Irbid, Jordan*

Background: Studies show that women and early career faculty members have less access to career development opportunities and leadership positions. These disparities slow the process of change and may affect leadership roles, promotions, and career advancements in academic medicine. Here, we provide the first analysis of speakers' gender and early faculty disparities in hematology and medical oncology board review series. **Methods:** We performed a cross-sectional analysis of speakers at all major hematology and/or oncology board review series meetings, which were held in the United States between January 2017 and December 2021. Six major board review series were involved: Baylor/M.D. Anderson Cancer Center, the Brigham and Dana-Farber, George Washington School of Medicine and Health Sciences, Memorial Sloan Kettering Cancer Center, Seattle Cancer Care Alliance, and the American Society of Hematology. Details of the lectures were acquired via accessing brochures available on the institutions' official websites. Data on board certification and maintenance of certificate (MOC) were obtained from the American Board of Internal Medicine (ABIM) website. We extracted the number of publications from the PubMed website (MEDLINE). **Results:** Our analysis included 1224 board review lectures presented by 386 speakers. Of which, 315 (81.6%) were American Board of Internal Medicine (ABIM) certified, and MOC was active in 56.1% of speakers. Females accounted for 37.7% of all speakers, with a representation of less than 50% in 5 out of 6 board review series. The least proportion of female participation was among lectures discussing malignant hematology topics (24.8%), followed by solid tumors (38.9%), and benign hematology topics (44.1%). Faculty members with more than 15 years of experience since initial certification presented more than half of the lectures. The median time from initial hematology or medical oncology certification to lecture presentation was 12.5 years and 14 years, respectively, which varied significantly among different series ($p < 0.001$). Speakers' median number of publications was 84. We also investigated how frequently the same speaker gave lectures. Thirteen male speakers conducted more than or equal to 10 lectures across all board review series, compared to only two female speakers who did the same. An upward trend of improvement in females participation was found at all board review conference meetings across the years. **Conclusions:** Our data suggest that women and early career faculty members are underrepresented in hematology and oncology board review series. Therefore, efforts should be made to ensure equal participation of them in such important activities needed to advance academic careers. Research Sponsor: None.

11061 **Poster Session**

Comparison of methodology in the collection of gender and race/ethnicity in hematology and oncology journal editorial boards. *First Author: Shruti Rajesh Patel, Stanford University, Stanford, CA*

Background: Reporting on disparities is strongly influenced by the methodology used to collect race/ethnicity and gender data. Incorporating gender and race into research has its challenges, as these variables are difficult to define. As underrepresentation of minorities and women continues to persist in many facets of academia, it is important to assess the accuracy of differing methodologies. While asking individuals to self-identify their race and gender remains the gold standard of reporting, low response rates and response bias have been shown to affect results. In our initial study on representation in editorial boards, gender and race/ethnicity were determined based on publicly available data which can lead to misclassification of editors. We aimed to add to our study by asking editors to self-report their gender and race in hopes to validate our methodology given the importance of considering gender and race in academia. **Methods:** Of the 60 highest impact journals in oncology, hematology, radiation oncology, and surgical oncology identified, race/ethnicity and gender determinations were made using two methods. All senior editors were sent a survey via email asking participants to self-report their gender, race/ethnicity, age, and job characteristics. Gender and race were also assigned to the editors by a diverse coding team based on publicly available data and the NIH's OMB Directive 15 as a framework. The self-reported data was then compared to data that was assigned by our team. **Results:** 66 of the 793 (8.3%) editorial board members included in the study responded to the survey. Of the 66 respondents, gender was assigned correctly 100% (66/66) of the time and race was assigned correctly 95.5% (63/66) of the time. Of the 66 respondents to the self-survey of the 793 editorial board members surveyed. A significantly lower proportion of men responded to the survey compared to the gender breakdown of the 793 editorial board members (54.5% vs 72.6%; $p = 0.000279$). The three incorrectly identified respondents self-identified as Native Hawaiian, White, and Middle Eastern. **Conclusions:** Multiple recent reports have demonstrated high rates of sexual harassment, gender bias, and exclusion in the field of oncology. Collecting data on racial/ethnic groups and gender is imperative to understand the academic landscape of oncology and work towards a more equitable environment. Notably, this data from our study supports the methodology of a diverse coding team assigning gender and race based on publicly available data and the NIH's OMB Directive 15 as a framework as an alternative to self-report. Our study also demonstrates the low response rates and significant discrepancies in the demographic of respondents seen in survey-based identification. Research Sponsor: None.

11500 **Oral Abstract Session**

Primary efficacy and safety of letetresgene autoleucel (lete-cel; GSK3377794) pilot study in patients with advanced and metastatic myxoid/round cell liposarcoma (MRCLS). *First Author: Sandra P. D'Angelo, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Lete-cel is an autologous T-cell therapy targeting NY-ESO-1 tumors using a genetically modified, high-affinity T-cell receptor. MRCLS is a sarcoma with poor response to current immunotherapy approaches and limited treatment options. The cancer testis antigen NY-ESO-1 is expressed in 80–90% of MRCLS tumors, making this a promising target. This report summaries the primary efficacy and safety results of a pilot study of lete-cel in patients (pts) with advanced or metastatic MRCLS. **Methods:** This is an open label, study of lete-cel in pts with advanced or metastatic MRCLS following reduced-dose (Cohort 1 [C1]; 30 mg/m^2 fludarabine [flu] x 3d + 600 mg/m^2 cyclophosphamide [cy] x 3d) or standard dose (Cohort 2 [C2]; 30 mg/m^2 flu x 4d + 900 mg/m^2 cy x 3d) lymphodepletion (LD). Key eligibility criteria were: age ≥18 y; HLA-A*02:01; A*02:05, or A*02:06; advanced or metastatic NY-ESO-1+ MRCLS (≥30% of cells 2+/3+ by IHC); prior anthracycline treatment, and measurable disease. The transduced T cell dose range was 1– 8 $\times$ 10^9. Response was assessed at weeks 4, 8, 12, 24, then every 3 months (mo) until disease progression, death, or withdrawal. Investigator-assessed (IA) ORR by RECIST v1.1 was the primary efficacy endpoint. Secondary endpoints included safety, independently assessed ORR by RECIST v1.1, time to response (TTR), duration of response (DOR), progression-free survival (PFS). Overall survival (OS) was an exploratory endpoint. **Results:** 23 pts enrolled from March 2017 to February 2020. The median age was 47.0 yrs (range 33 to 72). 20 pts were dosed with T cells, 10 in each cohort with a median transduced T cell dose of 4.6 x 10^9. 8 of 20 pts (40%) had 1 line of prior therapy, 6 pts (30%) had 2 lines, and 6 pts (30%) had ≥3 lines. The median follow-up was 5.6 (C1) and 12.9 (C2) mo. In C1 the IA ORR was 20%, with best response (BR) of partial response (PR) in 2 pts and BR of stable disease (SD) in 8 pts. The median TTR was 1.9 mo, median DOR was 5.3 mo (95% CI: 1.9-8.7), and median PFS was 5.4 mo (95% CI: 2.0-11.5). In C2 the IA ORR was 40%, with BR of PR in 4 pts and BR of SD in 5 pts. The median TTR was 1.9 mo, median DOR was 7.5 mo (95% CI: 6.0-NE), and median PFS was 8.7mo (95% CI: 0.9-NE). OS is not yet mature. All pts experienced at least 1 treatment-emergent adverse event (TEAE). 55% of pts experienced serious TEAEs. 90% of pts had Gr ≥3 TE neutropenia, with 83% probability of resolution of initial Gr ≥3 occurrence by Day 30. Cytokine release syndrome occurred in 80% of pts, of which 25% were Gr 3, with 1st onset within 5d of infusion and median duration 7.5d. No Graft-vs-host disease, immune effector cell–associated neurotoxicity syndrome, Guillain-Barré Syndrome were reported. **Conclusions:** Treatment with a single dose of lete-cel showed anti-tumor activity, including response and long median PFS with an acceptable safety profile in pts with advanced and metastatic MRCLS. Clinical trial information: NCT02992743. Research Sponsor: GlaxoSmithKline.

LBA11501 **Oral Abstract Session**

Randomized phase II study of neoadjuvant checkpoint blockade for surgically resectable undifferentiated pleomorphic sarcoma (UPS) and dedifferentiated liposarcoma (DDLPS): Survival results after 2 years of follow-up and intratumoral B-cell receptor (BCR) correlates. *First Author: Emily Zhi-Yun Keung, The University of Texas MD Anderson Cancer Center, Houston, TX*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

11502 **Oral Abstract Session**

Phase I clinical trial to assess safety, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy of NY-ESO-1–specific TCR T-cells (TAEST16001) in HLA-A*02:01 patients with advanced soft tissue sarcoma. *First Author: Xing Zhang, Melanoma and Sarcoma Medical Oncology Unit, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: NY-ESO-1 is a cancer/testis antigen with expression in a wide range of tumor types. TAEST16001 cells are genetically engineered autologous T cells that express high-affinity NY-ESO-1-specific T-cell receptor (TCR) targeting NY-ESO-1+ soft tissue sarcoma in the context of HLA-A*02:01. Here, we report preliminary results of TAEST16001 cells from an ongoing, dose-escalation and expansion study in HLA-A*02:01 positive patients with advanced soft tissue sarcoma expressing NY-ESO-1 antigen. **Methods:** This is an open, single arm, dose-escalation and expansion study to evaluate safety, tolerability, PK, PD and preliminary efficacy of TAEST16001 cells in patients with soft tissue sarcoma. Enrolled patients underwent apheresis, and their isolated T cells were expanded in vitro after transducing with a lentiviral vector containing NY-ESO-1 TCR. Prior to TAEST16001 cells infusion, patients were to receive lymphodepleting chemotherapy consisting of cyclophosphamide (15 mg/kg/day ´3 days) and fludarabine (20 mg/m^2/day´3 days). TAEST16001 cells were administered at 5 $\times$ 10^8 ± 30% (dose level 1), 2 $\times$ 10^9 ± 30% (dose level 2), 5 $\times$ 10^9 ± 30% (dose level 3) and 1.2 $\times$ 10^{10} ± 30% (dose level 4/expansion) transduced cells. After TAEST16001 cells infusion, patients were to receive interleukin-2 subcutaneous injection for 14 days. Tumor responses were assessed by RECIST/iRECIST. **Results:** As of 31 December 2021, 12 patients with advanced soft tissue sarcoma were enrolled (M:F 7:5; mean age = 37.9; median prior regimens = 2 (range 1-3)). TAEST16001 cells were well-tolerated with no dose limiting toxicity. The most frequently reported grade ^{3} 3 adverse events were lymphopenia (n = 12), leukopenia (n = 10), neutropenia (n = 11), anemia (n = 4), thrombocytopenia (n = 1), hypokalemia (n = 1), and fever (n = 1). Two patients presented with cytokine release syndrome (grades 2) and resolved after symptomatic treatment. None of the patients had neurotoxicity, or serious adverse events related to cell infusion. The maximum tolerated dose (MTD) was not reached. PK modelling indicated that T_{max} of TAEST16001 cells were 6.23 days after cells infusion, and there were no relationship between clinical response and C_{max}/$AUC_{0\text{-}28}$. Among 12 efficacy-evaluable patients, 5 patients had a partial response, 5 patients had stable disease, and 2 patients had progressive disease. The overall response rate was 41.7%. The median time to an initial response was 1.9 month (range, 0.9 to 3.0), and the median duration of response was 14.1 months (range, 5.0 to 14.2). **Conclusions:** TAEST16001 cells showed an acceptable tolerability profile overall. MTD was not reached. Emerging efficacy data encouraged the continued expansion study of TAEST16001 cells in advanced soft tissue sarcoma. Clinical trial information: NCT04318964. Research Sponsor: Guangzhou Xiangxue Pharmaceutical Company limited.

11503 **Oral Abstract Session**

A phase I/II study of prexasertib in combination with irinotecan in patients with relapsed/refractory desmoplastic small round cell tumor and rhabdomyosarcoma. *First Author: Emily K Slotkin, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Prexasertib (PRX) is an inhibitor of CHK1, prevents DNA repair leading to mitotic catastrophe, and can enhance the activity of DNA-damaging chemotherapy. Translocation driven sarcomas exhibit high levels of replication stress and have demonstrated susceptibility to CHK1 inhibition in preclinical models. Desmoplastic small round cell tumor (DSRCT) and rhabdomyosarcoma (RMS) are aggressive sarcomas of children, adolescents and young adults for which novel therapies are urgently required. **Methods:** We conducted a phase I/II trial of PRX with irinotecan (irino) in patients ≥ 12 months of age with relapsed or refractory DSRCT or RMS. Eligible patients could have any number of prior therapies, including irino. Dose level 1 was PRX 80 mg/m^2 on day 1 + irino 20 mg/m^2 for 10 days. Dose levels 2 and 2A were PRX 105 or 150 mg/m^2 (>21 years or ≤ 21 years) on day 1 and irino 20 mg/m^2 for 10 (level 2) or 5 (level 2A) days. All cycles were 21 days. The primary objectives were to determine the RP2D of PRX with irino, and to determine the best overall response rate (ORR) in 6 months at the RP2D (RECIST v1.1) in DSRCT, with 3 or more responses out of 16 considered promising. **Results:** 21 patients were enrolled (DSRCT: 19; 2 RMS:2). The RP2D was dose level 2A. Treatment was well tolerated with the most common adverse events being neutropenia (48%), nausea (48%), and fatigue (52%). Cytopenias were managed with the aid of growth factor support in all patients once the RP2D was established. The DSRCT expansion enrolled 13 of 16 planned patients due to discontinuation of PRX supply prior to study completion. Four patients remain on therapy at the time of this submission. Responses in DSRCT patients at all dose levels are shown in Table. Sixteen of 21 enrolled patients, and 5 of 6 patients achieving PR had previously received irino. The median (range) number of cycles was 7 (2-26). Both RMS patients treated at the RP2D experienced SD as best response. The estimated ORR at the RP2D was 23%, and lower boundary of the one-sided 90% confidence interval was 9%, exceeding the unpromising rate of 5%. The two-sided 90% confidence interval was 7 to 49%. In addition, 3 patients had a PR at doses lower than the RP2D, bringing the ORR for all dose levels (n = 19) to 32% (90%CI: 15 to 53%). **Conclusions:** The RP2D of PRX in combination with irino is PRX 105 or 150 mg/m^2 (>21 years or ≤ 21 years) on day 1 and irino 20 mg/m^2 for 5 days in 21 day cycles with myelosuppression successfully managed with growth factor support. The study met its primary objective to consider PRX + irino promising in DSRCT and should be further investigated. Clinical trial information: NCT04095221. Research Sponsor: Cycle for Survival.

Dose level	Overall, N = 19[1]	1, N = 3[1]	2, N = 3[1]	2A, N = 13[1]
Best response				
Partial response (PR)	6 (32%)	1 (33%)	2 (67%)	3 (23%)
Stable disease (SD)	9 (47%)	1 (33%)	1 (33%)	7 (54%)
SD**	3 (16%)	1 (33%)	0 (0%)	2 (15%)
Progressive disease (PD)	1 (5%)	0 (0%)	0 (0%)	1 (8%)
[1]n (%)				

**= RECIST SD but removed from treatment due to clinical progression.

11504 **Oral Abstract Session**

Outcomes following preoperative chemoradiation +/- pazopanib in non-rhabdomyosarcoma soft tissue sarcoma (NRSTS): A report from Children's Oncology Group (COG) and NRG Oncology. *First Author: Aaron R. Weiss, Maine Medical Center, Portland, ME*

Background: Pazopanib is a multi-targeted tyrosine kinase inhibitor (TKI) with activity in advanced soft tissue sarcoma. ARST1321 was a phase II study designed to compare the near complete pathologic response rate (≥ 90% necrosis) following preoperative chemoradiation +/- pazopanib in children and adults with intermediate/high risk chemotherapy-sensitive body wall/extremity NRSTS. Enrollment was stopped early following a predetermined interim analysis that found the rate of near complete pathologic response to be significantly greater with the addition of pazopanib. As a planned secondary analysis of the study, we now report the outcome data for this cohort. **Methods:** ARST1321 was a jointly designed COG and NRG Oncology study open to enrollment July 2014-October 2018. Eligible adult (≥18 years) and pediatric (< 18 years) patients with newly-diagnosed unresected body wall/extremity NRSTS were enrolled into the Chemotherapy Cohort (> 5 cm, FNCLCC grade 2/3, protocol-designated chemotherapy-sensitive histology). Following a dose-finding phase, patients were randomized to receive (Regimen A) or not receive (Regimen B) pazopanib (< 18 years: 350 mg/m^2/day; ≥ 18 years: 600 mg/day) in combination with ifosfamide (7.5 gm/m^2/cycle) and doxorubicin (75 mg/m^2/cycle) + 45 Gy preoperative RT followed by primary resection at week 13, then further chemotherapy to week 25. **Results:** Eighty-five eligible patients were enrolled in the Chemotherapy Cohort and randomized to receive or not receive pazopanib. Median age 22.1 years (range: 5.7-64.2 years); 30 patients < 18 years. Most common histologies were synovial sarcoma (n = 42) and undifferentiated pleomorphic sarcoma (n = 19). As of December 31, 2021, at a median survivor follow-up of 3.3 years (range: 0.1 – 5.8 years), the 3-year event-free survival (EFS) for all patients in the intent-to-treat analysis was 52.5% (95% CI: 34.8%-70.2%) for Regimen A and 50.6% (32%-69.2%) for Regimen B (p = 0.8677); 3-year overall survival (OS) was 75.7% (59.7%-91.7%) for Regimen A and 65.4% (48.1%-82.7%) for Regimen B (p = 0.1919). **Conclusions:** Although the rate of near complete pathologic response was significantly greater with the addition of pazopanib to preoperative chemoradiation in children and adults with intermediate/high risk body wall/extremity NRSTS, outcomes were not statistically significantly different between the two regimens. Pathologic response could be a TKI-related phenomenon and may not be a good surrogate marker of outcome in future studies. Clinical trial information: NCT02180867. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

11505 **Oral Abstract Session**

Long-term outcomes in patients with localized Ewing sarcoma treated with interval-compressed chemotherapy: A long-term follow-up report from Children's Oncology Group study AEWS0031. *First Author: Thomas Cash, Aflac Cancer & Blood Disorders Center, Children's Healthcare of Atlanta, Emory University School of Medicine, Atlanta, GA*

Background: Children's Oncology Group study AEWS0031 demonstrated superior 5-year event-free survival (EFS) in patients with localized Ewing sarcoma (ES) receiving interval-compressed (IC) chemotherapy (every 2 weeks) compared to standard timing (ST) chemotherapy (every 3 weeks). We assessed the long-term outcome of patients treated on AEWS0031 to determine whether the survival advantage of IC chemotherapy was maintained at 10 years. **Methods:** AEWS0031 enrolled 568 eligible patients with localized ES. Patients were stratified into four groups by age (<18 years and ≥ 18 years) and primary site (pelvic and non-pelvic), and randomized to receive 14 cycles of alternating vincristine-doxorubicin-cyclophosphamide and ifosfamide-etoposide given every 3 weeks (ST; Regimen A) vs. every 2 weeks (IC; Regimen B). For this updated report, one patient was excluded due to uncertainty of original diagnosis giving a total of 567 patients in this analysis. Data for tumor measurements and histologic response were collected retrospectively from institutional reports. EFS and overall survival (OS) were estimated using the Kaplan-Meier method and compared using the log-rank test and Gray's test for cumulative incidence (CI). **Results:** The 10-year EFS for patients treated with IC chemo was 70% compared to 61% for ST chemo (p = 0.03), and the OS was 76% with IC chemo compared to 69% for ST chemo (p = 0.03). The 10-year CI of second malignant neoplasms (SMNs) for ST chemo was 4.2% [95% confidence interval: 2.4-7.5] compared to 3.2% (95% confidence interval: 1.6-6.3) for IC chemo (p = 0.5). There was a trend towards improved 10-year EFS in those receiving IC chemo both with non-pelvic (N = 477; 71% vs. 64%) and pelvic (N = 90; 67% vs. 43%) primary tumors. Similarly, the 10-year EFS was superior for patients treated with IC chemo in both the < 18 years (N = 500; 73% vs. 64%) and ≥ 18 years (N = 67; 53% vs. 37%) age groups. Among the 184 patients with available histologic response data, the 10-year EFS from the time of local control was 76% for those with < 10% viable tumor and 56% for those with ≥ 10% viable tumor (p = 0.01). Additional analysis comparing patients with any viable tumor vs. no viable tumor (NVT) by treatment regimen demonstrated that patients with NVT who received IC chemo had 10-year EFS and OS from local control of 91% and 97%, respectively. In the 210 patients for whom tumor volume calculations were possible, there was no difference in the 10-year EFS for patients with tumors < 200 mL vs. ≥ 200 mL. **Conclusions:** With longer term follow-up, IC chemotherapy for localized ES is associated with superior EFS and OS without an increase in SMNs. This study suggests patients ≥ 18 years with poor necrosis or pelvic primary tumors remain at high risk for relapse despite IC chemo, emphasizing the need for alternative treatment strategies to improve their outcomes. Clinical trial information: NCT00006734. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

11506 **Oral Abstract Session**

A phase Ib/II study of the combination of lenvatinib (L) and eribulin (E) in advanced liposarcoma (LPS) and leiomyosarcoma (LMS) (LEADER): Efficacy updates. *First Author: Tom Wei-Wu Chen, Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan*

Background: There are limited treatment options for advanced LPS and LMS, the two most common histologies in soft tissue sarcoma. Patients (pts) treated with E had an improved overall survival (OS) compared to dacarbazine but with an unsatisfactory 4% objective response rate (ORR). Early studies of L, a multi-targeted anti-angiogenic inhibitor, had suggested efficacy in sarcoma pts. We hypothesized that the L+E could potentiate the treatment efficacy in advanced LMS and LPS. **Methods:** LEADER was a single-arm phase Ib/II study for advanced adult LMS and LPS pts who had received no more than 2 lines of systemic chemotherapy (NCT03526679). The phase Ib part (starting dose: L 18mg/day, E 1.1mg/m^2) had been reported and the recommended phase 2 dose (RP2D) was determined at L 14mg/day and E 1.1mg/m^2 D1, D8 every 21 days. The primary endpoint of the phase II part was ORR by RECIST 1.1, secondary endpoints included progression-free survival (PFS), 6-month PFS rate, and OS. Pts in phase Ib/II part were analyzed together for efficacy. **Results:** As of Nov 15 2021, 30 pts (F/M 20/10) had been treated with at least one cycle of L + E; 21 were LMS (9 uterine, 12 non-uterine) and 9 were LPS (5 dedifferentiated, 2 myxoid round cell, 2 pleomorphic). The median age was 59 (range 29-73); the median lines of treatment(s) received before enrollment was 1 (range 0-3). The ORR by RECIST 1.1 was 20 % (6/30) (95% CI 10-53%); the ORR for pts received L 18mg/day (2/6) and L 14mg/day (4/26) were not significantly different (p = 0.23). After a median FU time of 20.1 months, the median PFS and 6-month PFS rate was 8.56 mos (95% CI 4.40-not reached (NR)) and 59%, respectively. The median PFS for LMS (8.56 mos, 95% CI 4.17- NR) and LPS (11.36 mos, 95% CI 4.4-NR) were not significantly different (p = 0.73). The median OS and 12-month OS rate was 26.2 mos (95% CI 21.4-NR) and 89%, respectively, but LPS pts had significantly worse OS (HR 3.5, p = 0.04). Twenty pts experienced at-least one grade (gr) 3 or 4 adverse event (AE); gr 3 or 4 AEs occurred in > 1 pt included hypertension (n = 4); hand-foot-syndrome (HFS) (n = 5), proteinuria (n = 3), febrile neutropenia (n = 3), neutropenia (n = 11, without G-CSF support). Compared to L 18mg/day, pts treated with RP2D were associated with lower gr3/4 HFS and hypertension. There were no sustained grade 3/4 AEs for pts receiving long-term L+E. **Conclusions:** L + E had shown promising efficacy in advanced LMS and LPS. L at 14mg (vs 18mg) had a better AE profile without compromising activity. Future randomized study to confirm the efficacy of the combination is warranted. Clinical trial information: NCT03526679. Research Sponsor: National Taiwan University Hospital Clinical Trial Center, Pharmaceutical/Biotech Company.

11507 **Oral Abstract Session**

A phase 1b study of unesbulin (PTC596) plus dacarbazine for the treatment of patients with locally recurrent, unresectable, or metastatic relapsed/refractory leiomyosarcoma. *First Author: Brian Andrew Van Tine, Siteman Cancer Center, Washington University in St. Louis, St. Louis, MO*

Background: Leiomyosarcoma (LMS) is one of the most common subtypes of soft tissue sarcoma and is associated with high risk of relapse and a poor prognosis for advanced disease. In preclinical LMS models, unesbulin, a microtubule polymerization inhibitor, potentiated the activity of dacarbazine (DTIC) (Jernigan F, et al. *Mol Cancer Ther.* 2021;20:1846–1857). Here, we report preliminary safety and efficacy results from a Phase 1b dose escalation study evaluating the combination of unesbulin with DTIC in patients with advanced LMS (NCT03761095). **Methods:** In this single-arm, open-label, Phase 1b clinical trial, patients with advanced LMS received unesbulin orally at 200, 300, or 400 mg twice weekly (BIW) in combination with intravenous DTIC at 1,000 mg/m^2 once every 21 days. The primary objectives were to determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of unesbulin in combination with DTIC and to characterize the safety profile of the combination. The time-to-event continual reassessment model (TITE-CRM) was used for dose finding. An expansion cohort with up to 12 additional patients is currently being enrolled. **Results:** As of the data cutoff on January 6, 2022, 29 LMS patients have been treated. Median prior lines of therapy were 3 (range 1–6). Of 27 evaluable patients, 12 had non-uterine and 15 had uterine LMS. The MTD/RP2D of unesbulin was determined to be 300 mg BIW with DTIC 1,000 mg/m^2 every 21 days using the TITE-CRM. At the RP2D, the most common treatment-related adverse events included fatigue, diarrhea, neutropenia, and thrombocytopenia. In the intent-to-treat population, the overall response rate (ORR) was 17.2% (5/29) and the disease control rate (DCR) (DCR = complete response + partial response + stable disease at 12 weeks) was 58.6%. At the 300 mg dose level, the ORR was 19% (4/21) and the DCR was 57.1%. Patients received a median of four cycles (range 1–12). The study is ongoing, with patients continuing to receive treatment. **Conclusions:** Unesbulin 300 mg BIW in combination with DTIC 1,000 mg/m^2 every 21 days was well tolerated and demonstrated promising efficacy in a heavily pre-treated patient population with advanced LMS; these results support further investigation. Updated clinical results will be presented as the data mature. A randomized, placebo-controlled, Phase 2/3 trial is planned. Clinical trial information: NCT03761095. Research Sponsor: PTC Therapeutics.

11508 **Oral Abstract Session**

Neoadjuvant chemotherapy in high-risk soft tissue sarcomas: Results of the expanded cohort of myxoid liposarcoma of the randomized clinical trial from the Italian Sarcoma Group (ISG), the Spanish Sarcoma Group (GEIS), the French Sarcoma Group (FSG), and the Polish Sarcoma Group (PSG). *First Author: Alessandro Gronchi, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: An ISG, GEIS, FSG and PSG randomized trial on 3 cycles of neoadjuvant epirubicine+ifosfamide (EI) versus a histology-tailored (HT) regimen in selected localized high-risk STS showed some superiority of EI in all histologies with the exception of Myxoid Liposarcoma (MLPS) where EI and HT regimens seemed equivalent (J Clin Oncol 2020; 38:2178-86). This MLPS cohort was expanded with the aim to assess the non-inferiority of the HT regimen compared to EI. **Methods:** This was a multicenter European randomized trial comparing EI versus a HT regimen. Patients (pts) had localized high-risk (grade = 3; size >5 cm; deeply seated) undifferentiated pleomorphic sarcoma, leiomyosarcoma, malignant peripheral nerve sheath tumor, synovial sarcoma or MLPS of extremities or trunk wall. Primary end-point was Disease Free Survival (DFS). Secondary endpoint was Overall Survival (OS). The MLPS cohort was expanded after the results of the 3rd interim analysis (Lancet Oncol 2017; 18:812-22) in order to reject the hypothesis that HT regimen trabectedin is associated with a HR of relapse = 1.25 with a non-inferiority design. To this aim, a Bayesian monitoring approach was used until the probability that the true HR is higher than 1.25 was greater than 80% or smaller than 5%. **Results:** From May 2011 to June 2020, 101 pts affected by high-risk MLPS were randomized, 56 to EI and 45 to HT regimen. The median follow-up was 66 months (IQ range 37-89). Median size was 107 mm (IQ range 84-143), 108 mm (IQ range 86-150) in the EI and 106 mm (IQ range75-135) in the HT arm. The DFS and OS probabilities at 60 months were 0.86 and 0.73 (HR:0.60; 95%CI: 0.24-1.46; log rank p = 0.26 for DFS) and 0.88 and 0.90 (HR:1.20; 95%CI:0.37-3.93; log rank p = 0.77 for OS), in the HT and EI arm, respectively. 5-yr observed and Sarculator-predicted OS were 0.89 (95% CI 0.82-0.97) and 0.80 in all patients (p = 0.020), 0.90 (95% CI 0.81-1.00) and 0.79 in the EI arm (p = 0.049) and 0.88 (95% CI 0.77-1.00) and 0.81 in the HT arm (p = 0.204) respectively. **Conclusions:** In the expanded cohort of MLPS, the HT neoadjuvant therapy trabectedin was not inferior to EI. While survival in both arms was better than predicted by Sarculator, it is left to understand whether this patient population, who had on average a lower Sarculator-predicted risk of death compared with the rest of the trial population, may benefit from a neoadjuvant therapy. Clinical trial information: NCT01710176. Research Sponsor: Eurosarc FP7 278472.

11509 **Clinical Science Symposium**

Correlative results from NCI protocol 10250: A phase II study of temozolomide and olaparib for the treatment of advanced uterine leiomyosarcoma. *First Author: Sminu Bose, Columbia University Irving Medical Center, New York, NY*

Background: uLMS is an aggressive sarcoma subtype of smooth muscle origin. Chemotherapy provides limited benefit for advanced disease. 18-25% of uLMS harbor deleterious alterations in homologous recombination (HR) DNA repair genes. uLMS exhibits high levels of replicative stress. These findings prompted a phase 2 study of O+T in pretreated uLMS where O+T demonstrated activity: ORR 27%, mPFS 6.9 mos (Ingham M. et. al. ASCO 2021: #11506) **Methods:** NCI protocol #10250 is a single-arm, multicenter, phase 2 trial evaluating O+T in advanced uLMS pts with progression on ≥1 prior line. Pre-treatment (Pre) and on-treatment (On) biopsies were collected from 22 pts. In prespecified analysis, we evaluated for a relationship between clinical outcomes and HR gene alterations by whole exome sequencing (WES), SLFN11/MGMT expression by RNAseq, and RAD51 foci formation (functional assay). HRD scores were calculated from WES using scarHRD. Gene expression was evaluated using a Spearman rank-order correlation analysis to identify genes associated with PFS ($p < 0.01$) and overexpressed in sensitive (S: PFS > 240d) or resistant (R: PFS < 240d) pts. Gene set enrichment analysis (GSEA) was performed (q = FDR-adjusted p value). Pts with available results: WES/RNAseq (16), Pre HRD score (13), Pre RAD51 foci (12). **Results:** 31% (5/16) pts had a mutation (Mut) or homozygous deletion (Hd) in the HR panel: ATRX Mut (2), ATR Mut, PALB2 Hd, RAD51B Hd. Pts with PALB2 and RAD51B Hd had longest PFS on study. Recurrent alterations also occurred in TP53 (56%) and RB1 (19%). Median HRD score in Pre samples was 51 (range 36-66) and 10/13 had HRD scores ≥ 42. Pre and On SLFN11 and MGMT RNA expression were not correlated with ORR/PFS. 6/13 Pre samples were HR-deficient by the RAD51 foci assay. Of pts with PFS ≥ 200d, 4/6 were HR-deficient. In Pre samples, 81 genes were overexpressed in S pts and 73 in R pts. In On samples, 146 genes were overexpressed in S pts and 127 in R pts. In On samples, GSEA identified the epithelial-mesenchymal transition enriched in S pts (q = 3.38e-7) and cell cycle pathways (E2F targets, G2M checkpoint) in R pts (q = 7.43e-4). Only 2 genes, CXCL10 and PCDH15, were differentially expressed between paired Pre and On samples (both increased in On). Gene expression signatures for replicative stress showed borderline association with worse PFS. **Conclusions:** Most uLMS tumors exhibit HR defects as measured by HRD scores. A subset of pts with greater benefit from O+T were identified by WES for HR genes and the RAD51 assay. There was no correlation between SLFN11 and MGMT expression and outcomes. GSEA identified pathways differentially expressed in S and R pts in On samples. O+T induced CXCL10 which has been associated with T-cell trafficking to tumors. A randomized phase 3 trial of O+T versus investigator's choice is planned. These results provide insight into which pts may benefit most from this novel drug combination. Clinical trial information: NCT03880019. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

11510 **Clinical Science Symposium**

Presence of immune infiltrates, increased expression of transposable elements, and viral response pathways in sarcoma associate with response to checkpoint inhibition. *First Author: Benjamin Alexander Nacev, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Response to checkpoint inhibition (CPI) in sarcoma is overall low and varies between and within subtypes. Understanding tumor intrinsic determinants of this response may improve efficacy and patient selection. The de-repression of transposable elements (TEs), which are epigenetically silenced repetitive DNA elements of viral origin, is linked to anti-tumor immunity through an antiviral inflammatory response. We hypothesize that baseline expression of TEs and epigenetic regulators correlates with overall response rate (ORR) in sarcoma CPI clinical trials. **Methods:** This is a retrospective analysis of bulk RNA-sequencing data from pretreatment biopsies of patients on CPI trials in sarcoma (pembrolizumab plus talimogene laherparepvec, nivolumab plus bempegaldesleukin, and pembrolizumab plus epacadostat). Sixty-seven samples from unique patients representing 12 subtypes were analyzed. The MCP counter deconvolution method and unsupervised clustering were used to group samples by immune phenotypes resulting in immune 'hot' and 'cold' clusters. ORR was defined by RECIST. To determine if baseline expression of TEs and epigenetic regulators significantly predicted immune types, we implemented a lasso penalized logistic regression. **Results**: Immune 'hot' tumors were characterized by increased immune infiltrates including CD8+ T-cells, B-cells, and NK cells vs 'cold' tumors. Patients with 'hot' vs 'cold' tumors had an ORR of 30.5% (11/36) vs. 3.2% (1/31) (p = 0.003; chi-squared). The best predictors of 'hot vs 'cold' was the increased expression of multiple TE families including MER45A, MER57F, and LTR21B (respective lasso coefficients, 0.27, 0.07, and 0.07). Expression of *IKZF1*, a chromatin-interacting transcription factor, was also predictive (lasso coefficient, 0.35) and increased expression correlated with improved ORR (p = 0.003; unpaired t-test). TE and *IKFZ1* expression was significantly correlated with CD8+ T-cell signaling and antiviral response pathways such as cGAS-STING (MER57F, r^2= 0.43, padj = 1.75E-4; *IKZF1*, r^2= 0.63, padj = 6.28E-9) and type II interferon (MER57F, r^2= 0.67, padj = 2.51E-10; *IKZF1*, r^2= 0.60, padj = 7.19E-8). Increased expression of cGAS-STING (p = 3.9E-4; unpaired t-test) and type II interferon pathways (p = 1.89E-10; unpaired t-test) was significant in 'hot' tumors. **Conclusions:** Immune 'hot' baseline immune profiles of sarcoma are associated with improved ORR to CPI and with increased expression of TEs and *IKZF1*. These differences in gene expression correlate with increased inflammatory signaling, which suggests a response to TE-encoded viral-like sequences that are typically epigenetically silenced. Induction of TE de-repression and *IKZF1* expression through epigenetic targeting warrants pre-clinical investigation as a strategy to promote CPI response in sarcomas. Research Sponsor: Merck, Amgen, NEKTAR, Incyte, Bristol Myers Squibb, Cycle for Survival, Witherwax Fund.

11511 **Clinical Science Symposium**

Phase II trial of palbociclib in advanced sarcoma overexpressing *CDK4* gene excluding dedifferentiated liposarcoma (DD LPS): A study from the Spanish Group for Research on Sarcoma (GEIS). *First Author: Javier Martin Broto, Health Research Institute-Fundación Jiménez Díaz University Hospital, Autonomous University of Madrid (IIS-FJD, UAM), Madrid, Spain*

Background: CDK4/6 inhibitors showed a favorable progression-free survival (PFS) in DD LPS, a sarcoma bearing 12q 13-15 amplicon that implies *CDK4* amplification. The median PFS was 4 and 7 months (m) for palbociclib and abemaciclib, respectively. Preclinical experiments in 10 sarcoma cell lines and 6 PDX models, including only one DD LPS, showed higher efficacy of anti-CDK4 in cases with high expression of CDK4 and low expression of p16. This rationale supported the design of a phase II trial exploring palbociclib in a wide range of sarcomas, excluding DD LPS. **Methods:** Progressing pretreated advanced soft tissue sarcoma, excluding DD LPS, or osteosarcoma adult patients (pts), whose tumors overexpressed *CDK4* and underexpressed *CDKN2A* mRNA in a baseline mandatory biopsy, were enrolled. *CDK4* and *CDKN2A* expression were assessed by qRT-PCR, using an external control as reference (Universal human reference RNA; Agilent Technologies). The primary endpoint was 6-m PFS rate. Minimax Simon's two-stage with type 1 and 2 errors of 10%, and null and alternative hypothesis of H0 15%, H1 40%, 6-month PFS rates were specified. The study will warrant further investigation if 6 or more pts had a PFS > 6 m from 21 evaluable pts. Palbociclib was administered orally at 125 mg/ day 21 out of 28 days. Pre-screening intended to increase the probability of positive profile in the baseline biopsy. **Results:** A total of 214 pts with 236 *CDK4/ CDKN2A* determinations were assessed for enrolment; 141 for prescreening, in archive tumor sample, and 95 for screening, in a baseline biopsy. There were 38/141 (27%) and 28/95 (29%) pts with favorable mRNA profile from pre and screening, respectively. Twenty-two pts were enrolled with a median of previous systemic lines of 3 (1-5). There were 9 different sarcoma subtypes, including 2 osteosarcomas. With a median FU of 10 m (0.4-23.3), the median PFS was 4.2 m (95% CI 0.9-7.4), while the 6- and 12-m PFS rates were 30% (95% CI 9-51) and 18% (95% CI 12-48) respectively. From 19 evaluable pts (1 early death by COVID, 1 withdrew consent and for 1 it was too early to be assessed) 11 had stable disease (58%) and 8 progressed (42%) as the best response. Patients with CDK4 expression above the median value had significantly longer mPFS in the univariate analysis: 5.9 m (95% CI 1.4-10.4) vs 1.9 m (95% CI 0.6-3.2), p = 0.046; and longer OS: 15.5 m (95% CI 6.8-24.3) vs 10.6 m (95% CI 0-23.2), p = 0.047, respectively. The probability to find a positive profile in the screening was 29%, but this proportion increased up to 41% if in pre-screening had been positive. **Conclusions:** Palbociclib showed to be effective in a wide variety of sarcoma subtypes, other than DD LPS, selected by *CDK4/ CDKN2A* biomarkers. Clinical trial information: NCT03242382. Research Sponsor: Spanish group for research on sarcoma (GEIS), Pharmaceutical/Biotech Company.

11512 **Poster Discussion Session**

A phase 1, multicenter, open-label, first-in-human study of DS-6157a in patients (pts) with advanced gastrointestinal stromal tumor (GIST). *First Author: Suzanne George, Dana-Farber Cancer Institute, Boston, MA*

Background: GPR20 is selectively and abundantly expressed in GISTs, the most common sarcoma of digestive tract. DS-6157a is an anti-GPR20 antibody-drug conjugate with a novel tetrapeptide-based linker and DNA topoisomerase I inhibitor exatecan derivative (DXd). The target drug-to-antibody ratio is ~8. The DXd payload, when released, inhibits topoisomerase I and induces cell apoptosis. **Methods:** This study conducted in the US and Japan was designed to include a dose-escalation (Part 1) and a dose-expansion (Part 2) in adult pts with advanced GIST (NCT04276415). Part 1 evaluated safety, tolerability, efficacy, and pharmacokinetics (PK) to determine the maximum-tolerated dose (MTD) and/or recommended dose for expansion. Key eligibility criteria included ECOG PS of 0 or 1, measurable disease per RECIST v1.1, and adequate bone marrow, hepatic, and renal function. DS-6157a was administered every 3 weeks as monotherapy. Pts had tumor assessments per RECIST 1.1 every 6 weeks (wks) for 36 wks, then every 9 wks thereafter. **Results:** At data cutoff, 34 pts were available for full analysis: median treatment duration was 9.9 wks (range, 3-56 wks) and 5 pts (14.7%) were ongoing; median age 60.5 years (y) (range, 29-81 y); 19 pts (56%) were male; 47% of pts were Asian and 47% were white. Baseline GPR20 expression was highly prevalent, and dose-dependent PK exposure was confirmed within the range of dose levels. The MTD was 6.4 mg/kg. One pt with SDH-deficient GIST with both SDH B and NF1 mutations, had a confirmed PR with shrinkage of -75%; 18 pts (53%) experienced stable disease and 10 pts (29%) experienced progressive disease as best response. Median progression-free survival across all dose levels was 3.6 months (95% CI, 1.6, 6.9). Treatment-emergent AEs (TEAEs) occurred in all pts and treatment-related TEAEs (TRAEs) in 32 pts (94%). The most common (≥25%) all-grade (Gr) TEAEs were nausea (82%), decreased appetite (59%), fatigue (47%), anemia (44%), constipation (38%), decreased platelets (35%), and vomiting (32%). Gr ≥3 TRAEs occurred in 14 pts (41%); the most common were decreased platelets (21%) and anemia (18%). Serious TEAEs (SAEs) occurred in 9 pts (27%) and related SAEs in 4 pts (12%). Related Gr 4 SAEs in 2 pts included abnormal hepatic function, neutropenia, thrombocytopenia and leukopenia. There was 1 treatment related death (hepatic failure). Further investigations are on-going to understand the modest clinical efficacy observed. The study did not proceed to Part 2, because the data from Part 1 did not meet efficacy targets. **Conclusions:** DS-6157a was generally well tolerated with early signs of moderate clinical activity. While there were no objective responses in pts with KIT-mutant GIST, tumor shrinkage was observed in all 4 pts with KIT wild-type GIST treated at different doses, including a confirmed PR at the MTD in a pt with SDH-deficient GIST with both SDH B and NF1 mutations. Clinical trial information: NCT04276415. Research Sponsor: Daiichi Sankyo, Inc.

11513 **Poster Discussion Session**

Promising antitumor activity of olverembatinib (HQP1351) in patients (pts) with tyrosine kinase inhibitor- (TKI-) resistant succinate dehydrogenase- (SDH-) deficient gastrointestinal stromal tumor (GIST). *First Author: Haibo Qiu, Sun Yat-Sen University Cancer Center, Guangzhou, China*

Background: GIST is a rare mesenchymal tumor whose management has been transformed by approvals of TKIs. However, treatment resistance is a formidable challenge in managing locally advanced or metastatic GIST. Pts with SDH-deficient GIST are not sensitive to imatinib and other TKIs, are frequently multifocal, and typically have a multinodular architecture. Olverembatinib is a novel, potent, orally active third-generation TKI with promising activity against GIST in multiple preclinical GIST models. **Methods:** The aim of this phase Ib/II study was to evaluate the safety/tolerability, pharmacokinetics (PK), and efficacy (assessed per RECIST v1.1) of olverembatinib (NCT03594422) in pts with metastatic GIST whose disease was resistant or failed to respond to imatinib or other TKIs. Olverembatinib was administered orally once every other day (QOD) in 28-day repeated cycles. After 3 pts were treated at 20 mg, other pts were randomly allocated in a 1:1:1 ratio to 30, 40, and 50 mg regimens. **Results:** On the cutoff date of January 30, 2022, 39 pts (median age 52 [range 19-72] years) had received at least 1 dose of olverembatinib. The average (range) treatment period was 5.0 (0.2-35) months. PK analyses indicated an approximately dose-proportional increase in systemic exposure over the dose range of 20 to 50 mg. Thirty-one pts had *KIT* or *PDGFRA* mutations, 13 had stable disease for at least 2 cycles as the best response, 8 withdrew early, and 10 had progressive disease before Cycle 3. Very interestingly, 6 of 8 pts with *KIT* wild-type GIST were confirmed as SDH deficient: 2 pts had partial responses (PRs), 1 patient's tumor had shrunk by 35.9% and lasted for 16 cycles, and another patient's tumor had shrunk by 54.2% in the first evaluation. Four pts had stable disease as best response for 2, 6, 14, and 36 cycles. A total of 36 (92.3%) pts experienced treatment-emergent adverse events, most of which were mild or moderate. Ten (25.6%) pts experienced serious adverse events, of which intestinal obstruction attributed to GIST was the most reported. Common treatment-related adverse events (≥ 20%) included increased leukocyte (59.0%) and neutrophil (46.2%) counts, anemia (20.5%), constipation or asthenia (35.9% each), hyperuricemia (25.6%), hypoalbuminemia (23.1%), and elevated AST or ALT (20.5% each). **Conclusions:** Olverembatinib was well tolerated at doses of up to 50 mg QOD and showed antitumor activity in pts with TKI-resistant SDH-deficient GIST, with 2 PRs in 6 evaluable pts with SDH-deficient GIST and 1 with stable disease for 36 cycles. These promising findings warrant further investigation. Clinical trial information: NCT03594422. Research Sponsor: Ascentage Pharma Group Corp Ltd (Hong Kong).

11514 **Poster Discussion Session**

***KIT* resistance mutations identified by circulating tumor DNA and treatment outcomes in advanced gastrointestinal stromal tumor.** *First Author: Steven Bialick, University of Miami Miller School of Medicine/Sylvester Comprehensive Cancer Center, Miami, FL*

Background: Tyrosine kinase inhibitors (TKIs) are the cornerstone treatment for advanced GIST via pharmacologic targeting of driver oncogenes such as *KIT*. Detection of *KIT* alterations through tissue-based next-generation sequencing (NGS) is common, but circulating tumor DNA (ctDNA)-based NGS is a less invasive alternative to identify driver and resistance mutations in advanced GIST. Patients (pts) with *KIT*-mutant GIST benefit from first-line (1L) imatinib; however, *KIT* resistance mutations may confer imatinib-resistance and differential sensitivity to subsequent TKIs. We sought to analyze ctDNA from GIST pts to determine whether certain resistance mutations were associated with superior outcomes with particular TKIs in the second-line and beyond (2L+). **Methods:** Under an approved institutional review board protocol, a retrospective analysis was performed with available ctDNA NGS results (Guardant360; Redwood City, CA) from pts (N = 104) who progressed on 1L imatinib between 2017-21. Using R statistical programming, we identified pts with primary *KIT* alterations (N = 64) and known resistance mutations in *KIT* exons 13 (N = 25) and 17 (N = 35). We studied the median time to treatment failure (mTTF), defined as the time from treatment start to treatment end (months) due to progressive disease or toxicity, for each 2L+ drug. Using Kaplan-Meier methods, we calculated Cox proportional-hazard ratios (HR) with confidence intervals (CI) and p-values for statistical significance. **Results:** 49% were male (median age 66; range, 31-94). Driver oncogenes were detected in 80% (N = 83), including *KIT*, *NF1*, *PDGFRA* and *BRAF*. Of those with a *KIT* alteration, 12 (19%) had *KIT* exon 9 mutations and 52 (81%) had *KIT* exon 11 mutations. *KIT* resistance mutations were observed in *KIT* exons 13 (N = 25; V654), 14 (N = 2; T670), and 17 (N = 45; D816, D820, N822, Y823). Pts with *KIT* resistance mutations received 2L+ therapy with avapritinib, dose-escalated imatinib, nilotinib, pazopanib, ponatinib, regorafenib, ripretinib, or sunitinib. mTTF for *KIT* exon 13 V654 pts treated with 2L+ sunitinib, imatinib 800mg, or other was 10.8, 7.5, and 3.7 months, respectively. TTF for sunitinib vs other 2L+ drugs showed a HR of 0.51 (CI 0.33-0.8), p = 0.003. mTTF for *KIT* exon 17 (non-V654) pts treated with 2L+ regorafenib, imatinib 800mg, or other was 4.6, 1.2, and 6.3 months, respectively. Comparison of mTTF for regorafenib vs other 2L+ drugs was not statistically significant. **Conclusions:** ctDNA is a noninvasive tool for detecting driver and resistance mutations in pts with advanced GIST. GIST pts with *KIT* exon 13 V654 resistance mutations had superior outcomes in the 2L+ setting with sunitinib. Regorafenib was not superior to other 2L+ TKIs in pts with *KIT* exon 17 resistance mutations, possibly due to their own activity against exon 17 resistance alterations. ctDNA-guided therapy warrants evaluation in a prospective clinical trial. Research Sponsor: None.

11515 **Poster Discussion Session**

INT230-6 monotherapy and in combination with ipilimumab (IPI) across a broad spectrum of refractory soft tissue sarcomas (STS) [Intensity IT-01; BMS#CA184-592]. *First Author: Matthew Ingham, Columbia University Irving Medical Center, New York, NY*

Background: INT230-6 is a novel intratumoral (IT) agent with a dual anti-cancer mechanism (tumor cytoreduction while stimulating antigen presentation and recruitment of T-cells). The drug is comprised of cisplatin (CIS) and vinblastine (VIN) co-formulated with an amphiphilic molecule that enables drug dispersion throughout tumors and passive diffusion into cancer cells following IT delivery. In the neoadjuvant setting, a single injection can cause necrosis in > 95% of the tumor and recruit TILs. Combining with anti-CTLA-4 improved responses in preclinical models. **Methods:** INT230-6 dose is set by the tumor's longest diameter and is proportional to the injected disease volume. INT230-6 is administered IT Q2W for 5 treatment sessions followed by maintenance every 9 weeks as monotherapy or with IPI 3mg/kg IV Q3W for 4 doses. Biopsies from injected tumors are obtained pretreatment and Day 28 for immunoprofiling. **Results:** 22 subjects with various advanced STS histologies with a median age of 64 and a median of 3 prior systemic therapies were enrolled (11 INT230-6 alone, 11 IPI combination). There were 178 image-guided IT INT230-6 injections (107 to deep tumors) at INT230-6 doses ranging from 5 to 242 mL (121mg CIS, 24.2mg VIN, doses which vastly exceed the usual IV doses of these drugs). PK analysis showed that > 95% of drug agents remain in the tumor. The most common (> 25%) all-grade related adverse events (AEs) in evaluable monotherapy subjects (n = 10) were pain (80%), decreased appetite (40%), nausea (40%), anemia (30%), fatigue (30%) and vomiting (30%). Tolerability was similar for the combination with IPI. Most events were low grade. The incidence of grade 3 AEs for the INT230-6 arm was 30% and for the IPI combination was 10%. There were no related grade 4 or 5 AEs in either cohort. RECIST metrics may not accurately reflect clinical benefit with this treatment given large volumes of INT230-6 is repeatedly injected into a tumor and local inflammation may occur. Paired biopsies showed reduction in proliferating tumor cells and an increase in T-cell infiltrates. The disease control rate at the first imaging timepoint for evaluable INT230-6 subjects (n = 9) was 56% and for evaluable IPI combination (n = 5) was 80%. Abscopal effects were seen in 2 monotherapy subjects, though most uninjected tumors were not tracked. The estimated 1-year overall survival was 88% for the IPI combo and 60% for the monotherapy cohort. **Conclusions:** IT INT230-6 is well tolerated as monotherapy and combined with IPI. STS, which is typically not sensitive to immunotherapy, may be amenable to INT230-6 or IPI combo to create antigens and promote a systemic immune response. Preliminary efficacy using INT230-6 alone is encouraging and will be evaluated in a global phase 3 trial. Further evaluation is needed to determine whether the addition of IPI may improve patient outcomes. Clinical trial information: NCT03058289. Research Sponsor: Intensity Therapeutics, Inc.

11516 **Poster Discussion Session**

A phase I/II trial of the PD-1 inhibitor retifanlimab (R) in combination with gemcitabine and docetaxel (GD) as first-line therapy in patients (Pts) with advanced soft-tissue sarcoma (STS). *First Author: Evan Rosenbaum, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: In a phase III trial, GD had similar response and survival rates to doxorubicin when administered as first-line therapy to advanced STS pts. G and D have each demonstrated synergy with PD-1 blockade in pre-clinical or clinical studies. We hypothesized that GD plus R would be safe, tolerable, and have synergistic activity in STS. **Methods:** This is an ongoing open-label, single-center, phase I/II trial of R (INCMGA00012) combined with GD in pts with treatment-naïve unresectable or metastatic high-grade STS. Herein, we report the phase I results, which included a safety run-in followed by a 3+3 dose de-escalation design. G (900 mg/m^2) was administered on days 1 and 8 and D (75 mg/m^2) on day 8, in 21-day cycles. R (210 mg IV flat dose on the run-in portion and 375 mg on the dose de-escalation portion) was administered on day 1 of each cycle starting in cycle 2 and continued as monotherapy after completion of 6 cycles of GD. The primary endpoint of the phase I was to determine the recommended phase 2 dose (RP2D) of R plus GD. Secondary endpoints included describing the safety, assessing best overall response rate (ORR) by RECIST 1.1, disease control rate (DCR), and progression-free survival (PFS). **Results:** Thirteen pts were treated, 7on the run-in and 6 on the de-escalation portion. One pt progressed prior to starting R and was replaced. Median pt age was 53 (range 28 – 74) and 7 were female. Histologies included leiomyosarcoma (n = 6), undifferentiated pleomorphic sarcoma (2), dedifferentiated liposarcoma (2), pleomorphic liposarcoma (1), angiosarcoma (1), and myxofibrosarcoma (1). The Table lists treatment-related adverse events (TRAEs) that occurred in ≥ 20% pts in descending order of frequency. Additional Grade (Gr) 3 TRAEs occurring in 1 pt each, included: infusion reaction, leukopenia, anorectal infection, neutropenia, and pyelonephritis. Gr 3 pyelonephritis was the only dose-limiting toxicity. There were no Gr ≥ 4 TRAEs. One pt (Gr 3 elevated AST/ALT) required corticosteroids and cessation of study therapy. The RP2D was determined to be 375 mg of R plus GD. Twelve pts were evaluable for response. ORR was 17% (1 of 6; 95% CI 1 - 64%) and 50% (3 of 6; 95% CI 19% - 81%) in the run-in and de-escalation cohorts, respectively. DCR was 100% (6 of 6; 95% CI 52 - 100%) and 83% (5 of 6; 95% CI: 36 - 99%). PFS rates at 24 weeks were 60% (95% CI: 29 - 100%) and 44% (95% CI: 17 - 100%). **Conclusions:** R plus GD was generally safe and well tolerated with no unexpected safety signals to date. The phase II portion evaluating efficacy of R plus GD at the RP2D is ongoing. Clinical trial information: NCT04577014. Research Sponsor: Incyte Corporation.

TRAE	Grade		
	1	2	3
Anemia	2	4	3
Elevated AST/ALT	6		1
Fatigue	7		
Myalgia	3	2	
Peripheral sensory neuropathy	2	1	1
Alkaline phosphatase increased	3	1	
Alopecia	4		
Diarrhea	3	1	
Edema limbs	4		
Rash	3	1	
Lipase increased	1	1	1
Flu like symptoms	2	1	
Hypothyroidism	1	2	
Pruritus	2	1	
Skin hyperpigmentation	3		

n = pt(s) with TRAE.

11517 **Poster Discussion Session**

Interim analysis of a phase I study of SNK01 (Autologous Nongenetically Modified Natural Killer Cells with Enhanced Cytotoxicity) and avelumab in advanced refractory sarcoma. *First Author: Sant P. Chawla, Sarcoma Oncology Research Center, Santa Monica, CA*

Background: For patients (pts) with advanced sarcomas in the relapsed/refractory setting, there are very few if any effective salvage treatment options. The likelihood of response and/or tumor control only diminishes with each subsequent line of therapy. Monotherapy of PD-L1 inhibitors has shown modest to no activity in most sarcomas, especially in tumors that have little to no PD-L1 expression. Natural killer (NK) cells have recently been implicated in the antitumor response to immune checkpoint inhibitors with some evidence suggesting a role in PD-L1 negative tumors. SNK01 is a first-in-kind, autologous nongenetically modified NK cell therapy with highly enhanced cytotoxicity and over 90% activating receptor expression which can be consistently produced from heavily pretreated pts. Avelumab is an anti-PD-L1 immunotherapy with dual engagement of both the adaptive and innate immune systems. We hypothesized that this combination would be safe, and together better overcome the immunosuppressive tumor microenvironment. **Methods:** In this Phase I study (NCT03941262), cohort 4 is comprised of up to 18 pts treated with 800 mg of avelumab + 4 x 10^9 SNK01 cells every two weeks via IV Infusion. Pts were eligible regardless of PD-L1 status and permitted to continue treatment indefinitely until progression or unacceptable toxicity. The primary endpoint is safety. The secondary endpoints include overall response rate (ORR), progression free survival (PFS), and overall survival (OS). **Results:** As of February 1, 2022, 15 pts with advanced refractory sarcoma have been enrolled. Median age is 50 (range 20-75) and 8 were male. Pts had a median of 5 lines of prior therapy (range 1-8). The subtypes included 6 leiomyosarcoma, 2 osteosarcoma, 1 pleomorphic liposarcoma, 1 Ewing's sarcoma, 1 epithelioid sarcoma, 1 epithelioid mesothelioma, 1 endometrial stromal sarcoma, and 1 sarcoma NOS. There were three Grade 2 or 3 adverse events related to avelumab, but unrelated to SNK01. Best objective response by RECIST 1.1 was PR in 2 pts (ORR of 13.3%) and SD in 3 pts. Median PFS is 11.14 weeks. Several pts had PD-L1 negative disease and response appears to be independent of PD-L1 status. Of pts who progressed in this cohort, several reported an overall improvement in their QoL and some pts became eligible to be treated with additional salvage chemotherapy, resulting in some additional clinical response. **Conclusions:** SNK01 combined with avelumab was safe and well tolerated and appears to have some clinical activity against several types of heavily pretreated advanced sarcoma, independent of PD-L1 status. It may also keep rapidly progressing disease stable enough to allow additional cytotoxic chemotherapy. A proposed study expansion is planned. Clinical trial information: NCT03941262. Research Sponsor: NKGen Biotech.

11518 **Poster Discussion Session**

GALLANT: A phase 2 study using metronomic gemcitabine, doxorubicin, nivolumab, and docetaxel as second/third-line therapy for advanced sarcoma (NCT04535713). *First Author: Noufil Adnan, Sarcoma Oncology Center, Santa Monica, CA*

Background: In our experience, combinatorial therapy with lower doses of doxorubicin, gemcitabine, and docetaxel has been effective with a manageable toxicity profile in patients with advanced soft tissue sarcomas. Hypothesis: The addition of nivolumab will have synergistic effects and improve treatment outcomes. **Methods:** Primary objective: To assess progression-free survival; Secondary objectives: (1) To evaluate best overall response during treatment period confirmed in a 6-week follow-up, (2) PFS rate at 6 and 9 months, (3) Overall survival rate at 6, 12 months, and (4) Incidence of treatment-related adverse events (TRAEs). Inclusion criteria: Previously treated male and female subjects, > 18 years of age, pathologically confirmed diagnosis of locally advanced, unresectable, or metastatic sarcoma, measurable disease by RECIST v1.1, and acceptable hematologic and organ functions. Exclusion Criteria: History of autoimmune disorder. Treatment schedule: Metronomic doses of gemcitabine (600 mg/m2 max:1000 mg), doxorubicin (18 mg/m2; max: 32 mg), docetaxel (25 mg/m2; max:42 mg) on Day 1 and Day 8, and nivolumab (240 mg) on Day 1 only. Repeat treatment cycles may be given every three weeks if toxicity grade is <1. **Results:** This is an Interim Report on the modified Intent-to-treat population (n = 43). This population completed at least one treatment cycle and had a follow-up CT or MRI scan at week 6. The most common histological subtypes in this group include leiomyosarcoma (n = 15), pleomorphic sarcoma (n = 4), synovial sarcoma (n = 4), liposarcoma (n = 3), osteosarcoma (n = 3) and other (n = 10). Best Overall Response = 2 CR (surgical CR), 6 PR, 30 SD, 5 PD. The disease control rate (CR+PR+SD) was 88.4%. Median PFS was > 4.6 (range: 1-27) months; 4 month PFS rate 60%. Median OS 6.2 months, with 4-month OS 74%. Historically, the median PFS on preceding lines of therapy was 2 (range: 1-14) months. There were no unexpected side effects noted in this study. The most common grade 3/4 TRAEs include Fatigue (n = 13), Nausea (n = 9), Neutropenia (n = 8), thrombocytopenia (n = 6), Anemia (n = 6). **Conclusions:** The GALLANT protocol using metronomic Gemcitabine, Doxorubicin (Adriamycin), Nivolumab, and Docetaxel (Taxotere) (1) is an effective regimen as second/third-line therapy for advanced sarcoma with no unexpected side effects, and (2) may have synergistic activity when this metronomic chemotherapy is combined with an immune checkpoint inhibitor. Clinical trial information: NCT04535713. Research Sponsor: None.

11519 **Poster Discussion Session**

Phase I study of pegylated liposomal doxorubicin in combination with cyclophosphamide and vincristine in pediatric patients with relapsed/refractory sarcoma and other malignant solid tumors. *First Author: Suying Lu, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Pegylated liposomal doxorubicin (PLD) was found to have improved toxicity profile, especially with regards to reduced cardiotoxicity. The objectives of this study were to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of PLD in combination with cyclophosphamide and vincristine (PCV regimen) and describe the toxicities and response of this regimen. **Methods:** This was an open-label, single-center, single-arm phase I study utilizing a "3 + 3" design. The primary endpoint was the MTD of PLD, and the secondary endpoints included safety, objective response rate (ORR), disease control rate (DCR), and progression-free survival (PFS). Efficacy was evaluated using RECIST 1.1. PFS was defined as the time from treatment until disease progression or death. This study included cohort A and cohort B. Three dose levels were studied in cohort A, PLD 30 mg/m^2 (L1), 40 mg/m^2 (L2) or 50 mg/m^2 (L3) d1 + cyclophosphamide and mesna at 1 g/m^2/d d1-2 + vincristine 1.5 mg/m^2/d (≯2mg) d1 every 3 weeks. As the endpoint of the study could not be reached, we changed the dose of cyclophosphamide and mesna to 1.5 g/m^2/d d1 in cohort B. **Results:** Eleven in cohort A and 34 in cohort B were enrolled, the median age was 6 years (range 1-15). Forty-three patients were eligible and evaluable for toxicity, and 35 (77.8%) patients were evaluable for response. Diagnoses were rhabdomyosarcoma (n = 29, 64.4%), Ewing's sarcoma (n = 4), and others. The median number of prior regimens was 2 (range 1-5). The most common adverse event (AE) was grade 3 or grade 4 neutropenia with a proportion of 90.9% and 65.5% in cohort A and cohort B, respectively. There was no significant difference in ORR (60% vs. 48%) and DCR (90% vs. 88%) between the two cohorts. The ORR (60% vs. 0, P = 0.019) and DCR (96.7% vs. 40%, P = 0.006) were significantly higher in Group 1 (rhabdomyosarcoma, Ewing's sarcoma, Wilm's tumor, fibrosarcoma, undifferentiated sarcoma) compared with Group 2 (neuroblastoma, osteosarcoma, embryonal sarcoma, epithelioid sarcoma, extrarenal rhabdoid tumor). The 12-month PFS of Group 1 was also better than Group 2 (79% vs. 60%, P = 0.041). **Conclusions:** The PCV regimen demonstrated an acceptable toxicity profile and promising clinical efficacy in pediatric patients with R/R rhabdomyosarcoma, Ewing's sarcoma, Wilm's tumor, fibrosarcoma, and undifferentiated sarcoma. Increasing the dose of cyclophosphamide did not improve the efficacy, but increased the toxicity. The RP2D for future studies is PLD 30 mg/m^2/d for one day. Clinical trial information: NCT04213612. Research Sponsor: None.

Response	Cohort A (n = 10)	Cohort B (n = 25)	P	Group 1 (n = 30)	Group 2 (n = 5)	P
CR, n	1 (10)	2 (8)	0.849	3 (10)	0	0.460
PR, n (%)	5 (50)	10 (40)	0.589	15 (50)	0	0.036
SD, n (%)	3 (30)	10 (40)	0.580	11 (36.7)	2 (40)	0.886
PD, n (%)	1 (10)	3 (12)		1 (3.33)	3 (60)	
ORR, n (%)	6 (60)	12 (48)	0.521	18 (60)	0	0.019
DCR, n (%)	9 (90)	22 (88)	0.867	29 (96.7)	2 (40)	0.006

11520 **Poster Discussion Session**

Gemcitabine-docetaxel in patients with relapsed high-grade osteosarcoma after first-line treatment with high-dose ifosfamide: A retrospective multicenter study. *First Author: Maria Grazia Pionelli, Pediatric Onco-Hematology, A.O.U Città della Salute e della Scienza, University of Turin, Torino, Italy*

Background: Currently, there is no accepted standard chemotherapy regimen for recurrent osteosarcoma. We performed a retrospective study to evaluate the effectiveness, toxicity and clinical benefit of second line therapy with Gemcitabine (G) in combination with Docetaxel (D), in patients with relapsed high-grade osteosarcoma who have been previously treated with High-dose Ifosfamide (HD-IFO) during first-line treatment (ClinicalTrials ID: NCT04651179). **Methods:** Patients were eligible to the analysis according to the following criteria: episode of first relapse of osteosarcoma, previous first line treatment according to poor responders' arm of ISG-AIEOP OS 2 Protocol based on methotrexate, cisplatin, doxorubicin and HD-IFO (3gr/m2/day, day 1-5) ± Mifamurtide, presence of measurable disease according to RECIST 1.1, treatment with at least two cycles of Gemcitabine 900 mg/m2/day, days 1 and 8 and Docetaxel 75 mg/m2 day 8 every 21 days. Primary objective: overall survival (OS) at 12 months; secondary objectives: overall response rate (ORR) (complete response + partial response), progression-free survival (PFS) at 6-12 months, toxicity and quality of life. **Results:** 14 patients were included in the analysis. All patients were previously treated according to poor responders' arm of ISG-AIEOP OS 2 Protocol, 7/14 (50%) of them received Mifamurtide. Most of patients (12/14, 86%) received 4 GD cycles and the total number of cycles administered was 60. Median OS was 20 months (range 11-69); OS at 12 and 24 months was 84% (95% CI 65-100) and 51% (95% CI 22-79), respectively; ORR were 35,7% after six cycles. Median PFS was 12 months (range 2-69); 6-months and 12-months PFS were 86% (95% CI 67-100) and 56% (30-83) respectively. For 8/14 (57%) patients a surgical approach was feasible after 2 and 6 GD cycles. Previous use of Mifamurtide correlate with a better 6-months PFS rate (100% vs 57%, P = 0.0011). Also, amelioration of ECOG/Lansky score showed a positive correlation with both PFS (P = 0.01) and OS (P = 0.04). No extra-hematological toxicities grade ≥3 was observed according to CTCAE v4.03 criteria. **Conclusions:** This trial confirms that GD combination has an anti-tumor activity for relapsed high-grade osteosarcoma with a well-tolerated toxicity profile. Furthermore, GD guarantee a surgical tumor remotion for patients with a chemo-resistant disease such as patients previously treated with a poor responders' arm improving their OS and PFS rate. Promising results for patients previously treated with Mifamurtide need to be confirmed in future trials. Clinical trial information: NCT04651179. Research Sponsor: None.

11521 **Poster Discussion Session**

NRG-DT001 phase Ib trial of neoadjuvant navtemadlin (previously AMG232 and KRT232) concurrent with preoperative radiotherapy in wild-type p53 soft tissue sarcoma of the extremity and body wall. *First Author: Meng Xu Welliver, The Ohio State University James Cancer Center, Columbus, OH*

Background: NRG-DT001 is a phase Ib trial evaluating neoadjuvant navtemadlin with preoperative radiation therapy (RT) in patients (pts) with wild-type (WT) p53 soft tissue sarcoma (STS). The primary objective is to evaluate the safety and tolerability of the MDM2 inhibitor navtemadlin in combination with standard-dose RT in STS in two cohorts (A, extremity or body wall; B, abdomen/pelvis/retroperitoneum) to determine the maximum tolerated dose/recommended phase II dose (MTD/RP2D) of navtemadlin in combination with RT. This report contains the results for cohort A. **Methods:** Eligible pts had grade 2-3 STS ≥ 5 cm, age ≥ 18, and Zubrod performance status 0-1. Dose levels were 120 mg 2x/week (DL-1), 120 mg 3x/week (DL1), 4x/week (DL2), and 5x/week (DL3) 1 week prior to and during RT (50Gy/5 weeks). Surgery was 5-8 weeks after RT. A 3+3 design was used to make dose escalation/de-escalation decisions at each dose level. Five additional pts were enrolled to the MTD to ensure safety (expansion cohort) with a dose limiting toxicity (DLT) rate of ≤ 1/5 considered safe. The DLT observation period was from the start of navtemadlin until 4 weeks after completion of drug+RT. Tumor Tp53 mutation status was determined by NGS sequencing. All eligible and treated p53 WT pts who experienced DLT or completed the observation period were considered DLT-evaluable. DLT included all grade 4-5 AE definitely, probably, or possibly related to navtemadlin. Any grade 3 AE definitely, probably, or possibly related to navtemadlin was also considered DLT if any of the 2 following situations occurred: a delay of treatment > 2 weeks or ≥ 2 dose reductions due to the grade 3 AE. The decision to escalate or de-escalate was made by consensus of the study team in accordance with the protocol. **Results:** Between 11/3/2017 and 9/10/2021, 4 (3 WT), 7 (4 WT) and 7 (4 WT) pts were enrolled at DL1, DL2, and DL3 respectively. An additional 9 (5 WT) pts were enrolled on DL3 expansion cohort. Preoperative RT was completed for all except 1 pt (pt refusal/DL3). On DL1 and DL2, 100% of pts completed navtemadlin. On DL3 (including expansion cohort), 78% (7/9) completed navtemadlin (1 AE, 1 pt refusal). On DL1, DL2, and DL3, 3/3, 3/4 (1 disease progression), and 5/6 (1 consent withdrawal; 3 pending) completed surgery. There were no DLTs in any dose level (DL1 0/3, DL2 0/4, DL3 0/9), establishing DL3 as the MTD/RP2D. Tumor necrosis rates will be reported at the time of presentation. **Conclusions:** Neoadjuvant navtemadlin concurrent with standard dose preoperative RT is well tolerated in patients with WT p53 STS at extremity or body wall, and the 120 mg PO daily of navtemadlin, 5 days per week dose should be used to design future trials of RT with extremity STS. Incorporating NGS sequencing results as an integral biomarker in a clinical trial of neoadjuvant radiotherapy and a radiosensitizer is feasible. Clinical trial information: NRG-DT001 NCT03217266. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

11522 **Poster Discussion Session**

Preliminary results of a phase IB study of olaparib with concomitant radiotherapy in locally advanced/unresectable soft-tissue sarcoma from the French Sarcoma Group. *First Author: Paul Sargos, Institut Bergonié, Bordeaux, France*

Background: The poly(ADP-ribose) polymerase (PARP) inhibitor olaparib (O) has radiosensitizing properties in several tumor models including sarcomas. We studied safety and activity of O with external beam radiation therapy (EBRT) in patients with locally advanced soft-tissue sarcomas (STS). **Methods:** This phase I study first assessed four dose levels (DL1:25 mg, DL2:50 mg, DL3:100 mg, DL4:150 mg BID) of O administered in combination with EBRT (59.4 Gy in 33 fractions of 1.8 Gy) using a TITE-CRM design. Next, we recruited 15 additional patients in an expansion cohort to assess the tumor response or the histological response for patients with resectable disease. Tumor response was assessed by investigators according to RECIST 1.1 criteria. **Results:** A total of 41 patients (17 men, 24 women) were enrolled in both cohorts, of whom 19 (46.3%) underwent post-treatment surgery. We observed 1 DLT at DL1 (n = 5), 1 at DL2 (n = 7), 0 at DL3 (n = 11) and 1 at DL4 (n = 3) during the dose escalation. The recommended dose (RP2D) was 100 mg BID. Most common adverse events related to O and/or EBRT were acute dermatitis (G1/2 63.4% of patients, G3/4 34.1%), edema limbs (G1/2 36.6%), fatigue (G1/2 36.6%), nausea (G1/2 31.7%) and myositis (G1/2 29.3%). Among the 22 patients assessed for tumor response, 3 unconfirmed partial responses, 12 stable diseases, 5 progressive diseases, and 2 non-evaluable responses were recorded as best overall responses. The 6-month non-progression rate in that population was 9.1% [95%CI 1.1%-29.2%]. Six (31.6%) good histological responses and 9 (47.4%) poor responses were observed on the 19 patients who underwent surgery (4 responses non-available). **Conclusions:** This study shows that the combination of O with EBRT is well tolerated and lead to encouraging down-staging. A little less than half of the population was able to benefit from surgery with positive results in more than 30% of the cases and the rest of the population showed a promising stability of the disease at 6 months. We are currently awaiting a minimum of one year follow-up for the expansion cohort to assess survival. Clinical trial information: NCT02787642. Research Sponsor: Institut National du Cancer (INCa, Clip^2 program).

11523 **Poster Discussion Session**

Results of a phase I dose escalation and expansion study of tegavivint (BC2059), a first-in-class TBL1 inhibitor for patients with progressive, unresectable desmoid tumor. *First Author: Lee D. Cranmer, University of Washington/Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: Desmoid tumors are known to have increased nuclear β-catenin levels. Tegavivint selectively disrupts the interaction of β-catenin and TBL1/ TBLR1, resulting in specific degradation of nuclear β-catenin. The primary objectives of this study were to determine the maximum tolerated dose (MTD), safety, and preliminary efficacy of tegavivint in patients (pts) with desmoid tumors. **Methods:** This study (*NCT03459469*) utilized an accelerated dose escalation schema for the first two dose levels followed by a 3+3 design to determine the MTD/recommended phase 2 dose (RP2D) of tegavivint, followed by a dose expansion phase. The study included adult pts with sporadic desmoid tumors that were progressive (20% increase in tumor volume, recurrent in one year from surgery, or symptomatic), unresectable, and measurable via WHO criteria. Tegavivint was administered IV weekly (three weeks on, one week off) up to two years. **Results:** 24 pts were enrolled. Dose escalation enrolled 17 pts in six dose levels from 0.5 - 5 mg/kg. In dose expansion, 7 additional pts were enrolled. Dose expansion cohort also included 6 pts in dose escalation that were escalated to RP2D and 3 pts treated at RP2D in dose escalation (n = 16 total). Median age was 43 years (18-66). Median time from diagnosis was 3.1 years with median of one prior systemic treatment (range 0-6). Median time on study was 9.4 months; 3 pts remain on study at data cut-off. No dose-limiting toxicities were observed; MTD was not determined. RP2D was declared at 5 mg/kg based on pharmacologically relevant plasma concentrations and preliminary efficacy. Trough plasma concentrations (C_{min}) exceeded *in vitro* IC_{50} efficacy estimates at 4 mg/kg and 5 mg/kg. Median half-life was 38 hours supporting once weekly administration. Treatment-related adverse events (TRAEs) occurring in ≥20% of pts included fatigue (71%), headache (38%), nausea (33%), constipation (21%), decreased appetite (21%), and dysgeusia (21%), mostly Grade 1-2. Grade 3 TRAEs of hypophosphatemia, stomatitis, increased ALT, diarrhea, and headache occurred in 5 separate pts. There were no grade 4-5 adverse events (AEs). One serious AE of Grade 2 extravasation occurred. Objective response rate (ORR) of 17% across all dose levels and 25% at RP2D (WHO and RECIST criteria) were observed. Median duration of response was 8.1 months (range 6 to 11.8 months) with all responses ongoing. The 9-month progression free survival rate was 76% (95% CI: 54 - 90%) among all pts and 79% (95% CI: 51 – 93%) among those treated at RP2D. Patient reported outcomes and correlative science will be included in the presentation. **Conclusions:** Tegavivint is well tolerated with mostly Grade 1/2 AEs and no serious toxicity associated with WNT inhibition. The ORR of 25% at the RP2D warrants continued development of tegavivint in desmoid tumors. Clinical trial information: NCT03459469. Research Sponsor: Iterion Therapeutics.

11524 **Poster Session**

A report on the review of archived osteosarcoma and EWING sarcoma specimens at the Biopathology Center, BONE Sarcoma Committee, Children's Oncology Group. *First Author: Sonja Chen, Nationwide Children's Hospital, Columbus, OH*

Background: The Children's Oncology Group (COG) Biorepository at the Biopathology Center (BPC), Nationwide Children's Hospital, Columbus, OH contains archived tumor specimens submitted for COG study protocols. The BPC repository is utilized for numerous biology study aims with the goal of improved understanding of tumor pathophysiology, and impacts future clinical trials design and patient care. BPC pathologists perform quality assurance (QA) reviews of archival material before biospecimens are released for study. Since QA reviews are not routinely included in the submission process into the BPC, the quality and utility of tissue is often unclear. Therefore, a pathology quality assurance review was conducted to explore the utility of future testing on banked formalin fixed paraffin embedded (FFPE) Ewing Sarcoma and Osteosarcoma specimens. **Methods:** The BPC staff retrieved archival tumor cases for review between 06/2020 and 1/2022. One hematoxylin and eosin-stained slide per FFPE tissue block was digitally scanned for whole slide image (WSI) analysis and uploaded with a de-identified pathology report on a virtual slide-viewing platform. Five board certified pediatric pathologists with sarcoma expertise (AA, JB, SC, AS, JD) designed a digital QA review form and performed reviews. The QA review data collection form included diagnosis, volume of viable tumor, decalcification techniques, ancillary molecular/cytogenetic studies and a comment box to include additional noteworthy information. **Results:** During the study period, of the 1379 digitally prepared cases, 486 case reviews were completed, totaling 1192 digital slides reviewed. Of the reviewed cases, 465 (95%) were concordant with the diagnosis and had variable volumes of viable tumor (scant to adequate), while 33 (7%) of cases had no viable tumor (extensive necrosis or no tumor on the slide) and 21 (4%) had an alternative diagnosis (e.g. tumor submitted as osteosarcoma, re-classified as a chondromyxoid fibroma). Of the reviewed concordant cases, 271 (58%) were consistent with OS, 187 (40%) were consistent with ES and 7 (2%) were consistent non-ES round cell sarcomas (e.g. *BCOR* or *CIC*- rearranged sarcomas). **Conclusions:** Over ninety percent of reviewed specimens passed QA review, whereas the remaining failed due to diagnostic discordance or lack of viable tumor. Among cases with diagnostic concordance, variable volumes of tumor were present, including cases with scant viable tumors. Although QA reviews are time consuming, these results suggest QA reviews at tissue submission could potentially improve tissue quality available and timeliness of sample delivery for research. In addition, it would provide an opportunity for follow-up with sites to request submission of higher quality specimens and mitigate storage of tissue without potential for future use. Research Sponsor: COG.

11525 **Poster Session**

Age as a factor in the molecular landscape and the tumor-microenvironmental signature of osteosarcoma. *First Author: Andreas Seeber, Department of Internal Medicine V (Hematology and Oncology), Medical University of Innsbruck, Comprehensive Cancer Center Innsbruck, Innsbruck, Austria*

Background: Osteosarcoma (OS) incidence is characterized by a bimodal age distribution, with peaks in early adolescence and in adults > 65 years of age. In contrast to adolescents, OS in adults is frequently considered as a secondary neoplasm (i.e., transformation of Paget's disease of the bone, radiation induced). Yet, the literature is scarce regarding the impact of age on the molecular landscape of OS. Herein, we sought to explore the association between age and the genomic profile as well as the tumor immune microenvironment (TME) in a large cohort of OS patients. **Methods:** 208 specimens were centrally analysed at the Caris Life Sciences laboratory with DNA seq (NextSeq, 592 gene panel or NovaSeq, whole-exome sequencing), RNA seq (Archer fusion panel or whole-transcriptome sequencing) and immunohistochemistry (IHC). RNA deconvolution and differential expression analyses were performed using the Microenvironment Cell Populations counter method for quantification of immune cell populations and gene expression profiling. The cohort was stratified into three distinct age groups (< 25 years [n = 83], 25-45 years [n = 58], > 45 years [67]). **Results:** Overall, the most frequently detected mutations were in *TP53* (37%), *RB1* (13%), *ATRX* (9%), *TERT* (6%), *PTEN* (5%), *PIK3CA* (4%) and *KMT2D* (3%). Copy number alterations were most frequently detected in *CDK4* (12%), *LRIG3* (11%), *FLCN* (11%), *MDM2* (9%), *CCND3* (9%), *VEGFA* (8%), *TFEB* (8%). Interestingly, age-based stratification revealed an increased frequency of *FLCN* (19.7 vs 4.7%, $p < 0.01$), *CCND3* (13.9 vs 3.1%, $p < 0.05$), and *HSP90AB1* (11.3 vs 0.0%, $p < 0.01$), alterations in patients < 25 years compared to > 45 years. TME analysis revealed that patients > 45 years have decreased B-cell abundance compared to patients < 25 years (2.9-fold decrease, $p < 0.05$) and 25-45 years (4.8-fold decrease, $p < 0.05$). Although not statistically significant, median transcriptional expression of PD-L1 was numerically increased in patients > 45 years (1.8-fold compared to 25-45 years, $p = 0.17$; 2.0-fold compared to < 25 years, $p = 0.27$), which was consistent with increasing rates of IHC PD-L1 expression with age (5.3%, 9.4%, and 17.5%, respectively, $p = 0.06$). **Conclusions:** To the best of our knowledge, this study represents the largest cohort of molecularly characterized OS. Age-associated differences in the genetic landscape and TME composition, including increased gene amplifications observed in younger patients and decreased B-cell abundance in older patients, might suggest fundamental underlying molecular and biological differences. Research Sponsor: None.

11526 **Poster Session**

Metzolimos metronomic cyclophosphamide (CP) and methotrexate (MTX) combined with zoledronic acid (ZA) and sirolimus (SIR) in patients with advanced solid tumor with bone metastasis and advanced pretreated osteosarcoma (OSS): A phase Ib study. *First Author: Maud Toulmonde, Institut Bergonié, Bordeaux, France*

Background: Advanced pretreated OSS has a very poor prognosis. Metronomic CP and MTX have shown little activity in pediatric cancers, including OSS. Preclinical data suggest that ZA could have a synergic effect when combined with mTOR inhibition in OSS. **Methods:** This is a prospective phase Ib study investigating the combination of SIR with CP, MTX and ZA trough a dose-escalation phase (3 + 3 design) in patients ≥ 18 years with bone metastatic solid tumors (part I) and an expansion cohort dedicated to patients ≥ 13 years with advanced pretreated OSS (part II). SIR was given at two dose levels (4 mg and 6 mg) continuously, in combination with CP 50 mg x 2 per day, 1 week on / 1 week off, MTX at 2.5 mg x 2 per day, on day 1 and day 4 every week, and ZA 4mg IV every 4 weeks. Primary endpoints were dose limiting toxicities (DLT), maximum tolerated dose and recommended phase II dose (RP2D) of SIR combined with CP, MTX and ZA for Part I, and 6-month non-progression rate (NPR) according to RECIST v1.1 for part II. Secondary endpoints included safety, 6-month objective response rate (ORR), one-year progression-free (PFS) and overall survivals (OS), and pharmacodynamics biomarker analyses. At least one non-progression at 6 months after centralized review of imaging was needed among 14 patients to consider activity of the combination. **Results:** From February 2015 to March 2021, 23 patients were included in the three participating centers. In part I, nine patients with breast (56%), prostate (33%) or biliary duct carcinoma (11%) were included. Median number of cycles was 2 (1-6). Two DLT were reported at dose level 2: one grade 3 neutropenia and one grade 3 anemia, therefore dose level 1 was the RP2D for part II. In part II, 14 OSS patients were included. Median age was 27 years (14 - 80). Median number of previous lines in the advanced disease was 1 (1-3). At the time of analysis, 11 patients had died. Reason for study discontinuation was progressive disease for 10 patients (72%), toxicity for two (14%) (one grade 2 platelet count decrease and one grade 5 unrelated lung infection), and investigator decision for two (14%), including one for cryotherapy of a residual lesion after an excellent partial response. Overall, 64 adverse events related to study drugs were reported, of which 14 (22%) grade 3, and 2 grade 4 (3%). They were mainly asthenia, nausea, mucositis oral, anemia, lymphocyte and platelet count decrease. Median follow up was 27.5 months [95% CI : 12.8-27.5]. Two non-progressions at 6 months (14%) were observed, including a partial response (7%). One-year PFS was 21.4% [95%CI 5.2-44.8] and median OS was 12.8 months [95% CI : 2.8-20.4]. **Conclusions:** The combination of SIR at 4 mg daily with CP, MTX and ZA has an acceptable toxicity profile and reached the initial targeted efficacy rate in advanced pretreated OSS patients. Clinical trial information: NCT02517918. Research Sponsor: Anticancer Funds.

11527 **Poster Session**

The efficiency of anlotinib in osteosarcoma with chemoresistance: Exploratory therapy based on PDX models and next-generation sequencing. *First Author: Zuoyao Long, General Hospital of Northern Theater Command, Shenyang, China*

Background: It's urgent to find a new approach for the treatment of progressed osteosarcoma in neoadjuvant chemotherapy. Using patient-derived xenograft (PDX) models and next-generation sequencing (NGS), we have explored the efficiency of anlotinib in these patients. **Methods:** Frozen osteosarcoma tissues were used to establish PDX models. Ten samples of each PDX model were randomized to treatment or control group. The treatment group were gavaged at a volume of 0.1 ml/10g body weight for 4 weeks, while the control group were administered with vehicle at the same dose orally. Tumor volume and body weight were measured every 3 days, and the tumour were removed and weighed after 28 days. The number of mitotic cells and tumor necrosis rate were detected by Hematoxylin-Eosin (HE) staining. Immunohistochemistry (IHC) was used to evaluate the number of apoptotic cells and the expression of VEGFR-2, PDGFR-β, FGFR-1, c-Kit and their phosphorylated proteins, CD 31. Additionally, patients who had progressed during neoadjuvant chemotherapy (NAC) were treated with combination of anlotinib. After four cycles NAC, we performed salvage surgery and maintained with anlotinib. The change of tumor size was evaluated for tumor response. We used IHC and NGS to analyze the expression of drug targets. **Results:** 21 PDX models were established successfully from 43 samples. Tumor specimens from patients, who had pulmonary metastasis, local recurrence or chemoresistance, were easier to establish PDX models ($P < 0.001$, $P = 0.046$, $P = 0.013$). Six models were selected randomly for anlotinib. After anlotinib administration, the tumor inhibition rates were 18.82%, 45.98%, 85.86%, 83.38%, 84.57% and 86.42%. Anlotinib could not only inhibit the mitosis, induce tumor cell apoptosis and necrosis, but also decrease the expression of drug targets. The expression of VEGFR-2, PDGFR-β and CD31 were positively associated with tumor response. Five patients had received anlotinib during NAC. Four patients had tumor regression (69.4%, 28%, 19%, 8.7%), including two with high expression of VEGFR-2 mRNA or/and PDGFR-β and one with medium expression. **Conclusions:** Based on the results of PDX models and NGS, we suggested that osteosarcoma with high expression of VEGFR-2 or/and PDGFR-β was sensitive to anlotinib, which was alternative for patients progressed during NAC. Research Sponsor: None.

11528 **Poster Session**

A phase 2 study of anti-PD-L1 antibody (atezolizumab) in grade 2 and 3 chondrosarcoma. *First Author: Mohamad Adham Salkeni, National Cancer Institute, Bethesda, MD*

Background: Chondrosarcoma is one of the most common bone malignancies in adults, and the third most common in pediatric patients (pts). The most prevalent subtype, conventional chondrosarcoma, is a slow growing tumor that is historically known to be refractory to chemotherapy. Anecdotal reports indicated a role for anti-PD-(L)1 in the treatment of this disease. This is the first prospective report on the efficacy of the PD-L1-targeting agent, atezolizumab, in this rare disease. **Methods:** Patients (pts) ages 2 and older with unresectable grade 2 or 3 conventional chondrosarcoma were eligible. No prior anti-PD-(L)1 treatment was allowed, otherwise pts were eligible irrespective of prior therapies as long as protocol-specified washout period requirements were met. Pts received atezolizumab 1200 mg (15 mg/kg with 1200 mg cap in pediatric pts) once every 21 days. Imaging was carried out at end of cycle 3, and then every two cycles. Research biopsies were collected from adult pts prior to C1D1, prior to C3D1, and at progression. Immuno-pharmacodynamic (IO-PD) studies were performed on paired tumor samples and circulating immune cells to help elucidate signaling pathways mediating the immune response, with focus on subsets of effector cells in the tumor microenvironment. **Results:** A total of 9 pts (7 males, 2 females) were enrolled in 6 centers across the US and Canada. Six pts were Caucasian/White, 1 Asian, 1 Hispanic, and 1 unknown. Median age was 49 years (42-72). No objective responses were seen. Three pts (33%) experienced disease stability (SD) per RECIST 1.1, for a median duration of 21 weeks as of data cutoff (January 2022). A patient with SD remains on active treatment (tx) for 35 weeks. Three patients had no tx-related adverse events (AEs). Six pts (67%) experienced at least one tx-related AE. Two patients experienced > G2 AEs, but only one was considered tx-related (lymphopenia). Immune-related AEs were all G1/2 and included hepatitis (2), hypothyroidism (1), hyperthyroidism (1), and maculopapular rash (1). IO-PD studies are ongoing and will be reported at the conference if available. **Conclusions:** Atezolizumab was well-tolerated but demonstrated limited activity in this cohort of pts with few treatment options. Ongoing IO-PD studies will provide insight into atezolizumab's effect upon immune cell content and activation in the tumor microenvironment that will help design future immunotherapy trials in this disease and other sarcoma types. The study was funded by NCI Contract HHSN261201500003I. Clinical trial information: NCT04458922. Research Sponsor: U.S. National Institutes of Health, Supported in part by Roche/Genentech Inc. through a Cooperative Research and Development Agreement.

11529 **Poster Session**

Checkpoint inhibitor and multireceptor tyrosine kinase inhibitor combination in relapsed refractory sarcomas: A single institution series. *First Author: Nupur Mittal, Rush University Medical Center, Chicago, IL*

Background: Adolescent and young adults (AYA) with primary metastatic and relapsed bone and soft tissue sarcomas (BST) have poor prognosis with progression free survival (PFS) rates < 15% and overall survival (OS) < 20%. These outcomes have not improved in the past three decades, highlighting the need for new treatment paradigms. Immunotherapy is effective for multiple malignancies via blockade of CTLA4 or PD-L1 by immune checkpoint inhibitors (CPI), like nivolumab (NIVO). Sarcomas often express PD-L1 as part of their complex pathogenic pathway. Additionally, combination with oral targeted therapies is an emerging strategy for adult malignancies. Encouraging early phase results with multi-tyrosine kinase inhibitors (TKI) of several pathogenic sarcoma pathways – including lenvatinib (LEN), cabozantinib (CABO), and pazopanib – have prompted our team to offer CPI in combination with a TKI for BST patients without chemotherapy options. **Methods:** Retrospectively identified AYA patients with relapsed heavily pre-treated BST who received CPI/TKI combination at our institution between January 2018 to date. **Results:** This is the first reported series of prolonged survival in metastatic and multiply relapsed BST with CPI and TKI therapy. Table summarizes the demographics, disease features, and survival for all patients. The regimen was well tolerated in all patients, except for a rash (n = 1) that resolved by reducing the CABO dose by 25%. All patients had previously been offered palliative care before this regimen. **Conclusions:** Our preliminary experience with CPI/TKI combination in multiply relapsed BST shows a PFS exceeding prior PFS periods with other therapies for all patients. The overall survival is more than historical controls for initial metastatic ASPS, initial metastatic EWS, and recurrent metastatic OST. Our report will inform colleagues about the potential of CPI/TKI combination for these patients with few options. Research Sponsor: None.

Patient	Primary diagnosis, age, sex	# of relapses	Regimen CPI+TKI	Interventions prior to CPI+TKI	Best response by RECIST 1.1	PFS (months)	Prior PFS periods (months)	# cycles of CPI+TKI received / months	OS (months since diagnosis)
1	Localized Osteosarcoma (OST), 10, F	5	NIVO-LEN	Surgery, chemotherapy x3 regimens, radio-ablation, radiation, samarium,	SD	31	15, 5, 5, 3, 15	30, 31	74
2	Localized OST, 12, M	2	NIVO-LEN	Surgery, chemotherapy x2 regimens	continued CR	11	20, 4	24, 11	41
3	Metastatic Ewing Sarcoma (EWS), 15, M	4	NIVO-CABO	Chemotherapyx4 regimens, radiation, radio-ablation, surgery	continued CR	15	32, 18, 3, 12	20, 15	88
4	Metastatic Alveolar soft part sarcoma (ASPS) 19, M	2	NIVO-CABO	Surgery, radiation, sorafenib	PR	12	3, 6	23, 12	23
5	Localized OST, 15, M	2	NIVO-LEN	Chemotherapy(MAP), radiation, pembrolizumab	SD	6	13, 6	6, 6	27
6	OST, 16, M	2	NIVO-pazopanib	Chemotherapy (MAP), surgery	PD (non-adherence)	5	15, 7	7, 5	49

11530 **Poster Session**

Real-world experience of tyrosine kinase inhibitors in patients (pt) with recurrent bone tumours (BT): A CanSaRCC study. *First Author: Tushar Shailesh Vora, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada*

Background: Survival after relapse in osteosarcoma (OST), Ewing Sarcoma (ES) and chondrosarcoma (CS) remains dismal. Recent reports suggest a role of tyrosine kinase inhibitors (TKI) including regorafenib (R) and cabozantinib (C). We conducted a retrospective multi-centre pan-Canadian study to assess real-word outcomes with these novel treatments in recurrent BT. **Methods**: After ethics approval, data from pts treated in 7 different institutions was extracted from the CanSaRCC (Canadian Sarcoma Research and Clinical Collaboration) Database. Pt characteristics, treatment and outcomes were analyzed. Response was assessed per RECIST 1.1. PFS, OS were estimated using Kaplan-Meier. TTP was defined as time from TKI start to progression. **Results**: From June 2018-Dec 2021, 44 pts received R or C and best response by histology are listed in Table, with an overall clinical benefit rate of 63.6%. Median time to best response was 2.3 mo (range 1 – 17). 15 pts (34.1%) required dose reduction; most common reasons were hand-foot syndrome (13.6%), mucositis (9.1%) and hypertension (9.1%). At median FU of 6.4 mo (range 1.6 – 29), 25 pts (56.8%) died, 19 (43.2%) were alive with disease (AWD). Median PFS was 4.1 mo (95%CI 2.9 – 5.7), for OST was 5.0 (N = 25, 95%CI 2.6 – 10.6), for ES was 4.1 (N = 10, 95%CI 2-5.9), and for CS 4.0 (N = 9, 1 Progressed). Median OS was 10.5 mo (95%CI 7 – 14). By univariate analysis, age, line of therapy, gender, location of primary, or R vs. C did not correlate with PFS. **Conclusions**: Consistent with previous published studies, our pan-country real-world analysis shows that TKI have meaningful activity in the setting of recurrent BT with acceptable toxicities. Inclusion in earlier lines of treatment and/or maintenance therapy could be questions for future research. Research Sponsor: None.

		Total 44 (n, % of 44)	R (n = 16, 36.4%) N (% of R)	C (n = 28, 63.6%) N (% of C)
Age at TKI start	<18 years	11 (25%)	5 (31.2%)	6 (21.4%)
	>=18 years	33 (75%)	11(68.8%)	22 (78.6%)
N (%)	**OST**	25 (56.8%)	14 (87.5%)	11(39.3%)
	ES	10 (22.7%)	0	10 (35.7%)
	CS	9 (20.5%)	2 (12.5%)	7 (25.0%)
Gender	Male	24 (54.5%)	6 (37.5%)	18 (64.3%)
Line of therapy	**1st**	1 (2.3%)	0	1 (3.6%)
	2nd	16 (36.4%)	6 (37.5%)	10 (35.7%)
	3rd	16 (36.4%)	8 (50.0%)	8 (28.6%)
	>=4	11 (24.9%)	2 (12.5%)	9 (32.1%)
Median Starting Dose		60 (40 – 160)	120 (40 – 160)	60 (40 – 60)
	Dose Reduction	15 (34.1%)	7/16 (43.7%)	8/28 (28.6%)
Best Response	CR	1 (2.3%)	0	1 (3.6%), ES1
	PR	7 (15.9%)	2 (12.5%) OST1, CS1	5 (17.8%) OST3, ES2
	SD	20 (45.5%)	8 (50%) OST7, CS1	12 (42.8%) OST4, ES4, CS4
	PD	16 (36.4%)	6 (37.5%)	10 (22.7%)
Outcome	AWD	19 (43.2%)	3/16 (18.7%) OST: 2/14 (14.3%) ES: – CS: 1/2 (50%)	16/28 (57.1%) OST: 5/11 (45.4%) ES: 4/10 (40%) CS: 7/7 (100%)
	Deceased	25 (56.8%)	13/16 (81.2%) OST: 12/14 (85.7%) CS: 1/2 (50%)	12/28 (42.8%) OST: 6/11 (54.5%) ES: 6/10 (60%) CS: 0/7 (0%)
Median TTP mo (Range)	OST	3.7 (1.5 -19.5)	3.94 (1.4 -19.4)	2.92 (1.8 – 8.4)
	ES	3.84 (2 – 7.1)	–	3.84 (2 – 7.1)
	CS	2.27 (1.4 – 4)	4*	2.05 (1.4 – 3.3)

* N = 1.

11531 **Poster Session**

Value of adjuvant radiotherapy in patients with localized Ewing sarcoma at the extremities: Report from the Ewing 2008 trial. *First Author: Philip Heesen, University of Zurich, Zurich, Switzerland*

Background: In patients with Ewing Sarcoma (EWS), adjuvant radiotherapy is often performed after surgery that could not obtain wide margins or after poor histological response to surgery. However, the benefit of adjuvant radiotherapy needs further investigation. Therefore, we compared event-free survival (EFS) between surgery (SX) alone and SX combined with radiation therapy (RT), performed a subgroup analysis and identified independent prognostic factors. **Methods:** The data from localized EWS patients with tumors at the extremities that were treated in the Ewing 2008 trial from 2009-2018 were included in this analysis. Patients received induction chemotherapy according to the protocol and then underwent local therapy. Patients receiving SX or adjuvant RT (combined SX/RT) were included in this analysis. Hazard ratios (HRs) (95% Confidence Intervals (CIs)) were calculated using Cox regression. **Results:** 360 out of 863 patients (41.7%) presented with an EWS at the extremities with 81 tumors at the upper extremity, and 279 tumors at the lower extremity. Most patients were treated with surgery only (223, 61.94%), while 125 patients (34.72%) were treated with SX plus RT. Adjuvant radiotherapy was conducted after a median time of 69 days (1st quartile, 3rd quartile; 54, 109). Median EFS at 5-years for all patients was 0.74 (0.69, 0.80), 0.76 (0.70, 0.83) for patients after surgery only, and 0.73 (0.64, 0.83) after combined RT/SX. After adjusting for sex, age, tumor volume, histological response and surgical margins, the HR for combined RT/SX vs SX alone was 0.69 (0.37, 1.26), p = 0.22. In patients with poor histological response to surgery (≥10% vital tumor cells) and with high tumor volume (≥ 200mL), additional radiotherapy did not decrease the hazards of any event, HR 0.72 (0.25, 2.06), p = 0.54. We identified high tumor volume, poor histological response to surgery as well as intralesional resection of the tumor as independent prognostic factors after adjusting for other known prognostic factors with HRs of 1.73 (1.04, 2.90), p = 0.03; 2.79 (1.69, 4.62), p < 0.0001 and 215.9 (13.17, 3538.61), p = 0.0002, respectively. Surgical complication was not a prognostic factor after adjusting for above mentioned variables, HR 0.85 (0.31, 2.34), p = 0.75. **Conclusions:** In our cohort, adjuvant radiotherapy was not superior compared to surgery alone in all patients with localized EWS at the extremities and neither in a subgroup of patients with high-risk factors. Poor histological response, intralesional tumor resection as well as high tumor volume were identified as independent negative prognostic factors. Clinical trial information: NCT00987636. Research Sponsor: None.

11532 **Poster Session**

Spine high-grade osteosarcoma in the era of radiotherapy with high-energy charged particles: A single institution retrospective analysis. *First Author: Gisberto Evangelisti, Spine Surgery Department, Orthopaedic Institute Rizzoli, Bologna, Italy*

Background: Limited are data on high-grade osteosarcoma occurring in the spine. Wide resection is recommended, but it is a difficult and high morbidity procedure in the spine. High-energy particle therapy has been recently used. The goal of this study was to examine treatment and outcome of patients with osteosarcoma in the mobile spine. **Methods:** Spine high grade osteosarcoma patients who underwent surgery at the Rizzoli Institute between 2009 and 2020 were identified. Treatment, outcome, and prognostic factors in patients treated in a single institution were examined. **Results:** Characteristics of the 20 patients (8 female; 12 male) included: median age, 39.7 years (range, 14-71 years), 5 (25%) with tumors in the cervical spine, 6 (30%) with tumors in the thoracic spine, and 9 with tumors in the lumbar spine (45%); 14 (70%) patients with localized disease and 6 (30%) with metastatic disease at the time of presentation. Nineteen patients (95%) underwent chemotherapy, the majority were treated with MAP (methotrexate, doxorubicin, cisplatin) regimen. In 12 patients undergoing preoperative chemotherapy (n = 11) or chemotherapy and radiotherapy (n = 1), the median tumor % necrosis was 20 (IQR 20 - 40), with none achieving a good histologic response (> 90%). All patients underwent surgery. Adequate surgical margins were achieved in 5 patients (25%). In patients with positive margins, radiotherapy was administered to 8 (40%) patients. Four patients with positive margins after resection received photon neoadjuvant or adjuvant therapy. Four patients received high-energy particles as adjuvant therapy after planned gross total excision. The median overall survival rate was 10.5 months (IQR 5.8 - 15.0) for patients with metastatic disease and 25.5 months (IQR 8.3 - 46.0) for patients with localized disease (P = .0501). Patients treated with planned intralesional gross total resection followed by adjuvant high-energy particle therapy had a significant higher disease-specific survival than patients with positive margins after resection with or without additional conventional radiotherapy (P = .023). **Conclusions:** Metastatic disease, is a poor prognostic factor for high grade osteosarcoma of the spine. Post-operative high-energy particle therapy improved overall survival in patients undergoing a planned gross total resection compared to intralesional resection in this series. Chemotherapy induced necrosis was low underscoring the need of more aggressive multidisciplinary approaches for these patients. Research Sponsor: None.

11533 **Poster Session**

Subclonal somatic copy number alterations emerge and dominate in recurrent osteosarcoma. *First Author: Michael David Kinnaman, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Multiple large-scale tumor genomic profiling efforts have been undertaken in osteosarcoma, however little is known about the spatial and temporal intratumor heterogeneity and how it may drive treatment resistance. **Methods**: We performed 30-80x whole genome sequencing (WGS) of 37 tumor samples from 8 patients with relapsed or refractory osteosarcoma. A set of high confidence single nucleotide variants (SNV), copy number alterations (CNA), structural variations (SV) were called for each sample using our pediatric expanded genomics pipeline and an evolutionary analysis was performed using a custom pipeline of computational tools. **Results**: Of the 8 patients in our cohort, 4 had localized disease at diagnosis (OSCE4, OSCE5, OSCE6, OSCE9) and 4 had metastatic disease at diagnosis (OSCE1, OSCE2, OSCE3, OSCE10). There were 17 samples from primary sites, 7 were pretreatment biopsies, 10 from on therapy primary resections. 20 samples came from metastatic sites, 15 of which were from lung metastases. Driver gene SNV's were identified in 5 of 8 patients, including *TP53* (OSCE1), *ATRX* (OSCE3, OSCE10), *RB1* (OSCE4), and *CDKN2A* (OSCE9). No new driver SNV's emerged post-therapy in any patient. HATCHet, an algorithm which infers clone specific copy number alterations, identified subclonal CNAs in all but one patient (OSCE2). In the 7 patients with subclonal CNAs, 6 had two copy number clones identified, and 1 patient (OSCE10) had three copy number clones identified. In 5 patients (OSCE1, OSCE4, OSCE5, OSCE6, OSCE10) there is a copy number clone that is subclonal in the primary tumor which emerges and dominates at subsequent relapses. The resistant clone in each of these cases had either *MYC* gain/amplification. Amplifications in CCNE1 (OSCE1), RAD21 (OSCE4, OSCE5, OSCE10), VEGFA (OSCE1, OSCE9), IGF1R (OSCE6) were also identified as potential drivers in the resistant copy number clones. In two of these patients (OSCE1, OSCE6), the treatment resistant subclone becomes the dominant copy number clone by the time of primary resection. SNV based phylogenies revealed monoclonal and polyclonal seeding of metastases and monophyletic and polyphyletic modes of dissemination. Over half the new mutations acquired in recurrent disease were attributed to HRD or cisplatin mutational signatures. **Conclusions:** Subclonal copy number clones emerge and dominate in relapsed osteosarcoma, with MYC gain/amplification a defining characteristic in our cohort. Selective pressure from neoadjuvant chemotherapy reveals this clone at the time of primary resection, implying genomic profiling at this timepoint may be more reflective of its metastatic potential. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology, Other Foundation.

Sample	Pre-Treatment Biopsy	Primary Resection	Metastasectomy	First Relapse	2nd Relapse	3rd Relapse	4th Relapse	5th Relapse	Total
OSCE1	*	*		*	*		*	*	6
OSCE2	*	*	* *						4
OSCE3	*	*	* * * *						6
OSCE4	*			*	*	*			4
OSCE5	*					*	*		3
OSCE6	*	*		*					3
OSCE9		*		* *					3
OSCE10	*	* * * * *	*	*					8

11534 **Poster Session**

Platelet derived growth factor receptor alpha (*PDGFRA*) mutant gastrointestinal stromal tumours (GISTs): Clinicopathological characteristics and outcomes from a regional centre in the United Kingdom. *First Author: David M Favara, University of Cambridge, Cambridge, United Kingdom*

Background: GISTs are the most common mesenchymal tumours of the gastrointestinal tract with an annual incidence of 10-15 per million. 10% of GISTS have activating mutations in the *PDGFRA* gene. We report our 13 year experience of all the *PDGFRA*-mutated GISTs in our regional centre in Cambridge. **Methods**: *PDGFRA*-mutant GISTs were identified from the Cambridge GIST database. Demographics, clinical and histopathological features, survival and response to tyrosine kinase inhibitors of all the patients from 2008-2021 were reviewed. **Results:** n = 50 (male:female 1.5:1) Median age 68 years (range 19-87). 8% of patients were under the age of 40 years. Tumour size ranged from 1-26 cm with a median of 5 cm. Mitotic index ranged from 1-51 with a median of 1 mitosis/5mm2. 52% of GISTs were located in the gastric body. Histological subtypes: 44% epithelioid, 36% mixed and 20% spindle cell. 38% of cases had high KIT expression (immunohistochemistry), whilst 48% had patchy expression and 14% were negative. Most were DOG1-positive (94%). 76% had radical surgery, 60% had laparoscopic resection. 24% were assessed as being high risk GISTs using the modified AFIP model contrasted to 13% being high risk with prognostic contour mapping. 13% developed metastatic disease with liver being the most common metastatic site. The table shows *PDGFRA* mutational analysis results: 58% had a D842V mutation. None had a *KIT* mutation. With a median follow up of 55.1 months, 82% were alive. 6 patients died from metastatic GIST and 3 from other causes. Median time to metastatic disease in resected GISTs was 30.1 months and median time from metastatic diagnosis to death was 18.5 months. Patients who presented with metastatic disease had poor survival compared with patients with localised disease (p=0.001). 8 patients were treated with tyrosine kinase inhibitors including imatinib, sunitinib and regorafenib prior to 2020 with no objective responses. 3 patients were treated with Avapritinib since 2020 within the compassionate use programme. All 3 patients had partial responses and 2 patients are continuing Avapritinib with no grade 3 adverse events. **Conclusions:** We report the largest single centre *PDGFRA*-mutant GIST cohort from Europe. Male preponderance and exclusive gastric location were observed. KIT expression was patchy to negative in the majority of patients. 58% had *PDGFRA* D842V mutations for which Avapritinib has been recently approved. No objective responses were seen with imatinib, sunitinib or regorafenib. Our early experience with Avapritinib is promising. Research Sponsor: None.

PDGFRA mutation	Exon 18 D842V	Exon 18 non-D842V	Exon 14	Exon 12
	58%	28%	4%	10%

11535 **Poster Session**

Discontinuation of imatinib in patients with oligo-metastatic gastrointestinal stromal tumor who are in complete radiological remission: A prospective multicenter phase II study. *First Author: Ivar Hompland, Oslo University Hospital, Oslo, Norway*

Background: Life-long tyrosine kinase inhibitor (TKI) treatment is recommended for patients (pts) with metastatic GIST. We investigated whether highly selected pts with metastatic GIST may remain in durable complete remission after imatinib discontinuation. **Methods:** In this 1-group, prospective, multicenter phase II trial (NTC02924714) selected pts with overtly metastatic GIST discontinued imatinib treatment. Eligible pts had been treated with imatinib > 5 yrs for oligo-metastatic (≤3 metastases) disease, had no GIST progression and had undergone either R0/R1 resection or radiofrequency ablation (RFA) of all metastases, and had no longer detectable metastases on CT/MRI imaging, The primary endpoint was 3-yr progression-free survival (PFS), overall survival was a secondary endpoint. We estimated to achieve an improvement from 15% to 35% in 3-yr PFS compared to pts treated in the BRF-14 trial with a sample size of 31 pts. **Results:** The trial closed early due to slow accrual. Between January 5, 2017, and June 5, 2019, 12 pts (males, 7) with a median age of 67 yrs (range, 50-85) were enrolled. All pts had their primary tumor surgically removed (stomach, 4; small bowel, 6; large bowel/rectum, 2). Seven pts had *KIT* exon 11 mutation, 2 *KIT* exon 9 mutation, 1 *PDGFRA* exon 12 mutation, 1 had no mutation in *KIT/PDGFRA*, and 1 pt had unknown GIST mutational status. Eight pts had liver metastases, 3 peritoneal metastases, and 1 had both. Prior to enrollment all pts were in macroscopic complete remission after surgical metastasectomy (n = 7), RFA (n = 2), or both (n = 1), and 1 pt achieved complete radiological response with imatinib. At enrollment, 8 pts had imatinib 400 mg/d and 4 had < 400 mg/d. The median time of imatinib treatment before study entry was 8 yrs (range, 5-17). After imatinib discontinuation 7 (58%) pts progressed; the median time to progression was 10 mos (range, 2-31 mos). Five (42%) patients were progression-free after a median follow-up time of 42 mos (range, 30-59 mos). Median PFS was 23 mos and the estimated 3-year PFS 39%. Patients who progressed all achieved a second remission after restarting imatinib and were alive after a median follow-up time of 48 mos (range, 32 to 61 mos). **Conclusions:** The findings suggest that discontinuation of imatinib is safe in highly selected patients with oligo-metastatic GIST and that such patients may survive without detectable GIST progression for several years. The findings need to be viewed with caution due to the small pt numbers. Further study on imatinib discontinuation seem warranted. Clinical trial information: NCT02924714. Research Sponsor: None.

11536 **Poster Session**

Second primary malignancies (SPM) in patients with gastrointestinal stromal tumors (GIST): 10-year experience from the Ottawa Hospital (TOH). *First Author: Abdulhameed Alfagih, Division of Medical Oncology, Department of Medicine, The Ottawa Hospital, The University of Ottawa, Ottawa, ON, Canada*

Background: The secondary malignancies in patients with GIST are relatively high. We present our 10-year experience of SPM in patients with GIST from a regional Cancer Centre in Canada. **Methods:** A retrospective cohort study was performed in all GIST patients treated at TOH between January 2011 and December 2021. Patients were identified using ICD-10 codes and electronic medical records reviewed. Clinicopathological data were analyzed. Logistic regression analysis was used to evaluate associated factors with SPM. Survival analysis was estimated with the use of the Kaplan-Meir method and compared by log-rank test. **Results:** In total, 248 patients with GIST were identified. Of these patients, 61 (25%) had SPM; synchronous (9, 15%) and metachronous (52, 85%). Nine patients had two additional primary cancers other than GIST, and four patients had three additional primary cancers. The median age at diagnosis was 70 (range 44 – 90) years, and males were (59%). The most common SPMs were skin cancer (14, 17%), melanoma (5), and non-melanoma (9), followed by prostate cancer (13, 16%) and breast cancer (12, 15%). Colorectal cancer and hematological malignancies were found in (5, 11%) patients each, while RCC was found in (4, 6%). Thyroid cancer, lung cancer, neuroendocrine tumor, bladder cancer, thymoma, and other types of cancers were collectively found in 15 patients (24%). The majority (57%) of SPM diagnosed before GIST, 30% after GIST. The most common primary GIST locations were in the stomach (62%), followed by the small bowel (30%), and the most common histology was spindle cell (69%), followed by mixed histology (13%). The majority of GIST were localized (46 patients, 75%). Based on Miettinen risk classes for non-metastatic GIST, 74% had zero to low-risk disease, while 26% had moderate or high-risk disease. There was no association between SPM and GIST primary site (p = 0.4), TNM stage (p = 0.8), histology (p = 0.2), Mitosis (p = 0.5), and Miettinen risk class (p = 0.6). The median follow-up time was 53 months (range 1 – 132), and four patients lost follow-ups. Five years overall survival of SPM group vs. non SPM, 79.8% vs. 94.1%, (p = 0.03). Cox regression did not reveal a significant association with the covariants **Conclusions:** We observed that one out of four GIST patients have SPM. Skin, prostate, breast cancers were the most common SPM associated with GIST. Molecular studies are needed to explore the association/underlying mechanisms of GIST with these malignancies. Research Sponsor: None.

11537 **Poster Session**

Regorafenib third-lined therapy in advanced GISTs: A single center analysis based on different genotypes. *First Author: Sile Chen, Dept of GI Surgery, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China*

Background: The relationship between primary and secondary mutational status and efficacy of regorafenib in third-line therapy on GISTs is yet clear. **Methods:** From Jun 2017 to Dec 2021, a total of 62 patients with advanced GIST refractory to imatinib and/or sunitinib were enrolled in this study from the First Affiliated Hospital, Sun Yat-sen University. **Results:** Primary mutational was most common in KIT exon 11(40/62, 64.5%) , followed by *exon 9* (19.4%), *exon 17* (4.8%). Six cases (9.7%) belonged to *SDH* deficiency and one case (1.6%) was NF1-associated GISTs. Before receiving treatment of regorafenib, specimens obtaining for secondary mutations were as follows: 39 cases from surgery，12 from core-needle biopsy; ctDNA alone was performed in 9 cases and 2 patients refused to secondary mutational test. Excluding 6 patients with *SDH* deficiency, 14 patients (25.8%) had mutations in *exon 11+13*, 15 (27.7%) in *exon 11+17*, 7 (13.0%) in *exon 9+17*, 4 (7.4%) in *exon 11+13+17*. Exon 11 + 18, exon 11 + 13 + 18, exon 11 + 13 + 17 + 18, exon 9 + 16, exon 11 + 17 + 18 and NF-1 were found in 1 case, respectively (1.9%). Eight (14.7%) patients with primary *KIT* mutation were not detected any secondary mutation (2nd-not-detected) . There was no complete response, 4 of partial response (4/54, 7.4%), 27 of stable disease (50.0%). Progression disease was seen in 23 patients (42.6%) and 8 were not applicable (no assessable lesion) to imaging response assessment due to R0/1 surgery before using regorafenib. The median follow-up time was 19.0 months. The median progression-free survival (mPFS) was 5.4 months (0.2-29.1 months) and the median overall survival (mOS) was 20.3 months (0.2-37.0 months). For primary mutation analysis, it was found that *SDH*-deficient patients had longer mPFS (29.1 months) than those with mutations in *exon 9* or *exon 11* (5.4 and 4.8 months, respectively; P= 0.013). In terms of secondary mutations, patients with activation loop mutations *(exon 17+18)* showed both longer mPFS (7.3 months vs 1.9 months, P= 0.001) and longer mOS (20.3 months vs 7.7 months, P= 0.059) than those patients with non-activation loop mutations. Not any specific or new adverse reaction was found in all patients. By Cox-regression analysis, response to regorafenib and mutational status were independent predictors of PFS，response to regorafenib was also an independent predictor of OS. **Conclusions:** Regorafenib seems to have better treatment efficacy in GIST patients with *SDH* deficiency compared to those with primary KIT mutations, and better with secondary mutations in activation loop than those with non-activation loop mutations. It is necessary to carry out clinical research for later-line treatment choice based on different genotypes for imatinib-resistant GISTs. Research Sponsor: None.

11538 **Poster Session**

A randomized phase 2 study of continuous or intermittent dosing schedule of imatinib re-challenge in patients with tyrosine kinase inhibitor-refractory gastrointestinal stromal tumors. *First Author: Hyung-Don Kim, Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea*

Background: Resumption of imatinib is one of the available therapeutic options for patients with gastrointestinal stromal tumors (GIST) refractory to tyrosine kinase inhibitors (TKIs). Intermittent dosing of imatinib was suggested to delay outgrow of the imatinib-resistant clones in a preclinical study. **Methods:** A randomized phase 2 study was performed to evaluate the efficacy and safety of continuous or intermittent schedule of imatinib in GIST patients whose disease had progressed to at least imatinib and sunitinib. Patients were randomly assigned (1:1) to the intermittent dosing group that received 400mg daily imatinib based on a 1 week-on and 1 week-off schedule or the continuous dosing group that received imatinib 400mg daily without drug holiday. Disease control rate (DCR) rate at 12 weeks was the primary endpoint. Plasma samples were collected for circulating tumor DNA analysis at baseline, at 3 months of continuous or intermittent imatinib treatment and at the time of progressive disease. **Results:** Fifty patients received at least one dose of imatinib and were included in the full analysis set. Most patients (n = 46) had received prior regorafenib. DCR rate at 12 weeks was 34.8% and 43.5% in the continuous and intermittent groups, respectively. Median progression-free survival was 1.68 months and 1.57 months in the continuous and intermittent groups, respectively. The frequency of any grade anorexia, dysphagia, diarrhea, decreased neutrophil was lower in the intermittent group, whereas that of abdominal pain was higher in the intermittent group. Two patients in the continuous imatinib group underwent dose modification, and there was no patient who discontinued the study treatment because of adverse events related to study treatment. **Conclusions:** We confirmed that imatinib re-challenge was effective in TKI-refractory GIST patients. Intermittent dosing schedule may also be a clinically feasible treatment option for imatinib resumption in TKI-refractory GIST patients. Clinical trial information: NCT02712112. Research Sponsor: None.

11539 **Poster Session**

Interruption of imatinib in advanced gastrointestinal stromal tumor after prolonged imatinib maintenance in the absence of gross tumor lesions. *First Author: Yoon-Koo Kang, Asan Medical Center, University of Uslan College of Medicine, Seoul, South Korea*

Background: Although current guidelines recommend indefinite imatinib treatment in advanced gastrointestinal stromal tumor (GIST) patients, prolonged imatinib treatment is often challenging. Imatinib-refractory progression-free survival (PFS) and overall survival were reportedly not different between those who interrupted imatinib and those did not. **Methods:** Clinical outcomes of 77 consecutive patients with recurrent or metastatic GIST who interrupted imatinib treatment after maintaining around 5 years of imatinib treatment in the absence of gross tumor lesions were retrospectively analyzed. Association between clinical factors and progression-free survival (PFS) following imatinib interruption was analyzed. **Results:** Median time from the absence of gross tumor lesions to imatinib interruption was 61.5 months (range 41.4–122.7 months). Since imatinib interruption, median PFS was 19.6 months, and the PFS rate at 60 months was 26.3%. Among patients who had progressive disease following interruption, imatinib re-introduction led to 88.6% objective response rate and 100% disease control rate, with the median imatinib-refractory PFS since re-introduction of 112.4 months. Complete removal of initial gross tumor lesion(s) (hazard ratio [HR] 0.32, 95% confidence interval [CI] 0.12–0.81, P = 0.016) and complete removal of residual gross tumor lesion(s) (HR 0.45, 95% CI 0.21–0.94, P = 0.033) by local treatment (vs. no local treatment or residual lesions after local treatment) were independently associated with favorable PFS. **Conclusions:** Interruption of imatinib may be considered with close surveillance in selected patients who maintained years of imatinib treatment in the absence of gross tumor lesions, especially for those who had complete removal of gross tumor lesions by local treatment. Research Sponsor: None.

11540 **Poster Session**

Selective internal radioembolization (SIRT) allows to control liver metastases of gastrointestinal stromal tumors (GIST) failing treatment with tyrosine kinase inhibitors (TKI). *First Author: Peter Hohenberger, Division of Surgical Oncology and Thoracic Surgery, Mannheim University Medical Centre, University of Heidelberg, Mannheim, Germany*

Background: The liver and the peritoneum are the main area of metastatic spread in GIST. Liver resection does not play a role for hepatic metastases in comparison to f.e. colorectal cancer. If hepatic metastases are the only or major area of tumor progression and are resistant to available TKIs due to a missing mutation in *KIT/PDGFRA/SDH* ('wildtype') or after treatment with $1^{st}/2^{nd}/3^{rd}/4^{th}$ line therapy, interventional radioembolization with yttrium-90 (^{90}Y) microspheres are promising treatment options, as radiation doses as high as 200Gy can be applied locally. We analyzed the long-term results of SIRT with respect to hepatic-progression-free survival (HEP-PFS) in a consecutive cohort of patients **Methods:** From 1/2008 to 1/2018, 2^6 pts (12f, 14m) with biopsy proven liver metastases of GIST which were the only (n = 13) or the dominant site of progression (n = 12) were treated by SIRT. Median age at GIST diagnosis had been 51.8 yrs and when receiving SIRT was 57.6yrs (range, 18–75yrs). The mutational status was 'wildtype' (n = 7, 2 NF-1), exon 11 (n = 7), exon $11+2^{nd}$ mutation (n = 7), exon 9 (n = 3), exon $9+2^{nd}$mut (n = 1), and, exon 13 (n = 1). All patients except of two had prior TKI therapy: 1 line n = 3, 2 lines n = 11, 3-4 lines n = 9. Follow-up after SIRT was done via dynamic MRI and contrast-enhanced (CE)-CT, the median follow-up is 33.6 mos (range, 12-108mos) and all patients were followed until death **Results:** .The median hepatic-progression free survival (HEP-PFS) after SIRT was 17 months (range, 5-53+, 95%CI 10.7-23.8 mos). Of the patients with concomitant extrahepatic disease, the extraHEP-PFS was median 10 months. Twelve patients received next-line TKI therapy for progressive extrahepatic disease, whereas six patients required this for progressive liver metastases. When comparing the results according to the mutational status, patients with a 'wildtype' tumor showed a better median HEP-PFS of 19 mos (range, 12-53+, 95%CI 16.7-21.2 mos.) in comparison to *KIT* exon 9/11/13 mutated patients with only 14 months (range, 4-34 mos., 95%CI 6.5-21.4 mos), $p < 0.11$ (Wilcoxon). **Conclusions:** 90Y radioembolization (SIRT) offers a safe and effective treatment for patients with liver metastases of GISTs being the dominant site of tumor progression and with no drug treatment options available. In patients known to have no mutation in *KIT/PDGFRA* (wt, also NF-1 associated) it looks whether the results might be even more promising and SIRT could be used in earlier treatment lines. Research Sponsor: None.

11541 **Poster Session**

Patient reported outcomes and tolerability in patients receiving ripretinib versus sunitinib after imatinib treatment in INTRIGUE: A phase 3 open-label study. *First Author: Hans Gelderblom, LUMC Leids Universitair Medisch Centrum, Leiden, Netherlands*

Background: Ripretinib (R) is a switch-control tyrosine kinase inhibitor (TKI) indicated for the treatment of patients (pts) with advanced gastrointestinal stromal tumor (GIST) after prior treatment with ≥3 TKIs. In the INTRIGUE study (NCT03673501) there was no significant difference in median PFS (primary endpoint) between R and sunitinib (S). We present exploratory analyses of tolerability data and selected pt reported outcomes (PROs). **Methods:** Pts were randomized 1:1 to R 150 mg QD or S 50 mg QD 4 weeks on/2 weeks off.Dose modification was allowed for toxicity management. The event of interest was severe or life-threatening (grade ≥3) treatment-related adverse event prior to progression (sTRAE). Days with at least one sTRAE were summed for all treated pts and for pts with ≥1 sTRAE event. PROs were assessed using questions from EORTC QLQ-C30 and Dermatology Life Quality Index (DLQI) at cycle 1 (C1) day 1 (D1), D15, and D29; D1 and D29 of all other cycles; as well as at end of treatment. Differences in PRO scores between baseline and later assessments were calculated across visits. Long-term data will be presented. **Results:** Pts receiving R (n = 223) versus (vs) S (n = 221) experienced fewer sTRAEs (24% vs 51%, respectively). For all treated pts, the mean time with sTRAEs was 11 days for R and 42 days for S (ratio 0.27, P<0.0001). For pts with ≥1 sTRAE, the mean number of days with a sTRAE was 48 days for R vs 81 days for S (ratio 0.59, p = 0.037). Completion of PRO assessments across the two treatment arms was similar (baseline: R [n = 199], S [n = 199]; C1 D29: R [n = 167], S [n = 177]). Significant differences in self-reported functioning and symptoms were observed by C1 D29. For PROs relating to commonly reported sTRAEs, except constipation, pts in the R arm reported better outcomes than pts in the S arm. Pts in the R arm reported significantly (p<0.05) less decline compared to baseline in pt-reported role function as well as less increase, or improvement, in symptoms of fatigue, appetite loss, diarrhea, nausea/vomiting, and pain vs pts in the S arm. Moderate or severe effect of skin toxicity on pt life, as measured by DLQI in the R arm (n = 165) and in the S arm (n = 175), was observed in 6.6% of pts in the R arm vs 14.8% of pts in the S arm (p = 0.015). **Conclusions:** In the INTRIGUE study the total number of days with sTRAEs was fewer for pts receiving R vs S. Pts in the R arm also reported significantly less decline in pt-reported role function and less increase in symptoms related to commonly reported sTRAEs, except constipation, vs pts in the S arm. Medical writing provided by Costello Medical. Clinical trial information: NCT03673501. Research Sponsor: Deciphera Pharmaceuticals, LLC.

11542 **Poster Session**

Outcomes in late-line systemic treatment in GISTs: Does sequence matter? *First Author: Prapassorn Thirasastr, University of Texas MD Anderson Cancer Center, Department of Sarcoma Medical Oncology, Houston, TX*

Background: Ripretinib (R) is approved for 4^{th} line treatment of GIST based on superior PFS and OS compared to placebo in a phase 3 study, with RR of 11.8% and PFS of 6.3 months (mo). In addition to having high potency against PDGFRA D842V, avapritinib (A) showed activity in 4^{th} or later lines for KIT mutated patients (pts). The RR was 17% and median duration of response was 10.2 mo from a phase 1 study. It is not known if pts receiving R benefit from A after progression or vice-versa. We retrospectively reviewed outcomes of R and A to determine if sequence affects outcomes. **Methods:** Pts diagnosed with GISTs and treated with both R and A at UTMDACC from Jan 2016 to Dec 2021 were included. Pts were separated into R-A (RA) or A-R sequence (AR) and outcomes were tabulated. Descriptive statistics were used to summarize characteristics and genetic profiles. Differences between RA and AR groups were calculated using Fisher's exact. Response was evaluated using RECIST. Kaplan-Meier and Log-rank test were used to estimate and compare PFS and OS between groups. **Results:** Twenty pts were included in the study; 12 in RA and 8 in AR. Median age was 55 years (R:29.7-76.3). Most pts had small bowel primary (11/20, 55%) followed by stomach (4/20, 20%). All baseline characteristics and mutations were equitably distributed between RA and AR. RR of R was 17% and 14% in RA and AR groups, respectively and RR of A was 33% and 29% in RA and AR, respectively (Table). None of the pts with secondary exon 13 mutations responded to R or A. The drug administration sequence did not affect RR (p = 0.7, 0.62 in R, A). The PFS of the second drug administered, was shortened. PFS did not differ based on type of KIT mutation. Median OS from diagnosis in RA and AR groups were 121.8 (58.2-NR) and 171.3 (73.3-NR) mo, respectively and median OS from start of RA and AR was 43.9 (23.0-NR) and NR (11.5-NR) mo, respectively. Neither difference was statistically significant. **Conclusions:** Both R and A are efficacious in later lines of treatment, with greater benefit from the agent used first. Although, the combined PFS was numerically higher in AR compared to RA (20.5 vs 15.2 mo), the OS was not different. Currently, R is the only drug approved in the 4^{th} or later lines in KIT-mutated GIST. Research Sponsor: None.

RA: n = 12	PR	SD	PD	mPFS (mo,95%CI)
R	2 (16.7)	9 (75.0)	1 (8.3)	10.08 (1.8-17.0)
Exon 11, 13 (1)	0	1	0	
Exon 11, 17 (1)	1	0	0	
Exon 11, 13, 17 (1)	0	1	0	
Exon 11 (3)	1	2	0	
Exon 9 (2)	0	2	0	
Exon 9, 11 (1)	0	1	0	
PDGFRA D842V (2)	0	2 0	0 1	
Exon 11, PDFRA D842V (1)	0			
A	4 (33.3)	5 (41.7)	3 (25.0)	5.12 (1.7-10.6)
Exon 11, 13 (1)	0	0	1	
Exon 11, 17 (1)	1	0	0	
Exon 11, 13, 17 (1)	0	0	1	
Exon 11 (3)	0	2	1	
Exon 9 (2)	1	1	0	
Exon 9, 11 (1)	0	1	0	
PDGFRA D842V (2)	2 0	0 1	0 0	
Exon 11, PDFRA D842V (1)				
AR: n = 8	PR	SD	PD	mPFS
A*	2 (28.6)	4 (57.1)	1 (14.3)	3.67 (1.8-NR)
Exon 11, 13 (1)	0	1	0	
Exon 11, 17 (1)	0	1	0	
Exon 11 (1)	0	1	0	
Exon 9 (3)	2 0	0 1	1 0	
PDGFRA D842V (1)				
R*	1 (14.3)	5 (71.4)	1 (14.3)	6.51 (4.7-NR)
Exon 11, 13 (1)	0	1	0	
Exon 11, 17 (1)	0	1	0	
Exon 9 (4) PDGFRA D842V (1)	0 1	3 0	1 0	

*RR was calculated in 7 pts as drug was stopped due to toxicity with no follow-up scan in 1pt of each group.

11544 **Poster Session**

Health-related quality of life in patients with resectable undifferentiated pleomorphic sarcoma treated with neoadjuvant checkpoint blockade in a single institution randomized phase II clinical trial. *First Author: Heather G. Lyu, MD Anderson Cancer Center, Houston, TX*

Background: In SARC028, patients with undifferentiated pleomorphic sarcoma (UPS) had a 40% overall response rate to pembrolizumab. Based on this, we conducted a randomized, phase II, non-comparative trial of combination nivolumab (nivo/RT) and ipilimumab (ipi/nivo/RT) and demonstrated an 89% major pathologic response. Here, we report the health-related quality of life (HRQoL) metrics. **Methods:** In this study (NCT03307616), patients with resectable UPS were randomized (1:1) to receive one dose of nivo (3mg/kg) or one dose of combination nivo (3 mg/kg) and ipi (1 mg/kg), followed by combination of nivo (3 doses, 3mg/kg every 2 weeks) plus 50 Gy in 25 fractions (both arms). HRQoL was assessed using the MD Anderson Symptom Inventory (MDASI), European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLC) Core 30, and the Functional Assessment of Cancer Therapy – General (FACT-G) questionnaires. Questionnaire completion rates were calculated using the number of patients with at least one baseline and post-baseline assessment. Analyses included mean change from baseline scores to week 11 (preoperative) and week 54 (postoperative). **Results:** Ten patients were randomized from October 2017 to February 2020. HRQoL were collected at baseline (n = 10) and at week 11 for five (83%) nivo/RT and three (60%) ipi/nivo/RT patients. Three (60%) nivo/RT and three (100%) ipi/nivo/RT patients had week 54 assessments. MDASI scores indicative of symptom severity and interference of daily life both decreased for patients undergoing ipi/nivo/RT (0.8→0.67 and 0.9→0.46, respectively) while both increased in the nivo/RT group (1.6→2.22 and 1.9→3.33, respectively). Both arms had similar increases at 54 weeks. Patients undergoing ipi/nivo/RT experienced a greater decline in EORTC-QLC global health status at 54 weeks than those undergoing single agent therapy (-22.92 vs -8.33). The mean change in total FACT-G score did not differ between the two arms at 11 weeks (-4.0 vs -4.5), however, there was a significant decline for patients undergoing ipi/nivo/RT at 54 weeks (-20.3 vs -5.7). **Conclusions:** For patients with resectable UPS, combination immune checkpoint blockade with ipi/nivo/RT is associated with an improvement in short term HRQoL compared to single-agent nivo/RT. This finding warrants further study with more patients, controlling for baseline symptom scores. Combination therapy was associated with a slower recovery to baseline function, with ongoing decline in HRQoL at 54 weeks post treatment. Our study demonstrates the feasibility of collecting HRQoL metrics, which can be key factors in guiding patient management decisions. Clinical trial information: NCT03307616. Research Sponsor: Bristol Myers Squibb.

11545 **Poster Session**

Extended progression-free survival and long-term safety of nirogacestat in patients with desmoid tumors. *First Author: Geraldine Helen O'Sullivan Coyne, Developmental Therapeutics Clinic/Early Clinical Trials Development Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD*

Background: Desmoid tumors are rare, locally invasive, soft-tissue neoplasms that can cause significant morbidity and frequently recur despite surgery or radiation. The ongoing phase II trial of nirogacestat, a gamma-secretase inhibitor, in patients (pts) with recurrent, refractory desmoid tumors (NCT01981551), has reported disease stabilization and multiple partial responses as assessed by RECIST criteria (Kummar JCO 2017). Herein, we report long-term outcomes, tolerability, and safety of this study. **Methods:** A total of 17 pts enrolled in this open label, single arm, phase II study, completing accrual in 2014. Pts received 150 mg nirogacestat orally twice a day in continuous 3-week cycles. Objective treatment response was defined by RECIST 1.1 at cycle 1 and every 6 cycles thereafter using CT (affected area) per the primary study objective; optional MRI assessment was concurrently performed. Yearly CT scans of the chest, abdomen, and pelvis were performed on pts starting in 2016. **Results:** As of Dec. 31, 2021, 4/17 (23%) pts remain on nirogacestat treatment for over 7 years. The objective response rate has not changed since the 2017 publication [31.25% (5/16 evaluable patients), with an exact two-sided Clopper-Pearson 95% confidence interval of 11.0-58.7%], but the observed extended progression-free survival (PFS) is notable; no RECIST disease progression has been observed for any of the 16 evaluable patients at any point on study. Median time on treatment was 4.14 years (range: 0.17-7.99 years). Most common adverse events remain hypophosphatemia (13/17, 76%; 8 grade 3 [gr3], 5 gr2), diarrhea (13/17, 76%; 1 gr3, 4 gr2, 8 gr1), nausea (11/17, 65%; 11 gr1), AST increase (11/17, 65%; 1 gr2, 10 gr1), and lymphopenia (11/17, 65%; 2 gr2, 9 gr1); no pts required a dose reduction after the second year of therapy. Bone fractures (fx) were reported in 4 pts (3 female/1 male) during the first 4 years of treatment (1 hip fx, 1 rib fx, 2 metatarsal stress fxs). Two of these 4 pts experienced a further fx approximately 1 year later (contralateral metatarsal; hip). Both pts with hip fx were > 10 years post-menopausal. Given median age at enrollment (34 years; range: 20-69 years) and reported fx events, bone health was evaluated with findings in keeping with expected range for age. No secondary malignancies have been identified to date. **Conclusions:** No patients receiving nirogacestat have progressed after a median of more than 4 years of treatment. The long duration of responses and lack of tumor progressions observed in this trial has informed the design of a phase III trial in pts with progressing desmoid tumors (NCT03785964) that is currently underway. Clinical trial information: NCT01981551. Research Sponsor: U.S. National Institutes of Health.

11546 **Poster Session**

Serum glycoproteomic signatures and association with survival in patients with bone and soft tissue sarcoma treated with immune-checkpoint inhibitor therapy. *First Author: Daniel Serie, Venn Biosciences Corporation, Redwood City, CA*

Background: Glycosylation is one of the most ubiquitous and functionally important forms of post-translational modification. The role of differential glycosylation in serum proteins has so far been limited by the technical complexity inherent in generating and interpreting this information. InterVenn has built a novel platform that combines liquid chromatography/mass spectrometry with a proprietary artificial-intelligence-based data processing engine, allowing for highly scalable and reproducible interrogation of glycoproteins with site- and glycan-specificity. **Methods:** Using this platform, we interrogated 519 glycopeptide (GP) biomarkers derived from 70 serum proteins in pre-treatment samples from a cohort of 103 individuals (56 females, 47 males, age ranging from 18 to 84 years) presenting with one of 20 solid cancer types. All patients were treated with durvalumab and tremelimumab immune checkpoint inhibitor (ICI) therapy. Median follow-up for overall survival (OS) was 11.4 months, with 70 events total observed. OS associations were assessed for individual GPs via Cox regression models and leave-one-out-cross-validation (LOOCV) was employed to generate penalized multivariable prediction scores. Notably, 43 patients had a primary diagnosis of bone and soft tissue sarcoma, and stratified analyses were carried out in this population. **Results:** We identified 154 biomarkers significantly associated with OS in the full dataset after adjusting for multiple comparisons (FDR < 0.05). Of these, 7 were statistically significant at $p < 0.01$ in the sarcoma-only subset. LOOCV models built in all cancer types resulted in held-out scores that discriminated those likely to exhibit long-term survival post-ICI therapy from those unlikely to benefit (HR = 4.0, p = 4.91E-08, with 4 GPs included in the final model). Furthermore, LOOCV models including only sarcoma patients demonstrated even stronger predictive attributes (HR = 8.22, p = 2.10E-05, employing 2 glycopeptides). All 9 sarcoma patients with extreme glycosylation signatures for prediction of poor survival displayed quick clinical progression with little benefit from ICI therapy. Relative signal strength and comparative analyses demonstrated strong histotype-specificity inherent in the biomarkers employed for sarcoma vs all cancers. **Conclusions:** Our results indicate that glycoproteomic liquid biopsy holds potential as a predictive biomarker for identifying sarcoma patients who will derive the greatest benefit from ICI therapy. Research Sponsor: None.

11547 **Poster Session**

Circulating tumor DNA (ctDNA) detection of molecular residual disease (MRD) as a potential biomarker in localized soft tissue sarcoma (STS). *First Author: Abdulazeez Salawu, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada*

Background: Surgery and (neo)adjuvant radiotherapy are the mainstay curative treatments for localized STS. Despite treatment, approximately 50% of STS patients (pts) experience metastatic relapse and routine use of adjuvant systemic therapy (AST) remains controversial. The presence of ctDNA following curative treatment of STS is a potential biomarker for MRD and may identify patients who benefit from AST. Given the genomic heterogeneity of STS, a histology-agnostic approach to ctDNA detection in this population is desirable. **Methods:** Pts with localized, high risk (size ≥ 5cm, grade ≥ 2) disease were enrolled prior to (neo) adjuvant radiotherapy and surgery. Blood for ctDNA was collected at diagnosis; post-radiotherapy, post-surgery and every 3 months for up to 2 years. Whole exome sequencing (WES) of archival tumor- and matched buffy coat-DNA were carried out to identify somatic variants. Personalized and tumor-informed, multiplex PCR next generation sequencing-based ctDNA assay (Signatera™ assay) was performed on plasma obtained at the serial timepoints. A sample level positive call required ≥ 2 variants above a confidence calling threshold. Absolute ctDNA levels were expressed as mean tumor molecules per milliliter (MTM/ml) of plasma, based on variant allele frequencies and quantity of cell free DNA. Standard radiologic surveillance (every 3 months) was performed following surgery. The primary endpoint was a ctDNA detection rate of 70% at diagnosis. Secondary endpoints included MRD detection and correlation of ctDNA levels with disease relapse. **Results:** Seventy-six plasma samples from 10 pts [8 males and 2 females; median age 64 years (range 46–84)] were obtained prospectively. STS subtypes were undifferentiated pleomorphic sarcoma (n = 4), myxofibrosarcoma (n = 2), dedifferentiated liposarcoma (n = 2), myxoid liposarcoma (n = 1), and pleomorphic liposarcoma (n = 1). All tumors successfully underwent WES with adequate data quality for Signatera™ assay design. The personalized ctDNA assay was performed on a median of 7 plasma samples per patient (range: 5 – 10). ctDNA was detected in 7 pts (70%) at diagnosis, with median ctDNA level of 1.6 MTM/ml (range: 0.2 – 137.8), achieving the study primary endpoint. Immediate post-surgery samples were negative in all pts. However, ctDNA was detected in 2 out of 2 pts who developed metastatic disease during follow-up. **Conclusions:** Personalized tumor-informed ctDNA assays in localized high-risk STS at diagnosis are feasible. In this series, all patients had undetectable levels of ctDNA post-surgery and patients who experienced disease relapse demonstrated a detectable rise in ctDNA levels. Further interrogation of this approach for detection of post-treatment MRD as a possible biomarker of benefit from AST is ongoing. Research Sponsor: University Health Network, Toronto, Natera.

11548 **Poster Session**

Pan-sarcoma analysis of DNA damage response pathway alterations and deficiency. *First Author: Steven Bialick, University of Miami Miller School of Medicine/Sylvester Comprehensive Cancer Center, Miami, FL*

Background: Alterations in DNA damage response (DDR) pathways contribute to genomic instability and malignant progression and have been shown to be of clinical significance in several carcinomas and solid tumors. While some studies have identified ostensibly pathogenic variations in known and novel cancer genes with implications for sarcoma risk and treatment opportunities, there is limited information regarding the role of DDR pathway alterations in sarcoma. We identified a gene alteration in *ERCC2*, a gene that codes for a DNA helicase in the nucleotide excision repair pathway, in a patient with multiply relapsed epithelioid sarcoma (ES), prompting an investigation of DDR pathway alterations in sarcoma samples using a global next-generation sequencing (NGS) platform. **Methods:** Sarcoma patient samples (N = 5310), representing 38 pediatric and adult histologic subtypes, underwent NGS of DNA (592 gene panel or whole exome) and RNA (whole transcriptome sequencing, N = 3612) at a CLIA-certified laboratory (Caris Life Sciences, Phoenix, AZ). A threshold of 10 mut/Mb was used to identify high tumor mutational burden (TMB-H). IHC was performed for PD-L1 (SP142; 2+I5% = positive). Homologous recombination deficiency (HRD) scores were calculated as a composite of loss of heterozygosity, telomeric allelic imbalance, and large-scale transitions, using a positive threshold of 42 (N = 2138). HRD score association with biomarker status was evaluated overall and in sarcoma subtypes. **Results:** A pathogenic DDR pathway mutation was noted in 842 (15.9%) of the total samples. *ATRX* was by far the most commonly altered DDR gene (10% of all samples), with mutations observed across 25 sarcoma subtypes (11 subtypes with > 10% mutation rate: leiomyosarcoma [LMS], perivascular epithelioid cell tumor [PEComa], pleomorphic sarcoma [PLSARC], uterine sarcoma [OUSARC], osteosarcoma, spindle cell sarcoma, angiosarcoma, mesenchymal chondrosarcoma, sarcoma NOS, fibrosarcoma and ES). *CHEK2*, *ATM*, and *MUTYH* mutations were observed in 1-2% of sarcoma samples. More than 20 histologic subtypes showed distinct gene signatures with mutations occurring in > 3% of the samples investigated. *ERCC2* was mutated in 3% of ES and 6.5% in PEComa. Median HRD scores ranged between 20-58 across sarcoma subtypes. High rates of deficient HRD (HRDd ≥ 42) were observed in PLSARC (83.2%), OUSARC (73.7%), and dedifferentiated chondrosarcoma (71.4%), while low rates of HRDd were observed in Ewing sarcoma (0%) and clear cell sarcoma (10%). In the overall cohort, *ERCC2*, *ATRX* and *BRCA2* were significantly associated with increased HRD scores (p = 0.01). **Conclusions:**DDR pathway alterations are present in numerous histologic subtypes of sarcoma. A more comprehensive analysis of individual histologic subtypes is in progress. Further research will evaluate the clinical implications of these known and novel mutations to guide risk stratification and potential therapeutic options. Research Sponsor: None.

11549 **Poster Session**

Prognostic value of *EZH2* expression for immunotherapy-based schemes in advanced soft-tissue sarcoma: A translational research from Spanish Group of Research on Sarcoma (GEIS). *First Author: David Silva Moura, Group of Advanced Therapies and Biomarkers in Sarcomas, Health Research Institute-Fundación Jiménez Díaz University Hospital, Madrid, Spain*

Background: Immunotherapy-based treatments had shown to be active in several solid tumors, including in selected subtypes of sarcomas. IMMUNOSARC (NCT03277924) is a phase Ib/II trial [from Spanish (GEIS) and Italian (ISG) sarcoma groups], that tested the combination of nivolumab (anti-PD-1 inhibitor) plus sunitinib (anti-angiogenic agent) in advanced sarcomas. Among the 65 soft-tissue sarcoma (STS) patients (pts) enrolled, 48% were free of progression at 6 months, meeting the trial's primary endpoint. EZH2 is the catalytic subunit of the Polycomb Repressive Complex 2 and it has been described to play an important role in the transcriptional repression of genes involved in T-cell migration and T-cell-mediated anti-tumor activity. The aim of this study was to explore the value of *EZH2* gene expression as potential prognostic biomarker of the activity of immunotherapy-based schemes. **Methods:** The expression of *EZH2* was evaluated in 64 paraffin tumor blocks, by direct transcriptomics, using HTG EdgeSeq Oncology Biomarkers Panel (HTG Molecular Diagnostics, Inc.; Tucson, AZ, USA). Data was normalized with DESeq2 and the cut-off of *EZH2* expression was calculated with MAXSTAT R package. Gene expression was correlated with progression-free survival (PFS) by RECIST, overall survival (OS) and clinical benefit (patients with response or stable disease vs patients with progressive disease as best response). **Results:** Among the 64 pts analyzed, 52 (81%) showed overexpression of *EZH2*, considering a cut-off of 570.15 read counts. Undifferentiated pleomorphic sarcoma (UPS) and epithelioid sarcoma were the subtypes with higher expression of *EZH2* with a median of read counts of 1888.04 (n = 10) and 1261.79 (n = 7), respectively. The lowest expressions were observed in extraskeletal myxoid chondrosarcoma (ECM) and alveolar soft-part sarcoma (ASPS) with a median of read counts of 461.42 (n = 4) and 680.84 (n = 7), respectively. Low expression of *EZH2* was associated with better PFS (16.8 months vs. 3.9 months; p = 0.001) and better OS (NR vs. 20.0 months; p = 0.006). Moreover, low expression of *EZH2* was also significantly associated with a clinical benefit of the patients treated with nivolumab plus sunitinib [relative risk (RR): 13; 95% CI: 3.0-56.9; p = < 0.001). **Conclusions:** Low expression of *EZH2* was associated with better outcome in advanced STS patients treated with immunotherapy-based schemes. These results might support the rationale for the combination of EZH2 inhibitors with immune-modulating agents for future studies. Research Sponsor: Sarcoma Foundation of America, Pharmaceutical/Biotech Company.

11550 **Poster Session**

Clinical utility of circulating tumor DNA sequencing with a large panel in patients with advanced soft-tissue sarcomas. *First Author: Julie Blanchi, Institut Bergonie, Bordeaux, France*

Background: Preliminary studies have suggested that the detection, quantification, and profiling of ctDNA in patients with sarcoma is feasible and may improve prognostication, measure treatment response, and detect relapse. However, data related to impact of ctDNA profiling to tailor therapy in patients with advanced disease are lacking. **Methods:** Patients with advanced soft-tissue sarcomas (STS) have been included in two ongoing institutional molecular profiling studies (BIP: NCT02534649, STING: NCT04932525). Genomic analysis (ctDNA in all cases and tissue when available) was performed by using the Foundation One Liquid CDx Assay (324 genes, tumor mutational burden [TMB], microsatellite instability status). Each individual genomic report was reviewed and discussed weekly by a multidisciplinary tumour board dedicated to precision medicine, attended by experts in clinical oncology, molecular biology, and clinical genetics. Actionable targets were defined by the MTB according to the existing level of evidence (ESCAT), and molecular-based treatment suggestions were proposed where possible. **Results:** Between December 2020 and August 2021, 98 patients with metastatic STS underwent ctDNA profiling. Median time to assay results was 12 days. Results were contributive for 86 patients (88%). At least one actionable target (range 1-4) was detected in 35 patients (36%) including high tumor mutational burden (> 16 mutations/Mb) for 1 patient (1%) and alteration of the DNA repair response pathway for 12 patients (12%). Overall, the MTB recommended a matched therapy for 27 patients (28%). 40 patients underwent also NGS of tissue besides ctDNA profiling. The number of actionable alterations was similar in 26 (65%), whereas it was higher in tissue for 10 (25%) and in liquid for 4 (10%) patients. **Conclusions:** This large-scale study demonstrates that liquid biopsy with a large NGS ctDNA panel is an efficient approach to match patients to genomically directed clinical trials/targeted therapies in patients with advanced STS. Outcomes of patients treated with matched therapy will be presented at the meeting. Research Sponsor: None.

11551 **Poster Session**

Using pan-sarcoma multiomic analysis for identifying sarcoma subtypes with immunogenic potential. *First Author: Galina Lagos, Brown University, Providence, RI*

Background: Immune checkpoint inhibitors (ICI) have limited efficacy for most sarcomas. Yet, responses are seen in particular sarcoma subtypes, highlighting the need for better predictive biomarkers. The T cell inflamed score (TIS), a gene expression signature reflective of an active tumor immune microenvironment, is associated with ICI response in multiple solid tumors. We evaluated the TIS across a large database of sarcomas to identify which histologic subtypes may benefit from ICI. **Methods:** Next generation sequencing of DNA (592 gene or whole exome)/RNA (whole transcriptome) was performed for 3605 sarcoma patient samples, representing 45 histologic subtypes (Caris Life Sciences, Phoenix, AZ). TIS (18 gene weighted coefficient composite value; Cristescu 2018) was calculated and the Microenvironment Cell Populations-counter tool (Becht 2016) was used to quantify immune cell populations. Results were compared to melanoma (n = 1255), a representative immunogenic tumor type. High TIS was defined as a score within the upper quartile of melanoma TIS (> 5.5). Percentage with high TIS are reported with 95% CI. **Results:** Median TIS was highest in inflammatory myofibroblastic tumor (IMT), epithelioid sarcoma (EPIS), myxofibrosarcoma (MFS), well differentiated liposarcoma, and solitary fibrous tumor (SFT). These did not differ significantly from melanoma (p > 0.06). Median TIS was lowest in embryonal rhabdomyosarcoma, desmoid tumor (DES), synovial sarcoma (SYNS), and Ewing sarcoma (ES). Histologic subtypes where > 10% of samples had a high TIS included IMT (29.9% ± 21.7%), MFS (23.3% ± 12.6%), pleomorphic sarcoma (PLSARC) (21.9% ± 5.8%), cutaneous angiosarcoma (ANGS) (18.4% ± 13.9%), spindle cell sarcoma (17.5% ± 7.6%), liposarcoma (LPS) (17% ± 10.7%), EPIS (15.4% ± 19.6%), visceral ANGS (13.2% ± 10.7%), pleomorphic LPS (13.6% ± 14.3%), fibrosarcoma (12.5% ± 13.2%), leiomyosarcoma (11.6%± 3.4%), malignant peripheral nerve sheath tumor (MPNST) (10.2% ± 7.7%), and perivascular epithelioid cell tumor (PEComa) (10% ± 10.7%). The relative abundance of immune and stromal cell populations was highly variable across sarcoma subtypes, yet a strong positive correlation between TIS and immune cell populations was observed for most subtypes (e.g. T cells, Spearman R range: 0.56 [P = 0.08] - 0.96 [P < 0.0001]). A notable exception was SFT, which had a relatively high median TIS but low abundance of CD8+ T cells and B cells. **Conclusions:** We found high median TIS and/or significant proportions of samples with a high TIS in sarcoma subtypes with previously demonstrated responsiveness to ICI, including MFS, PLSARC, LPS, and ANGS, while unresponsive tumor types such as RMS, DES, SYNS, and ES had low TIS. We further identified subtypes with high TIS but limited prior clinical data supporting ICI use, such as IMT, EPIS, MPNST, SFT, and PEComa. Our results warrant prospective exploration of TIS as a predictive biomarker for ICI use in sarcoma. Research Sponsor: None.

11552 **Poster Session**

Distinct oncogenic signatures in malignant PEComa and leiomyosarcoma identified by integrative RNA-seq and H3K27ac ChIP-seq analysis. *First Author: Krinio Giannikou, Center for Functional Cancer Epigenetics, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*

Background: Malignant perivascular epithelioid cell tumor (PEComa) and leiomyosarcoma (LMS) are two sarcomas with overlapping morphologic and immunophenotypic features which can make their diagnostic distinction challenging. We aimed to characterize the transcriptional and epigenetic landscape of PEComa and LMS to identify distinguishing features. **Methods:** We performed whole transcriptome RNA-sequencing on 19 PEComas and compared their gene expression profile to 259 sarcomas from The Cancer Genome Atlas (TCGA) including 104 LMS. ChIP-sequencing for H3K27ac, a histone modification associated with activation of nearby genes/open chromatin, was conducted on 9 malignant PEComas and 12 LMS and were compared with publicly available data from 4 other sarcoma subtypes (chordoma; osteosarcoma; undifferentiated pleomorphic sarcoma; rhabdomyosarcoma; n = 29 tumors). **Results:** Genome-wide epigenetic and transcriptional analyses revealed overlapping patterns between PEComa and LMS, which were distinct from other sarcomas. However, we also identified a set of highly expressed and epigenetically distinct transcripts which may represent diagnostic?biomarkers: e.g., *DAPL1, MLANA, SULT1C2, GPR143,* and *CHI3L1* for PEComa; and *MYOCD, WDFC2, DES, MYH11,* and *CNN1* for LMS; each of which showed >17x fold higher expression for each tumor entity by DESeq2 (FDR<0.0001). Gene Set Enrichment Analyses (GSEA) demonstrated enrichment in the KEGG Lysosome pathway for PEComa (FDR=0.11), whereas myogenesis and smooth muscle contraction pathways were enriched in LMS (FDR=0.09). Integrative transcriptomic and epigenetic analyses revealed a unique set of master core transcription factors for each tumor type including among others MYOCD for LMS; MITF for PEComa, which require further functional investigation. Twelve selected genes including new as well as known and standard diagnostic markers (e.g., DAPL1, MLANA, GPR143, PNL2, CHI3L1, DES, MYH11, ER, CD68, PU.1, pS6 and CNN1) were validated by immunohistochemistry (IHC) in multiple sections from PEComa and LMS (n = 26). The combination of three melanocytic markers (HMB45, MLANA, PNL2) and pS6 can distinguish LMS from PEComas (**** p<0.0001). IHC for CD68 and PU.1 macrophage markers did not show any difference regarding the degree of immune infiltration in PEComa vs. LMS. **Conclusions:** Our studies revealed novel epigenetic signatures translating into lysosomal and melanocytic proteins for PEComa and myogenic proteins for LMS, which may serve as useful diagnostic biomarkers in the distinction of these two sarcoma subtypes. Research Sponsor: U.S. National Institutes of Health, Other Foundation, U.S. National Institutes of Health.

11553 **Poster Session**

A phase 1 dose-escalation/expansion clinical trial of mocetinostat in combination with vinorelbine in adolescents and young adults with refractory and/or recurrent rhabdomyosarcoma: Interim results. *First Author: Noah Federman, David Geffen School of Medicine UCLA Jonsson Comprehensive Cancer Center, Los Angeles, CA*

Background: Rhabdomyosarcoma(RMS) is the most common soft tissue sarcoma in children. Relapsed/refractory(R/R) RMS has a poor outcome and remains an area of unmet need. Histone deacetylase (HDAC) inhibitors have been shown to have activity in preclinical models of RMS. Mocetinostat (Mirati Pharmaceuticals) is an investigational oral HDAC inhibitor, that targets HDACs 1, 2, 3 and 11. Mocetinostat displayed high activity in in vitro RMS cell lines, RMS xenograft models and exerted synergistic activity in combination with vinorelbine. We report early interim results of the Phase 1 trial of mocetinostat with vinorelbine in R/R RMS. **Methods:** An investigator initiated Phase 1,open-label, dose escalation/expansion clinical trial. A modified intent to treat approach is used for efficacy analysis for a target accrual of 20 subjects in the dose expansion cohort. Subjects with R/R RMS were age ≥ 18 years old(yo) for the phase 1 dose escalation cohort and ≥12 yo for the phase 1 dose expansion. Mocetinostat 40mg, 70mg or 90mg was taken orally 3 times weekly with vinorelbine 25mg/m^2 IV on day 1,8, and 15 in 21 day cycles. Maximum tolerated dose of mocetinostat in the dose escalation phase was 40mg, which was selected for dose expansion. Subjects were treated until disease progression by RECIST 1.1 or unacceptable toxicity. **Results:** A total of 8(6 FOXO translocation(+), 1 (FOXO-), and 1 unknown) have been enrolled at time of submission. 5 in dose escalation cohort, and 3 in dose expansion. Median age was 19 yo(range 16-63), Median prior treatment regimens were 2(range 1-4). All patients had measurable metastatic disease. 6 of 8 subjects had prior exposure to vinorelbine in prior salvage chemotherapy or maintenance chemotherapy. As of 20JAN2022 safety cutoff, most common AEs (all grades) observed in 7 evaluable treated patients include neutropenia (n = 5), anemia(n = 5), and nausea(n = 4). The only grade 3 or 4 treatment related AEs were neutropenia, lymphopenia and anemia. Myelosuppression was transient, reversible and responsive to growth factors. No SAEs related to mocetinostat and/or vinorelbine have been reported. As of efficacy cutoff 20JAN2022, 7 of 8 patients are evaluable for response. 4 subjects had a partial response (PR), 2 subjects had stable disease (SD) and 1 subject had progressive disease for a clinical benefit rate of 86% (CR+PR+SD). Rapid responses were seen in the majority of patients at median of 1.5 months(mos). Of the 6 responders, 4 had duration of responses (DOR) > 6 mo with a median DOR of 8 mos (range 4-16mo). **Conclusions:** In this interim analysis, Mocetinostat plus vinorelbine shows high efficacy and acceptable safety profile in this heavily pretreated group of R/R RMS patients. This study is open to accrual and enrollment is ongoing. Clinical trial information: NCT04299113. Research Sponsor: Phase One Foundation, Pharmaceutical/Biotech Company.

11554 **Poster Session**

A phase II study of gemcitabine docetaxel combination in metastatic/unresectable locally advanced relapsed synovial sarcoma. *First Author: Ghazal Tansir, All India Institute of Medical Science (AIIMS), Delhi, India*

Background: Synovial sarcoma (SS) is one of the commonest non-Rhabdomyosarcoma Soft Tissue Sarcomas (STS) in Adolescent and Young Adults. It is a chemosensitive, high-grade tumor with a tendency for local and metastatic recurrence. While the frontline therapy is doxorubicin, treatment options in later lines are scarce. Gemcitabine docetaxel combination has demonstrated its role in relapsed STS and promising potential in frontline setting in recent times. The major STS types in previous trials included leiomyosarcomas and pleomorphic sarcomas but in SS, this regimen has not been explored. We conducted this study on gemcitabine and docetaxel combination in relapsed metastatic/locally advanced unresectable SS. **Methods**: This is a phase II, single-arm study in patients (pts) of metastatic/locally advanced unresectable SS relapsed post atleast one line of treatment aged between 15-75 years, ECOG performance status (PS) 0-2, adequate organ function and measurable disease by RECIST 1.1. Treatment was gemcitabine 900 mg/m^2 on days 1 and 8 plus docetaxel 75 mg/m^2 on day 8 with G-CSF prophylaxis for maximum 6 cycles. Adverse event (AE) profile was analyzed by CTCAE 5.0, quality of life (QoL) assessed 4-weekly by EORTC QLQ-C30 questionnaire and response assessed by RECIST at 12 weeks. Primary endpoint, 3-month Progression-free survival rate (PFR) was required to be 40%. **Results:** 22 pts were enrolled between 3/2020 – 9/2021 with median age 32 (range 15-60 years); 13 (59%) patients were male; ECOG PS was 1 in 13 (59%) and 2 in 9. Extremity and lung were the commonest primary and metastatic sites respectively with 20 (90.9%) pts having metastases. 50% pts received the study treatment in 2nd line, 36.3% in 3rd line and the remaining in 4th line. The 3-month PFR was 45.4%, median PFS was 3 months, OS 67% at 7 months follow-up and Overall Response Rate (ORR) was 4.5% (1 PR). There was statistically significant worsening in QoL parameters of cognitive functioning, fatigue, dyspnea, appetite loss, nausea/vomiting at 12 weeks. Progression-free pts had better QoL in cognitive and emotional function, fatigue, pain and global health status. Beyond 12 weeks, 7 out of 10 non-progressors continued the treatment (1 patient each discontinued treatment due to death, change to TKI and enrolment in another trial). The most common AEs were fatigue, nausea/vomiting, mucositis, diarrhea, alopecia, anemia, transaminitis; Grade > 3 AEs (31.8%) included anemia, neutropenia, hyperbilirubinemia, transaminitis, mucositis. There was no febrile neutropenia. **Conclusions:** This is the first prospective study on gemcitabine docetaxel in patients of SS. The trial met its primary endpoint of 3-month PFR more than 40% which is promising in relapsed population. The improved QoL among progression-free pts is encouraging. Gemcitabine docetaxel regimen exhibits efficacy and safety to be considered for use in relapsed SS. Clinical trial information: CTRI/2020/02/023612. Research Sponsor: None.

11555 **Poster Session**

Activity of regorafenib in patients with non-adipocytic soft tissue sarcoma (NASTS): Evaluation of heterogeneity of treatment effect on the updated analysis of pooled cohorts. *First Author: Marie-Cecile Le Deley, Centre Oscar Lambret, Lille, France*

Background: Results of the double-blind randomized phase 2 trial (NCT01900743), showed that regorafenib (REG) is an active treatment in patients (pts) previously treated with chemotherapy for an NASTS (cohorts B-leiomyosarcoma, C-synovial sarcoma, D-other sarcoma, Mir 2016), and in pts previously treated with pazopanib (PAZ) (cohort E, Penel 2019). We now present an updated analysis of progression-free survival (PFS) in all NASTS pts to assess the heterogeneity of treatment effect according to histological subtype and prior exposure to PAZ. **Methods:** Pts received REG 160 mg/d, 21/28 d, or placebo (PB). Pts receiving PB were offered optional cross over in case of centrally confirmed disease progression. The primary endpoint was PFS, according to RECIST-1.1, based on full blinded central review of imaging (including a re-review for cohorts B, C and D, because first analysis was based on a partial central review in these cohorts). Overall survival (OS) was a secondary endpoint. We performed a pooled analysis of cohorts B, C, D and E, on the intent-to-treat dataset, including a multivariate analysis with interaction terms to assess the heterogeneity of treatment effect according to covariates. **Results:** From 06/2013 to 10/2017, 175 pts were randomized (87 REG vs 88 PB; 56, 27, 55, 37 pts in cohorts B, C, D and E, respectively). The median age was 59 yrs (range, 20-81). There were 101 women (58%). Histological subtype was leiomyosarcoma in 80 pts (LMS; 41 REG vs 39 PB; 56 in cohort B and 24 in cohort E), synovial sarcoma in 28 (SS; 13 REG vs 15 PB; 27 in cohort C and 1 in cohort E), and other sarcoma in 67 (33 REG vs 34 PB; 55 in cohort D and 12 in cohort E). The median number of prior lines of systemic treatment was 2 (range, 1-6). Overall, 43 pts had received prior PAZ (21 REG vs 22 PB). Out of 88 pts assigned to PB, 69 switched to REG after progression (79%). We confirmed a significant PFS-benefit associated with REG in multivariate analysis of the pooled study population, with a HR = 0.48 (95%CI, 0.35–0.66, p < 0.001); median PFS = 2.1 vs 1.0 months, respectively. This benefit appears significant in each histological subtype. However, we observed a borderline interaction between histological subtype and treatment effect (p = 0.09): PFS benefit appears larger in pts with SS (HR = 0.21, 0.10-0.48, p < 0.001) and other sarcoma (HR = 0.49, 0.30-0.81, p = 0.006) than in LMS (HR = 0.59, 0.37-0.93, p = 0.022). PFS benefit appears rather homogeneous across strata of pts with vs without prior exposure to PAZ (interaction test, p = 0.26). Overall, in this study, regorafenib does not show any statistically significant OS-benefit (HR = 0.77, 0.57–1.05, p = 0.10), likely due to the fact that 79% of PB pts crossed over to REG at progression. **Conclusions:** The present study confirms the clinical PFS benefit associated with regorafenib in all NASTS pts, regardless of prior treatment with pazopanib. Clinical trial information: NCT01900743. Research Sponsor: Bayer HealthCare.

11556 **Poster Session**

Excess of blood TNFa-R as a sign of recurrence of G1 soft tissue sarcomas in older men and G3 soft tissue sarcomas in older women. *First Author: Irina V. Kaplieva, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation*

Background: Tumor necrosis factor alpha (TNFa) and its receptor (TNFa-R) play an important role in tumor genesis. However, their involvement in the recurrence of sarcomas is poorly studied. The purpose of this study was to analyze levels of TNFa and TNFa-R in the blood of patients with recurrent soft tissue sarcomas. **Methods:** The study included 64 male and female patients, mean age 63.4±5.2 years. Main groups included patients with recurrent G1 and G3 soft tissue sarcomas T2bN0M0; comparison groups included patients with primary G1 and G3 soft tissue sarcomas T2bN0M0. 95% of tumors were liposarcomas, with solitary rhabdamyosarcomas, myxofibrosarcomas, epithelioid and undifferentiated sarcomas. All recurrent patients had previously underwent surgical and radiation treatment for primary sarcomas and their relapses (up to 2 episodes), with the last surgery more than 1 year ago. Control groups (n = 10 each) included healthy donors of similar age. Levels of TNFa and TNFa-R were measured in the blood serum by ELISA before the treatment. **Results:** No significant differences were found between TNFa levels in patients with primary and recurrent soft tissue sarcomas and in donors. Levels of TNFa-R in men with primary G3 sarcomas were 1.5 times (p < 0.05) higher compared with donors, 1.7 times (p < 0.05) higher than in men with primary G1 sarcomas, and 1.3 times (p < 0.05) higher than in women with primary G3 sarcomas. TNFa-R increased by 1.7 times (p < 0.05) in all men with recurrent sarcomas regardless of the tumor grade, compared with the levels in healthy men; however, in G1 it was 1.9 times (p < 0.05) higher than in men with primary G1 sarcomas, while in G3 it did not differ significantly from the levels in men with primary G3 sarcomas. TNFa-R in women increased only in recurrent G3 sarcomas by 2.5 times compared to healthy women. No differences were observed in TNFa-R levels between men and women with recurrent G3 sarcomas. **Conclusions:** An excess of TNFa-R in the blood is characteristic for the recurrent soft tissue sarcomas G1 in older men and G3 in older women. At the same time, high grade tumors in men are accompanied by an increase in TNFa-R in the blood in both primary and recurrent sarcomas. Research Sponsor: None.

11557 **Poster Session**

Surufatinib in U.S. patients with soft tissue sarcoma. *First Author: Sujana Movva, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Surufatinib is an inhibitor of VEGFR1, 2, & 3, FGFR1, and CSF-1R. A manageable safety profile, and statistically significant improvement in progression-free survival (PFS) in patients (pts) treated with surufatinib have previously been demonstrated in pts with advanced NETs of extrapancreatic (epNET) and pancreatic (pNET) origin in 2 phase 3 randomized trials conducted in China (SANET-ep; NCT02588170 & SANET-p; NCT02589821). Similar safety and efficacy were demonstrated in this phase 1 study (NCT02549937) in pts with NETs. Here we report the results of surufatinib in pts with soft tissue sarcoma. **Methods:** This study is a phase 1, dose escalation (ESC)/expansion (EXP) study to evaluate the safety and efficacy of surufatinib in the US and Europe (EXP only). ESC previously reported the recommended phase 2 dose as 300mg once daily. Enrollment into advanced, adult, soft tissue sarcoma EXP cohorts is ongoing. The primary endpoint is PFS rate at 4 months (mo). Soft tissue sarcoma histological subtypes include: angiosarcoma (AS), epithelioid sarcoma (ES), leiomyosarcoma (LMS), pigmented villonodular synovitis (PVNS), synovial sarcoma (SS) and undifferentiated pleomorphic sarcoma (UPS). **Results:** 32 adults with soft tissue sarcoma were enrolled (2 each AS and ES; 10 LMS; 1 PVNS; 9 SS; 8 UPS). The median age across all subtypes was 56.5 years (range 26-77), and the majority of pts were female (68.8%). 59.3% of pts received ≥ 3 prior lines of therapy (Tx) (median lines of Tx: 3 [range 1-6]). As of 15 Nov 2021, 1 pt (PVNS) remained on Tx. The PFS rate at 4 mo was 17.5%. The median PFS was 2.56 mo (95% CI; 0.92-2.92). The median duration on treatment (mDoT) for all pts was 11.2 weeks (wks) (0.4-39.0). The mDoT for LMS pts was 11.6 wks (3.1-36.0), mDoT for SS pts was 11.9 wks (0.4-27.9), and mDoT for UPS pts was 8.2 wks (2.7-27.9). Of 29 pts with ≥ 1 post baseline assessment, 6 pts (20.7%) achieved stable disease of ≥ 8.0 wks from start of Tx. No pts achieved a partial or complete response. The safety profile of surufatinib remains consistent with previously completed trials. All pts (n = 32) reported ≥ 1 adverse event (AE), and 21 pts (65.6%) reported AEs ≥ grade 3. The most common AEs of any grade were fatigue (53.1%), hypertension (43.8%), diarrhea (40.6%), anemia (25.0%), blood bilirubin increase (25.0%), headache (21.9%), and proteinuria (21.9%). The most commonly reported AEs ≥ grade 3 in > 1 pt were hypertension (21.9%), fatigue (12.5%), and anemia (9.4%). AEs leading to Tx discontinuation occurred in 9.4% of pts. **Conclusions:** Surufatinib demonstrated minimal antitumor activity as a single agent in heavily pretreated pts across various types of soft tissue sarcoma. The safety profile in pts with soft tissue sarcoma remains consistent with previously reported and ongoing studies with surufatinib. Clinical trials are ongoing with surufatinib globally, with active recruitment in PD-L1 combination studies. Clinical trial information: NCT02549937. Research Sponsor: HUTCHMED International Corporation.

11558 **Poster Session**

Handling missing covariates in observational studies: An illustration with the assessment of prognostic factors of survival outcomes in sarcoma in irradiated fields (SIF). *First Author: Noémie Huchet, Institut Bergonié, Comprehensive Cancer Center, Bordeaux, France*

Background: Missing covariates are common in observational research. They can result in biased estimations and loss of power to detect associations. Limited data regarding prognostic factors of survival outcomes of SIF are available. We assessed prognostic factors of overall (OS), progression-free (PFS) and metastatic- progression-free (MPFS) survivals in SIF using 3 methods to account for missing covariates. **Methods:** We relied on the NETSARC database of the French Sarcoma Group: Cox models for OS/PFS and competitive hazard survival models for MPFS. Prognostic factors investigated were age, sex, tumor characteristics (histology, size, depth, grade), metastasis, surgery, surgical resection, expertise of the surgeon (NETSARC/other), pre-surgical imaging (Y/N) and neoadjuvant treatment. To account for missing covariates, we used multiple imputation (MI) by fully conditional specification (Bartlett 2015). The observed data are used to estimate the missing covariate and subsequently replace (impute) the missing value by that estimate. With the "missing-data modality" alternative approach, a category "missing" was created (e.g. yes/no/missing). With the "complete-case" alternative approach, analysis was restricted to patients with all covariates available. **Results:** Among the 504 patients, 169 had all covariates available (33%). Rate of missing data was greater than 20% for imaging, neoadjuvant treatment, and surgical resection. In the complete-case analysis (N = 169), factors associated with OS included R1/R2 (vs R0) surgical resection (p = 0.03). In opposite, MI (N = 504) revealed an association with metastasis (p = 0.03), and a time-varying effect for surgical resection (p < 0.001), with a risk increasing over time for R1/R2 vs R0). For PFS and MI, associated factors included higher grade and ungradable tumors (p = 0.002) and R1/R2 vs R0 resection (p < 0.001), not found with the complete-case analysis. For MPFS and MI, factors included metastasis (p = 0.03), higher grade tumor (p = 0.007) and R1/R2 resection (p = 0.001). Grade and resection were not found in the complete-case analysis. The missing-data modality led to slight differences with MI, including significant association due to missing covariate (e.g. tumors with size missing associated with shorter PFS). **Conclusions:** We identified prognostic factors of survival outcomes for SIF. The complete-case analysis led to reduced statistical power and population was non-representative of the full sample, introducing bias. In non-randomized studies, as the outcome may be related to variables with missing values, the missing-data modality method will typically result in biased estimates. Appropriate statistical methods for missing covariates, such as MI, should be considered in particular for observational studies. Research Sponsor: None.

11559 **Poster Session**

Prevalence of ultra-rare undifferentiated round cells sarcoma of bone and soft tissue after genomic classification. *First Author: Emanuela Palmerini, Osteoncology, Bone and Soft Tissue Sarcomas and Innovative Therapies, Orthopaedic Institute Rizzoli, Bologna, Italy*

Background: Over the last decade, the category of undifferentiated round cell sarcomas (URCS), defined by the absence of Ewing sarcoma-associated translocations, has emerged. Aim of this study was to assess prevalence of each entity and outcome after genomic classification. **Methods:** Ewing sarcoma and other URCS diagnosed between 1920 and 2020 were reviewed. All URCS with available material were analyzed with FISH, RT-qPCR and/or Archer FusionPlex Sarcoma Panel. Demographic and treatment were collected. Survival was analyzed in patients with available follow-up. **Results:** 1995 cases identified, 20 cases lacked material for further genetic analysis and were excluded. 1975 cases were classified as follows: 1925 Ewing sarcomas (97.47%), 25 CIC-rearranged sarcomas (1.27%), 16 BCOR-CCNB3 rearranged sarcomas (0.81%), 2 EWSR1-NFATC2 sarcoma (0.1%), one each as CIC-LEUTX and FUS-NFATC2 rearranged sarcoma (0.05% each), and 5 as *unclassified* URCS (0.25%). A different presentation according to tumor type was shown in 43/50 ultra-rare tumors (Table). Forty-one/50 cases had available follow-up: 20/41 patients underwent surgery, 14/41 surgery+radiotherapy, 6 radiotherapy only, and no local treatment for 1 patient. Chemotherapy was administrated to 36/41 patients (Ewing sarcoma drugs in 16/22 CIC-DUX-4 and 8/11 BCOR-CCNB3; osteosarcoma drugs in 2/11 BCOR-CCNB3, and doxorubicin/ifosfamide in 2/22 CIC-DUX4 and 2/5 URCS; not specified in 6 cases). The 3-years overall survival (OS) was 32.7%f for CIC-rearranged sarcomas (75% in localize disease, 7,7% for the advanced disease, p 0.0084), 81.8% for BCOR-CCNB3 sarcomas (87.5% localized, 66.7% advanced; p 0.0734), and 60% for URCS (p 0.057). 1 patient with CIC-LEUTX sarcoma presenting with metastases died 13 months from diagnosis, 1 patient with FUS-NFATC2 and 1 with EWSR1-NFATC2 rearrenged sarcomas were alive without disease at 8 and 5 years from onset. **Conclusions:** Prevalence of URCS characterized by a combination of morphologic observation ad molecular techniques is provided. The majority of the cases underwent surgery or surgery combined with radiotherapy, and Ewing-like chemotherapy. The survival difference among different entities underscores the need of accurate subclassification of round cell sarcomas. Novel drugs for CIC-DUX-4 sarcomas presenting with metastases are needed. Research Sponsor: None.

Clinical presentation of ultra-rare sarcoma.

	CIC-DUX4 (n = 23)	BCOR-CCNB3 (n = 11)	URCS (n = 5)	EWSR1-NFATC2 (n = 2)	CIC-LEUTX (n = 1)	FUS-NFATC2 (n = 1)	P value *
Age y, median (range)	33 (11-76)	14 (5-58)	55 (4-61)	11, 71	69	56	0.0029
Sex, F/M	16/7	0/11	3/2	2/0	0/1	1/0	0.0002
Site, Soft tissue/Bone	21/2	2/9	5/0	0/2	1/0	0/1	<0.0001
Stage, Localized/Advanced	9/14	8/3	3/2	2/0	0/1	1/0	0.0007

*Excluding EWSR1-NFATC2 (n = 2), FUS-NFACTC2 (n = 1), CIC-LEUTX (n = 1).

11560 **Poster Session**

Synergistic activity of PARP inhibitors (PARPi) in combination with standard chemotherapy (CTx) in leiomyosarcoma. *First Author: Olga Vornicova, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Leiomyosarcomas (LMS) are genetically heterogeneous tumors that arise from smooth muscle. Currently, the mainstay of systemic treatment for patients with advanced/metastatic disease is doxorubicin (Dox) based CTx. Several genomic analyses of LMS reveal defects in homologous recombination (HR) DNA repair pathway in about half of patients, consistent with a druggable "BRCAness" phenotype. Thus, we sought to determine which combinations of standard CTx and PARPi might be synergistic promising therapeutic strategies for LMS. **Methods:** Dox, Docetaxel (Doc), Temozolomide (Tmz) were evaluated in combination with PARPi (Olaparib [Ola], Niraparib [Nira] and Talazoparib [Tala]) at 12 different drug concentrations. Four LMS cell lines of different origins (gynecological - GY, abdominal - A, extremity - E) were tested in a high throughput manner. All drug concentrations were chosen according to EC_{50}. Cells were incubated with each combination for 7 days. Viability was assessed by ATPlite Luminescence Assay System.Evaluation of drug combination effect was performed using a Bliss synergy score. This system quantifies the degree of synergy as multiplicative effect of single drugs as if they acted independently. With a synergy score of -5 to 5, the interaction between two drugs is considered as additive; <-5 antagonistic and > 5 synergistic, and therefore a promising combination. **Results:** Anticancer activity, ranging from additive to synergistic was seen with all combinations. Results were consistent among all cell lines, independent of site of cell line origin (Table) Most synergistic combination in the majority of LMS cell lines were Dox or Tmz when combined with Tala, reaching up to 15 % and 27% above Bliss respectively. In contrast, Doc showed only additive effect with all analyzed PARPi. **Conclusions:** The data suggest that the combination of Dox or Tmz with PARPi may represent promising treatment options for LMS patients. Recent clinical studies support this notion in uterine LMS. Importantly these results suggest that such approach may be extended to all sites of LMS. Pre-clinical studies are underway to identify the most promising combinations for future clinical trial design. Research Sponsor: Canadian Institute of Health Research (CIHR).

Value of synergy of CTx and PARPi in analyzed drug combinations.

	Dox (0.026-10 μM)*			Tmz (0.1-40 μM)*			Doc (0.02-50 nM)*		
0.026-10 μM*	**Tala**	**Ola**	**Nira**	**Tala**	**Ola**	**Nira**	**Tala**	**Ola**	**Nira**
STS 39	**5-12%**	2-4%	**4-6%**	**10-20%**	**2-10%**	**2-7%**	3-6%	4-6%	*-10-0%*
STS 137	**10-15%**	**4-8%**	**4-7%**	**2-8%**	**7-14%**	**5-13%**	*-10-0%*	2-4%	2-4%
STS 210	**5-8%**	**3-7%**	2-5%	**9-27%**	**5-15%**	*-10-5%*	**6-11%**	*-10-0%*	3-5%
SKLMS1	-5-0%	2-6%	**4-7%**	*-10-0%*	**10-13%**	**6-8%**	*-10-0%*	*-10-0%*	2-4%

Legend: Evaluation of synergy between CTx and PARPi in LMS cell lines (STS 39-GY, STS 137-E, STS 210- A, SKLMS1- GY). BLISS calculation for combination therapy is typographically emphasized – synergy, additive, or antagonistic effect. *Drug range represented in values, used for all 12 concentrations.

11561 **Poster Session**

Results of a phase I trial of ganitumab plus dasatinib in patients with rhabdomyosarcoma (RMS). *First Author: Srivandana Akshintala, Pediatric Oncology Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD*

Background: Antibodies against the insulin-like growth factor type 1 receptor (IGF1-R) have shown transient objective partial responses (PR) in patients with RMS followed by rapid development of resistance. Preclinical data demonstrate that activation of the SRC family kinase YES acts as a bypass resistance mechanism to IGF-1R targeting. Co-targeting IGF-1R and YES results in sustained responses in murine RMS models. We developed a phase I/II trial of the anti-IGF-1R antibody ganitumab combined with the multi-kinase inhibitor dasatinib in patients with RMS (NCT03041701). During the phase II part of the study, ganitumab became unavailable, and the trial was terminated early. We report here the results of the completed phase I study. **Methods:** Patients with relapsed/refractory alveolar or embryonal RMS and measurable disease were eligible. A 3+3 dose escalation design was used to determine the maximum tolerated dose (MTD), and evaluable patients were assessed for response using RECISTv1.1 criteria. All patients received ganitumab 18 mg/kg intravenously every 2 weeks. Dasatinib was administered orally on a continuous schedule. Dose level (DL)1 was 60 mg/m^2/dose (max 100 mg) once daily; DL2 was 60 mg/m^2/dose (max 70 mg) twice daily. MTD was determined based on cycle 1 dose-limiting toxicities (DLTs) and responses were assessed every 2 cycles. **Results:** Thirteen eligible patients (5M, 8F), median age 18 years (range 8-29 years) with embryonal (n = 6) and alveolar (n = 7) RMS were enrolled at DL1 (n = 7) and DL2 (n = 6). Median number of prior systemic therapies was 3 (range 1-6), all had received prior radiation, 5 prior surgery, and 2 prior high dose chemotherapy with stem cell rescue. Of 11 patients evaluable for toxicity, 1/6 had a DLT at DL1 (grade 3 diarrhea) and 2/5 had DLTs at DL2 (grade 3 pneumonitis and grade 3 hematuria) confirming DL1 as MTD. Common non-DLTs at least possibly attributed to dasatinib, ganitumab, or both included thrombocytopenia (n = 12), anemia (n = 10), lymphopenia (n = 8), hypophosphatemia (n = 7), hypocalcemia (n = 6), elevated transaminases (n = 5), fatigue (n = 5), nausea (n = 5), and vomiting (n = 5). The most common grade 3-4 adverse events were cytopenias and electrolyte abnormalities. Of 9 patients evaluable for response, 1 had a confirmed PR at DL2 sustained for 5 cycles, and 1 had prolonged stable disease (SD) for 6 cycles at DL1. Patients received a median of 1.5 cycles (range 0-6). Analysis of correlative biology studies of ctDNA and target expression are ongoing. **Conclusions:** The combination of dasatinib and ganitumab was safe and tolerable at DL1 in patients with relapsed and refractory RMS. Once daily dasatinib at 60 mg/m^2/dose (max 100 mg) combined with 18 mg/kg ganitumab every 2 weeks was determined to be the MTD. PR and SD for > 4 months were observed in this phase I trial suggesting that the addition of a YES-targeting agent may delay the development of acquired resistance to IGF-1R antibody therapy in RMS. Clinical trial information: NCT03041701. Research Sponsor: U.S. National Institutes of Health.

11562 **Poster Session**

Identification of response stratification factors from pooled efficacy analyses of afamitresgene autoleucel ("Afami-cel" [Formerly ADP-A2M4]) in metastatic synovial sarcoma and myxoid/round cell liposarcoma phase 1 and phase 2 trials. *First Author: Sandra P. D'Angelo, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Afami-cel is an autologous, HLA-A*02-restricted, specific peptide enhanced affinity receptor, T-cell therapy engineered to target MAGE-A4+ solid tumors. The pivotal, 2-cohort, single-arm, Phase 2, SPEARHEAD-1 trial (NCT04044768) with afami-cel met its primary endpoint based on Cohort 1 data. As of September 1, 2021, in 47 patients (pts) with metastatic synovial sarcoma (SyS) or myxoid/round cell liposarcoma (MRCLS), the overall response rate (ORR) per independent review was 34% with encouraging durability (Van Tine, et al. Paper 30: CTOS 2021; Virtual). To identify potential stratification factors for response and assess whether response is a proxy for progression-free survival (PFS), we present pooled analyses using data from the prior Phase 1 trial (NCT03132922) and Cohort 1 of the SPEARHEAD-1 trial. **Methods:** Eligible pts (16–75 years) were HLA-A*02+ with MAGE-A4+ tumors. Pts received afami-cel after lymphodepleting chemotherapy. The pooled analyses evaluated ORR per RECIST v1.1 by investigator review, stratified by 7 factors, and safety. **Results:** In the pooled data, 69 pts received afami-cel ($2.12–9.99\times10^9$ transduced T-cells) and were evaluable for response (Phase 1, n = 18; Phase 2, n = 51); all expressed one eligible HLA-A*02 allele. Median (range) for: age was 42 years (19–76), number of prior lines of therapy was 2 (1–12), and tumor MAGE-A4 H-score was 230 (60–300). Median (range) H-score was higher in SyS (256 [60–300]) than in MRCLS (180 [112–230]). The pooled investigator-assessed ORR was 36.2% (40.7% in SyS; 10.0% in MRCLS). Responses occurred across a wide MAGE-A4 H-score range (134–300). Median (range) duration of response was 52 weeks (8.29–75.14). Response rate was higher in the 59 pts with SyS: with ≤2 vs ≥3 prior lines of therapy (55.2% vs 26.7%), baseline target lesion sum of longest diameters <10cm vs ≥10cm (53.1% vs 25.9%), MAGE-A4 H-score ≥200 vs <200 (46.3% vs 27.8%), without vs with bridging therapy (48.6% vs 29.2%), who were female vs male (46.4% vs 35.5%), aged ≥40 vs <40 years (45.7% vs 33.3%), and from North America vs Europe (42.6% vs 33.3%). In responders vs non-responders with SyS, respectively, median PFS was 58.3 vs 11. 0 weeks (log-rank p-value <0.0001); the probability of being progression-free at 24 weeks was 0.8 vs 0.2. The pooled benefit:risk profile of afami-cel was similar to that in the SPEARHEAD-1 trial (Van Tine, et al. Paper 30: CTOS 2021; Virtual.). **Conclusions:** We show that baseline tumor burden, prior systemic treatment history, and MAGE-A4 tumor expression levels are potential factors associated with response to afami-cel, although their true predictive value for response status awaits confirmation. Our findings will inform the ongoing clinical development of afami-cel in sarcoma, especially for prognostic studies with PFS or overall survival endpoints. Clinical trial information: NCT04044768, NCT03132922. Research Sponsor: Adaptimmune.

11563 **Poster Session**

Phase 1b study of weekly split-dose selinexor in soft tissue sarcoma (STS). *First Author: Abdulazeez Salawu, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada*

Background: Selinexor has demonstrated clinical activity in a variety of tumors including STS. Selinexor dosing at 60mg twice a week or 80mg once a week in later phase trials was associated with gastrointestinal and hematologic toxicities requiring frequent dose interruption and reduction. Preclinical *in vivo* studies show that selinexor use in a split-dose regimen or sustained-release formula is associated with less toxicity. This phase 1b study aimed to evaluate the safety and tolerability of split-dose selinexor in patients (pts) with advanced STS. **Methods:** Eligible pts with advanced STS of any histologic subtype, and ECOG performance status (PS) ≤ 1 were treated with split-dose selinexor (40mg, 20mg, 20mg in the morning, afternoon, and evening, respectively) on days 1, 8, 15 and 22 of a 28-day cycle, until unacceptable toxicity or disease progression. Antiemetic prophylaxis (oral dexamethasone and ondansetron) was given to all pts. The primary endpoint was the rate of grade ≥ 3 treatment-related adverse events (TRAE) by CTCAE v5.0. The secondary endpoint was assessment of quality of life (QoL) using the EORTC QLQ-c30 tool v3. Descriptive analyses of Global Health Status (GHS) QoL scores at screening (baseline) and cycle 2 day 1 (C2D1) were performed. Radiologic tumor assessments (by RECIST v1.1) were performed every 8 weeks while on treatment. **Results:** Nineteen pts [12 female and 7 male; ECOG 0/1, 8/11; median age 61 years (range 41 – 83)] were enrolled. The most frequent of 12 STS subtypes was leiomyosarcoma (n = 7, 37%). Among 18 patients evaluable for toxicity, there were no grade ≥ 3 TRAE. The most common grade ≤ 2 TRAE were dysgeusia (n = 11, 61%), nausea (n = 11, 61%), fatigue (n = 10, 56%) and vomiting (n = 10, 56%). Grade ≤ 2 hematologic TRAE were thrombocytopenia (n = 6, 33%), neutropenia (n = 4, 22%) and anemia (n = 1, 6%). Dose reduction was required in 3 pts (17%) due to intolerable grade 2 TRAE (fatigue, nausea, thrombocytopenia). No serious adverse event due to selinexor was noted. QoL scores were evaluable for 15 pts. The mean (± SEM) change in GHS QoL score from baseline to C2D1 was -10.6 (± 4.8). Among 16 pts evaluable for radiologic response, the best response was stable disease (SD) in 10 pts (63%), and progressive disease (PD) in 6 pts (37%). Durable clinical benefit (SD for > 16 weeks) was seen in 5 pts (31%; 95%CI 11.0 – 58.7%) The median PFS was 3.6 months (95%CI 1.7 – 7.3). **Conclusions:** Split-dose selinexor was well tolerated in this heterogeneous group of pts with advanced STS and warrants further interrogation. Updated toxicity, safety, efficacy and QoL data will be presented at the meeting. Clinical trial information: NCT04811196. Research Sponsor: University Health Network, Toronto, Pharmaceutical/Biotech Company.

11564 **Poster Session**

Trabectedin and hypofractionated radiation for high-risk, localized, and metastatic soft tissue sarcoma: A retrospective study. *First Author: Narine Wandrey, University of Colorado Cancer Center, Aurora, CO*

Background: Soft tissue sarcomas (STSs) are a heterogeneous group of cancers with high unmet need. Trabectedin (T) is an FDA-approved chemotherapy that blocks cell cycling and DNA repair pathways. Combination T and conventional radiation (XRT) in STS nonrandomized phase 1/2 trials demonstrated objective response rates (ORR) of 36-72% in localized and low burden metastatic disease, while pre-treated metastatic STS treated with T alone has an ORR of 10-14%. We hypothesize that the combination of T and hypofractionated radiation (hXRT) will exhibit a tolerable safety profile and improve ORR relative to historical outcomes with T or hXRT alone. Here we report our experience in the treatment of oligometastatic STS with combined T and hXRT. **Methods:** We reviewed our institutional experience to identify patients treated with T and XRT. We included patients with high risk localized or metastatic STS (majority of patients had metastatic disease at time of treatment). All patients received at least 1 cycle of T and concurrent XRT to at least 1 lesion. ORR and local control rate (LCR) were determined for irradiated lesions by RECIST 1.1. **Results:** Between 2020 – 2021, 9 STS patients with 21 tumors were treated at the University of Colorado with XRT and concurrent T. The median age was 39.2 (range 26.0 – 64.6) years. 8 patients had metastatic disease at the time of treatment. Treated tumor sites included 1 lung,1 extremity, 2 liver, 2 retroperitoneal, 5 bone, and 10 peritoneal. The following histologic subtypes were included: myxoid liposarcoma (3), uterine leiomyosarcoma (2), non-uterine leiomyosarcoma (1), dedifferentiated liposarcoma (1), undifferentiated pleomorphic sarcoma (1), and synovial sarcoma (1). All metastatic patients were pre-treated with a median of 3 lines of systemic therapy. The median number of T cycles delivered was 5 (range 1 – 20). The median XRT prescription dose was 3000cGy (range 2000cGy – 5000cGy), with 8 patients having received hXRT (5 -10 fractions) and 1 having received conventionally fractionated XRT. 8 patients underwent 1 course of XRT, while 1 received 3 courses in combination with T. All patients had a Karnofsky performance status equal to or greater than 60. After a median follow-up 5.4 months, the LCR of treated lesions was 90.5%. The ORR (CR or PR) was 57.1% and median decrease in tumor diameter at time of maximum response was 52.0%. The median time until maximum response was 3.7 months. 2 patients experienced grade 3 toxicity (LFT elevation) attributable to T, and 2 patients experienced grade 3 toxicity due to XRT. There were no grade 4 or 5 toxicities. **Conclusions:** T in combination with hXRT appears to be safe and feasible in this patient population. Based on these data, a phase 1/2 prospective clinical trial is being planned in oligometastatic and high risk localized STS. Research Sponsor: None.

Local Control Rate	# of Treated Tumors (n = 21)
SD	7 (33.4%)
PR	7 (33.3%)
CR	5 (23.8%)
PD	2 (9.5%)

11565 **Poster Session**

Radiomics of MRI scans enables differentiation of benign from malignant soft tissue sarcoma. *First Author: Lin Li, Case Western Reserve University, Cleveland Heights, OH*

Background: Accounting for >15,000 cases annually, soft tissue sarcomas (STSs) represent a large spectrum of tumors with varying histology and clinical course. However, diagnosis of STSs on MRI is challenging due to its heterogeneous imaging phenotypes, such as surrounding soft tissue edema, vascular lesion characteristics, and specific imaging signs, such as splitting of fat between muscles. The goal of this study was to evaluate the utility of radiomic feature analysis for characterizing subtle heterogeneity patterns on T2-weighted MRI to distinguish benign and malignant STSs. **Methods**: T2-weighted MRI of N = 176 patients with STS were retrospectively obtained from a single institution. (Table) Tumor regions were manually annotated by a radiologist. The radiomic features included textural features, e.g. gray-level co-occurrence matrix features, which quantify the correlation between textural patterns within annotated regions. Maximum relevance minimum redundancy feature selection was employed to identify top 10 radiomic features that are associated with STS malignancy. Then, the identified features were integrated to generate a radiomic risk score (RRS) via logistic regression on a 10-fold cross validation to differentiate benign and malignant STS. Multivariate analysis and the area under the receiver operating characteristic curve (AUC) were employed to evaluate the association of RRS and clinical parameters, including age, gender, and STS location, with STS malignancy. **Results**: Multivariate analysis illustrated that age and RRS are independent variables in predicting STS malignancy ($p < 0.05$). The RRS yielded AUC as 0.76 (confidence interval (CI): 0.69-0.83), age 0.71 (CI: 0.64-0.79) and the combination of the RRS and age 0.84 (CI: 0.78-0.90). **Conclusions:** The RRS generated by radiomic features was found to be a significant predictor of STS malignancy. Furthermore, RRS could provide complementary information to the clinical parameters in differentiating benign and malignant STSs. Research Sponsor: U.S. National Institutes of Health, Other Government Agency.

Demographic and disease characteristics.

Clinical data		*number of patients*
Age	54 (7-86)	
Gender	male	83
	female	93
Aggressiveness	malignant	94
	benign	82
Location	Trunk	34
	Extremity	134
	Both	8

11566 **Poster Session**

Epitheliod hemagioendothelioma (EHE) patient-derived model (PDX): Drug activity assessment and validation of novel biomarkers. *First Author: Silvia Stacchiotti, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: EHE is an ultra-rare sarcoma marked by two specific fusions, *WWTR1-CAMTA1* (~90%) and *YAP1-TFE3* (~10%). The clinical course of EHE ranges from indolent to highly aggressive, often associated with systemic paraneoplastic symptoms. Molecular predictors of clinical outcome are unknown. While surgery is the mainstay of treatment in the localized setting, management of advanced disease is challenging due to the rarity and poor sensitivity to conventional chemotherapy. This hampers the conduct of large prospective clinical trials. We report herein the first available EHE PDX (developed at the Istituto Nazionale Tumori, Milan, Italy) (INT), to assess the activity of old and new anticancer agents in EHE and inform future clinical studies. We also report on the preliminary results of a prospective observational study, ongoing in collaboration with The EHE Rare Cancer Charity (UK) and The EHE Foundation (US) aimed at identifying prognostic factors. **Methods:** A PDX of EHE in SCID mice was generated at INT from a patient (pt) suffering with the aggressive clinical variant, presenting with systemic symptoms. The PDX fully reproduces the originating clinical tumor in terms of morphology, biology (*WWTR1-CAMTA1* positive), overall transcriptomic profile. 2D (monolayer) and 3D (sferoids) cell cultures were established following PDX disaggregation. We have started assessing the comparative activity of currently available drugs (doxorubicin, sirolimus), while the efficacy of novel agents is undergoing. In parallel, we analyzed the presence of a selection of inflammatory cytokines in prospectively collected blood samples from EHE pts who entered an international observational study and we looked at their presence and modulation in the PDX model. **Results:** PDX experiments showed almost negligible activity of doxorubicin while sirolimus induced an 80% tumor volume inhibition. Biochemical analysis in tumors explanted from sirolimus-treated mice confirmed the down-regulation of mTOR downstream signaling. Among all cytokines, Growth and Differentiation Factor-15 (GDF-15) was found significantly over-expressed in serum of EHE pts (n = 23), particularly those with the most aggressive clinical variant, compared to healthy subjects (n = 23; $p< 0.01$). Consistently, EHE PDX and cell culture were found to release in the blood/culture medium GDF-15. Sirolimus was found to down-regulate GDF-15 release in both *in vivo* and *in vitro* EHE models. **Conclusions:** Our preliminary results indicate that this EHE PDX model is suitable *i)* for comparatively assessing the activity of anticancer drugs, and *ii)* for identifying and pre-clinically validating novel biomarkers. The role of GDF-15 in EHE progression deserves further investigation. Research Sponsor: Grant by the EHE Rare Cancer Charity (UK) and The EHE Foundation (US).

11567 **Poster Session**

LTX-315 and adoptive cell therapy using tumor-infiltrating lymphocytes in patients with metastatic soft tissue sarcoma. *First Author: Morten Nielsen, National Center for Cancer Immune Therapy, Department of Oncology, Copenhagen University Hospital, Herlev, Denmark, Herlev, Denmark*

Background: Adoptive cell transfer (ACT) with tumor-infiltrating lymphocytes (TILs) is a potent treatment that can induce complete and durable tumor regression as documented in patients with metastatic melanoma. To our knowledge, ACT has not been utilized for patients with metastatic soft-tissue sarcoma (STS). LTX-315 is an oncolytic peptide that has been shown to increase TILs in malignant tumors after intratumoral injection. In this trial, patients with metastatic sarcoma were treated with the combination of LTX-315 and TIL - based ACT. **Methods**: Patients with progressive metastatic STS after a minimum of one systemic treatment were eligible for inclusion. In step 1, patients received up to five treatments over 2-3 weeks with LTX-315 injections. Afterwards, the injected tumor was surgically removed, and TILs were expanded *in vitro*. In step 2, patients received preparative chemotherapy followed by infusion of the expanded TILs, and follow-up treatment with subcutaneous IL-2. The impact of LTX-315 on tumor microenvironment was assessed by immunohistochemistry (IHC) on biopsies collected before and after injections. Clinical effect of the treatment was assessed by follow-up CT-scans using RECIST 1.1. Exploratory analyses aimed at identifying tumor reactive T cells in the expanded TILs and in peripheral blood (PBMC) in the patients before and after treatment. Expanded TILs or PBMC were cocultured with autologous tumor or selected neo-peptides and reactivity was assessed by measurement by Elispot or flow cytometry. **Results**: Six patients received intratumoral injections with LTX-315. In 3 out of 5 samples available for IHC, increased infiltration of CD4+ cells following LTX-315 injections was observed. Four patients received the full treatment with both LTX-315 injections and ACT. Total number of infused cells was 44-63x10^9, comprising 0,4-52% CD8+ T cells. Treatment was tolerated with manageable toxicity. After completed treatment, all four patients had stable disease as best overall response. Two patients with leiomyosarcoma and solitary fibrous tumor had stable disease for 25 and 20 weeks, respectively. In these two patients, and one additional patient, Elispot analyses showed presence of tumor-reactive cells in the PBMC following treatment. **Conclusions**: This trial demonstrates that the combination of LTX-315 and ACT is feasible and tolerable with manageable toxicity. CD4+ and CD8+ TILs can be expanded *in vitro* from sarcomas that have been pretreated with the oncolytic peptide LTX-315. Furthermore, the data suggest that LTX-315 can modulate the tumor microenvironment in sarcomas, thus potentially affect the expanded TILs that can be used for ACT. Further optimization of the treatment schedule will position LTX-315 as technology to invoke tumor specific T cells that can be cultured and infused as part of an adoptive transfer regimen for several subtypes of soft tissue sarcoma. Clinical trial information: NCT03725605. Research Sponsor: Lytix Biopharma AS.

11568 **Poster Session**

Randomized, placebo-controlled, double blind, phase II study of zaltoprofen for patients with diffuse-type and unresectable localized tenosynovial giant cell tumors. *First Author: Akihiko Takeuchi, Department of Orthopaedic Surgery, Graduate School of Medical Sciences, Kanazawa University, Kanazawa, Japan*

Background:A tenosynovial giant cell tumor (TGCT) is a locally aggressive benign neoplasm arising from intra- or extra-articular tissue, and categorized localized (L-TGCT) or diffuse-type (D-TGCT). D-TGCT most commonly develops in the knee or ankle. We revealed that zaltoprofen, a nonsteroidal anti-inflammatory drug possessing the ability to activate peroxisome proliferator-activated receptor gamma (PPARγ), can inhibit the proliferation of TGCT stromal cells via PPARγ. PPARγ is a ligand-activated transcription factor that belongs to the nuclear hormone receptor superfamily. Therefore, we conducted a randomized trial to evaluate whether zaltoprofen was effective for patients with TGCT. **Methods:**This study was a randomized, placebo-controlled, double-blind, multicenter trial to evaluate the safety and efficacy of zaltoprofen for patients with L-TGCT or D-TGCT. For the treatment group, zaltoprofen 480 mg/day was administered for 48 weeks. The primary outcome was the progression-free rate (PFR) at week 48 after treatment administration. Disease progression was defined as follows requiring surgical interventions: 1) repetitive joint swelling due to hemorrhage; 2) limited range of joint motion; 3) invasion of adjacent cartilage or bone; 4) severe joint space narrowing; or 5) increase in tumor size (target lesion). This study was registered at the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN000025901). **Results:**We allocated forty-one patients to zaltoprofen (n = 21; Z) or placebo (n = 20; P) groups. The mean age was 44 years (range, 26 to 66) in the group Z and 47 years (range, 24 to 69) in the group P. TGCTs located at a knee in 26 patients and at an ankle in 15 patients. The primary outcome of PFR for the group Z was not higher than that for the group P at week 48 (84.0% vs. 90.0%; p = 0.619). The objective tumor response was graded as partial response (PR) in 1 patient, stable disease (SD) in 19, and progressive disease (PD) in 1 for the group Z, and SD in 17 and PD in 3 for the group P. The mean musculoskeletal tumor society scoring system for group Z was significantly improved from baseline to week 48 (83.8% vs. 93.0%, p = 0.02), whereas that for the group P was not significantly improved (82.2% vs. 86.8%; p = 0.167). During the study period, one severe adverse event was observed (grade 3 hypertension) in the group Z. **Conclusions:**To our knowledge, this was the first study to evaluate the efficacy of zaltoprofen in patients with TGCT. The TGCT patients in zaltoprofen group did not have higher PER compared with those in the placebo group at week 48. Zaltoprofen appeared to improve the limb-function. Both groups presented with a stable disease course for 48 weeks, therefore, the long-term clinical course of TGCT should be clarified. Further analysis with long-term administration of zaltoprofen is considered for the future study. Clinical trial information: UMIN000025901. Research Sponsor: Japan Agency for Medical Research and Development (AMED).

11569 **Poster Session**

The comparison of tumor microenvironment characteristics of well-differentiated and dedifferentiated liposarcoma and the association between immune cell infiltrations and recurrence of tumor. *First Author: Yuhong Zhou, Department of Medical Oncology, Zhongshan Hospital, Fudan University, Shanghai, China*

Background: Well-differentiated liposarcoma (WDLPS) and dedifferentiated liposarcoma (DDLPS) are common malignancies of adipocytic origin, which are in different differentiation stages. Both of them are characterized by high local recurrence rate. The tumor microenvironment (TME) is associated with the prognosis of tumor and immune-related cell infiltrations has been proved to be one of the mechanisms affecting the efficacy of immunotherapy. However, the difference between TME characteristics of WDLPS and DDLPS as well as the association between immune cell infiltrations and recurrence of WD/DDLPS has not been fully studied. **Methods:** 37 Chinese patients with liposarcoma were enrolled in this study, including 24 patients with WDLPS and 13 patients with DDLPS. Tissue samples from these patients were examined, who experienced previous recurrence or no recurrence. The density and percentage of the immune-related cell subsets in the TME were identified by multiplexed immunohistochemistry and multispectral imaging. Twenty cell lines derived from patients with liposarcoma in our center were used to analyze the correlation of immune-related cells content between patient tissues and cell lines. **Results:** Overall, DDLPS had more immune cell infiltrations than WDLPS. Compare to WDLPS, the density of CD8+ (the cytotoxic T cells identification) cells and CD163+ (M2 macrophages identification) cells and the percentage of FOXP3+ (Treg cells identification) cells was significantly more in DDLPS, with a Wilcoxon p-value of 0.02, 0.04 and 0.03, respectively. There was no significant difference in other protein markers between WDLPS and DDLPS. According to the multiple cut-off values (tertiles, quintile and tenths) of immune-related cells, the Chi-square test results equally suggested more immune infiltrations in patients with DDLPS. PD-1+ cells was significantly more (Wilcoxon p = 0.02), while FOXP3+ cells were significantly fewer (Wilcoxon p = 0.04) in patients without recurrence than those in patients with previous recurrence. Patients without recurrence had more CD3+ cells (the total T cells identification) and CD163+ cells infiltrations, although the both Wilcoxon p-value were not statistically significant. The total T cells, CD4+ T cells and Treg cells were more distributed in tumor tissues with no recurrence or recurrence for once, but less in patients with two or more recurrence. In addition, no strong correlation of immune-related cells content between patient tissues and cell lines were observed in our analysis. **Conclusions:** Our findings suggested that patients with DDLPS might benefit more from immunotherapy than patients with WDLPS due to the infiltrating TME of DDLPS. The increase of recurrence times might lead to a more repressive TME in liposarcoma. Research Sponsor: None.

11570 **Poster Session**

Dose intensity and outcomes of VDC/IE chemotherapy for adolescent and adult patients with Ewing's family sarcoma. *First Author: Danielle Klingberg, Prince of Wales Hospital, Sydney, NSW, Australia*

Background: Ewing's family sarcoma (EFS) is a rare and aggressive malignancy with peak incidence in the second decade of life. Treatment is multimodal, involving local surgery and/or radiotherapy, and chemotherapy, typically with VDC/IE (Vincristine, Doxorubicin, Cyclophosphamide alternating with Ifosfamide, Etoposide). There is paucity of data in the adult setting, with treatment protocols extrapolated mainly from the paediatric setting. We assessed chemotherapy dose intensity and outcomes across four Australian sarcoma centres (three adult and one paediatric centre). **Methods:** Using the Australia New Zealand Sarcoma Association national database (ACCORD) and medical records, we identified patients aged ≥10 years diagnosed with EFS between 2010-2020. Clinical characteristics, treatment and survival information were collected for those receiving Ewing protocol with VDC/IE backbone. Received Dose Intensity (RDI) of chemotherapy was calculated using planned and actual doses received and time taken. RDI ≥85% was considered acceptable, consistent with published literature. We compared survival outcomes based on RDI. Clinical predictors of achieving an acceptable RDI were explored using logistic regression. **Results:** Of 146 patients with EFS identified, 76 received VDC/IE (59% male). The median age was 25 years, with age distribution 24% aged 10-19, 58% aged 20-39, and 18% aged 40-59. Majority had extraskeletal Ewing's (57%), non-extremity primary site (64%) and localised disease (stage, II 37%; III 28%; IV 28%). Treatment received included surgery (74%), radiotherapy (66%) and chemotherapy (100%). Over two-thirds (70%) completed their scheduled chemotherapy and 57% achieved an acceptable RDI (67% aged 10-19, 61% aged 20-39, 29% aged 40-59). Compared to those aged 10-19, the odds ratio (OR) of an acceptable RDI for patients aged 20-39 was 0.79 (95% CI 0.24-2.46, p = 0.70) and for patients aged 40-59 was 0.20 (95% CI 0.04-0.86, p = 0.04). The median number of chemotherapy cycles was 14 (range, 2-17). Dose reductions were mostly within 20% cumulative target dose (91%), and were predominantly for neutropenia (47%), thrombocytopenia (30%) and/or anaemia (28%), and less frequently for cardiotoxicity (7%). Median follow-up was 37.3 months. Two-year progression-free survival (PFS) rates were 56% for acceptable RDI, compared to 30% for low RDI (p = 0.001), with two-year overall survival (OS) rates respectively 88% versus 49% (p < 0.001). After adjustment for age, gender, Ewing's type, primary site and stage, RDI remained an important prognostic factor (PFS HR 0.39, 95% CI 0.18-0.82; OS HR 0.25, 95% CI 0.10-0.63). **Conclusions:** Survival outcomes in EFS were contingent on achieving an acceptable RDI. It was more difficult to maintain VDC/IE chemotherapy dose intensity in adults aged over 40 years, due to myelosuppression. Optimal treatment strategy for older adults remains to be defined. Research Sponsor: None.

11571 **Poster Session**

PEC-PRO: A new prognostic score from a series of 93 patients with localized perivascular epithelioid cell neoplasms (PEComas) treated with curative intent. *First Author: Justine Gantzer, Medical Oncology Department, ICANS, Strasbourg, France*

Background: Perivascular Epithelioid Cell Neoplasms (PEComas) encompass a heterogeneous family of mesenchymal tumors. The current understanding of their natural history is limited. Previously described clinicopathological factors aimed to define benign or malignant variants, but there is a lack of prognostic factors associated with recurrence of surgically resected tumors, preventing the development of a prognostic score to better optimize patient's management. **Methods**: This is a retrospective analysis of clinicopathological features from patients diagnosed with a localized PEComa, within all centers from the French Sarcoma network and one center in Belgium. We analyzed 12 clinicopathological factors in a Cox proportional hazard framework to derive a multivariate prognostic risk model for progression-free survival (PFS). We built the PEComa PROgnostic score (PEC-PRO) ranging from 0 to 5, based on the coefficients of the multivariate model. Three different prognostic groups were identified: low risk (score = 0), intermediate risk (score = 1) and high risk (score ≥2). **Results**: Ninety-three patients were analyzed with a median follow-up of 46 months (range, 3-253). At diagnosis, the median age was 54 years (range, 13-84), with female predominance (72%). Most common primary locations were uterus (n = 15;16%) and kidney (n = 15;16%). Median tumor size was 6.2 cm (range, 0.8-30). Among patients with reported surgical margins, 64 (73%) and 23 (27%) had R0 and R1-2 margins, respectively. The median PFS was 26 months (IC95, 2.9-124.4), with 1- and 5-year overall survival (OS) rates of 95.7% and 69.9%, respectively, while the median OS was not reached. Using univariate analyses, male gender, primary tumor size > 5 cm, high nuclear grade and cellularity, high mitotic rate > 1/50 HPF, necrosis, vascular invasion, nodal invasion, and R1-2 margins were associated with a shorter PFS. Among those, male gender (HR = 2.88; IC95 1.12-7.411, p = 0.03), vascular invasion (HR = 3.14; IC95 1.10-8.96, p = 0.034), necrosis (HR = 3.93; IC95 1.35-11.47, p = 0.015), and R1-2 margins (HR 4.47; IC95 1.60-12.46, p = 0.007) remained associated with PFS in the multivariate analysis and were included in the multivariate model. Median PFS in patients with high PEC-PRO score was 16 months as compared to 104 months and not reached for patients with intermediate and low PEC-PRO scores, respectively (p < 0.001). We also confirmed the prognostic relevance of the PEC-PRO score in terms of OS. **Conclusions**: Using a weighted combination of clinicopathological features, the PEC-PRO score reliably predicts the post-operative recurrence risk in patients with localized PEComas. It has the potential to better improve follow-up strategies and personalize adjuvant treatments. The findings of this retrospective analysis require validation in a prospective trial. Research Sponsor: None.

11572 **Poster Session**

Which angiosarcoma subtypes may benefit from immunotherapy? *First Author: Stefan G van Ravensteijn, Department of Medical Oncology Radboud University Medical Centre, Nijmegen, Netherlands*

Background: Angiosarcomas (AS) are aggressive mesenchymal tumors arising from cells with endothelial properties. They include de novo primary AS (pAS), and secondary AS (sAS) due to prior radiotherapy, UV exposure or chronic lymphedema. Treatment options are limited and their prognosis is poor. Development of new treatment strategies is difficult due to the heterogeneity and rarity of AS. We hypothesize that immunological and genomic profiles are significantly different between pAS and sAS and may result in different immune checkpoint inhibition (ICI) based treatment strategies. **Methods:** Tumor samples from AS patients were retrospectively collected. Patients were categorized as pAS or sAS. Lymphocytes were analyzed using multiplex immunohistochemistry on tissue microarrays. Genomic profiling was performed in a selected subgroup with "TruSight Oncology 500", a Next Generation Sequencing panel containing 523 cancer related genes. **Results:** Immunological data were analyzed from 257 AS patients. The cohort comprised 80 pAS patients and 177 sAS patients. The median density of CD3+ T cells was 250 cells/mm^2 in pAS vs 452 cells/mm^2 in sAS (p< 0.001). Median CD4+ T helper cell density was 128 cells/mm^2 in pAS vs 246 cells/mm^2 in secondary AS (p< 0.001). The median density of CD8+ cytotoxic T cells was 85 cells/mm^2 in pAS vs 111 cells/mm^2 in sAS (p= 0.057). Density of FoxP3+ T regulatory cells was higher in sAS (median 42 cells/mm^2) compared to pAS (median 23 cells/mm^2) (p< 0.001). The median count of CD20+ B cells in pAS was 24 cells/mm^2 compared to 32 cells/mm^2 in sAS (p= 0.533). Genomic analysis was performed on tumor DNA from 51 patients (25 pAS and 26 sAS). Median tumor mutational burden (TMB) was 3.2 (range 0.8-11.9) mutations per megabase (mut/Mb) in pAS vs 3.9 (range 0.0-99.6) in sAS (p= 0.485). No microsatellite instability was detected. A pathogenic mutation, gene amplification or gene loss was identified in 82% of all patients (n = 42, 70% of pAS vs 100% of sAS (p< 0.01)). In 36 patients (71%) at least one (likely) pathogenic mutation was detected (54% pAS vs 88% sAS, (p= 0.013)). In 20 patients (39%) mutations in the DNA damage response (DDR) pathway were detected (12% pAS vs 68% sAS (p< 0.01)). The most frequently found mutated genes were *TP53* (10%), *BRAF* (6%), *ERCC4* (6%), *PTPRD* (6%), *WETD2* (6%) and *SETD2* (6%). Amplifications were found in 49% (n = 25) of all patients (15% pAS vs 84% sAS, (p< 0,01)). *MYC* amplifications were most common and were detected in 15% of pAS and 68% of sAS. Immune profiles of the 51 genomically characterized patients are currently under further investigation. **Conclusions:** We showed a clear distinction in immunological and genomic profiles between pAS and sAS. The potential benefit of ICI seems to be most promising in sAS with a T cell inflamed tumor microenvironment, frequent MYC amplifications, DDR mutations, and high mutational load, while in pAS boosting strategies to enhance susceptibility to ICI might be interesting for further investigation. Research Sponsor: Sarcoma Foundation of America.

11573 **Poster Session**

Five-year results of a phase 2 trial using ipilimumab (I), nivolumab (N), and trabectedin (T) for previously untreated advanced soft tissue sarcoma (NCT03138161). *First Author: Erlinda Maria Gordon, Sarcoma Oncology Research Center, Santa Monica, CA*

Background: Understanding the bifunctional role that the immune system plays in tumor eradication vs growth promotion is critical in the design and timing of tumoricidal and immunologic therapies for sarcomas. Hypothesis: Immune checkpoint inhibitors that promote sustained T cell activation would be most effective when given as first line therapy, together with a tumoricidal agent. **Methods:** Eligible patients for this Phase 2 study are males or females ≥ 18 years of age with locally advanced unresectable or metastatic soft tissue sarcoma, previously untreated, with measurable disease by RECIST v1.1. Treatment protocol: (I) mg/kg i.v. q 12 wks, (N) 3 mg/kg i.v. q 2 wks, (T) 1.2 mg/m2 CIV q 3 wks. Treatment Outcome Parameters: (1) Best objective response rate by RECIST v1.1, (2) Progression-free survival (PFS), (3) Overall survival (OS), and (4) Incidence of treatment-related adverse events. **Results:** Ninety-nine patients were enrolled. Efficacy analysis (n = 88): There were 8CR (1 surgical CR), 11PR, 58SD, 11PD. Overall response rate was 21.6%, Disease Control Rate, 87.5%. The median PFS was 7 (range:1-44) months, median OS, 14 (range: 1-46) months. Grade 3 TRAEs include fatigue (n = 8), adrenal insufficiency (n = 1), dehydration (n = 1), hyponatremia (n = 2), increased AST (n = 8), increased ALT (n = 24), increased ALP (n = 2), port site infection (n = 2), psoriasis exacerbation (n = 1), anemia (n = 9), thrombocytopenia (n = 2), and neutropenia (n = 5). Grade 4 TRAES include anemia (n = 1), neutropenia (n = 1), thrombocytopenia (n = 2), increased AST (n = 2), increased ALT (n = 2), and increased CPK (n = 2). Grade 5 TRAES include rhabdomyolysis (n = 1). There was no incidence of alopecia nor cardiac toxicity reported. **Conclusions:** Taken together, these data indicate that first-line combinatorial therapy with Ipilimumab, Nivolumab, and Trabectedin (1) may be more effective than standard first line therapy (doxorubicin/ifosfamide/mesna), and (2) is safer than standard first line therapy for advanced soft tissue sarcoma. Clinical trial information: NCT03138161. Research Sponsor: None.

11574 **Poster Session**

***nab*-Sirolimus for patients with advanced malignant PEComa with or without prior mTOR inhibitors: Biomarker results from AMPECT and an expanded access program.** *First Author: Mark Andrew Dickson, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Malignant perivascular epithelioid cell tumor (PEComa) is a rare and aggressive sarcoma. *nab*-Sirolimus is an albumin-bound intravenous (IV) mTOR inhibitor (mTORi) approved for the treatment of adult patients with locally advanced unresectable or metastatic malignant PEComa. The AMPECT trial (NCT02494570) was the first prospective study in advanced malignant PEComa. In exploratory biomarker analyses, *TSC1* or *TSC2* alterations were associated with response. We report data from the final analysis of AMPECT patients, who were naïve to mTORi, and in patients with malignant PEComa with prior mTORi exposure treated with *nab*-sirolimus in an expanded access program (EAP) (NCT03817515). **Methods:** In AMPECT, patients with malignant PEComa naïve to mTORi received *nab*-sirolimus (100 mg/m^2 IV days 1 and 8 of every 21-day cycle) until progression or unacceptable toxicity. The primary endpoint was ORR by independent radiology review. Other endpoints included duration of response (DOR) and disease control rate (DCR), defined as complete response (CR), partial response (PR), or stable disease (SD) at ≥12 weeks. In the EAP, patients with malignant PEComa and prior mTORi exposure received the same dose of *nab*-sirolimus as in AMPECT. Responses and DCR were evaluated post hoc via electronic medical record review. Genetic profiling, including *TSC1* or *TSC2* status, was assessed in both protocols, but no specific mutation criteria were required for enrollment. **Results:** Data include 47 total efficacy-evaluable patients, 31 in AMPECT and 16 with malignant PEComa and prior mTORi exposure treated in the EAP from July 2019–July 2021. Prior mTORi on the EAP included sirolimus, everolimus, temsirolimus, or sapanisertib; 12 patients had exposure to 1 prior mTORi and 4 to ≥2 prior mTORi, and 50% had had progressive disease as best response on mTORi. In AMPECT, ORR was 39% (12/31 patients), and DCR was 71%. Median DOR was not reached after 3 years of follow-up. On the EAP, 4/16 patients (25%) achieved PR (DOR range: 1.3+–25.2+ months, 3 ongoing), and 8/16 (50%) had SD as best response; the DCR was 63% (10/16). Of patients with known *TSC1* or *TSC2* inactivating alterations in the combined datasets (n = 23), 57% had a response (AMPECT, 64%; EAP, 44%). There were no Grade 4 or 5 treatment-related adverse events on either protocol **Conclusions:** *nab*-Sirolimus provided durable responses in mTORi-naïve patients with malignant PEComa and clinical benefit in an expanded access protocol for patients with malignant PEComa with prior mTORi therapy. Although AMPECT and the EAP cannot be directly compared, response rates showed similar trends regardless of prior mTORi exposure and in patients with *TSC1* or *TSC2* alterations. Based on the emerging biomarker results, a tissue-agnostic study in patients with *TSC1* and *TSC2* alterations has been initiated (NCT05103358). Clinical trial information: NCT02494570, NCT03817515. Research Sponsor: AADi Bioscience.

11575 **Poster Session**

Trabectedin in advanced retroperitoneal well differentiated/dedifferentiated liposarcoma and leiomyosarcoma (TRAVELL): Results of a phase 2 study from Italian sarcoma group (ISG). *First Author: Roberta Sanfilippo, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: To further explore the activity of T as second/further line treatment in retroperitoneal leiomyosarcoma (LMS) and well differentiated/dedifferentiated liposarcoma (LPS). The primary endpoint of the study was the growth modulation rate (GMR) defined as the ratio between the time to progression under T (TTP) and during previous chemotherapy treatment (TTP-1). The secondary end-points were objective response rate as per RECIST and PFS. **Methods:** This was a multicenter, single-arm Phase 2 study, conducted in 20 Italian centers. Patients with locally relapsed or metastatic disease, already treated with one or more previous systemic treatments with anthracyclines and/or ifosfamide, were enrolled. T was administered at a dose of 1.3-1.5 mg/mq with a top dose of 2.6 mg per cycle. T was administered as a 24h continuous infusion until progressive disease, major toxicity, patient's intolerance or medical decision. As per protocol, patients were considered responders if the GMR was > 1.33, non-responders if < 0.75 and neither if 0.76-1.32. Eighty evaluable patients were needed to detect an odds of trabectedin response ≥ 2.5, corresponding to 71.4% of patients with a GMR > 1.33 (80% power, one-sided alpha 2.5%). **Results:** From August 2014 to February 2019, 104 patients were registered and 91 were evaluable for the primary endpoint (32 pts with LMS and 59 with LPS). Overall, the median number of cycles received was 6.0 (q1-q3 3.0-12.0), the main reason for treatment discontinuation was disease progression in 72% of patients, followed by medical decision (8%). The median TTP was 6.0 months (6.2 and 6.0 for LMS and LPS), while the median TTP-1 was 7.5 months (8.1 and 6.4 for LMS and LPS). Thirty three patients (52% 95%CI: 36-58, p = 0.674, odds of response = 1.1) had a GMR > 1.33 (LMS: 46%, 95%CI 26-67,odds = 0.85; LPS 56%, 95%CI 40-72, odds = 1.3).Overall, response rate (CR+PR) was 16% (24% for LMS and 12% for LPS). Overall, in LPS we observed 15/47 patients with GMR < 0.5 and 15/47 with GMR > 2. Among LMS patients, 9/26 had a GMR < 0.5 and 10/26 > 2. Between LPS six patients had a GMR > 5. Previous treatment had been based on anthracyclines and/or ifosfamide in 85% of patients (91% in LPS population). **Conclusions:** While the primary end point of the study was not met, we noticed a subgroup of patients with a markedly discrepant TTP with T in comparison to previous therapy (GMR < 0.5 or > 2, the latter including some pts with a long TTP with T). Efforts are ongoing to assess the pathologic counterparts of such discrepancies. T seems to be selectively active in poorly understood subgroups, with a pattern of activity distinct from other available agents. Clinical trial information: 2012-005428-14. Research Sponsor: Pharmamar, Italian sarcoma Group.

11576 **Poster Session**

Genetic abnormalities and aberrant expression of genes involved in chromosome segregation and mitosis in patients with chromosomally unstable malignant soft tissue tumors haboring extensive somatic loss-of-heterozygosity (LOH). *First Author: Katsuhito Takahashi, Kameda Medical Center, Center for Multidisciplinary Treatment of Sarcoma, Department of Sarcoma Medicine, Kamogawa, Japan*

Background: Malignant soft tissue tumor is a rare cancer with few therapeutic options. Recent genomic analysis of soft tissue sarcoma (STS) revealed a high degree of chromosomal instability (CIN) including genome-wide copy number alteration, aneuploidy, whole genome doubling and chromothripsis. In STS patients, we observed extensive somatic LOH, a hallmark of CIN, which is haploid of germline mutations/variants in cancer-related genes. CIN of STS genome implicates abnormalities in chromosome segregation and mitosis. So far, studies on this issue, however, have not been reported in STS patients. **Methods:** We recruited 155 patients with metastatic/recurrent malignant soft tissue tumors (135 female and 20 male, mean age 51 at analysis, 100 LMS, 19 LPS, 4 ESS, 3 UPS, 3 AS, 3 MPT, 3 GIST and others) with information of familial cancer burden. Whole exome sequencing and analysis were performed in both blood and tumor samples as described in 2018ASCO. KIF18A expression was assessed by immunohistochemistry. **Results:** Patients with tumors harboring less than 33% somatic LOH in a total of somatic and LOH mutations/variants in 595 COSMIC genes (n = 54) have a better prognosis than those (34-66%, n = 49, 67-100%, n = 52) with tumors harboring more LOH genes (5-year OS; 71% vs 52% or 46%, p = 0.0299, p = 0.0117, respectively). Neither TMB nor MSI status was associated with LOH. Of the genes involved in chromosome segregation and mitosis, we found that a family of ARHGAP genes which play a role in the spindle assembly and Aurora A kinase activation was frequently mutated in both tumor and germline genomes (n = 81 in a total of 155). Damaging ARHGAP mutations/variants in tumors are correlated with higher LOH values (54±3.4%, n = 81 vs. 39±3.3%, n = 74. mean±SE, p = 0.0021) and poor prognosis of patients (5-year OS; 58% n = 81 vs. 41% n = 74, p = 0.0098). We also found that elevated and robust expression of a mitotic kinesin KIF18A in tumors harboring higher LOH and/or damaging ARHGAP mutations/variants (n = 12) but not in lower LOH tumors without ARHGAP mutations/variants (n = 4). **Conclusions:** This study, for the first time, demonstrates that genetic abnormalities and aberrant expression of genes involved in chromosome segregation and mitosis in patients with malignant soft tissue tumors. The results reveal a novel target of drug discovery for incurable STS because CIN tumor cells are shown to be particularly vulnerable to KIF18A inhibition, while somatic, diploid cells are not. Research Sponsor: Promotion fund for genomic medicine of rare cancers by Japan Sarcoma Association, Research Grant from Osaka Foundation for the Prevention of Cancer and Cardiovascular Diseases.

11577 **Poster Session**

Efficacy and safety of eribulin in the treatment of advanced adult soft tissue sarcoma (STS): First real-world data in Chinese population. *First Author: Xi Guo, Department of Medical Oncology, Zhongshan Hospital, Fudan University, Shanghai, China*

Background: Eribulin has shown efficacy in STS, especially for the L-type sarcomas, including liposarcoma (LPS) and leiomyosarcoma (LMS). We investigated the efficacy and safety of eribulin in the treatment of advanced adult STS in Chinese population. **Methods:** The study retrospectively analyzed data from patients diagnosed as advanced STS and received eribulin monotherapy or combination regimens in the Department of Oncology, Zhongshan Hospital affiliated to Fudan University from January 2020 to February 2021. Primary endpoint was objective response rate (ORR) by RECIST v1.1. Secondary endpoints included disease control rate (DCR), progress-free survival (PFS) and treatment-related adverse events (TRAE) by CTCAE v5.0. **Results:** A total of 40 patients who received at least two doses of eribulin and underwent at least one post-baseline response assessment were included in analysis. The mean age was 48 years. 82.5% (33/40) had L-type sarcomas, and 17.5% (7/40) had non-L-type sarcomas. Overall, 25% (10/40) of patients received eribulin alone; and 75% (30/40) received combination regimens. Drugs used with eribulin included gemcitabine, tyrosine kinase inhibitors (TKIs), anti-PD-1 antibodies, or TKIs plus anti-PD-1 antibodies. For the 40 patients, the ORR was 27.5% (11/40) and the DCR was 60% (24/40). The ORR for myxoid liposarcoma was especially encouraging: 54.5% (6/11) and the DCR was 72.7% (8/11). 10 patients received the combined therapy of anti-PD-1 antibodies, TKIs, and eribulin and showed a likely better ORR of 30% (3/10) and DCR of 70% (7/10). After a median follow-up time of 12.57 months (IQR, 8.43-16.30), the median PFS was 4.13 months (95% CI, 2.17-8.40). 10 out of 33 (30.3%) patients with L-type sarcomas had achieved PR and the median PFS was 2.67 months, 1 out of 7 (14.3%) patients with non-L-type sarcomas had achieved PR and the median PFS is 4.45 months. Common TRAEs were bone marrow suppression (42.5%), hypertriglyceridemia (25%), fatigue (10%), hypertension (7.5%). No treatment-related death happened. Logistic regression analysis of the multiple factors influencing ORR revealed no difference between taxane-treated and taxane-naïve patient groups. **Conclusions:** This study presents the first real-world data on the use of eribulin in STS in Chinese population. Eribulin monotherapy or combination therapy were likely more effective in this population, as well-tolerated as with Study 309, especially in treating liposarcoma. Eribulin used in combination with TKI and anti-PD-1 antibody showed potential efficacy in STSs. Further clinical exploration of front-line eribulin monotherapy and combination strategies in this setting is warranted. Research Sponsor: None.

11578 **Poster Session**

Clinical markers of immunotherapy outcomes in sarcoma. *First Author: Marium Husain, The Ohio State University Medical Center, Columbus, OH*

Background: Despite immunotherapy's promise in oncology, its use for sarcoma remains challenging. There are no sarcoma-specific biomarkers for immune checkpoint inhibitors (ICI). Previously, we reported our institutional experience highlighting ICI activity in 29 patients with sarcoma. In this updated study, we further explore responses to ICI based on ICI regimen and other covariates to identify significant clinical factors in sarcoma outcomes. **Methods:** Patients in the Ohio State University Sarcoma clinics were enrolled in the Sarcoma Retrospective ICI database from January 1, 2015 through November 1, 2021. Data included treatment regimen (single agent ICI or ICI+combination) along with covariates: stage, age, gender, histology, change in neutrophil-to-lymphocyte ratio (NLR), number of cycles of ICI and immune-related adverse events (irAE). ICI+combination was further categorized into ICI+chemotherapy, ICI+radiation, ICI+surgery or ICI+multiple (more than 2 modalities). Statistical analysis included log rank tests and proportional hazard regression. The primary objective was to evaluate overall survival (OS) and progression-free survival (PFS). **Results:** One hundred and thirty-five patients met inclusion criteria. We demonstrated improved OS in patients treated with ICI+combination ($p = 0.014$, median 64 weeks), but no effect on PFS ($p = 0.471$, median 31 weeks). Whether patients had received single agent or combination ICI, those who received more than 3 cycles of ICI had an improved OS and PFS ($p < 0.05$ for both). Patients who received single-agent ICI and whose change in NLR was less than 5 had an improved OS ($p = 0.002$); this was not seen in patients who received ICI+combination therapy ($p = 0.441$). Patients who had a documented irAE of dermatitis had improved OS but only in the ICI+combination cohort ($p = 0.021$). There were no differences in OS based on age, gender, histology or sub-categories of ICI+combination. This was not the case for PFS; patients who received any ICI regimen and were younger than 70 had a worse PFS ($p = 0.036$). Patients who developed an irAE, specifically colitis ($p = 0.009$), hepatitis ($p = 0.048$) and dermatitis ($p = 0.003$) had an improved PFS. There were no differences in PFS based on ICI regimen (or subcategories of ICI+combination), gender, histology, change in NLR or grade of irAE. Our ICI cohort results are consistent with historical data from our previous study. Further, irAEs are similar to historical data. **Conclusions:** This retrospective study demonstrates that ICI+combination therapy can improve OS in sarcoma. This is consistent with our prior results of ICI in sarcoma. Benefits in OS/PFS were seen in patients who received more than 3 cycles of ICI and developed certain irAE. These results can direct the optimal duration of ICI therapy. Those with decreased change in NLR also had improved OS, demonstrating a potential prognostic biomarker. Further studies are needed to validate our findings. Research Sponsor: None.

11579 **Poster Session**

The emerging fifth epidemiologic subtype of Kaposi sarcoma in HIV-negative men who have sex with men at a tertiary care center in NYC from 2000 to 2021. *First Author: Ayana E Morales, Weill Cornell Medical College, New York, NY*

Background: Kaposi sarcoma (KS) is a vascular tumor caused by human herpesvirus 8, also known as Kaposi sarcoma herpesvirus. There are 4 widely accepted distinct epidemiologic subtypes of KS: classic, endemic, iatrogenic, and epidemic (HIV-associated) forms. An emerging 5th subtype is increasingly recognized: non-epidemic KS in men who have sex with men (MSM) who are HIV-negative and have no other known causes for immunodeficiency. **Objectives:** To characterize a cohort of non-epidemic KS seen at the Sarcoma Medical Oncology or Dermatology Clinics at Memorial Sloan Kettering Cancer Center in New York City from 2000 to 2021 to identify risk factors, presentation, treatment course, and prognosis of these patients. **Methods:** Following IRB approval, a retrospective observational study was performed. Eligible patients were identified through the Electronic Health Records (EHR). The patients were characterized based on age at presentation, sex, gender identity, comorbidities, coinfections, and treatments and outcomes amongst other factors. Study data were collected and managed using REDCap electronic data capture tools. **Results:** Seventy-two patients were identified. The median age at time of diagnosis was 58 (range: 32-83). At initial diagnosis, 46% (33/72) of patients underwent observation, 50% (36/72) received localized treatment (i.e. excision, cryotherapy or topical therapy), and 4% (3/72) received systemic treatment with chemotherapy. The median duration of follow-up was 22 months. In follow-up, 43% (31/72) of patients had progression of disease requiring recurrent treatment: 24% (17/72) received localized treatment while 18% (13/72) received chemotherapy. Patients who received chemotherapy, predominantly pegylated liposomal doxorubicin, received treatment for a median duration of 13 months (range: 2-72 months). By the end of the follow-up period, 7 patients had died, of which 2 deaths were attributed to KS. During follow up, 10% (7/72) of patients were diagnosed with a lymphoproliferative disorder. **Conclusions:** This study is the largest yet, to our knowledge, to characterize the non-epidemic KS subtype in HIV-negative MSM. It is important to recognize this KS subtype to identify these individuals, who despite not having HIV are at increased risk for KS. Accurate recognition of this subtype may also allay patient concerns regarding overall prognosis, given that the majority of these patients present with indolent disease and have favorable outcomes compared to the epidemic variant of KS. Additional research is needed to understand the potential increased risk of lymphoproliferative disorders. Research Sponsor: U.S. National Institutes of Health.

11580 **Poster Session**

DNA damage response pathways in synovial sarcoma. *First Author: Priscila Barreto Coelho, University of Miami Miller School of Medicine/Sylvester Comprehensive Cancer Center, Miami, FL*

Background: Synovial sarcomas (SS) harbor a specific, balanced, reciprocal translocation t(X;18) leading to the oncogenic SS18-SSX fusion. Defective DNA damage response (DDR) is a hallmark of cancer leading to genomic instability and is associated with chemosensitivity. Efforts have been made to identify a genetic signature that predicts SS progression, treatment response, and survival in order to identify more accessible and effective treatments. This investigation explores the role of DDR in pathogenesis of SS. **Methods:** Patients with the diagnosis of SS from 2013 to 2021 within the Caris Life Science database were included in the study. A combination of NGS of DNA and RNA at a CLIA-certified laboratory (Caris Life Sciences, Phoenix, AZ) was performed on archival tumors. Homologous recombination deficiency (HRD) scores were calculated as a composite of loss of heterozygosity, telomeric allelic imbalance, and large-scale transitions, using a positive threshold of 42. This study was approved by the University of Miami (UM)-Sylvester IRB and all the data collected was de-identified. **Results:** A total of 120 patients were identified with 49 of these patients from UM-Sylvester. Mean age of diagnosis on the sample was 46 years old (range of 15-86) and 45.8% were female. Among the 49 patients from UM-Sylvester, mean age was 60 years old (range of 35-84), 28 patients had a gene alteration identified (57%) and 6 of them a homologous recombination deficiency (HRD) gene (12%). A total of 63 different genes were identified with the most common *TP53* (49%), *LOH* (12.2%), *ATRX* (10.2%) and *RB1* (6.1%). Other HRD genes identified were *MLH1* (4%) and *CHEK2* (4%). There was no correlation identified between the age (15-65 vs elderly $\geqslant$ 65 years) or the gender (female vs male) and the presence of a mutated DDR ($p = 0.615$; $p = 0.091$ respectively). Within the entire Caris database ($N = 120$), we identified 11 patients ($N = 120$, 9%) whose tumor tested positive for any DDR gene alteration. The most common were *ATM* (2.6%), followed by *ATRX* (1.6%) and *CHEK2* (0.9%). The median HRD score was 22 within the sample. **Conclusions:** We report here the most common genes altered on molecular profile for a large cohort of SS samples. The prevalence of predicted pathogenic DDR gene mutation carriers in our cohort (9%) suggests that constitutional defects in this pathway may be associated with SS. We found higher rates of positive DDR on the UM-Sylvester cohort, and this could be associated with specifics of our population, given high frequency of Hispanic patients. Work is ongoing to associate our findings with race, ethnicity, survival and response to treatments. Work is ongoing to associate our findings with race, ethnicity, survival and response to treatments. These correlations will be reported in the final abstract. Cytotoxic therapy remains gold standard for metastatic SS, but better understanding of the molecular profile can pave way for further options, including targeted therapy and immunotherapy. Research Sponsor: None.

11581 **Poster Session**

Efficacy of liposomal doxorubicin in patients with intra- and extra-abdominal desmoid fibromatosis. *First Author: Rodney Dixon Dorand, Vanderbilt University Medical Center, Nashville, TN*

Background: Desmoid tumors (DT) or aggressive fibromatosis are rare growths of fibroblastic connective tissue that can be locally aggressive but without metastatic potential. Most cases are sporadic, but 5-20% of cases are associated with Familial adenomatous polyposis (FAP). Despite numerous systemic options, optimal choice is unclear, and there is a paucity of studies comparing efficacy based on tumor site. Liposomal doxorubicin (LD) can be an appealing option for DT patients (pts) given its favorable schedule and toxicity profile. In this study, we compared outcomes in pts with intra-abdominal (IA) and extra-abdominal (EA) DT who received LD. **Methods:** We identified pts with DT who were treated with LD between 1/2010 - and 2/2022 at two sarcoma centers. Tumor and pt characteristics and outcomes were clinically (symptom improvement) and radiologically (RECIST 1.1) assessed. **Results:** 40 pts with DT treated with LD were identified; 58% female and 42% male. Pt characteristics and outcomes are summarized in Table 1. Primary tumor site was IA in 21 (53%) pts. FAP was present more commonly in pts with IA vs EA DT, 8/21 (43%) and 4/19 (21%), respectively. In the IA cohort, LD was given as first (15/21, 71%), second (10%) or third (19%) line therapy. LD was used more commonly as a later line in the EA cohort with 16%, 52%, 16%, and 16% receiving it in first, second, third, and fourth lines, respectively. 37 pts were evaluable for response. Response rate in the IA cohort treated in first-line was 50% (8 of 16) and 10 of 12 evaluable pts had symptomatic improvement. No first-line responses were seen in the EA cohort. As later lines of therapy, 7/12 pts had disease control in the second line, 6/8 pts in the third line, and 1/2 pts in the fourth line with LD in the IA cohort. 1 patient had fourth line response to LD in the EA cohort. Disease control rate with LD was 72.5% across all pts. Reasons for early discontinuation of LD included progression or lack of symptom improvement (20%), allergic reaction (12.5%), adverse effects (7.5%), or infection (2.5%). No acute or long-term cardiotoxicity was reported. 2 pts had no signs of recurrence or symptoms at follow-up, 33 pts were alive with symptomatic DT, 1 patient died from disease, and 3 were lost to follow-up. **Conclusions:** In our study, LD provided tumor response, disease control, and symptomatic improvement regardless of location or prior therapy, with responses most frequently seen in IA DT in first line setting. Further studies should include comparison of efficacy, adverse effects, and patient-reported outcomes while accounting for tumor location and line of therapy. Research Sponsor: U.S. National Institutes of Health.

	All Cases	IA	EA
Number of Patients	40	21	19
FAP	12	8	4
Median Age (Range)	32 (1-78)	36 (14-78)	34 (1-65)
Median Tumor Size (cm)	8.9	11.2	6.3
Sex (Number)	F (23), M(17)	F (11), M (10)	F (12), M(7)
Surgery % (Pos Margin)	53% (71%)	48% (60%)	58% (82%)
Radiation %	27.5%	14.3%	42.1%
First Line LD	45%	71.4%	15.8%
Response Rate (RECIST 1.1)	37.5%	66.7%	5.26%

TPS11582 **Poster Session**

A randomized, placebo-controlled, phase 2 trial of INBRX-109 in unresectable or metastatic conventional chondrosarcoma. *First Author: Sant P. Chawla, Sarcoma Oncology Research Center, Santa Monica, CA*

Background: Chondrosarcomas (CS) are the third most common type of primary bone cancer after myeloma and osteosarcoma. Conventional CS represent 85–90% of all cases and are typically treated with surgical resection. However, there are no approved systemic treatment options for patients with unresectable or metastatic conventional CS, and outcomes remain poor. INBRX-109 is a precision-engineered, tetravalent death receptor 5 (DR5) agonist antibody designed to overcome the limitations of earlier-generation agonists and exploit the tumor-specific cell death induced by DR5 activation. DR5 is one of two pro-apoptotic receptors for the trimeric tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). Early clinical activity of INBRX-109 was observed in an ongoing phase 1 trial and warrants further investigation. INBRX-109 has been granted an FDA fast-track designation for conventional CS. **Methods:** This is a multicenter, randomized, blinded, placebo-controlled phase 2 study in patients with unresectable or metastatic conventional CS, measurable disease by RECIST 1.1, and radiologic disease progression within 6 months prior to screening. Any number of prior lines of therapy are allowed, except for prior DR5 agonists. Patients must be ≥18 years of age and have an ECOG performance status of 0/1 and have archival or fresh tissue available. Approximately 201 patients will be randomized (2:1) to INBRX-109 (3 mg/kg intravenously, every 21 days) or placebo, stratified by histologic grade (Grade 1/2 vs 3), isocitrate dehydrogenase (IDH)1 R132/IDH2 R172 status (wildtype vs mutation), and line of systemic therapy (none vs prior). Treatment will continue until disease progression/unacceptable toxicity. Patients treated with a placebo will have the option to cross over to INBRX-109 upon disease progression. The primary endpoint is progression-free survival (PFS) by independent radiology review. Secondary endpoints are overall survival, PFS by investigator assessment, quality of life, overall response rate, duration of response, disease control rate, safety, pharmacokinetics, and immunogenicity. Adverse events will be recorded and graded by NCI CTCAE Version 5.0. Median PFS of 7.0 months is projected for INBRX-109 and 4.0 months for placebo (corresponding hazard ratio of 0.571); INBRX-109 will be declared superior if the 1-sided p-value from the stratified log-rank test is <0.025. More than 50 sites are planned across the US/Europe. The study is actively enrolling. Clinical trial information: NCT04950075. Research Sponsor: Inhibrx, Inc, La Jolla, CA, USA.

TPS11583 **Poster Session**

Phase 2 study to evaluate palbociclib in combination with irinotecan and temozolomide in pediatric patients with recurrent or refractory Ewing sarcoma. *First Author: Theodore Willis Laetsch, Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, PA*

Background: Palbociclib (PD-0332991) is a highly selective, reversible, small molecule inhibitor of cyclin-dependent kinases (CDK) 4 and 6, administered orally. Functional dependence of Ewing Sarcoma (EWS) cell lines and tumor xenografts on Cyclin D1/CDK4 via genetic knockdown has shown both Cyclin D1 and CDK4 as critical dependencies for EWS cell line proliferation. The phase 1 portion of the study established the recommended Phase 2 dose (RP2D) with two chemotherapy backbones in children with solid tumors. The Phase 2 portion of the study now enrolls patients with EWS. The primary objective of this portion of the study is to determine whether the addition of palbociclib to irinotecan (IRN) and temozolomide (TMZ) will prolong event-free survival (EFS) of pediatric and young adult patients with recurrent or refractory EWS. **Methods:** Patients with recurrent or refractory EWS are randomized 2:1 to receive either palbociclib in combination with IRN and TMZ or IRN and TMZ alone. Randomization is stratified by type and time of disease recurrence (primary refractory or 1st recurrence <2 years vs. 1st recurrence ≥2 years or 2nd or greater recurrence). The primary efficacy endpoint is EFS per investigator assessment. Secondary efficacy endpoints include objective response, progression-free survival and overall survival. An interim futility analysis will be conducted to allow for early stopping of the study due to futility/no signal of activity based on the primary endpoint of EFS. Safety and planned interim efficacy data will be assessed by an Independent Data Monitoring Committee (DMC). Key eligibility criteria include: recurrent or refractory EWS with evaluable disease, no known bone marrow metastases, histopathological confirmation of EWSR1-ETS or FUS-ETS rearrangement or availability of formalin fixed paraffin embedded (FFPE) tumor tissue sample for central testing, age ≥2 and <21 years at the time of study entry. Treatment intervention: Patients randomized to palbociclib with IRN and TMZ treatment arm will receive palbociclib at the RP2D of 75 mg/m^2 orally (either as a capsule or oral solution) once daily on Days 1-14 of each 21-day treatment cycle. TMZ will be administered orally once daily at 100 mg/m^2 on Days 1-5 (intravenously (IV) if patient cannot swallow the TMZ capsule). IRN will be administered IV at 50 mg/m^2 on Days 1-5. Patients randomized to the chemotherapy only treatment arm will receive IRN and TMZ at the same doses on Days 1-5 of the 21-day treatment cycle. Treatment will continue until disease progression, patient and/or legal guardian refusal, unacceptable toxicity, or up to 24 months of treatment, whichever occurs first. The Phase 2 enrolment has been initiated and 1/75 patients has been enrolled as of Jan 2022. Clinical trial information: NCT03709680. Research Sponsor: Pfizer Inc.

TPS11584 **Poster Session**

A phase 1/2 dose-escalation and dose-expansion study of ZN-c3 in combination with gemcitabine in adult and pediatric subjects with relapsed or refractory osteosarcoma. *First Author: Viswatej Avutu, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Osteosarcoma (OS) is the most common primary bone malignancy of childhood and adolescence with 5-year survival rates of 65-70% for localized disease and < 30% for de novo metastatic disease or recurrent disease. Pooled analysis of previous phase 2 trials by the Children's Oncology Group has determined a 4-month event-free survival (EFS) of 12%. The Wee1 kinase helps regulate DNA damage repair at the G2-M checkpoint. In the presence of DNA damage, the Wee1 kinase is activated, arresting cells in the G2 phase and preventing entry into the M phase. Inhibition of the Wee1 kinase abrogates the G2-M checkpoint, forcing cancer cells to undergo unscheduled mitosis even in the presence of DNA damage, leading to mitotic catastrophe. However, the Wee1 kinase is often upregulated in OS, preserving the G2-M checkpoint and allowing tumor growth and metastases. Additionally, up to 90% of OS tumors have alterations in p53, a critical protein in the regulation of the G1-S checkpoint, especially in relapsed or refractory cases. With a dysfunctional G1-S checkpoint, cancer cells further rely on G2-M checkpoint to repair DNA damage and preserve genomic integrity. Prior studies have demonstrated that pharmacologic inhibition of the Wee1 kinase produced cell death in OS cell lines and patient-derived xenografts. While p53 mutational status appeared to modulate efficacy of the Wee1 kinase inhibitor, activity was observed in p53 wild type, mutant and null cell lines. Combination therapy studies have also been performed, demonstrating potential synergism with gemcitabine. As expected, by precipitating DNA damage, susceptibility to inhibition of the G2-M checkpoint is further increased. **Methods:** NCT04833582 is an ongoing, open label, multicenter, phase 1/2 clinical trial to evaluate the activity of ZN-c3, an oral Wee1 inhibitor, in combination with gemcitabine in subjects ≥12 years and ≥40 kg, with relapsed, refractory OS. Subjects are dosed once daily, continuously with ZN-c3 and receive gemcitabine 1000 mg/m^2 on days 1 and 8 of 21-day cycles. Up to 18 subjects are expected to enroll in the phase 1 portion based on a typical 3 + 3 escalation design; ~60 subjects will be enrolled in the phase 2 portion, consisting of three stages: futility, promising clinical activity, and improved precision for clinical activity. The first two stages follow a Simon two-stage optimal design with 30 subjects, to differentiate an EFS rate at 18 weeks between 12% and 36% (which may be considered a more suitable endpoint for OS, compared with radiographic response). Tumor and skin punch biopsies are incorporated into the trial to identify potential biomarkers of treatment response. Subjects must be able to swallow oral tablets and have measurable disease by RECIST v1.1; prior exposure to gemcitabine is allowed. Global enrollment began August 1, 2021, and is ongoing. Clinical trial information: NCT04833582. Research Sponsor: Zentalis Pharmaceuticals.

TPS11585 **Poster Session**

REGOMAIN: A randomized, placebo-controlled, double-blinded, multicenter, comparative phase II study of the efficacy of regorafenib as maintenance treatment in patients (pts) with high-grade bone sarcomas (HGBS) at diagnosis or relapse and without complete remission after standard treatment. *First Author: Mehdi Brahmi, Centre Léon-Bérard, Lyon, France*

Background: Primary metastatic osteosarcoma (OS) patients are treated with a curative intent following the same principles of non-metastatic OS, while the treatment of recurrent OS is primarily surgical in the case of isolated lung metastases. When complete removal of all metastases cannot be achieved, the prognosis remains poor, with a median Progression-Free Survival (PFS) between 3 to 8 months, and therefore there is a clinical need to reduce the risk of progression after the initial treatment sequence. The REGOBONE study reported a significant PFS benefit of regorafenib (REG) compared to placebo (in osteosarcomas: median PFS: 16.4 *versus* 4.1 weeks) and a manageable safety profile in patients with histologically confirmed HGBS (i.e., osteosarcoma or other bone sarcomas with the exception of Ewing sarcomas, chondrosarcoma and chordoma). **Methods:** This multicenter trial is ongoing to study the efficacy and safety of maintenance REG in pts > = 16 years old with HGBS, without complete remission but with no progressive disease after standard treatment, either at diagnosis or at relapse. Sixty pts will be randomly allocated in a 1:1 ratio to receive either oral REG at a daily dose of 120mg or its matching placebo, continuously for a maximum of 12 months. Randomization is stratified according to the setting of the disease: initial diagnosis versus relapse. The primary objective is to compare the efficacy (PFS) between the 2 arms. The expected 4-month PFS rates are 30% in the control arm and 60% in the REGO arm (HR = 0.42). Fifty-two events will provide 87% power to show significant improvement in PFS, using a 2-sided log-rank test at a 5% level. Secondary endpoints include Overall Response Rate (ORR), Disease Control Rate (DCR), Time to Treatment Failure (TTF), Overall Survival (OS), Quality of Life (QoL), and safety profile. Radiological endpoints will be evaluated using the RECIST 1.1 with tumor assessments every 2 months (first 6 months) and then every 3 months. Translational objectives will identify predictive biomarkers for efficacy of REG as maintenance therapy. Pts of the control arm who experience disease progression may switch to receive open label REG. As of Feb 1st, 2022, 3 patients have been randomized. 14 sites of the French Sarcoma Group will participate. An amendment is being implemented to lower the age limit (12 years old) and to expand tumor types to other HGBS (Ewing sarcomas, chondrosarcomas, Undifferentiated Pleomorphic Sarcomas, Leiomyosarcomas and angiosarcomas). Clinical trial information: NCT04698785. Research Sponsor: Programme Hospitalier de Recherche Clinique.

TPS11586 **Poster Session**

A phase II/III, randomized, open-label, multicenter study of BI 907828 compared to doxorubicin in the first-line treatment of patients with advanced dedifferentiated liposarcoma (DDLPS): Brightline-1. *First Author: Patrick Schöffski, Department of General Medical Oncology, Leuven Cancer Institute, University Hospitals Leuven, Leuven, Belgium*

Background: The standard of care in the first-line treatment of patients (pts) with unresectable/metastatic DDLPS is doxorubicin, despite only moderate efficacy and many associated adverse events (AEs). BI 907828 is a mouse double minute 2 (MDM2)–p53 antagonist that binds to MDM2 and blocks its interaction with p53, leading to p53 stabilization, *TP53* target gene induction, cell-cycle arrest and apoptosis in *TP53* wild-type tumor cells. In a Phase I study, BI 907828 monotherapy demonstrated a manageable safety profile and preliminary signs of efficacy, particularly in pts with DDLPS (Gounder et al, ESMO 2021). **Methods:** NCT05218499 is a Phase II/III, randomized, open-label, international, multicenter study (~125 sites) that aims to evaluate whether BI 907828 is superior to doxorubicin in the first-line treatment of advanced/metastatic DDLPS. In the Phase II part, ≤180 pts will be randomized 1:1:1 to receive BI 907828 30 mg or 45 mg orally every 3 weeks (q3w), or doxorubicin 75 mg/m^2 intravenously q3w to a maximum cumulative dose of 450 mg/m^2. Main inclusion criteria include: ≥18 years of age; histologically proven advanced/metastatic, unresectable DDLPS; positive MDM2 immunohistochemistry or amplification; ≥1 measurable target lesion (RECIST v1.1); and ECOG PS 0/1. Exclusion criteria include a known *TP53* gene mutation and prior systemic therapy for liposarcoma. In the experimental arm, treatment will continue until disease progression, unacceptable AEs, or consent withdrawal. Pts who receive doxorubicin may cross-over to receive BI 907828 after confirmed progressive disease. The primary endpoint is progression-free survival (PFS; based on blinded independent central review), defined as the time from randomization to tumor progression (RECIST v1.1) or death from any cause, whichever occurs first. Secondary endpoints are objective response (OR), duration of OR, overall survival, disease control, and pt-reported health-related quality of life. In Phase II, an interim analysis (based on the totality of safety and PK/PD data) will be used to select the optimal BI 907828 dose. Subsequently, an interim futility analysis will be performed after ~56 PFS events using a log-rank test stratified by the extent of disease (locally advanced vs metastatic). If the selected BI 907828 dose passes the futility boundary, the trial will proceed to Phase III. In the Phase III part, ≥120 additional pts will be randomized 1:1 to receive the selected BI 907828 dose or doxorubicin. The primary PFS analysis will be performed after ~92 and ~65 PFS events in pts enrolled before and after the interim futility analysis, respectively, using a weighted inverse normal method combining one-sided p-values from a stratified log-rank test. Enrollment is ongoing. Clinical trial information: NCT05218499. Research Sponsor: Boehringer Ingelheim.

TPS11587 **Poster Session**

A phase II study, with a safety lead-in, to evaluate ATX-101, a peptide drug targeting PCNA, in advanced dedifferentiated liposarcoma and leiomyosarcoma. *First Author: Sminu Bose, Columbia University Irving Medical Center, New York, NY*

Background: Soft tissue sarcoma (STS) is a heterogeneous malignancy of mesenchymal origin; leiomyosarcoma (LMS) and liposarcoma (LPS), two of the most common adult STS, are treated with first-line chemotherapy with objective response rates (ORRs) of 15-20%. There is an urgent need for novel therapeutics. ATX-101 is a small peptide comprised of a novel human AlkB homolog 2 proliferating cell nuclear antigen (PCNA) interacting motif termed APIM coupled to cellular and nuclear delivery domains. Via APIM, PCNA interacts with many cellular proteins important in the cellular stress and DNA damage responses, as well as intracellular signaling, apoptosis, metabolism, and anti-tumor immunity. In preclinical studies, ATX-101 demonstrated single-agent activity and potentiated other cytotoxic and targeted agents across multiple cancer models *in vitro* and *in vivo*, including LMS and LPS. In a phase I safety and pharmacokinetic study in solid tumors, ATX-101 was well tolerated and demonstrated prolonged disease stabilization in patients (pts) with heavily pretreated malignancies. This study will evaluate preliminary efficacy and further establish the safety profile of ATX-101 in advanced LMS and LPS. **Methods:** This is a single-arm, open-label, Simon 2-stage, phase II clinical trial of ATX-101 in pts with advanced LMS and LPS. Eligible pts have ECOG PS ≤2, progression on ≥1 prior line of therapy and disease measurable by RECIST v1.1 and amenable to image-guided biopsy. Pts receive ATX-101 60 mg/m2 IV weekly in continuous 21-day cycles. The 1° endpoint is progression free rate at 12 weeks (PFR12). A Simon 2-stage design is used to evaluate for improvement in PFR12 of ≤ 30% (null hypothesis) versus ≥ 55% (alternative hypothesis). The design calls for 34 pts with a safety lead-in among the first 10 pts enrolled. If 15/34 meet the PFR12 endpoint, the treatment is promising. This design yields 85% power and 1-sided type I error of 5%. 2° endpoints include progression free survival, ORR, and safety. 10 pts undergo tumor biopsies pre-treatment and during cycle 2. Tissue is used for correlative analysis interrogating ATX-101's effects on the immune microenvironment through multiplex immunohistochemistry, DNA damage response through whole exome sequencing/RNAseq to evaluate for alterations in HR pathway component genes, and intracellular signaling pathways by Western blot for AKT/mTOR components. The study opened to accrual 12/2021. Clinical trial information: NCT05116683. Research Sponsor: APIM Therapeutics.

TPS11588 **Poster Session**

A pilot study of lenvatinib plus pembrolizumab in patients with advanced sarcoma. *First Author: Sujana Movva, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: New treatment options are needed for sarcomas. Pazopanib is the only targeted agent approved for multiple soft tissue sarcoma (STS) subtypes with a response rate of 6% and a PFS of 4.6 months. Immunotherapy has a limited role in STS, as the SARC028 study of pembrolizumab demonstrated an overall response rate of 18%, with the highest response rate seen in the undifferentiated pleomorphic sarcoma (UPS) cohort at 23%. Lenvatinib is an oral, multi-tyrosine kinase inhibitor approved for the treatment of multiple cancer types including progressive, radioiodine-refractory thyroid cancer and unresectable hepatocellular carcinoma with inhibitory activity against the receptor tyrosine kinases VEGFR 1-3, FGFR 1-3, KIT, PDGFR alpha/beta, and RET. Early outcomes with the combination of lenvatinib and pembrolizumab suggest that this regimen could be broadly superior to PD-1 targeting alone for several tumor types as high rates of objective response have been noted. The rationale for this study is based on preclinical work demonstrating the immunosuppressive effects of VEGF in the tumor immune microenvironment including inhibition of dendritic cell maturation, recruitment of immunosuppressive Tregs, MDSCs and TAMs and up-regulation of PD-1 on CD8+ cells. **Methods:** This is a pilot study evaluating the efficacy of lenvatinib and pembrolizumab in the treatment of select metastatic and/or unresectable sarcomas. Patients will be enrolled in one of five cohorts: Cohort A: leiomyosarcoma; Cohort B: UPS; Cohort C: vascular sarcomas (including angiosarcoma and epithelioid hemangioendothelioma); Cohort D: synovial sarcoma and malignant peripheral nerve sheath tumor; and Cohort E: bone sarcomas (limited to osteosarcoma and chondrosarcoma). Eligible patients should have had at least one prior therapy for unresectable and/or metastatic disease, but no more than three prior lines of therapy. Prior treatment with angiogenesis inhibitors or immunotherapy is excluded. Archival tissue is required for eligibility. Patients enrolled in the study will be treated initially with a 2 week run-in of lenvatinib 20 mg orally daily which will be continued daily thereafter. Subsequently, they will start pembrolizumab 200 mg intravenously every 21 days. The primary endpoint for each cohort is best overall response rate documented by RECIST v1.1 Criteria at 27 weeks. A sample size of 10 patients is planned for each of the five histological cohorts. If 2 or more confirmed responses are observed among the 10 patients in an arm, the drug combination will be considered positive and worthy of further investigation for that arm. Secondary endpoints are PFS, OS, duration of response and safety/tolerability of the combination. On-treatment biopsy and blood samples will be required for correlative assessments. Accrual in all cohorts is ongoing. Clinical trial information: NCT04784247. Research Sponsor: Parker Institute, Sarcoma Foundation of America, Linn Fund, Witherwax, EHE Foundation.

TPS11589 **Poster Session**

MANTRA: A randomized, multicenter, phase 3 study of the MDM2 inhibitor milademetan versus trabectedin in patients with de-differentiated liposarcomas. *First Author: Mrinal M. Gounder, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY*

Background: Murine double minute 2 (MDM2) is a negative regulator of tumor suppressor protein p53. MDM2 induces degradation of p53 and promotes tumorigenesis. *MDM2* amplification occurs in many cancers but is documented in up to 100% of well-differentiated or dedifferentiated liposarcomas (WD/DDLPS) [Cancer Genome Atlas Research Network. Cell 2017]. Inhibition of the MDM2-p53 interaction is a promising therapeutic approach to restore p53 tumor suppressor activity in WD/DDLPS. Milademetan (RAIN-32) is a small-molecule MDM2 inhibitor that inhibits the MDM2-p53 interaction and restores p53 function at nanomolar concentrations. In a phase 1 study, milademetan showed promising efficacy in 53 patients with WD/DDLPS when administered on an intermittent schedule (260 mg QD on Days 1–3 and 15–17 on a 28-day cycle), with a median progression-free survival (PFS) of 7.4 months [Gounder et al. AACR-NCI-EORTC 2020]. WD/DDLS are relatively resistant to chemotherapy, and systemic treatment options for patients with advanced disease are limited. MANTRA (RAIN-3201) is a randomized, multicenter, open-label, phase 3 registration study designed to evaluate the efficacy and safety of milademetan versus trabectedin in patients with unresectable or metastatic DDLPS with disease progression on ≥ 1 prior systemic therapies. **Methods:** Eligible patients are ≥ 18 years of age with histologically confirmed unresectable and/or metastatic DDLPS, with or without a WD component, who have received ≥ 1 prior systemic therapies, including ≥ 1 anthracycline-based regimen, with radiographic evidence of progression by RECIST v1.1 within 6 months before study entry. Prior treatment with trabectedin or an MDM2 inhibitor is not permitted. Patients will be randomly assigned (1:1) to receive milademetan (260 mg once daily orally Days 1–3 and 15–17 on a 28-day cycle) or trabectedin (1.5 mg/m^2 as a 24-hour intravenous infusion every 3 weeks). Randomization is stratified by Eastern Cooperative Oncology Group performance status (0 or 1) and number of prior treatments for WD/DDLPS (≤ 2 or > 2). Tumor response will be evaluated by RECIST v1.1 at Weeks 8, 16, 24, and 32, and then every 12 weeks. Primary endpoint: PFS by blinded independent central review. Secondary endpoints: overall survival; disease control rate; objective response rate; duration of response; PFS by investigator assessment; safety; health-related quality of life. Exploratory endpoints: molecular markers in peripheral blood and/or tumor tissue; milademetan pharmacokinetics. To demonstrate a 3-month increase in PFS (from 3 to 6 months) corresponding to a hazard ratio of 0.5, approximately 160 patients will be required to observe 105 events with 93.9% power and 2-sided significance level of 5%. Clinical trial information: NCT04979442. Research Sponsor: Rain Therapeutics, Inc.

TPS11590 **Poster Session**

MOTION: A randomized, phase 3, placebo-controlled, double-blind study of vimseltinib (DCC-3014) for the treatment of tenosynovial giant cell tumor. *First Author: William D. Tap, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Tenosynovial giant cell tumor (TGCT) is a rare, locally aggressive neoplasm that occurs in the synovium of joints, bursae, or tendon sheaths. TGCT is caused by upregulation of the colony-stimulating factor 1 (CSF1) gene, resulting in aberrant CSF1 expression and the recruitment of CSF1 receptor (R)-dependent inflammatory cells. Resection is the primary treatment, but nonsurgical treatment options are necessary for patients with symptomatic TGCT not amenable to surgical resection. Vimseltinib is an oral switch control TKI specifically designed to selectively and potently inhibit CSF1R. In a Phase 1/2 study in patients with TGCT, vimseltinib showed encouraging antitumor activity with an overall objective response rate (ORR) of 42% in the cohort receiving 30 mg twice weekly (recommended phase 2 dose; Gelderblom et al, ESMO 2021 Poster). Vimseltinib was also well tolerated, and the majority of the common (≥15%) treatment-emergent adverse events (TEAEs) were Grades 1–2. Among these common TEAEs, the only Grade 3–4 event in the Phase 2, twice-weekly, 30-mg cohort was increased blood creatine phosphokinase (CPK); however, this elevated CPK was not associated with any symptoms (Gelderblom et al, ESMO 2021 Poster). Phase 1/2 efficacy and safety data support further development of vimseltinib; here, we describe the ongoing Phase 3 study for patients with TGCT not amenable to surgical resection. **Methods:** MOTION (NCT05059262) is a Phase 3, randomized, placebo-controlled, double-blind study that aims to evaluate the efficacy and safety of vimseltinib for the treatment of TGCT not amenable to surgical resection. Participants must be at least 18 years of age and have histologically confirmed and symptomatic TGCT for which surgical resection will potentially cause worsening functional limitation or severe morbidity. Prior CSF1R therapy is not permitted (previous imatinib and nilotinib is allowed). In Part 1 of the study, eligible participants will be randomized 2:1 to receive either vimseltinib 30 mg twice a week or matched placebo for 24 weeks. The primary outcome measure is ORR assessed by central read using Response Evaluation Criteria in Solid Tumors version 1.1 at 25 weeks. Secondary outcome measures include ORR per tumor volume score, range of motion, and patient-reported outcomes. Participants assigned to placebo in Part 1 will have the option to receive vimseltinib in Part 2, a long-term treatment phase in which participants will receive open-label vimseltinib. This international study plans to randomize 120 participants and is currently enrolling. Clinical trial information: NCT05059262. Research Sponsor: Deciphera Pharmaceuticals, LLC.

TPS11591 **Poster Session**

ARST2031: A study to compare early use of vinorelbine and maintenance therapy for patients with high risk rhabdomyosarcoma. *First Author: Wendy A Allen-Rhoades, Mayo Clinic, Rochester, MN*

Background: Patients with high-risk rhabdomyosarcoma (HR-RMS) continue to have poor outcomes with 3-year event free survival (EFS) rates of 30% or less despite chemotherapy dose intensification on recent cooperative group RMS trials. Vinorelbine (VINO) has demonstrated clinical activity in RMS patients with relapsed/refractory disease and shown to provide a survival benefit when given with oral cyclophosphamide as maintenance chemotherapy for a select group of patients that achieved first complete remission. **Methods:** ARST2031 is a randomized Phase 3 trial with the primary aim to compare event-free survival (EFS) of patients with HR-RMS treated with vincristine, dactinomycin and cyclophosphamide (VAC) followed by maintenance with vinorelbine and oral cyclophosphamide (VINO-CPO) or vinorelbine, dactinomycin and cyclophosphamide (VINO-AC) followed by maintenance with VINO-CPO. Patients are stratified by histology and randomly assigned to VAC followed by VINO-CPO maintenance or VINO-AC followed by VINO-CPO maintenance. To be eligible, patients must be ≤ 50 years of age at the time of enrollment with newly diagnosed RMS except adult-type pleomorphic, based upon institutional histopathologic classification. All patients must have Stage 4 disease and patients diagnosed with embryonal RMS (ERMS) must be ≥ 10 years of age. Patients with malignant cytology in cerebrospinal fluid, intra-parenchymal brain metastases, or diffuse leptomeningeal disease are excluded. The study was activated on September 13, 2021 and is anticipated to enroll approximately 4 patients per month. The planned sample size is 100 patients, with approximately 50 patients randomized to each arm. Safety and feasibility of VINO-AC will be assessed in the first 8 patients prior to randomization. The study will have power of 0.8 to detect a hazard ratio of 0.61 (74 events in total) when the one-sided Type I error rate is 0.10, with 30 months of accrual and 2 years of follow-up. The hazard ratio of 0.61 was determined by assuming piecewise exponential distributions and specifying the 2-year EFS of 46% vs. 28% and long-term EFS of 32% vs. 16%, based on prior outcome data. Biospecimens will be collected and banked for future use. Clinical trial information: NCT04994132. Research Sponsor: U.S. National Institutes of Health.

TPS11592 **Poster Session**

A phase 1b lead-in to a randomized phase 2 trial of lurbinectedin plus doxorubicin in leiomyosarcoma (LMS). *First Author: Gregory Michael Cote, MGH, Boston, MA*

Background: Single agent or combination chemotherapy regimens, typically including doxorubicin or gemcitabine, represent standard of care options for first- and second-line therapy in patients (pts) with metastatic LMS. However, response rates (ORR) and progression-free (PFS)/overall survival (OS) remain poor. Lurbinectedin (PharmaMar S.A. and Jazz Pharmaceuticals) uniquely binds DNA, inducing DNA double strand breaks leading to apoptosis and delaying progression through phase S/G2 of the cell cycle. Lurbinectedin is a novel structural analog of trabectedin with improved toxicity profile, potency, and pharmacokinetics. In a prior pilot study, we showed that the combination of lurbinectedin and doxorubicin (L+D) was safe, with early signs of clinical activity, particularly in LMS. Thus, we designed this investigator-initiated/investigator-sponsored phase 1b lead-in to optimize doses of L+D, to be followed by a randomized (1:1) phase 2 study of L+D versus doxorubicin monotherapy in anthracycline-naïve LMS. **Methods:** Pts age > 18 years with locally advanced or metastatic, unresectable LMS (non-GIST soft-tissue sarcoma histologies allowed in Phase 1b), without prior anthracycline or lurbinectedin/trabectedin, ECOG PS < 3, measurable disease by RECIST 1.1, and normal organ function, are eligible. Phase 1b dosing will include a fixed dose of lurbinectedin and two dose levels of doxorubicin. The Phase 1b lead-in follows a standard 3+3 design where dose escalation will occur if 0/3 or 1/6 patients experience a dose-limiting toxicity (DLT). Tumor assessments are conducted every two cycles. Once the recommended phase 2 dose (RP2D) is confirmed, Phase 2 will be initiated. Fifty pts will be randomized 1:1 including doxorubicin +/- lurbinectedin. Randomization will be stratified by uterine v. non-uterine origin of LMS. Pts progressing on single agent doxorubicin will be allowed to cross over to lurbinectedin monotherapy. The Phase 2 primary endpoint is PFS. Secondary endpoints include disease control rate, ORR, OS, PFS2 (for doxorubicin monotherapy patients who cross to lurbinectedin monotherapy). Archival tumor, germline DNA, and ctDNA will be collected for correlative studies exploring genomic markers of sensitivity/resistance. We will provide respective point estimate along with 90% confidence interval for each of the arms. Log-rank test will be performed to test the difference in survival (both PFS and OS) between groups. Regression analyses of survival data will be based on the Cox proportional hazards model. The first pt in dose-level 1 of the Phase 1b lead-in was enrolled in February 2022. Clinical trial information: NCT05099666. Research Sponsor: Jazz Pharmaceuticals.

TPS11593 **Poster Session**

TTI-621-03: A phase I/II study of TTI-621 in combination with doxorubicin in patients with unresectable or metastatic high-grade leiomyosarcoma (LMS). *First Author: Sant P. Chawla, Sarcoma Oncology Research Center, Santa Monica, CA*

Background: Doxorubicin is a standard of care agent for patients with advanced soft tissue sarcoma, with a response rate of around 15%, progression-free survival of 5-7 months and cumulative cardiac toxicity that limits its use. TTI-621 is a recombinant soluble fusion protein that combines the N-terminal portion of human SIRPα (the binding domain for CD47) with the Fc region of human IgG1, generating a decoy receptor for CD47 on the surface of tumor cells that both over-rides CD47-mediated inhibition of phagocytosis and provides a pro-phagocytic stimulation. Many solid tumors express high levels of CD47 which is associated with poor prognosis, thought to be the result of CD47-mediated inhibition of macrophage phagocytosis and escape of immune-mediated clearance. Interruption of the CD47-SIRPα signaling pathway using monoclonal antibodies to CD47 has shown anti-tumor activity in animal models and in some early clinical trials. The combination of doxorubicin with CD47-targeted antibodies results in enhanced anti-tumor activity and increased macrophage-mediated cell killing in animal models and macrophage-mediated phagocytosis of cancer cell lines *in vitro*, suggesting that combining TTI-621 with doxorubicin might be more effective than doxorubicin alone in tumor types that express CD47 and have high numbers of macrophages, such as LMS. Thus, a Phase 1/2 study was initiated to evaluate this combination in patients with advanced soft tissue sarcoma, including LMS. **Methods:** TTI-621-03 is a Phase 1/2, open-label study of TTI-621 in combination with doxorubicin in patients with anthracycline-naïve disease. The Phase 1 dose escalation evaluates doses of TTI-621 (0.2 to 2.0 mg/kg) in combination with doxorubicin at 75 mg/m^2 in patients with high-grade soft tissue sarcomas. Expansion cohorts will evaluate TTI-621 (0.2 and 2.0 mg/kg) with doxorubicin in patients with LMS, with pathology confirmed at a central laboratory. The primary goals of this study are evaluation of safety of TTI-621 administered in combination with standard-of-care doxorubicin and to further evaluate clinical activity (ORR, PFS, OS), safety, PK and patient-reported quality of life in the LMS subpopulation. The dose escalation portion of the study has been completed without DLT. Enrollment to the expansion portion of the study is underway. Clinical trial information: NCT04996004. Research Sponsor: Trillium Therapeutics Inc, a Pfizer Company.

TPS11594 **Poster Session**

A phase II multi-arm study to test the efficacy of oleclumab and durvalumab in specific sarcoma subtypes. *First Author: Neeta Somaiah, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Anti-PD 1/PD-L1 blockade alone or in combination with anti-CTLA4 have yielded suboptimal results in most sarcoma subtypes. CD73, an ectonucleotidase, catalyzes the rate-limiting step for adenosine production in the extracellular space, which then aids tumors in evading immune recognition and destruction. Oleclumab, a monoclonal antibody (mAb) selectively binds and inhibits the activity of CD73, and preclinical data suggests additive activity with durvalumab, a mAb that blocks PD-L1. We designed a trial combining oleclumab and durvalumab in certain sarcoma subtypes, selected based on modest activity with anti-PDL-1 and intense staining with CD73 in the tumor microenvironment. **Methods:** This phase 2 study (NCT04668300) is enrolling patients with age ≥18 years with recurrent/metastatic angiosarcoma (cohort 1) or dedifferentiated liposarcoma (DLPS) (cohort 2) and ≥12 years with recurrent/metastatic osteosarcoma (cohort 3), who have received at least one prior systemic therapy but are checkpoint inhibitor naïve and have measurable disease. Each treatment cycle is 28 days with oleclumab administered at 3000 mg i.v. every 2 weeks x 5 doses, and then every 4 weeks and durvalumab administered at 1500 mg i.v every 4 weeks. Tumor assessments are based on RECIST 1.1 and immune-related response criteria (irRC) and performed at baseline, and every 8 weeks after start of therapy, with an additional scan at 12 weeks for confirmation of response. Planned sample size is ≤ 25 pts in each arm. The primary efficacy endpoint for cohorts 1 and 2 is response rate (RR) at 4 months (per RECIST 1.1). The primary efficacy endpoint for cohort 3 is event free survival (EFS) rate at 4 months. If there is a high probability that the RR4 months is unlikely to be at least 20% for cohorts 1 and 2 or the EFS4 months is unlikely to be at least 40% for cohort 3 then the accrual of the corresponding cohort will be halted. The cohorts will be monitored separately for both futility and toxicity in groups of 5 after a minimum of 10 patients have been enrolled in each cohort. Secondary endpoints for the study include safety, best RR by RECIST and irRC, median PFS, and OS. Core needle biopsies and blood samples are collected at baseline and early on-treatment (week 6). Fresh flow cytometry is being performed to assess changes in T-cell activation, proliferation, and function and CD73 expression in the membrane and cytoplasm is being assessed by immunohistochemistry. Localization of tumor-infiltrating lymphocytes and engagement of the PD-1/PDL1 axis is being assessed using multiplex immunofluorescence staining. As of Jan 30th, 2022, twenty-two patients have initiated study treatment, 3 in cohort 1, 12 in cohort 2, and 7 in cohort 3. Clinical trial information: NCT04668300. Research Sponsor: Astra-Zeneca.

TPS11595 **Poster Session**

Phase 1/2 study of devimistat in combination with hydroxychloroquine (HCQ) in patients with relapsed or refractory (R/R) clear cell sarcoma (CCS). *First Author: Mark Agulnik, Northwestern University, Feinberg School of Medicine, Chicago, IL*

Background: CCS of the soft tissues is a rare and aggressive subtype of sarcoma that often starts in the tendons of the arms or legs. It is molecularly characterized by t(12;22)(q13;q12) translocation, resulting in EWSR1-ATF1 or EWSR1-CREB1 gene fusion. Despite reports of occasional responses to systemic therapies, currently available therapies have shown limited efficacy in advanced CCS. Therefore, there is a significant unmet medical need for more active agents in CCS. Devimistat is a stable intermediate of a lipoate analog that inhibits pyruvate dehydrogenase and α-ketoglutarate dehydrogenase enzymes of the tricarboxylic acid (TCA) cycle preferentially within the mitochondria of cancer cells. Devimistat induces autophagy in cancer cells. In a metastatic mouse model of CCS, treatment with devimistat in combination with chloroquine significantly suppressed tumor growth (Egawa et al, 2018). Based on this data, we hypothesized that inhibition of autophagy with HCQ may sensitize cancer cells to devimistat with increased efficacy and acceptable toxicity. Given its expected synergy, we have initiated a single-arm phase I/II prospective, multicenter, open-label, non-randomized study to evaluate maximally tolerated dose (MTD), safety, and efficacy of devimistat in combination with HCQ in patients with R/R CCS. **Methods:** In the phase 1 portion of the study, patients with R/R CCS and other fusion-positive R/R sarcomas will be enrolled and a standard 3+3 design will be followed to evaluate toxicity, MTD, and recommended phase 2 dose. There will be two patient groups based on weight, and dose escalation will be conducted separately for each group. Starting dose of HCQ will be 5mg/kg PO BID for patients < 45 kg and 200 mg PO BID for patients ≥45 kg on days 1 through 5 of every 28 days. The first dose of HCQ each day will be followed 2 hours later by 1,000 mg/m^2 devimistat (for patients < 45 kg) and 2,000 mg/m^2 of devimistat (for patients ≥ 45 kg) administered over 2 hours. A maximum of 36 patients will be enrolled for the phase I portion, 18 for each patient group. In the phase 2 portion of the study, only relapsed or refractory CCS patients will be enrolled, and the response rate will be determined using RECIST 1.1. In phase 2, pharmacokinetics, duration of response, clinical benefit rate, progression-free survival, overall survival, safety, and patient-reported outcomes will also be assessed. This portion of the study will utilize Simon's admissible two-stage design with 29 patients. This study started enrolling participants in November 2021 and has dosed six patients to date. The first two dose-escalation cohorts for patients ≥45 kg have been completed without DLT and the third dose level will be opening shortly. Clinical trial information: NCT04593758. Research Sponsor: Rafael Pharmaceuticals.

12000 **Oral Abstract Session**

Impact of acetaminophen on the efficacy of immunotherapy in patients with cancer. *First Author: Alban Bessede, ImmuSmol, Bordeaux, France*

Background: Pain is the most common symptom experienced by patients with advanced cancer. Acetaminophen (APAP, commonly known as paracetamol) alone or in combination with a weak opioid, such as codeine or tramadol, is usually considered as the first-line strategy to manage mild-to-moderate pain in this setting. Although generally considered to be safe, several evidences suggest that APAP may have negative immunomodulatory effects. Randomized studies have shown that APAP use is associated with blunted vaccine immune responses. Given its potential to impair vaccine effectiveness, the World Health Organization stated in 2015 that administration of APAP before or at the time of vaccination is not recommended. This study aimed to assess APAP impact on efficacy of immunotherapy in patients with cancer. **Methods:** Exposure to APAP was assessed by plasma analysis and was correlated with clinical outcome in three independent cohorts of patients with advanced cancer who were treated with immune checkpoint blockers (ICB): the CheckMate 025 trial, n = 297 (NCT01668784, sponsor: Bristol Myers Squibb), the institutional biomarker program BIP n = 34 (NCT02534649, sponsor: Institut Bergonié, Bordeaux, France) and the institutional biomarker program PREMIS n = 297 (NCT03984318, sponsor: Gustave Roussy, Villejuif, France). APAP immunomodulatory effects were evaluated on a pre-clinical tumor model (MC38) and on human peripheral blood mononuclear cells (PBMCs) from healthy donors. **Results:** Detectable plasma APAP levels at treatment onset was associated with a significantly worse clinical outcome in ICB-treated cancer patients (HR for progression-free survival : 1.43, 95% CI 1.07–1.91, p = 0.015; HR for overall survival: 1.78 95% CI 1.18–2.68, p = 0.006), independently of other prognostic factors (age, performance status, number of previous lines of treatment, tumor type, number of metastatic sites, presence of liver metastases, LDH levels). APAP significantly reduced ICB efficacy in the pre-clinical MC38 model, as well as the production of PD1 blockade-related interferon-γ secretion by human PBMCs. Moreover, reduction of ICB efficacy *in vivo* was associated with significantly increased tumor infiltration by regulatory T cells (Tregs). Administration of APAP over 24 h induced a significant expansion of peripheral Tregs in healthy individuals. In addition, interleukin-10, a crucial mediator of Treg-induced immune suppression, was significantly upregulated upon treatment with ICB in cancer patients taking APAP. **Conclusions:** This study provides strong preclinical and clinical evidence of the role of APAP as a potential suppressor of antitumor immunity. Hence, APAP should be used with caution in patients treated with ICB. Research Sponsor: None.

12001 **Oral Abstract Session**

Correlation of psychological distress with quality of life and efficacy of immune checkpoint inhibitors in patients with newly diagnosed stage IIIB-IV NSCLC. *First Author: Fang Wu, Department of Oncology, The Second Xiangya Hospital, Central South University, Changsha, China*

Background: Psychological distress is common among cancer patients and leads to activation of the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS) and continuous production of distress hormones, which may contribute to a highly immunosuppressive tumor microenvironment (TME). Meanwhile, preclinical studies have shown that psychological distress could undermine cancer therapies. Therefore, we investigate the prevalence of psychological distress in non-small-cell lung cancer (NSCLC) patients, identify its impact on quality of life (QoL) and efficacy of immune checkpoint inhibitors (ICIs), and explore the possible neuro-endocrinological mechanisms. **Methods:** Patients with newly diagnosed stage IIIB-IV NSCLC received ICIs as first-line treatment were included. The assessments of psychological distress including depression and anxiety symptoms were measured using the Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder-7 (GAD-7), respectively. The QoL was measured by Short Form Health Survey 36 (SF-36). Stress hormones including serum cortisol, adrenocorticotropic hormone (ACTH), plasma epinephrine (Epi), and norepinephrine (NE) were determined by ELISA kit before treatment. Objective response rates (ORR) and Median progression-free (PFS) were estimated using the Chi-square test, Kaplan-Meier, and Cox regression method. **Results:** 77 NSCLC patients with a mean age of 60.9 years were enrolled. Stage distribution included 50 (64.9%) stage IIIB/C and 27 (35.1%) stage IV. 44(57.1%) patients were present psychological distress. Psychological distress was associated with poorer QoL (P<0.001). The median follow-up time was 16.2 months. Compared with non-psychological distress patients, psychological distress patients had a significant lower ORR (35.9% vs 63.64%; *P*=0.033) and shorter PFS (median 12.63 vs 14.60 months; 95% CI: 0.36 to 1.98; *P*=0.026). Moreover, psychological distress was the only independent predictor for PFS (HR:2.71, 95%CI: 1.06~6.90; *P*=0.037) in multivariate Cox regression analyses. The patients with psychological distress had higher levels of serum cortisol (*P*=0.040) and plasma Epi (*P*=0.023). Additionally, the serum cortisol (*P*=0.043) and plasma Epi (*P*=0.025) concentrations were associated with inferior ICIs response. **Conclusions:** Psychological distress is common within stage IIIB-IV NSCLC patients. Patients with psychological distress are associated with worse QoL and inferior outcomes to ICIs and discover the potential mechanisms of neuro-endocrinological hormones in resistance to ICIs therapy. Research Sponsor: Beijing Xisike Clinical Oncologic Research Foundation (Grant No. Y-BMS2019-100), Beijing Xisike Clinical Oncology Research Foundation (Grant No. Y-HS202102-0130).

12002 **Oral Abstract Session**

Impact of age and frailty on acute care use during immune checkpoint inhibitor (ICI) treatment: A population-based study. *First Author: Lawson Eng, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: ICIs are a common therapeutic option across solid tumors. However, older adults were poorly represented in clinical trials evaluating ICIs, especially those who are very old or frail. Although ICIs are better tolerated than chemotherapy, some patients develop immune related adverse events (irAEs) that may require hospitalization. We performed a population-level retrospective cohort study to evaluate the impact of age and frailty among older adults on acute care use and irAE related hospitalizations. **Methods:** We used administrative data deterministically linked across databases to identify a cohort of cancer patients > 65 years of age receiving ICIs from June 2012 to October 2018 in Ontario, Canada and obtained data on socio-demographic and clinical covariates, and acute care utilization. Acute care use was defined as an emergency department visit or hospitalization from initiation to 120 days after the last ICI dose; hospitalizations were classified as irAE related based on ICD-10 codes. Frailty was assessed using the McIsaac Frailty Index. Multivariable competing risk analyses with Fine Gray subdistribution hazards evaluated the impact of age and frailty on both acute care use and irAE hospitalizations adjusted for sex, rurality, BMI, autoimmune history, hospitalization within 60 days prior to starting ICI and comorbidity score. **Results:** Among 2737 patients, median age 73 (18% age > 80, 50% age 70-79); 43% received Nivolumab, 41% Pembrolizumab and 13% Ipilimumab; 53% had lung cancer, 34% melanoma. 70% were robust, 26% pre-frail and 4% frail. Most patients (1962; 72%) had an acute care episode during the window, while 212 (8%) had an irAE hospitalization. Older age was associated with reduced risk of being hospitalized due to an irAE when measured as a continuous variable (aHR 0.97 per year [0.95-0.99] p = 0.01). Older adults, age > 80 years were also less likely to be hospitalized due to an irAE (age 70-79 vs 65-69, aHR 0.92 [0.66-1.27] p = 0.61, age > 80 vs 65-69, aHR 0.63 [0.39-1.01] p = 0.05). Age was not associated with acute care use as a continuous or categorical variable. Increasing frailty was associated with increased risk of acute care use during ICI treatment (pre-frail vs robust, aHR 1.20 [1.07-1.36] p = 0.003; frail vs robust, aHR 1.45 [1.12-1.86] p = 0.004) but was not associated with irAE hospitalizations. When evaluating both age and frailty in the same model, the identified associations remained significant. **Conclusions:** Among older adults receiving ICIs, age was not associated with acute care use but may be associated with reduced risk of experiencing an irAE related hospitalization. In contrast, frailty was associated with risk of acute care use but was not associated with risk of an irAE related hospitalization. Age and frailty may need to be considered independently when evaluating their use as potential factors influencing toxicity risk among older adults receiving ICIs. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

LBA12003 **Oral Abstract Session**

Bacterial decolonization to prevent acute radiation dermatitis: A randomized controlled trial. *First Author: Yana Kost, Department of Medicine, Division of Dermatology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

12004 **Oral Abstract Session**

A phase III, randomized, sham-controlled trial of acupuncture for treatment of radiation-induced xerostomia (RIX) in patients with head and neck cancer: Wake Forest NCI Community Oncology Research Program Research Base (WF NCORP RB) trial WF-97115. *First Author: Lorenzo Cohen, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The majority of head/neck (HN) patients who undergo radiotherapy develop RIX. Unfortunately, existing treatments are of limited benefit and have side effects. Initial small studies suggest acupuncture may treat chronic RIX. A multicenter, phase III, randomized, sham-controlled trial (NCT02589938) was conducted to compare true acupuncture (TA) with sham acupuncture (SA) and wait list control (WLC) group in treating chronic RIX. **Methods:** HN patients with chronic RIX at least 12 months post-RT were recruited through the WF NCORP RB network (2UG1CA189824). Patients must have received bilateral radiation therapy with subsequent grade 2 or 3 xerostomia per modified RTOG scale, with no history of xerostomia or other illness known to affect salivation prior to HN XRT. All patients received standard oral hygiene and were randomized to TA, SA, or WLC. Patients in TA and SA were treated 2 times per week for 4 weeks. Those experiencing a marginal response (10-19 point decrease on the Xerostomia questionnaire (XQ)) received another 4 weeks of the respective treatment. Patients who had no response (increase in XQ score or decrease of < 10 points from baseline), partial response (20 or more point decrease in XQ score from baseline), or complete response (XQ score = 0) did not receive further treatment. Patient outcomes including XQ and FACT-HN were collected at baseline, 4, 8, and 12 weeks; the primary endpoint was XQ at 4 weeks. A sample size of 80 per group (240 total), had 80% power to detect a difference of 10 points between groups, assuming two-sided alpha = 0.013 and 20% attrition. Analysis of covariance adjusted for baseline XQ and Bonferroni corrections for pairwise comparisons. **Results:** 258 from 33 different practices participated. Average age was 65 years, 78% male, and 67% had AJCC stage IV a,b disease. At week 4, there was a group main effect on the XQ (P = 0.02) revealing significant between group differences between TA and WLC (51.1 vs 56.8, P = 0.008), with marginal between group difference between TA and SA (51.1 vs 54.5, P = 0.066) and no difference between SA and WLC (P = 0.36). A similar pattern was seen at week 8 (TA = 48.3, SA = 50.8, WLC = 54.8; only TA vs WLC significant, P = 0.012) and 12 (TA = 48.6, SA = 49.3.8, WLC = 54.6; TA vs WLC, P = 0.02; SA vs WLC, P = 0.04; TA vs SA, P = 0.79). Incidence of clinically significant RIX (XQ scores > 30) followed a similar pattern. The FACT-HN at week 12 revealed statistically and clinically significant group differences for the total score and several subscales between TA vs SA and WLC with no differences between SA and WLC. Completer and mediation analyses will be presented. **Conclusions:** True acupuncture was more effective in treating chronic RIX and improving QOL one or more years after the end of XRT than sham acupuncture or standard oral hygiene. Clinical trial information: NCT02589938. Research Sponsor: U.S. National Institutes of Health.

12005 **Oral Abstract Session**

Evaluating risk for second primary cancers by radiotherapy technique in prostate cancer survivors. *First Author: Kishan Pithadia, NCI - DCEG, Rockville, MD*

Background: Radiotherapy-related adverse effects such as the development of subsequent neoplasms cause significant morbidity among prostate cancer survivors. Advances in radiotherapy techniques, including intensity-modulated radiation therapy (IMRT) and proton beam radiotherapy (PBRT), have aimed to reduce exposure to adjacent healthy tissues to reduce adverse effects. Initial reports based on small sample sizes and limited follow up (through 2011) have suggested reduced risks for subsequent colon and rectal cancers following IMRT compared to 3D conformal radiotherapy (CRT) for prostate cancer patients, but not for subsequent bladder cancer. We sought to extend previous reports with larger sample size and longer follow up. **Methods:** We conducted a retrospective cohort study within the linked database of Surveillance, Epidemiology and End Results (SEER) cancer registries and Medicare claims. The cohort included men diagnosed with first primary non-metastatic prostate cancer at ages 66-84 during 2002-2011; received initial IMRT, PBRT, or CRT; and survived without developing a second primary cancer ≥5 years after diagnosis (follow up through 2016). Cox regression models estimated risks of second primary solid tumors after IMRT and PBRT vs CRT, adjusting for age at prostate cancer diagnosis, tumor grade, race, Charlson comorbidity score, and receipt of initial prostate cancer therapy. **Results:** The cohort (median follow-up = 8.4 years) included 51,020 patients, of whom 19,536 received CRT alone, 29,868 received IMRT without PBRT, and 1,616 received PBRT. Compared to patients who received CRT (n = 1,348, 7.0%), both IMRT (n = 1,289, 4.3%; hazard ratio [HR] = 0.87; 95% confidence interval [CI], 0.80-0.95) and PBRT (n = 83, 5.1%; HR = 0.77; 95% CI 0.62-0.97) showed a decrease in risk of developing any second solid malignancy. In analyses by second cancer type, risks of colon cancer (HR = 0.70; 95%CI, 0.52-0.94) and bladder cancer (HR = 0.79; 95%CI, 0.65-0.97) were significantly lower after IMRT than CRT, whereas no association was observed for anorectal cancers (HR = 1.00; 95%CI, 0.65-1.53). Further investigation by time since prostate cancer diagnosis revealed a time-dependent decrease after IMRT compared to CRT in risk for bladder cancer (HRs = 0.94, 0.87, 0.61 for 5-7.4, 7.5-9.9, and 10+ years respectively) and anorectal cancer (HRs = 1.22, 0.97, 0.78), whereas the opposite trend was observed for colon cancer (HRs = 0.70, 0.68, 1.05). **Conclusions:** In this large cohort with increased follow-up time compared with previous reports, we observed reduced risk of colon and bladder cancer with IMRT overall, as well as time-dependent patterns for bladder and anorectal cancer that were consistent with improved tumor targeting. Further research is needed with larger sample sizes to evaluate long-term effects after PBRT. Our study supports the value of quantifying adverse effects as radiotherapy techniques evolve. Research Sponsor: U.S. National Institutes of Health.

12006 **Oral Abstract Session**

Open-labeled placebo for the treatment of cancer-related-fatigue in patients with advanced cancer: Results of a randomized controlled trial. *First Author: Sriram Yennu, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Despite the high frequency of cancer related fatigue (CRF) in patients with advanced cancer (PAdC), there are no effective pharmacological treatments. Our group previously found that the placebo response was 56% among PAdC participating in CRF trials. There are no clinical trials using open label placebo for CRF in PAdC. The purpose of this study was to determine the effects of open labeled placebo (OLP) compared to waitlist control (WLC) in reducing CRF in PAdC using Functional Assessment of Chronic Illness Therapy-Fatigue subscale (FACIT-F). **Methods:** In this randomized controlled trial, PAdC with fatigue ≥ 4/10 on ESAS were randomized to OLP one tablet twice a day or WLC for seven days (primary end point). After week 1 in patients of both arms received placebo for 3 weeks. Changes in FACIT-F from baseline to Day 8 (primary outcome), and changes after 21 days of placebo in both arms were assessed. Secondary outcomes included quality of life (QOL)[FACT-G], fatigue dimensions(MFSI-SF), depression(CES-D), and Fatigue cluster(ESAS fatigue, pain, and depression). **Results:** 82/90(91%) patients were evaluable. The adherence to placebo [mean%(SD)], was 93.6(18.6), and 88.1(20.2) at Day 8 and Day 29 respectively in OLP arm, and 89.9 (73) at Day 29 in WLC arm. The mean(SD) FACIT-F change at day 8 was 6.6 (7.6) after OLP, 2.1 (9.4) after WLC (p = 0.016). On days 15 and 29, when all patients received OLP, there was significant improvement of CRF but not difference between arms. FACT-G Total Score, FACT-G EWB, ESAS Fatigue, and Fatigue cluster score, all showed significant evidence of reduced CRF in the OLP arm on Day 8 of the study (p = 0.002, 0.030, 0.029, and 0.044, respectively). There was no significant difference in adverse events between the two groups. **Conclusions:** Open labeled placebo was efficacious in reducing CRF, fatigue cluster, and QOL in fatigued advanced cancer patients at the end of one week. The improvement in fatigue was maintained for 4 weeks. Further studies of this intervention are justified. Clinical trial information: NCT03927885. Research Sponsor: None.

12007 **Oral Abstract Session**

Randomized trial of diet and exercise on chemotherapy completion in women with breast cancer: The Lifestyle, Exercise, and Nutrition Early After Diagnosis (LEANer) study. *First Author: Tara B. Sanft, Yale School of Medicine, New Haven, CT*

Background: In observational studies, 25%-55% of women with breast cancer (BC) do not complete chemotherapy as initially prescribed, primarily due to toxicity. Relative dose intensity (RDI) is an integrated measure of chemotherapy dose delays and reductions and is associated with cancer mortality. Physical activity (PA) and diet may reduce treatment toxicity, but less is known about their effect on RDI. We conducted a randomized trial of a diet and PA intervention on RDI (primary endpoint) in women with newly diagnosed BC initiating chemotherapy. **Methods:** 173 women with Stage I-III BC were randomized to usual care (UC, n = 86) or a yearlong, 16-session, in-person or telephone-administered diet and PA intervention (n = 87) delivered by registered dietitians. Dates, doses and reason for dose-adjustments/delays of chemotherapy were abstracted from electronic medical records or obtained from treating oncologists. T-tests and Chi-square tests were used to examine the effect of the intervention vs. UC on RDI. **Results:** Participants were 53±11 years old, had a body mass index of 29.7+6.8 kg/m^2, 51% had stage I BC and 22% were under-represented minorities. 27 different chemotherapy regimens were prescribed. Participants randomized to intervention completed 94% of counseling sessions during chemotherapy and had statistically significant improvements in PA and diet compared to UC. Average continuous RDI was unexpectedly high in both groups, with 93%+14% of prescribed chemotherapy completed (p = 0.92). However, 17% and 15% of intervention and UC participants, respectively, had < 85% RDI (p = 0.70) and more than one-third had at least one toxicity-associated dose reduction and/or delay (> 7 days) for at least one chemotherapy drug (39% intervention and 37% UC, p = 0.80). In posthoc analyses, there was a benefit of the intervention on chemotherapy completion compared to UC in the 74 women receiving neoadjuvant chemotherapy (RDI: 95% intervention vs. 90% UC, p = 0.05). Among intervention women, a dose-response effect was seen with participants who achieved more PA and better diet quality via the Healthy Eating Index (above median) experiencing higher RDI vs participants who were below the median for PA and/or diet quality (97% vs 90% RDI, p = 0.05). **Conclusions:** A primarily telephone-based diet and PA intervention led to improved diet and PA, but did not improve RDI compared to UC. However, a dose-response effect of the intervention was observed with higher PA and diet associated with higher RDI. Future analyses will examine intervention effects on secondary endpoints of endocrine therapy adherence and patient-reported outcomes when all women reach the 1-year timepoint (end of intervention). Further study of diet and PA interventions in patients receiving neoadjuvant chemotherapy are necessary. Clinical trial information: NCT03314688. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

12008 **Oral Abstract Session**

A randomized control trial to determine necessary intervention elements to achieve optimal symptom outcomes for a remote symptom management system. *First Author: Kathi Mooney, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT*

Background: Interventions to improve patient-reported cancer symptom outcomes (PROs) are often multicomponent. In order to scale efficacious interventions, it is important to know if all components are needed to achieve the greatest benefit. We deconstructed the Symptom Care at Home (SCH) monitoring and management system, a multicomponent intervention found to be highly efficacious in reducing symptom burden for patients at home. SCH remotely monitors daily PROs, provides tailored automated self-management coaching based on the severity pattern reported for 11 monitored symptoms and alerts a nurse practitioner (NP) of poorly controlled moderate to severe symptoms. The NP follows up to intensify symptom care utilizing the SCH decision support system based on national guidelines. **Methods:** A 5 group randomized controlled design was utilized with 755 participants assigned to PRO assessment plus: Gp 1, (N = 143) automated self-management coaching, Gp 2, (N = 144) automated self-management coaching plus an activity tracker, Gp 3, (N = 147) NP follow up without decision support, Gp 4, (N = 154) NP follow up utilizing decision support or Gp 5, (N = 167) automated coaching plus NP follow up utilizing decision support- the complete SCH intervention. The primary outcome was maximum likelihood estimation of overall symptom severity over the duration of study participation (62 day median). **Results:** Patients were recruited from sites in Utah and Georgia. The majority of patients were female (60.3%), married (59.9%), 60.7% Caucasian and 34.9% Black, with a mean age of 59.4 years and Stage 3 or 4 cancer (65.7%). Most common diagnoses included breast (17.1%), lung (13.9%), colorectal (12.9%), pancreatic (8.6%) and ovarian (8.4%). Adherence rate for daily symptom reports was 73.8% with no differences between groups. 84.2% of patients reported one or more moderate or severe symptoms- most commonly fatigue (70.1%), pain (64.8%) and trouble sleeping (56.0%). Group 5- the complete SCH intervention had significantly greater symptom relief than any other group (Gp 5 vs Gp 1 or Gp 2 automated coaching both $p < .001$; Gp 5 vs Gp3 NP without decision support $p = .039$; Gp 5 vs Gp 4 NP with decision support $p = .017$). The two NP groups did not differ significantly but were significantly better than either automated coaching groups. The two automated coaching groups did not differ significantly from one another. **Conclusions:** PRO assessment with automated coaching and NP decision-supported follow-up for moderate to severe symptoms achieved better symptom reduction than the individual components. Better symptom relief can be obtained for patients at home through a synergistic, multicomponent intervention that combines a tailored symptom coaching component with notification and follow up by clinicians when symptoms rise to moderate or severe levels- both components contribute to better outcomes. Clinical trial information: NCT02779725. Research Sponsor: U.S. National Institutes of Health.

12009 **Clinical Science Symposium**

Association between an electronic health record (EHR)–embedded frailty index and survival among older adults receiving cancer chemotherapy. *First Author: Heidi D. Klepin, Wake Forest Baptist Comprehensive Cancer Center, Winston Salem, NC*

Background: Innovative strategies to facilitate rapid frailty screening are critically needed to enhance personalized oncology care among vulnerable older patients. An electronic frailty index (eFI) holds promise as a passive measure of frailty. The eFI was initially designed for primary care. The objective of this study was to establish feasibility, estimate prevalence of frailty, and evaluate the predictive value of the eFI for overall survival (OS) among older adults with cancer planned to receive chemotherapy. **Methods:** Consecutive patients (N = 509) aged 65+ with newly diagnosed lung, colorectal or breast cancer treated with chemotherapy were identified from our cancer registry between 2017 and 2020. Calculation of the eFI requires at least two ambulatory visits over a 2-year period and utilizes demographic information, vital signs, smoking status, ICD-10 diagnosis codes, select outpatient laboratory measurements, and functional information (if available from Medicare Annual Wellness Visits) during the 2 years prior to diagnosis. Frailty status is categorized as fit (eFI $\leq$0.10), pre-frail (0.10 < eFI$\leq$0.21), and frail (eFI > 0.21) based on the proportion of deficits present over the total number evaluated (score range 0-1). Non-calculable scores indicate insufficient historical primary care data within two years prior to cancer diagnosis. OS was estimated by eFI category using Kaplan Meier curves and compared using log rank testing. Cox proportional hazards models evaluated the adjusted association between eFI categories and mortality. **Results:** The cohort included 509 adults (median age 72.2 yrs, 55% female, 83.5% white, 13.4% black, 45.8% stage 4) with lung (N = 312), colorectal (N = 111) and breast (N = 86) cancer. Distribution of eFI categories at diagnosis were fit (25.9%), pre-frail (41.1%), frail (17.3 %) and not calculable (15.7%). The proportion of patients categorized as "fit" differed by disease type (19.9% lung, 30.6% colorectal, 41.9% breast, $p < 0.0001$). In univariate analyses, eFI frailty category was associated with OS (median OS for fit, pre-frail, frail and not calculable were > 54, 25, 19 and 10 months respectively, $p < 0.0001$.). Adjusting for age, gender, race, stage, and cancer type, the hazard of death was higher for pre-frail (Hazard Ratio, [HR] 1.7, 95% Confidence Interval [CI] 1.2-2.4), frail (HR 2.3, 95% CI 1.5-3.4) and not calculable eFI categories (HR 2.8, 95% CI 1.8-4.2) compared to fit patients. **Conclusions:** Calculating an EHR embedded eFI at the time of diagnosis among older adults treated with chemotherapy was feasible and identified nearly one-fifth of patients as frail. eFI-defined frailty status was associated with survival, with poorer survival among the most frail supporting eFI validity. The eFI is a promising scalable tool to efficiently conduct frailty screening in oncology clinical practice. Research Sponsor: U.S. National Institutes of Health.

12010 **Clinical Science Symposium**

Preliminary findings of implementing the G8 screening tool in an academic cancer center. *First Author: Kuang-Yi Wen, Thomas Jefferson University, Philadelphia, PA*

Background: Older patients often experience more toxicity from cancer treatments due to their functional age and co-morbidities. The G8 is a geriatric screening tool designed to identify patients who are appropriate for a comprehensive geriatric assessment (CGA) which will inform and optimize oncology therapeutic decision making, reduce toxicities and improve outcomes. Using a nurse-led assessment approach, we have implemented an EMR embedded G8 tool across our cancer center since June 2020. We aim to describe the characteristics of those patients who scored abnormal ($\leq$ 14) on the G8. **Methods:** The demographic and clinical characteristics were collected from the EMR for those who were $\geq$ 65 and have completed the G8 screening tool from June 2020 to Jan 2022. Summary statistics such as means, standard deviations and proportions were reported. Comparisons of various endpoints between dichotomized ($\leq$ 14 vs. > 14) G8 scores were performed using pairwise two-sample t-test, pairwise proportion test, Fisher's exact test and/or Pearson's chi-squared test. Selected stakeholders were elicited for their perspectives on the implementation process. **Results:** 544 patients age $\geq$ 65 completed G8 screening with a mean score of 13.4 ($\pm$ 2.3). The mean age was 75.2 ($\pm$ 7.0), and 55.7% were females and 78.3% were non-Hispanic White. The most frequent cancer type was breast cancer (21.3%), followed by lung/respiratory cancer (18.2%), and GI cancer (15.8%). The percentage of patients appropriate for a CGA (based on an abnormal G8 score) was 59% (n = 332), of which only 10% (n = 31) were referred. A spearman correlation of 0.4 ($p < 0.001$) between G8 scores and age was obtained. A statistically significant association between ECOG and G8 groups was found, but not for any comorbidities. The prevalence of current/former smoking and extreme polypharmacy (> 10) is significantly higher in the G8 abnormal group. Implementation process evaluation found new patients with cancer overwhelmed with information, a lack of patient education and provider engagement, and an unstandardized referral process to CGA, were barriers for CGA referral. **Conclusions:** The G8 is an effective tool identifying patients appropriate for a CGA. An EMR embedded G8 steadily improved the G8 utilization uptake but not referral for CGA at our institution. To further improve awareness, utilization and referral, we are redesigning a hybrid workflow integrating patient-mediated MyChart implementation and nurse navigator engagement. EPIC enhancements are being designed to inform the oncologist of the patient's G8 score, CGA referral status and the final CGA report. Research Sponsor: U.S. National Institutes of Health.

12011 **Clinical Science Symposium**

A decision curve analysis of the clinical usefulness of a two-step frailty assessment strategy in older patients with prostate, breast, colorectal, or lung cancer. *First Author: Adolfo Gonzalez Serrano, Université Paris Est Créteil, INSERM, IMRB, Créteil, Cedex, France*

Background: Geriatric Assessment (GA) is recommended to assess the health status and select the most appropriate cancer treatment in older patients. However, GA is resource- and time-consuming. Thus, a two-step approach using frailty screening has been recommended. We aimed to evaluate the usefulness of frailty screening over GA for identifying unfit individuals who need GA and reducing unnecessary GA in fit individuals in a population of older outpatients with cancer. **Methods:** We analyzed patients age 70 and older with prostate, breast, colorectal, or lung cancer included in the multicenter, prospective ELCAPA cohort study (NCT02884375) between February 2007 and December 2019. All patients had a GA at inclusion. GA was the reference test. We defined unfit patients as those having at least one abnormal score in the following domains: functional status, mobility, comorbidity, cognition, mental health status, nutrition, and polypharmacy. We defined unfit patients according to the G8 and modified G8 scores using the recommended cut-offs ($\leq$ 14 out of 17 points and $\geq$ 6 out of 35 points, respectively). We calculated each screening tool's sensitivity, specificity, and positive and negative predictive values. We used decision curve analysis to estimate the net benefit (the percentage of patients found to be unfit) of screening over GA. We assessed the avoided unnecessary GAs for each screening tool (reducing unnecessary GA in fit patients without decreasing the number of unfit patients undergoing [necessary] GA). We calculated these estimates across different threshold probabilities corresponding to the value of missing an unfit patient compared to exposing a fit patient to an unnecessary GA. A probability of 0.33 indicated that missing an unfit patient was two times worse than referring a fit patient to an unnecessary GA. A probability of 0.50 indicated that missing an unfit patient was the same as exposing a fit patient to an unnecessary GA. **Results:** We analyzed 1,648 patients with prostate (15%), breast (52%), colorectal (22%), or lung cancer (11%). The median age was 81 years, 559 patients (34%) had metastatic disease, and 1,428 patients (87%) were unfit. The sensitivity (95% CI) and specificity were 85% (84-87) and 59% (57-61) for the G8 score, and 86% (84-87) and 60% (58-63) for the modified G8 score. With a threshold probability of 0.33, the net benefit was 0.71 for the G8 score, 0.72 for the modified G8 score, and 0.80 for GA. With a threshold probability of 0.50, the net benefit was 0.68 for the G8 score, 0.69 for the modified G8 score, and 0.73 for GA. We did not observe a reduction in unnecessary GA of screening tools over GA. **Conclusions:** Frailty screening tools showed good diagnostic performances. However, our findings suggest that the GA-for-all strategy provides the higher clinical benefit in older patients with cancer. Research Sponsor: RINC4, EUR-LIVE Graduate School of Research "Life Trajectories and Health Vulnerability".

12012 **Clinical Science Symposium**

Rural-urban disparities in Geriatric Assessment (GA) impairments and mortality among older adults with cancer: Results from the Cancer and Aging Resilience Evaluation (CARE) Registry. *First Author: Mackenzie Fowler, University of Alabama at Birmingham, Birmingham, AL*

Background: Rural-urban disparities persist in cancer incidence and mortality, despite improvement in cancer screening and treatment. Older adults are at increased risk for cancer, represent the majority of cancer cases, and are more likely to reside in rural areas than younger adults are. GAs are recommended in clinical management of older adults with cancer, in part to identify aging-related impairments predictive of adverse outcomes; few studies have explored rural-urban disparities in GA impairments and mortality among older patients with cancer. **Methods:** We included 937 older adults (≥60y) from the CARE registry recently diagnosed with cancer who underwent GA at their first pre-chemotherapy visit to the UAB oncology clinic. Rural-urban status using Rural-Urban Commuting Area (RUCA) codes, classified the cohort by residence in metropolitan, micropolitan, and rural/small town areas. We included self-rated performance status (PS) (≥2 on Eastern Cooperative Oncology Group PS), instrumental activities of daily living (IADL) [≥1 impairment], physical and mental health-related quality of life (HRQoL) [t-score < 40 on PROMIS 10-item Global Health], and overall survival as outcomes. Logistic regression evaluated the association between rural-urban status and each outcome (except overall survival, where we used Cox regression analyses). Micropolitan residence was chosen as the reference category due to similar high risk in both rural and urban areas. **Results:** Median age at study participation was 69.0y (Interquartile range: 64.0-74.0); 12.4% resided in rural, 14.8% in micropolitan and 72.8% in urban areas; 22.5% were diagnosed with colorectal cancer, 19.0% with pancreatic, and 12.4% with hepatobiliary; 74.7% were Stage III/IV. Participants in rural areas were more likely to be white and less educated. After adjustment for age, sex, race, education and cancer type/stage, rural residence was associated with increased odds of impaired PS (OR = 1.93, 95% CI: 1.10-3.40), limitations in IADLs (OR = 1.79, 95% CI: 1.03-3.10), and impaired physical HRQoL (OR = 1.84, 95% CI: 1.05-3.22) compared to micropolitan residence. Urban residence was not significantly associated with any GA outcomes compared to micropolitan residence. Rural residence was associated with higher hazard of death compared to micropolitan residence (HR = 1.88, 95% CI: 1.09-3.24) as well as urban residence (HR = 1.67, 95% CI: 1.13-2.45). **Conclusions:** Among older adults with newly diagnosed cancer, rural residence was associated with impaired PS, limitations in IADLs, impaired physical HRQoL, and reduced overall survival. Implementation of routine GA among older adults in rural areas may aid in early identification and intervention on GA impairments to improve cancer outcomes. Research Sponsor: U.S. National Institutes of Health, Other Government Agency.

12013 **Poster Discussion Session**

Effectiveness of Active Living After Cancer (ALAC), a community-based physical activity program for underserved cancer survivors and their caregivers. *First Author: Scherezade K. Mama, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Physical activity (PA) improves physical functioning and quality of life in cancer survivors, yet few cancer survivors meet recommendations of ≥150 minutes/week of moderate intensity PA. Active Living After Cancer (ALAC) is a community-based program to improve the quality of life of cancer survivors by promoting PA and providing navigation services for survivorship issues. This study evaluates the impact of ALAC on PA, physical functioning, and quality of life in underserved cancer survivors who participated with and without a caregiver. **Methods:** Cancer survivors were recruited through community organizations to participate in ALAC, which consists of 12 weekly sessions, with or without a caregiver. Participants completed assessments of PA (Godin Leisure Time Exercise Questionnaire), physical functioning (30-sec sit-to-stand test), and quality of life (PROMIS physical and mental health) at baseline and follow-up. Paired samples t-tests were used to assess changes in physical activity, physical functioning and quality of life in cancer survivors and general linear models were used to compare changes between cancer survivors who participated with vs. without a caregiver. **Results:** Cancer survivors (N = 539; M age = 61.0±11.3 years) were mostly women (92.4%), Hispanic (57.3%) or non-Hispanic Black (21.5%), and medically underserved (85.3%). Most were breast cancer survivors (69.4%), diagnosed with Stage 0-III cancer (91.5%), and participated in ALAC without a caregiver (N = 463, 85.9%). From baseline to follow-up, the percent of cancer survivors meeting PA recommendations increased from 30.3% to 59.6% (Δ = 27.8 score, t= 16.4, p< .001), and the number of sit-to-stand repetitions in a 30-second period increased from 12.4 to 14.3 (Δ = 2.1, t= 8.6, p< .001). Cancer survivors also reported significant improvements in physical (Δ = 0.6, t= 2.4, p= .015) and mental (Δ = 1.0, t= 3.7, p< .001) health-related quality of life. Cancer survivors who participated with a caregiver reported improvements in physical (Δ = 0.7) and mental (Δ = 1.2) health-related quality of life, whereas those who participated without a caregiver reported slight decreases in physical (Δ = -0.2) and mental (Δ = -0.2) health-related quality of life. However, group x time interactions were not statistically significant [physical $F(1,412)$ = 1.9, p= .168; mental $F(1,412)$ = 49.2, p= .061]. **Conclusions:** Results confirm the effectiveness of ALAC among medically underserved cancer survivors for increasing PA and physical function and suggest that quality of life improvements may be enhanced by participating with a caregiver. Thus, community-based programs should encourage participation with a caregiver when possible to further increase PA, improve cancer survivorship, and reduce cancer health disparities among underserved cancer survivors. Research Sponsor: Cancer Prevention and Research Institute of Texas, U.S. National Institutes of Health.

12014 **Poster Discussion Session**

Association of parental cancer and minor child's unmet economic needs in food, housing, and transportation. *First Author: Zhiyuan Zheng, American Cancer Society, Atlanta, GA*

Background: A cancer diagnosis is associated with substantial economic burden among cancer survivors and their families. Some families make sacrifices that adversely affect food, housing, and transportation to offset high out-of-pocket medical expenses. Cancer survivors with minor children may be particularly vulnerable to financial hardship, even years after diagnosis. However, little is known about the extent to which parental cancer affects minor children's food insecurity, unmet housing needs, and delayed medical care due to transportation barriers. **Methods:** The 2013 to 2018 National Health Interview Survey was used to identify minor children (ages 5-17 years) living in families with a parental cancer history (n = 812, representing 860,488 children) and children without a parental cancer history (n = 22,129, representing about 24.5 million children). Multivariable logistic regressions were used to compare family-level food insecurity, parent's worry about ability to pay monthly bills and housing costs, and delayed medical care for the child because of no transportation between minor children with and without a parental cancer history. All analyses adjusted for child-, parent-, and family-related characteristics, including child's age group, sex, and race/ethnicity; parent's age group, sex, race/ethnicity, health insurance coverage, number of comorbid conditions, and obesity status; family's structure (married/cohabiting parents versus single parent families), highest educational attainment in the family, and family income as a percentage of the federal poverty level. **Results:** About 3.4% of minor children were living in families with a parental cancer history. In adjusted analyses and compared to children whose parents did not report a history of cancer, children of cancer survivors were more likely to live in families that experience shortages in basic economic needs, such as food bought did not last 26.0% (95% confidence intervals[CI]: 22.3%-29.7%) vs 16.7% (95CI: 16.1%-17.3%), inability to afford balanced meals 16.9% (95CI: 13.8%-20.0%) vs 13.3% (95CI: 12.8%-13.8%), worry about paying monthly bills 44.8% (95CI: 40.6%-48.9%) vs 37.9% (95CI: 37.1%-38.7%), and worry about housing costs 35.7% (95CI: 31.9%-39.5%) vs 30.7% (95CI: 30.0%-31.5%). Moreover, children with a parental cancer history were more likely to experience delayed medical care due to lack of transportation than children without a parental cancer history 3.6% (95CI: 2.2%-4.9%) vs 1.6% (95CI: 1.4%-1.9%), all p < .05. **Conclusions:** Parental cancer is associated with greater likelihood of food insecurity, worse housing and other living conditions, and transportation barriers to medical care for minor children. Efforts to identify minor children with a parental cancer history and develop strategies to attenuate their unmet economic needs are warranted. Research Sponsor: None.

12015 **Poster Discussion Session**

Bias reported by family caregivers of healthcare team support when assisting patients with cancer-related decision-making. *First Author: James Nicholas Dionne-Odom, University of Alabama at Birmingham, Birmingham, AL*

Background: Individuals receiving healthcare services often experience differential treatment based on their personal identity characteristics (e.g., age, race, gender), including in the context of shared decision making with clinicians. Yet, little is reported about the extent of bias experienced by family and friend caregivers from the clinician support they and patients receive when making cancer-related decisions. **Methods:** Analysis of data from a nationally-representative U.S. online survey conducted by CancerCare (2/2021-7/2021) of family caregivers of patients with cancer (N = 2,703). Bias experienced in decision support was assessed with the item: "Have you felt that the support you and the person with cancer have received for making cancer-related decisions by your doctor or healthcare team has been negatively affected by any of the following?" Check-all-that-apply response options included: age, race, language, education, political affiliation, body weight, insurance type or lack of insurance, income, religion, sexual orientation, and gender/sex. Chi-square was used to compare demographics and bias; regression analyses were used to identify relationships between bias and caregiver's psychological distress, measured by the GAD-2 and PHQ-2. **Results:** Out of 2,703 cancer caregiver respondents, 47.4% (n = 1,281) reported experiencing at least one type of bias when receiving healthcare team support for making cancer-related decisions, with body weight (24.7%), age (22.2%), and income level (19.9%) being the most commonly endorsed biases. Experiencing one or more types of bias differed by caregivers' age (p < .001; younger > older), gender (p < .001; male and transgender/gender nonconforming > females), race (p < .01; African American/Black and Alaskan Native, American Indian, Native Hawaiian, or Pacific Islander > White and Asian), ethnicity (p < .001; higher for Hispanic/Latino), education (p < .01; higher education > less education), and length of time providing care (p < .01; higher for longer time providing care). After covariate adjustment, the odds of having high anxiety (GAD-2 scores≥3) were 3 times higher for caregivers experiencing ≥1 types of bias compared to those experiencing none (adjusted OR, 3.12; 95% CI, 2.6-3.7); similarly, the odds of having high depression symptoms (PHQ-2 scores≥3) were also 3 times higher (adjusted OR, 3.29; 9% CI, 2.8-3.9). **Conclusions:** Half of caregivers involved in their care recipients' cancer-related decisions report bias in the decision support received from the healthcare team. Furthermore, experiencing bias was associated with increased odds of experiencing psychological distress. The pervasiveness of bias experienced by families involved in patients' cancer-related decisions suggests the priority need to critically evaluate and improve clinician decision support practices. Research Sponsor: None.

12016 **Poster Discussion Session**

Accounting for the high enrollment of African Americans in Winship Cancer Institute's myeloma clinical trials. *First Author: Tekiah McClary, Emory Healthcare, Winship Cancer Institute, Atlanta, GA*

Background: Multiple myeloma (MM) is twice as common in African Americans (AA) as in Whites, yet AA make up only 5% of multiple myeloma (MM) clinical trial participants nationwide. Multiple studies have attempted to identify the reasons why AA are underrepresented in clinical trials and have discovered that sociodemographic factors, a lack of understanding, mistrust of sponsors, and a variety of opportunity barriers all contribute to AA underrepresentation in clinical trials. At one cancer center, African Americans make up 33% of those enrolled in MM clinical trials. To begin to account for this success in enrolling AA in myeloma clinical trials, a survey was designed to determine whether the major barriers to AA clinical trial participation existed at this cancer center. **Methods:** The survey was open to any AA patient who had consented to a clinical trial. The Trust in Medical Research scale (TMR) developed by Hall et al., the Human Connection (THC) scale developed by Mack et al., and the Duke Intrinsic Religiosity Scale (DUREL) were the three main scales used in the survey. Adapted assessment questions from Advani et al were used to assess the importance of side effects in deciding to participate in clinical trials. **Results:** We offered the study to 76 patients and 80% (61/76) participated. The mean TMR score was 15.0 which is significantly greater than the 11.6 score observed for AAs at other institutions ($p < 0.001$). The mean human connection score was 57.7 which is significantly greater than the 54.6 observed in the population of the Mack study, which accrued mostly white participants ($p < 0.001$). The Pearson correlation coefficient between the TMR score and the human connection score is 0.37, indicating a significant positive correlation between human connection scores and trust scores (p-value = 0.002). The average score for the intrinsic religiosity section of the DUREL scale was 13 (score of 15 indicates high religiosity). The average score of importance of side effects was 8.574, significantly higher than the Advani AA response of 6.7 (p-value < 0.001). **Conclusions:** African Americans enrolled in clinical trials at the high enrolling cancer center had higher THC and TMR scale scores than reported nationally, both helping to facilitate trial enrollment. The high intrinsic religiosity score observed suggests that high religiosity had no impact on clinical trial participation, nor did concern about side effects. Furthermore, a high THC score was associated with a high trust score. Since this THC scale assesses whether participants believe their doctors listen carefully, care about them, offer hope, provide clear explanations, and so on, establishing a human connection may be one way to increase AA trust in providers, increase AA clinical trial enrollment and overcome other barriers. Research Sponsor: U.S. National Institutes of Health.

12017 **Poster Discussion Session**

Strategies for implementing an ePRO-based symptom management program (eSyM) across six cancer centers. *First Author: Michael J. Hassett, Dana-Farber Cancer Institute, Boston, MA*

Background: Electronic patient-reported outcome (ePRO)-based symptom management can improve cancer care outcomes. However, implementation is challenging as it requires 1) tremendous technical resources to integrate ePROs into the electronic health record (EHR), 2) substantial buy-in from clinicians and patients, 3) between visit symptom management, and 4) institutional investment to support engagement. **Methods:** The SIMPRO Consortium developed and deployed eSyM, an EHR-integrated ePRO-based symptom management program for medical oncology and surgery patients, at 6 cancer centers between September 2019-March 2022. Site teams document new and changes to implementation strategies monthly using REDCap (data collection is ongoing). Strategies are itemized using the Expert Recommendations for Implementation Change (ERIC) list and mapped to the Consolidated Framework for Implementation Research (CFIR) list of barriers. The SIMPRO Coordinating Center (Dana-Farber) reviews all ERIC-CFIR classifications for consistency. **Results:** To date, 162 distinct strategies have been documented. On average, sites have implemented 23 strategies, 5 preparing for go-live and 18 remaining active beyond go-live. Preparation of clinical staff, training, and routine program evaluation are consistent high impact strategies. Other adaptive strategies have varied across sites, including various approaches to patient and provider engagement. Foundational strategies have been deployed by the coordinating center to support the multi-center initiative. **Conclusions:** Methodical deployment using theory-based implementation strategies may foster adoption of novel health care delivery systems by patients, clinicians, and institutions. Attention to the specific high-value strategies identified by the SIMPRO Consortium could support similar ePRO deployment at other institutions. Research Sponsor: U.S. National Institutes of Health.

Strategy Type	ERIC Category	CFIR Domain (Construct)	Example
High-Impact (Universal)	Develop & implement quality monitoring tools	Process (reflect & evaluate)	Automated reports to capture usage rates
	Conduct educational meetings	Process (engage)	Training sessions with clinicians
	Purposefully reexamine the implementation	Characteristics of individuals (knowledge & beliefs about the intervention)	Meetings with stakeholders
Adaptive (Site-Specific)	Prepare patients to be active participants	Process (execute)	Phone calls, portal messages, and/or in-person approaches to assist patients
Foundational (Consortium-Wide)	Obtain & use patient/consumer feedback	Intervention characteristics (adaptability)	Modify questionnaires & alerts
	Create a learning collaborative	Outer setting (cosmopolitanism)	Monthly consortium meetings
	Assess for readiness; identify facilitators & barriers	Inner setting (implementation climate)	Stakeholder assessments pre and post go-live

12018 **Poster Discussion Session**

Psychological mobile app for patients with acute myeloid leukemia (AML): A randomized clinical trial. *First Author: Areej El-Jawahri, Massachusetts General Hospital, Boston, MA*

Background: Patients with AML experience substantial decline in their quality of life (QOL) and mood during their hospitalization for intensive chemotherapy. Yet, few interventions have been developed to enhance patient-reported outcomes during treatment. **Methods:** We conducted a randomized trial of a psychological mobile app (DREAMLAND) for patients with a new diagnosis of AML receiving intensive chemotherapy at Massachusetts General Hospital and Dana-Farber Cancer Institute. Patients were randomly assigned to DREAMLAND or usual care. DREAMLAND was tailored to the AML trajectory and included four required modules focused on 1) supportive psychotherapy to help patients deal with the initial shock of diagnosis; 2) psychoeducation to manage illness expectations; 3) psychosocial skill-building to promote effective coping; and 4) self-care. The primary endpoint was feasibility defined as at least 60% of eligible patients enrolling, and 60% of those enrolled completing at least 60% of the required modules. We assessed patient QOL (Functional-Assessment-of-Cancer-Therapy-Leukemia), psychological distress (Hospital-Anxiety-and-Depression-Scale [HADS] and Patient-Health-Questionnaire-9 [PHQ-9]), symptom burden (Edmonton-Symptom-Assessment-Scale), and self-efficacy (Cancer Self-Efficacy Scale) at baseline and day +20 post chemotherapy. We used ANCOVA to assess the effect of DREAMLAND on outcomes. **Results:** We enrolled 66.7% (60/90) of eligible patients and 62.1% completed ≥ 75% of intervention modules. At day +20 after intensive chemotherapy, patients randomized to DREAMLAND reported improved QOL (132.06 vs. 110.72, P = 0.001), lower anxiety (3.54 vs. 5.64, P = 0.010) and depression (HADS: 4.76 vs. 6.29, P = 0.121; PHQ-9: 4.62 vs. 8.35, P < 0.001) symptoms, and improved symptom burden (24.89 vs. 40.60, P = 0.007) and self-efficacy (151.84 vs. 135.43, P = 0.004) compared to the usual care group. **Conclusions:** A psychological mobile app for patients newly diagnosed with AML is feasible to integrate during hospitalization for intensive chemotherapy and may improve QOL, mood, symptom burden, and self-efficacy. Clinical trial information: NCT03372291. Research Sponsor: National Palliative Care Research Center.

12019 **Poster Discussion Session**

Efficacy of a password-protected, pill-dispensing device with mail return capacity to enhance disposal of unused opioids after cancer surgery. *First Author: Jacob C. Cogan, Columbia University Medical Center, New York, NY*

Background: Opioid misuse is a public health crisis. Initial opioid exposures often occur post-operatively, and 10% of opioid-naïve patients who undergo cancer surgery subsequently become long-term opioid users. It has been shown that 70% of opioids prescribed post-operatively go unused, but only 9% of unused pills are disposed of appropriately, which increases the risk of unintended use. We evaluated the impact of an inexpensive, password-protected pill-dispensing device with mail return capacity on disposal of unused pills after cancer surgery. **Methods:** We conducted a prospective, proof-of-concept pilot study among adult patients scheduled for major cancer-related surgery. Enrolled patients received opioid prescriptions in a pill-dispensing device (Addinex) from a specialty pharmacy. The mechanical device linked to a smartphone app, which provided passwords on a prescriber-defined schedule. Patients were able to enter unique passwords into the device to receive their pills if the prescribed time had elapsed. The smartphone app provided clinical guidance based on patient-reported pain levels, and suggested tapering strategies. Patients were instructed to return the device in a DEA-approved mailer when opioid use was no longer required for acute pain control. Unused pills were destroyed upon receipt. The primary objective was to determine the feasibility of device return, defined as > 50% within 6 weeks. We also explored total pill use and return, patterns of device use and patient satisfaction. **Results:** We enrolled 30 patients between October 2020 and December 2021. The median age was 46 (range 29–72). Surgical procedures included abdominal hysterectomy (13), mastectomy and reconstruction (10), and soft tissue tumor resections (7). Overall, the majority of participants (n = 24, 80%) returned the device, and more than half (n = 17, 57%) returned the device within 6 weeks of surgery. There were 19 patients who obtained opioids from the device. Among these patients, the majority were satisfied with the device (n = 14, 74%); felt the benefits of the device justified the added steps involved (n = 14, 74%); and would sign up to receive opioids in the device again (n = 13, 68%). The other 11 patients used no opioids. None of these non-users reported any opioid requirements for pain control, and all but one (n = 10, 91%) returned the device and unused pills. In total, 567 opioids were prescribed, and 170 (30%) were used. Of the 397 excess pills, 332 (84% of unused pills, 59% of all pills prescribed) were returned by mail. **Conclusions:** We found that use of an inexpensive pill-dispensing device with mail return capacity was a feasible and effective strategy to enhance disposal of unused post-operative opioids. Interestingly, a substantial number of prescribed pills were unused. This system also improves confidence with indicated opioid use while reducing diversion. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

12020 **Poster Discussion Session**

PEARL: A randomised phase 3 trial of palliative care early in advanced lung cancers (ALTG/TOGA 13/008). *First Author: Linda R. Mileshkin, Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia*

Background: Early referral to palliative care was associated with improved health-related quality of life (HRQL) and overall survival (OS) in a US phase 3 trial in lung cancer patients (pts). International studies in mixed cancer types have reported conflicting results. PEARL aimed to determine whether early referral to palliative care would improve HRQL, OS, and resource use in Australian pts with recently diagnosed, advanced thoracic cancers. **Methods:** Eligible participants (pts) in this unblinded, multi-centre, randomised, phase 3 trial had advanced thoracic cancers diagnosed within 60 days, and the ability to complete patient-rated outcome measures (PROMS). Pts were randomly allocated to early referral to palliative care (ER) or referral at clinician's discretion (DR). All pts received standard oncological care. PROMS were completed at baseline, every 3-4 weeks for 6 months, then 6-8 weekly. The primary objective was to determine the frequency of sustained, substantial improvements in HRQL, defined as a 5-point improvement in the FACT-L Trial Outcome Index (TOI) maintained for at least 2 consecutive assessments. Secondary outcomes included OS, documentation of advanced care plan (ACP), PROM scores at 12 weeks, anxiety/depression (PROMIS-ED), lung cancer symptoms (FACT-L), global HRQL (ICECAP-SCM), carer-satisfaction and burden, and understanding of illness and prognosis. The accrual target of 200 gave 80% power (alpha 0.05) to detect an absolute improvement of 20% in the proportion of pts achieving the primary endpoint. **Results:** 113 pts and 78 carers were recruited when the trial closed for slow accrual. Pt characteristics were well balanced: 88 (75%) had NSCLC, 18 (16%) small cell and 7 (6%) mesothelioma. Median age was 69 (IQR 62-74), 63 (56%) were male; systemic anti-cancer therapy ongoing or planned in 88 (78%). Median follow-up was 30 months. First consultations with a palliative care specialist within 60 days of diagnosis occurred in more pts assigned ER vs DR (57% vs 3.5%). Sustained substantial improvements in FACT-L TOI were reported by similar numbers of pts assigned ER vs DR: 33% vs 32%, p = 0.9. OS was similar among those assigned ER versus DR (median 12 vs 18.4 months, p = 0.11). A similar % had a written advanced care plan at death: 15/40 (39%) vs 15/33 (47%). We found no important differences between arms in global HRQL (ICECAP-SCM), depression/anxiety (PROMIS-ED), lung cancer symptoms (FACT-L), carer satisfaction (FAMCARE-2), carer burden (CRA), or understanding of illness by carers or pts. **Conclusions:** Early referral to palliative care, compared with discretionary referral, did not improve important outcomes for Australian thoracic cancer pts or carers. Our findings suggest that the palliative care needs of such pts were addressed equally well by delayed referral when clinically indicated, resulting in reduced burden for resource-limited specialist palliative services. Clinical trial information: ACTRN12617000166370. Research Sponsor: Cancer Australia 1101882_Mileshkin.

12021 **Poster Discussion Session**

Bereavement practices of gynecologic oncologists: Physician and care team practices compared to caregiver needs. *First Author: Lauren E. Harrison, University of Connecticut Health Center, Farmington, CT*

Background: Gynecologic cancers account for over 34,000 deaths in the United States annually. Family-centered care is beneficial to the family unit and patient throughout the illness course. Research is lacking regarding how physicians should approach family members or other caregivers after a patient dies. We aimed to assess how gynecologic oncologists are currently practicing and compare that to family members' needs during the bereavement period. **Methods:** We devised a set of paired surveys that were distributed to the Society for Gynecologic Oncology and to patient families. Families were recruited using social media, publicizing in local organizations, and advertising in University of Connecticut campus-wide emails. Likert-scale style questions with responses ranging from "1" to "10" were used to assess opinions on aspects of bereavement care and reported as means. Differences in means were assessed using ANOVA and T-tests and considered to be statistically significant if the P-value was < 0.05. **Results:** We received completed surveys from 129 physicians and 17 caregivers from different families. 48% of physicians reported contacting patient families, and, similarly, 47% of family members reported receiving contact from physicians. Physicians had a mean 6.21/10 confidence level (where 10 is maximum confidence) in providing bereavement care, while families reported 5.76/10 confidence in their physician's ability to provide bereavement support ($P = 0.493$). Factors that influenced physicians confidence in providing bereavement support were undergoing formal training in bereavement (6.84/10 vs 5.14/10 for physicians who had not been trained, $P < 0.001$) and being in practice for more than 11 years (5.65/10 for ≤10 years in practice, 7.05 for ≥11 years, P = 0.001). Physicians who contacted patients personally had a higher confidence level (6.98/10) in providing bereavement support compared with those who did not contact families (5.51/10, $P < 0.001$). Family members were nearly unanimous in reporting a desire for physicians to contact them personally (16/17), and stated that a phone call (56%) or a sympathy card (38%) were their preferred methods of contact. **Conclusions:** Our study suggests that although families appreciate contact from physicians after their loss, physicians do not have a high level of confidence in providing this support. Physicians who undergo bereavement training and who reached out after patients had died have higher confidence levels in interacting with family members. Based on these results, formal bereavement training should be incorporated into gynecologic oncology fellowships in order to increase the comfort levels and likelihood of gynecologic oncologists reaching out to families after a patient has died. Research Sponsor: None.

12022 **Poster Discussion Session**

Oral minoxidil for the treatment of late alopecia in cancer survivors. *First Author: Alyce Mei-Shiuan Kuo, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Late alopecia is defined as incomplete hair regrowth > 6 months following cytotoxic chemotherapy or from initiation of endocrine therapy. It has been reported in up to 25-30% of cancer survivors and is associated with decreased quality of life and reduced dose intensity of cancer therapies. Minoxidil is an aminopyridine potassium channel opener, resulting in vasodilation and premature entry of resting hair follicles into the anagen (growth) phase and increase in hair follicle size. This study aims to assess clinical outcomes and adverse events of oral minoxidil for the treatment of cancer therapy-related late alopecia. **Methods:** We retrospectively assessed all women with late alopecia treated with oral minoxidil (1.25 mg daily) evaluated at an oncodermatology referral program between 1/2018-5/2021. Outcomes were assessed by standardized photography (4 views) and trichoscopy (HairMetrix, Canfield Scientific, Inc.). Trichoscopy recorded hair density (hair count/cm^2) and hair thickness (shaft diameter) at uniform frontal and occipital target areas (12 and 36 cm midline from the glabella, respectively). Adverse events were recorded and graded using CTCAE v5.0. Descriptive statistics were used to summarize the patient demographics and clinical characteristics. Changes in trichoscopy measurements from baseline to follow-up were estimated using paired t-tests. **Results:** Two hundred and sixteen patients (mean age 57.8±13.7) were included for analysis. Thirty-one (14%) received chemotherapy alone, 65 (30%) endocrine monotherapy, and 120 (56%) chemotherapy followed by endocrine therapy. The majority of patients (n = 170, 79.1%) had a history of breast cancer. Standardized photography assessments (n = 119) after a median of 105 days (IQR = 70) on oral minoxidil revealed clinical improvement in 88 (74%). Trichoscopy assessments (n = 42) after a median of 91 days (IQR = 126) demonstrated increased frontal hair density (124.2 vs 153.2 hairs/cm^2, p = 0.008) and occipital hair density (100.3 vs 123.5 hairs/cm^2, p = 0.004). There was no statistically significant difference in average frontal or occipital hair thickness (69.3 vs 67.3 μm, p = 0.22, and 70.3 vs 69.9 μm, p = 0.84, respectively). No patients reported discontinuation of oral minoxidil due to adverse effects. **Conclusions:** Oral minoxidil may benefit both frontal and occipital late alopecia in cancer survivors treated with cytotoxic and/or endocrine therapy. This regimen was well tolerated by patients. Prospective, controlled studies are needed to confirm these observations. Research Sponsor: None.

12023 **Poster Discussion Session**

Vitamin D insufficiency as a peripheral neuropathy risk factor in white and black patients in SWOG 0221. *First Author: Ciao-Sin Chelsea Chen, University of Michigan, Ann Arbor, MI*

Background: Peripheral neuropathy (PN) is a treatment-limiting toxicity of paclitaxel. Black patients have higher rates of PN and vitamin D insufficiency, and our prior work suggests vitamin D insufficiency increases risk of paclitaxel-induced PN. The objective of this study was to validate that patients with vitamin D insufficiency have higher risk of paclitaxel-induced PN and investigate whether this explains racial disparities in PN risk. **Methods:** This retrospective validation study was conducted in the phase III SWOG 0221 (NCT00070564) trial comparing paclitaxel-containing chemotherapy regimens for early-stage breast cancer. Pre-treatment 25-hydroxy-vitamin D was quantified in cryopreserved serum. Males and patients who received less than a third of the paclitaxel treatment were excluded. The association between vitamin D insufficiency (≤20 ng/mL) and grade 3+ sensory PN was tested via logistic regression and then adjusted for self-reported race, age, paclitaxel schedule (QW vs Q2W), and body mass index. **Results:** Of the 1,116 female patients in the analysis, 169 (15.1%) experienced PN and 376 (33.7%) had vitamin D insufficiency. Vitamin D insufficiency was associated with higher PN risk (19.4% vs 13.0%, OR = 1.62, p = 0.005, Data Table). The association was borderline significant (OR = 1.44, p = 0.056) after adjustment for black race (OR = 2.41, p = 0.001), paclitaxel schedule (OR = 2.22, p < 0.001), and age (OR = 1.03, p = 0.005). Compared with white patients (n = 943), black patients (n = 99) had more prevalent vitamin D insufficiency (77.8% vs 28.6%, OR = 8.72, p < 0.001) and increased PN risk (29.3% vs 13.5%, OR = 2.66, p < 0.001); adjusting for vitamin D insufficiency decreased but did not eliminate the higher PN risk in black patients (OR = 2.23, p = 0.002). **Conclusions:** Vitamin D insufficiency increases risk of paclitaxel-induced PN and partially explains the higher risk of PN in black patients. Prospective trials are needed to test whether vitamin D supplementation lessens PN and reduces disparities in treatment outcomes. Research Sponsor: American Cancer Society, University of Michigan Rogel Cancer Center.

	Univariate Odds Ratio [95% Confidence Interval]	p-value	Multivariable Odds Ratio [95% Confidence Interval]	p-value
Vitamin D – Insufficient (n = 376) vs Sufficient (n = 740)	1.62 [1.16, 2.25]	**0.005**	1.44 [0.99, 2.08]	0.056
Race - Black (n = 99) vs White (n = 943)	2.66 [1.64, 4.23]	**< 0.001**	2.41 [1.43, 4.02]	**0.001**
Race - Asian (n = 32) vs White (n = 943)	1.48 [0.54, 3.45]	0.395	1.60 [0.58, 3.79]	0.322
Race - Other (n = 42) vs White (n = 943)	1.29 [0.51, 2.79]	0.555	1.34 [0.53, 2.95]	0.499
Paclitaxel Schedule - Q2W (n = 530) vs QW (n = 586)	2.20 [1.58, 3.11]	**< 0.001**	2.22 [1.58, 3.15]	**< 0.001**
Age, per year	1.02 [1.00, 1.04]	**0.017**	1.03 [1.01, 1.04]	**0.005**
Body Mass Index, per kg/m^2	1.01 [0.99, 1.03]	0.311	1.00 [0.98, 1.02]	0.978

12024 **Poster Discussion Session**

Differences in clinician and patient assessment of baseline neuropathy in patients receiving taxane-based chemotherapy enrolled to SWOG S1714 (NCT# 03939481). *First Author: Meghna S. Trivedi, Columbia University Irving Medical Center, New York, NY*

Background: Chemotherapy induced peripheral neuropathy (CIPN) can lead to treatment dose reduction or discontinuation and significantly impact quality of life and functional status. Clinical trials have historically excluded patients with pre-existing neuropathy. Thus, it is unknown how many patients start treatment with baseline neuropathy as well as the impact on the trajectory of neuropathy symptoms. There are several patient- and clinician-based methods to assess CIPN; however, there is no consensus on the best method to evaluate CIPN or whether clinician versus patient assessment differs at baseline. **Methods:** In SWOG 1714, we enrolled patients ≥ 18 years of age with Stage I-III non-small cell lung, breast, or ovarian/fallopian tube/peritoneal cancer starting treatment with a taxane. Patients with baseline neuropathy were eligible. Neuropathy was assessed with patient-reported outcomes (PROs), including the European Organization for Research and Treatment of Cancer QLQ-CIPN20 (CIPN-20) and the PRO version of the Common Terminology criteria for Adverse Events (PRO-CTCAE) for severity of and interference caused by numbness and tingling, and the clinician-assessed National Cancer Institute (NCI)-CTCAE Grading Scale Version 5.0 for nervous system disorders. **Results:** Of 1336 patients enrolled on S1714, 1322 (99.0%) were eligible. The median age was 55.7 years (range 23.9-85.5) and 98.9% were female. The cohort was racially/ethnically diverse with 73.6% White, 11.3% Black, 4.6% Asian, and 10.5% Other and 10.5% Hispanic/Latino. Most of the patients enrolled had breast cancer (91%) and 67 patients (5.1%) reported having a neurological condition. Paclitaxel was administered to 60.2% and docetaxel to 39.8% and 98.5% planned to start treatment with full dose of taxane. Based on clinician assessment with NCI-CTCAE, 87.6% of patients at baseline had Grade 0 peripheral sensory neuropathy, 10.2% Grade 1, 2.0% Grade 2, and 0.2% Grade 3. The mean baseline CIPN-20 sensory subscore (range 0-100, higher number indicating greater severity) was 5.68 (standard deviation 10.41). Using the PRO-CTCAE for severity of numbness and tingling, 75.4% reported no baseline symptoms, 18.2% "mild", 4.8% "moderate", 1.1% "severe", and 0.5% "very severe" symptoms. With respect to interference of numbness and tingling with daily activities, 88.5% reported "not at all", 8.3% "a little bit", 2.0% "somewhat", 0.9% "quite a bit", and 0.3% "very much". **Conclusions:** In this diverse cohort of predominantly breast cancer patients, there was limited evidence of significant pre-existing neuropathy. Clinician assessments of neuropathy may underestimate the symptoms of patients, emphasizing the importance of PROs in evaluating symptoms, particularly when baseline symptom is an exclusion criterion for clinical trials. Funding: NIH/NCI/NCORP grant UG1CA189974 Research Sponsor: U.S. National Institutes of Health.

12025 **Poster Session**

Influence of decision support persons on breast cancer treatment decisions among Latinas. *First Author: Krystal A Morales, University of Michigan, Ann Arbor, MI*

Background: Prior studies suggest that decision support persons (DSPs) involvement in breast cancer promotes greater deliberation and decision quality. Despite having the highest level of involvement, Latinx DSPs report the lowest satisfaction with their involvement. The reasons for this remain unknown. We examined the treatment decision-making experiences of Latinx DSPs, their influence on treatment deliberation, subjective decision quality (SDQ), and treatment received. **Methods:** Women with newly diagnosed early-stage breast cancer as reported to the Surveillance, Epidemiology, and End Results (SEER) registries of Georgia and Los Angeles County in 2014-2015 were surveyed. Participants identified the DSPs who played a key role in treatment decisions, who were also surveyed. We examined: (1) bivariate associations of DSP characteristics (e.g type, age, race/ethnicity, education, acculturation level) with DSP-reported level of engagement (informed about decisions, involvement (extent and satisfaction), and aware of patient preferences), (2) DSP engagement with patient-reported SDQ and treatment deliberation using multivariable linear regression with standardized scales (3), and treatment received by DSPs preferred treatment. **Results:** 2502 patients (68%) and 1203 eligible DSPs (70%) responded, resulting in 1,173 dyads, 292 where the patient identified as Latina, and 881 as non-Latina. Among Latina dyads, 78%, 17%, and 5% DSPs identified as Latinx, White, and Asian/Black/Other, respectively. Latinx DSPs within Latina/Latinx dyads were younger, had lower educational attainment and acculturation when compared to other dyads. The proportion of married/partnered status was not different across dyads, but the key DSP for the Latina-Latinx dyads was more often a daughter (37%), over a husband/partner (21%), compared to the other dyads. Latinx DSPs reported being more informed (adjusted mean 4.26, p = 0.058) compared to the other dyads, and being more informed was positively associated with higher patient SDQ (adjusted mean difference 0.176, p = 0.034), despite no difference in treatment deliberation. Overall, Latinx DSP had a higher preference for mastectomy, especially with reconstruction when compared to non-Latinx (40% vs 28%). Overall, 27% of Latinas (vs 13% non-Latina) underwent lumpectomy despite their DSP's preference for mastectomy. **Conclusions:** These findings reveal that the key DSP for many married Latinas is often a daughter over spouse/partner. Our results suggest that including daughter/DSPs in treatment decisions and tailoring strategies to meet their information needs may positively impact Latina SDQ. Potential areas of improvement include surgical options preferences, where notable discrepancy was seen between Latinas and non-Latinas. Awareness of these differences can minimize treatment regret, improve decision quality, and ultimately outcomes in Latinas. Research Sponsor: National Cancer Institute and American Cancer Society.

12026 **Poster Session**

Patients with cancer symptom and physical function reporting by caregivers as predictors of adverse clinical outcomes. *First Author: Elad Neeman, Hematology/Oncology Fellowship Program, Kaiser Permanente, San Francisco, CA*

Background: Informal caregivers are essential partners in the delivery of cancer care, and often can accurately identify and report symptoms and physical function of the patients they care for. We assessed whether such reporting by caregivers is predictive of adverse patient outcomes. **Methods:** In this prospective study, adult solid cancer patients on active intravenous systemic therapies and their informal caregivers were recruited from 18 Kaiser Permanente Northern California cancer centers. Using a study mobile app (TOGETHERCare), caregivers completed weekly surveys for 4 weeks, which were based on normalized NIH-PROMIS scores to report patients' physical function and PRO-CTCAE to report patients' symptoms. Patients' adverse clinical outcomes were abstracted from the medical record and included: emergency department (ED) visits or hospitalizations, grade 3-4 adverse events (AEs), and treatment delays, up to 1 month following the 4-week study period, as well as mortality and hospice referrals up to 6 months following the study period. Simple univariate logistic regressions were used to correlate caregiver reports (either at baseline or most proximal preceding an adverse outcome) with mortality and hospice referrals, and quasi-Poisson regressions were used for the other adverse outcome measures. **Results:** Fifty-four patient-caregiver dyads were enrolled, and 52 were included in this analysis. A third of patients had breast cancer and almost 75% had stage 3 or 4 disease. Caregivers predominantly identified as male (61.5%), spouse/partner (76.9%), and non-Hispanic White (63.5%). At least one adverse outcome was experienced by 36.5% of the patients. Caregiver-reported PRO-CTCAE consistently predicted ED/hospitalizations and mortality, and caregiver-reported PROMIS scores predicted hospice referrals (see Table). **Conclusions:** The results suggest that caregiver reporting of patients' symptoms and physical function could help provide early predictions of adverse patient outcomes. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

Association of survey measures and adverse outcomes.

Survey measure/outcome [RR, 95% CI, *P*Value]	Hospitalizations and ED Visits (N=7)	AEs and dose reductions (N=8)	Days of Treatment Delays (N=10)	Hospice Referral (N=8)	Died (N=7)
Count of severe/v. severe PRO-CTCAE at Baseline	1.5, 1.1-1.9, 0.003	1.3, 1.0-1.7, 0.051	1.3, 0.9-1.7, 0.176	1.4, 0.9-2.0, 0.123	1.5, 1.0-2.2, 0.070
Count of severe/v. severe PRO-CTCAE - Survey prior to event or final survey if no event	1.4, 1.2-1.7, 0.001	1.3, 1.0-1.6, 0.072	1.2, 0.9-1.5, 0.191	1.3, 0.9-1.8, 0.142	1.5, 1.0-2.1, 0.037
Normalized PROMIS score at Baseline	0.9, 0.8-1.0, 0.228	1.0, 0.9-1.1, 0.970	0.9, 0.8-1.0, 0.218	0.8, 0.6-0.9, 0.016	0.9, 0.8-1.0, 0.116
Normalized PROMIS score - Survey prior to event or final survey if no event	1.0, 0.9-1.0, 0.306	1.0, 0.9-1.1, 0.996	1.0, 0.9-1.1, 0.530	0.9, 0.8-1.0, 0.085	0.9, 0.9-1.0, 0.186

12027 **Poster Session**

Financial stress and burden among caregivers of cancer survivors in the United States. *First Author: Nicholas Theodoropoulos, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: United States caregivers perform annual services equating to nearly $500 billion, with three-quarters of family caregivers utilizing personal funds. Nearly a third of all caregivers of cancer survivors report using all or most of their savings to contribute to the cost of cancer care. Prior studies indicate the duration of caregiving is associated with an increase in caregiving burden. This study aims to further describe the financial stress and burden in relation to caregiving duration for people who provide care to cancer survivors. **Methods:** A retrospective cross-sectional study was conducted using the 2015 and 2020 National Alliance for Caregiving and American Association of Retired Persons survey data. Multivariable logistic regressions were used to examine differences in reporting financial stress between various racial/ethnic groups while adjusting for education, income, and employment. **Results:** A total of 2,998 caregivers were included, where 208 of them were caring for cancer patients. Caregivers of cancer patients who provided care > 21 hours/week were statistically more likely to be less educated, lower income, single, and unemployed compared to those who provided < 21 hours/week. Caregiving for > 21 hours/week compared to < 21 hours/week is associated with being more likely to report communicating with healthcare professionals about a recipient's care (87.7% vs. 75.9%; p = 0.038). It is borderline significant that caregivers who provided care for > 21 hours/week were more likely to advocate for recipients (68.7% vs. 56.8%; p = 0.086) and monitor condition severity to adjust care needs (84.9% vs. 70.7%; p = 0.100). After controlling for confounders (education, income, and employment), Non-Hispanic Black (odds ratio (OR) = 1.30; 95% CI: 1.02-1.65), Hispanic (OR = 1.39; 95% CI: 1.02-1.89), and Asian (OR = 1.51; 95% CI: 1.02-2.24) cancer caregivers had increased odds of reporting increased financial stress compared to Non-Hispanic White caregivers. **Conclusions:** Longer duration of caregiving to cancer survivors is associated with a greater burden for caregivers. Financial stress disparities related to caregiving exist between racial/ethnic groups, with non-white caregivers being more likely to report increased financial strain. Special financial programs are needed to assist caregivers of cancer survivors, a growing but understudied population. Research Sponsor: None.

12028 **Poster Session**

Medical assistance in dying (MAiD) in patients with cancer. *First Author: Sara Moore, The Ottawa Hospital Cancer Centre, Ottawa, ON, Canada*

Background: Medical assistance in dying (MAiD) was legalized in Canada in 2016. Cancer accounts for 60-70% of MAiD cases, though little is known about the demographic profile, cancer diagnoses, and treatments received in patients with cancer who pursue MAiD. We reviewed all patients with cancer who underwent MAiD through a large regional MAiD program, in order to better understand this population and identify gaps in the current system of care delivery. **Methods:** All patients with cancer who received MAiD through the Champlain Regional MAiD Network (CRMN) from June 1 2016 – November 30 2020 were reviewed. The CRMN provides the majority of MAiD services covering a population of 1.3 million in Eastern Ontario. Baseline demographic factors, diagnostic information, and treatment details were collected by retrospective review. The primary endpoint was the proportion of patients with an oncology consultation prior to MAiD. **Results:** During the study period, 255 patients with cancer underwent MAiD. Baseline characteristics included: median age at death 71 (range 31-100), 51% male, 56% married/common-law. The most prevalent solid tumors were gastrointestinal [GI] (n = 77, 30%), lung (n = 47, 18%), and genitourinary [GU] (n = 35, 14%). Most patients (n = 201, 79%) had metastatic disease at the time of MAiD. Of those without metastatic disease at time of death, common tumor sites included central nervous system (42%) and head and neck (23%). The majority of patients (n = 229, 89%) had seen an oncology specialist prior to MAiD; 226 (88%) had seen a systemic oncologist (medical, hematologic, or gynecologic oncologist), and 189 (69%) a radiation oncologist. Seventy-three percent of patients were followed by a systemic oncologist within 90 days of MAiD, and 44% within 30 days of MAiD. At least one line of systemic therapy was received by 159 (62%) patients, 138 (54%) received radiotherapy, and 61 (24%) best supportive care alone. Median time from last systemic therapy to MAiD was 85 days, and from last radiation therapy to MAiD was 137 days. Palliative care assessed at least 213 patients (84% [8% unknown]). Common reasons for pursuing MAiD included disease-related symptoms (33%), fear of future suffering or disability (19%), and ability to control the time and manner of death (17%). Among 26 patients who had not seen an oncologist, median age was 84 (range 61-100), 77% male, 42% GI primary / 19% GU / 15% lung. Most had seen a palliative care specialist (n = 23, 88%), and in the remaining 3 patients palliative care involvement was unknown. **Conclusions:** MAiD is a relatively new option for patients with cancer in Canada. The vast majority of patients with cancer who pursue MAiD are diagnosed with advanced/incurable disease, and most have met with an oncology specialist. As cancer treatments become more effective and more tolerable, collaboration between oncologists and MAiD providers is required to ensure patients are well informed of treatment options prior to MAiD. Research Sponsor: None.

12029 **Poster Session**

Prognostic impact of systemic anti-cancer therapy on patients with advanced cancer at end of life: Analysis of a multicenter prospective cohort study using propensity score methods. *First Author: Shuji Hiramoto, Peace Home Care Clinic, Otsu, Japan*

Background: Prognosis is said to worsen when systemic anti-cancer therapy (SACT) is administered until a patient's end of life (EOL) and professional palliative care is delayed. However, the prognostic impact of SACT at EOL is unclear. **Methods:** In this preplanned secondary analysis of a multicenter, prospective East Asian cross-cultural collaborative cohort study, consecutive patients with advanced cancer admitted to palliative care units between January and December 2017 were divided into four groups: patients who had and had not received SACT (SACT vs. non-SACT) and patients whose last administration of SACT was before or within 1 month of study enrolment (non-1M SACT vs. 1M SACT). The primary endpoint was difference in survival time from a palliative performance scale (PPS) of < 20 to death between the SACT and non-SACT groups, and the 1M SACT and non-1M SACT groups. The analysis was adjusted for age; sex; primary cancer site; metastatic site; comorbidity (Charlson comorbidity index); and history of radiotherapy, smoking, and psychiatric disorders. Weighting for inverse probability of treatment was applied. A secondary endpoint was to identify EOL symptom and care factors prognostic for survival time using a Cox proportional hazards model. **Results:** The 1396 study patients (712 men, 684 women; median age: 73 years) came from 21 institutions throughout Japan. Primary tumor sites were upper gastrointestinal (471 patients), lower gastrointestinal (193 patients), lung (241 patients), breast (93 patients), urologic (101 patients), gynecologic (82 patients), head and neck (56 patients), central nervous system (25 patients), and hematologic (39 patients). Metastatic sites were liver (554 patients), lung (522 patients), bone (373 patients), and brain (199 patients). The SACT, non-SACT, 1M SACT, and non-1M SACT groups consisted of 853, 539, 126, and 1270 patients, respectively. Survival time was significantly shorter in the SACT group (6.83 days, p = 0.03) than in the non-SACT group (9.01 days). No significant difference between the 1M SACT group (7.57 days) and the non-1M SACT group (7.36 days) was evident. Prognostic factors were use of opioids (HR 1.289), antipsychotics (HR 0.787), and anxiolytics (HR 0.867); infusion of more than 1 L daily (HR 0.727); and apnea (HR 0.874), dyspnea (HR 1.874), nausea (HR 0.612), fatigue (HR 1.284), and ascites (HR 1.236). **Conclusions:** Prognosis was shorter for patients with a history of SACT than for those without a history of SACT at EOL. However, SACT at EOL was not a prognostic factor. This information is useful in advance care planning for selecting and explaining treatment at EOL to patients and their families. Research Sponsor: Hospice Palliative Care Japan.

12030 **Poster Session**

The impact of primary palliative care on advance care planning in advanced cancer. *First Author: Michael Cohen, UPMC Cancer Center - Magee-Womens Hospital, Pittsburgh, PA*

Background: Palliative care specialists are experts in conducting advance care planning (ACP), but are a limited resource. We sought to determine the impact of a nurse-led primary palliative care intervention on ACP completion among patients with advanced cancer. **Methods:** We performed a secondary analysis of a cluster randomized controlled trial looking at the impact of nurse-based primary palliative care at community cancer centers. In the parent trial, patients with advanced cancer received either monthly primary palliative care visits with trained nurses within their cancer center or usual care. Nurses in the intervention arm received special training in addressing symptom management and ACP. ACP uptake was assessed at enrollment and 3 months later via validated questionnaire in the forms of an end-of-life conversation (EOLC) with one's oncologist or completion of an advance directive (AD). The present analyses were restricted to patients without ACP at baseline. Multivariable logistic regression tested differences in ACP uptake by treatment arm when adjusting for age, religious importance, education, time with current oncologist, and ECOG. **Results:** Of 672 patients enrolled, 182/336 in the intervention arm and 196/336 in usual care lacked an EOLC at baseline and completed three-month assessments. Of those, 82/182 (45.1%) in the intervention arm and 29/196 (14.8%) in the usual care arm reported having an EOLC at three months (Table). Similarly, 111/336 in the intervention arm and 105/336 in usual care lacked an AD at baseline and completed the three-month assessments. Of those, 48/111 (43.2%) in the intervention arm and 19/105 (18.1%) in usual care completed an AD over the study period (Table). For both types of ACP, the treatment effect suggested increased uptake of new ACP in the intervention arm after controlling for variables known to be associated with ACP (Table) **Conclusions:** Nurse-led primary palliative care increased the uptake of ACP among patients with advanced cancer. Training oncology nurses embedded within community cancer centers may represent a feasible mechanism to improve access to primary palliative care and uptake of advance care planning. Clinical trial information: NCT02712229. Research Sponsor: U.S. National Institutes of Health, Other Government Agency.

Odds of ACP with an oncology nurse-led primary palliative care intervention.

EOL Conversation	Odds Ratio	95% CI	P-Value
Unadjusted	4.72	(2.89, 7.71)	<0.001
Adjusted	5.28	(3.10, 8.97)	<0.001
Advance Directive			
Unadjusted	3.45	(1.85, 6.43)	<0.001
Adjusted	3.68	(1.89, 7.16)	<0.001

Adjusted for age, religious importance, education, time with current oncologist, and ECOG.

12031 **Poster Session**

Quality of end-of-life care for patients with multiple myeloma: A 12-year analysis of a population-based cohort. *First Author: Ghulam Rehman Mohyuddin, University of Utah, Salt Lake City, UT*

Background: Despite treatment advances, multiple myeloma (MM) remains a significant source of morbidity and mortality. The end of life for patients with MM has not previously been examined within the context of a population-based cohort in a publicly funded health system. **Methods:** We retrospectively analyzed patients with death attributable to MM between 2006-2018 using ICES linked databases in the public health care system in Ontario, Canada. Aggressive care was defined as two or more emergency department visits in the last 30 days before death, at least two new hospitalizations within 30 days of death, or an ICU admission within 30 days of death. Supportive care was defined as physician house call 2 weeks before death, or a palliative nursing or personal support visit at home in last 30 days before death. Multivariable logistic regression models were used to assess for factors predisposing to aggressive or supportive care. Patients were stratified based on receipt of autologous stem cell transplant (ASCT). **Results:** In total, 5095 patients were included (Table). Overall, 23.2% of patients received chemotherapy in last two weeks of life and 55.6% of patients died in the hospital. Most patients were admitted to hospital within the last 30 days of life (73.4%:ASCT cohort, 61.4%:non-ASCT cohort). A minority received aggressive care at end of life (28.3%:ASCT cohort, 20.4%:non-ASCT cohort), and a majority received supportive care at end of life (65.4%:ASCT cohort, 61.5%:non-ASCT cohort). Multivariate regression models showed that patients ≥ 80 years (compared to 60-69) were less likely to receive aggressive care (OR=0.54, 95% CI=0.42-0.68), and those with residence in smaller size community of < 10,000 were more likely to receive aggressive care (OR=1.89, 95% CI=1.5-2.4). Supportive care was significantly less likely to be received by patients (OR=0.72, 95% CI= 0.59 to 0.88) and more likely to be received by patients aged 18-49 (OR=1.9, 95% CI=1.2-3.1). Neighbourhoods with lowest income quintiles (OR=0.65, 95% CI=0.53-0.78) were less likely to receive supportive care. When trended over time, patients receiving supportive care at end of life increased (56.0% in 2006 to 70.3% in 2018). **Conclusions:** We demonstrate that despite improvements over time, a substantial number of patients with MM experience aggressive care and hospitalizations at the end of life. Despite this being a publicly funded system, disparities in end-of-life care based on age, income and area of residence are present. Research Sponsor: Canadian Cancer Society Research Institute via the Canadian Centre for Applied Research in Cancer Control (grant No. 2015-703549).

Patient characteristics.

Median age at death (IQR)		74 (65-81)
Sex	Female	2,258 (44%)
Prior ASCT	Yes	1,398 (27%)
	No	3,697 (73%)
Mean Years from diagnosis to death (SD)		3.6 (±3.7)
Area of Residence	Urban	4,436 (87%)
Treatment received at any time in disease course	Proteasome inhibitor	3,216 (63%)
	Immunomodulatory	2,038 (40%)
	Anti CD38	52 (1%)
	Alkylator	3,864 (76%)

SD= standard deviation, IQR= interquartile range.

12032 **Poster Session**

Death with dignity utilization among patients with thoracic, head, and neck cancer. *First Author: Natalie F. Uy, University of Washington, Seattle, WA*

Background: Death with Dignity (DWD) legislation, which took effect in 2009 in Washington state, allows terminally ill patients (pts) to self-administer physician-prescribed, life-ending medication. Thoracic, head and neck cancer (THN) pts are among the top cancer types requesting DWD; however, data describing this group are limited. **Methods:** This retrospective chart review, conducted at Seattle Cancer Care Alliance/University of Washington and Fred Hutch, collected demographics, disease, treatment, support services and steps of the DWD process. We tested the association between disease characteristics of interest and DWD completion using Fisher's Exact test. **Results:** Between Jan 2014 and October 2020, 498 pts inquired about DWD, and 108 (22%) were THN pts. Among THN pts, 51 (47%) only initiated the DWD request process, 35 (33%) only completed the DWD request process, and 22 (20%) completed the DWD request and self-administered the medication. Pts were white (n=90, 83%), male (n=64, 59%), primarily English speaking (n=103, 95%), nonreligious (n=69, 64%), single/divorced/non-partnered (n=55, 51%), and insured (n=103, 95%). Median age at request was 68 years (range 35-88). The table details THN DWD utilization. At time of DWD request, the median time from diagnosis was 14 months (range=0.2-242.7), and 62 (57%) had received ≥2 lines of therapy. Among 78 (72%) pts who received systemic therapy, 51 (65%) were ≥30 days from last therapy to time of death. Within 30 days prior to DWD request, 30 (28%), 25 (23%), and 7 (7%) pts saw social work, palliative care, and spiritual health respectively, and 35 (32%) were hospice-enrolled. Stage IV at diagnosis had higher rates of DWD medication use (p=0.05). There was no significant correlation between DWD medication use and primary site, ECOG score at request, insurance type, mental health diagnosis, use of depression/anxiety or pain medications, or hospice enrollment during DWD process. **Conclusions:** THN pts requesting DWD were predominantly white, nonreligious, insured males. Pts with advanced stage at diagnosis were more likely to use DWD medication. There was a higher proportion of DWD medication use with poorer performance status, and no association between use of depression/anxiety, pain medications, or utilization of supportive care services and DWD medication usage. Future research should investigate DWD utilization among THN pts in multiple centers and states to evaluate these patterns. Research Sponsor: This research was supported by Biostatistics, shared resource of the Fred Hutch/University of Washington Cancer Consortium (P30 CA015704).

DWD in the THN cancer population.

	Overall (n = 108)	Initiated/Completed DWD Request Only (n = 86)	DWD with Meds Self-Administered (n = 22)
Cancer Type			
Lung	80 (74%)	64 (74%)	16 (73%)
Head & Neck	23 (21%)	21 (24%)	2 (9%)
Unknown Primary	5 (5%)	1 (2%)	4 (18%)
Cancer Stage at Initial Diagnosis			
Stage I-III	41 (38%)	37 (43%)	4 (18%)
Stage IV	67 (62%)	49 (57%)	18 (82%)
ECOG at DWD Request			
Missing/Unknown	3 (3%)	2 (2%)	1 (5%)
ECOG 0-2	65 (60%)	56 (65%)	9 (41%)
ECOG 3-4	40 (37%)	28 (33%)	12 (55%)

12033 **Poster Session**

Cancer doesn't know what day of the week it is: Temporal trends in day of death, 2000-2017. *First Author: Kanan Shah, NYU Grossman School of Medicine, New York, NY*

Background: Improving end-of-life care is an opportunity to reduce trauma for both patients and caregivers. Studies support the existence of a psychosomatic phenomenon known as the "holiday effect," allowing critically ill patients to enter a bargaining phase and postpone death until a given event. We hypothesized that there may be a temporal trend as patients with cancer attempt to delay death until the arrival of family on weekends or the passage of a holiday. **Methods:** All deaths due to malignant neoplasms (ICD C00-C97) from 2000-2017 were collected from the National Center for Health Statistics. Outcomes were the days of week and months of year that death occurred. Weekend mortality was defined as death on Friday, Saturday, or Sunday. Holiday mortality was defined as death in December or January. Chi-squared tests were performed to determine differences in deaths by day or month. Logistic regression examined associations between day or month of death and age, education, race/ethnicity, location of death, marital status, race, and sex. Statistical analyses were performed using SAS statistical software, version 9.4 (SAS Institute Inc). **Results:** 10,305,990 deaths due to cancer were recorded from 2000-2017. Deaths were not uniform across day of week or month of year ($p < 0.001$ each). Each year, rates of death increased progressively from Monday to Thursday, peaked on Friday and Saturday, and declined on Sunday. There was a relative 3.4% difference in death rate between the peak on Friday and nadir of deaths on Monday. Each year there was a consistent increase in deaths in December and January, with a nadir in February with a relative difference of 10.2%. Multivariate logistic regression assessed associations in weekend and holiday cancer death. Non-hospital death (home, nursing facility, hospice) was more likely to occur on the weekend (aOR from 1.03-1.05, $p \leq 0.01$ for all). Hispanic patients (aOR 1.01, $p = 0.001$) were more likely to die on weekends. Females (aOR 0.99, $p = 0.02$), those who were divorced (aOR 0.99, $p = 0.04$) and those with pancreatic cancer (aOR 0.99, $p = 0.01$) were less likely to die on weekends. Non-hospital death was less likely to occur on Holiday months (aOR from 0.95-0.96, $p \leq 0.01$ for all). Those > 75 were more likely to pass away in Holiday months compared to younger age groups (OR 1.02-1.03, $p < 0.05$ for both). Cancer type was associated with holiday mortality; those with breast or prostate cancer were more likely to pass away (OR 1.01, $p < 0.05$ for both) during the holidays compared to those with lung cancer. **Conclusions:** There is a human element to death. The unequal distributions of deaths due to cancer in this study are small but significant; they suggest a non-biological variation that precludes cancer mortality from being strictly date agnostic. Temporal trends in cancer death highlight an opportunity to improve end of life care and demonstrate how care should shift focus to what matters to patients including time with family. Research Sponsor: U.S. National Institutes of Health.

12034 **Poster Session**

Geographic disparities in breast cancer mortality and place of death in the United States from 2003 to 2019. *First Author: Kelli Clemons, Medical College of Georgia, Augusta, GA*

Background: Breast cancer is the 2nd leading cause of cancer-related death in women with existing barriers in preventive services, access to treatment, and end-of-life care. There are unique sociopolitical challenges to rural healthcare with gaps in national health funding and hospice infrastructure. We investigated rural-urban disparities in age-adjusted mortality rates (AAMRs) and place of death in individuals dying from breast cancer. **Methods:** CDC WONDER database was utilized to analyze deaths from breast cancer from 2003 to 2019 using population classification per 2013 US Census: large metropolitan (≥1 million), small- or medium-sized metropolitan (50,000-999,999), and rural areas (< 50,000). We extracted AAMRs by geographic area, age, and race/ethnicity. We estimated annual percentage changes (APC) in AAMR using robust linear regression models of the log-scale AAMR, including population size as weights, and assessed differential changes over time by geographic area with interaction tests. We estimated the percent of all deaths occurring in medical, hospice, and nursing facilities, and home. Odds ratios (OR) for the association between each place of death and individual-level characteristics were calculated using logistic regression, adjusting for year of death. Differential changes in place of death over time by geographic region were assessed with interaction tests. **Results:** From 2003 to 2019, there were 676,532 breast cancer-related deaths (52.9% large metro, medium/small metro 30.3%, rural 16.8%). Total AAMR declined from 39.8 to 30.9 during this period with rural areas noting least improvement (APC -1.24, 95% CI [-1.39, -1.09], $p < 0.001$ for time trend) compared to large metropolitan (APC -1.74, 95% CI [-1.63, -1.46]). Non-Hispanic Black women had higher AAMRs among all racial/ethnic groups. Across all years, women in large metropolitan (OR 2.02, 95% CI [1.96, 2.07]) and medium/small metropolitan (OR 2.19, 95% CI [2.12, 2.25]) had higher odds of dying in a hospice facility compared to rural areas. Rural women died least often in a hospice facility (9.7% vs 14.5% large metropolitan vs 16.9% medium/small metropolitan in 2019), more often in a nursing facility (19.2% vs 12% large metropolitan vs 13.9% medium/small metropolitan) and slightly more often at home (44.6% vs 41.7% large metropolitan vs 43.4% medium/small metropolitan). Women in large metropolitan areas were most likely to die in a medical facility. **Conclusions:** Rural women with breast cancer experienced greater mortality and least annual improvement, with notable disparities in place of death. Our findings support interventions to improve access across cancer care continuum and congressional policy to urgently re-invest in cancer care access in rural areas. Research Sponsor: None.

12035 **Poster Session**

Sociodemographic factors associated with end-of-life palliative care utilization in female breast cancer: A national inpatient database analysis. *First Author: Tien-Chan Hsieh, Danbury Hospital, Danbury, CT*

Background: Palliative care (PC) has been shown to improve end-of-life quality in cancer patients. Nevertheless, several studies suggest that PC utilization is associated with socioeconomic factors. Patients with breast cancer, the most common neoplasm in women in the U.S., has lower PC utilization than those with other malignancies. We aim to investigate any sociodemographic barriers that are associated with the inpatient PC utilization in female breast cancer in the U.S. at the end of life. **Methods:** We used the National Inpatient Sample database of Healthcare Cost and Utilization Project, an all-payer inpatient care database in the United States, with data years 2014-2019. The end-of-life case was defined as hospitalized at least three days and passed away. We included all adult women (age at least 18 years old and female gender in electronic health records). The breast cancer cases were identified with International Classification of Diseases (ICD) 9th or 10th edition within the top three diagnoses. PC consultation could be identified with the ICD procedure code. Comorbidities were controlled with Charlson Comorbidity Index. After univariable analysis, the factors that were statistically associated with PC utilization would subsequently be added to the multivariable logistic regression model. **Results:** Between the year 2014 to 2019, we identified a total of 2,226 adult female patients who had breast cancer as their top three diagnoses and were hospitalized at least three days before death. 217 (9.7%) cases were 40-49 years old; 441 (19.8%) cases were 50-59 years old; and 1,455 (65.4%) patients were at least age 60 or above. The top three racial groups were Caucasian 1,420 (63.8%), African American 418 (18.8%), and Hispanic 166 (7.5%). 1,267 (56.9%) of all the cases had PC consult. African American (adjusted odds ratio [aOR]: 0.75; $p < 0.005$) and Hispanic (aOR: 0.62; $p < 0.05$) were significantly associated with less PC utilization than the Caucasian reference group in multivariable regression model. Lower PC prevalence was also observed at rural hospitals and Midwest region. Higher income group and private insurance no longer showed statistically significant higher PC utilization after adjusted for other variables. **Conclusions:** In end-of-life hospitalization with breast cancer as primary diagnosis, racial and hospital resource factors were significantly associated with the PC utilization. Cultural difference could be associated with the lower PC prevalence since adjusting income and insurance types could not explain the disparities in PC utilization among different racial groups. Future study should investigate and address the disparities of PC utilization in female terminal breast cancer. Research Sponsor: None.

12036 **Poster Session**

Comparative study of two cohorts of older adults with advanced cancer treated before and after implementation of a geriatric oncology service. *First Author: Tomohiro F. Nishijima, Geriatric Oncology Service/Medical Oncology, NHO (National Hospital Organization) Kyushu Cancer Center, Fukuoka, Japan*

Background: A comprehensive geriatric assessment (CGA) has been recommended by guidelines for older adults with cancer for whom chemotherapy is considered. As a quality assessment effort, we examined the effect of CGA conducted by a geriatric oncology service (GOS) in routine practice on clinical outcomes. **Methods:** This was a comparative study of two cohorts of consecutive patients aged ≥ 70 years with unresectable, locally advanced or metastatic cancer who were referred to medical oncology for first-line chemotherapy before (September 2015-August 2018) and after (September 2018-March 2021) the establishment of a GOS at a single institution in Japan. When the treating physician requested a consultation, the GOS conducted a CGA and provided recommendations for the oncologic treatment plan and geriatric interventions. We compared time to treatment failure (TTF) rates at 30, 60 and 90 days as well as 6-month overall survival (OS) rates between the two cohorts adjusting for potential confounders. TTF was defined as the time from start of first-line chemotherapy to discontinuation of first-line chemotherapy for any reason. **Results:** The study population consisted of 342 patients. Median age was 75 years (range: 70-95 years) and 85% had gastrointestinal tract cancer including gastroesophageal (43%) and colorectal (41%). Baseline characteristics of the patients treated before (n = 151) and after (n = 191) GOS implementation were similar with regard to age, sex, cancer type, and performance status. In the after GOS cohort, 82 patients (43%) received CGA before the treatment decision and oncologic treatment plans were changed after consultation in 49 patients (60%). For the majority of these patients, the treatment plan was adjusted to a less intensive option. Two hundred and eighty-two patients received chemotherapy (n = 128 before, n = 154 after GOS cohort) and 60 patients were treated with best supportive care only (n = 23 before, n = 37 after GOS cohort). More patients in the after GOS cohort were treated with reduced-intensity chemotherapy compared with those in the before GOS cohort (55% vs. 39%, P = 0.007). TTF event rates at 30 days (5.7% after vs. 14% before, P = 0.02), 60 days (13% after vs. 29% before, P = 0.001) and 90 days (26% after vs. 36% before, P = 0.06) were lower in the after GOS cohort compared to the before GOS cohort. Among patients receiving chemotherapy, significantly more patients were alive at 6 months in the after GOS cohort compared to the before GOS cohort (84% vs. 72%, P = 0.01). In all patients receiving CGA (n = 94), 219 interventions to address health problems were recommended and 97 interventions were conducted with an overall implementation rate of 44%. **Conclusions:** In this before-and-after quality assessment study, implementation of the GOS was associated with improved TTF and OS in older adults with advanced cancer receiving first-line chemotherapy. Research Sponsor: JSPS KAKENHI.

12037 **Poster Session**

The impact of diabetes on the performance of skeletal muscle density (SMD) in screening for frailty: Findings from the Cancer and Aging Resilience Evaluation (CARE) Registry. *First Author: Sydney T Thai, Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC*

Background: SMD is a marker of myosteatosis that can be obtained from routine computed tomography (CT) imaging and could be used to screen patients for further frailty evaluation. But diabetes (DM) is linked with myosteatosis in men and SMD utility for patients with DM is unknown. We assessed SMD performance as a frailty screening tool in older adults with primarily gastrointestinal cancer and compared performance in patients stratified by sex and DM. **Methods:** We analyzed CARE Registry patients at baseline, a sample with mostly late-stage, gastrointestinal malignancies. Frailty and DM were captured in the CARE tool, a patient-reported geriatric assessment. SMD was calculated from CT scans at L3 vertebrae. Analyses were run for each sex and by DM status. We used linear regression to assess crude associations of SMD and frailty score. SMD performance in classifying frail status (vs. non-frail) was analyzed with 1) area under the receiver operating characteristic curves (AUC) and confidence intervals (CIs); and 2) sensitivity and specificity for sex-specific SMD quartile cut-offs (Q1, median, Q3). Cut-off performance was compared between patients with DM vs. without using differences in sensitivity and specificity and CIs. CIs were estimated with 2,000 bootstrap replicates. **Results:** The analytic sample (N=874; 27% DM, 32% frail) was 39% female with median age 68 years. For each sex-DM subset, regression results had negative slopes indicating that low SMD was associated with higher frailty score. AUCs for women with and without DM were 0.57 (95% CI 0.45-0.69) and 0.62 (0.54-0.70). AUCs for men with and without DM were 0.68 (0.59-0.77) and 0.58 (0.52-0.65). Sex-stratified sensitivity and specificity results are below. Median cut-offs had both sensitivity and specificity >0.50; Q3 cut-offs had higher sensitivity but low specificity. **Conclusions:** SMD could be used to pre-screen older adults with and without DM for further clinical frailty assessment. With high-sensitivity cut-offs (Q3), 13% to 26% of frail patients could be missed. Compared to other groups, SMD pre-screening for men with DM may miss the fewest frail patients but would produce many false-positives. Research Sponsor: None.

Sex	SMD cut-off point, Houndsfield Units	Sensitivity [DM vs. No DM difference, 95% CI]	Specificity [DM vs. No DM difference, 95% CI]
Female	Q1: <31.1	DM = 0.35 No DM = 0.34 [0.01, -0.17 to 0.19]	DM = 0.70 No DM = 0.82 [-0.12, -0.26 to 0.02]
	Median: <38.1	DM = 0.60 No DM = 0.59 [0.02, -0.17 to 0.20]	DM = 0.52 No DM = 0.55 [-0.03, -0.19 to 0.12]
	Q3: <44.1	DM = 0.74 No DM = 0.85 [-0.11, -0.27 to 0.05]	DM = 0.34 No DM = 0.28 [0.06, -0.09 to 0.21]
Male	Q1: <33.0	DM = 0.52 No DM =0.29 [0.23, 0.08 to 0.38]	DM = 0.84 No DM = 0.80 [0.03, -0.06 to 0.13]
	Median: <39.8	DM = 0.65 No DM = 0.54 [0.10, -0.05 to 0.26]	DM = 0.56 No DM = 0.53 [0.03, -0.09 to 0.15]
	Q3: <47.3	DM = 0.87 No DM = 0.78 [0.10, -0.02 to 0.21]	DM = 0.26 No DM = 0.29 [-0.03, -0.14 to 0.07]

12038 **Poster Session**

Modified CARG score using data from the electronic health record to predict chemotherapy toxicity in older adults. *First Author: Jasmine L Martin, Geisinger Health Systems, Danville, PA*

Background: Older adults starting chemotherapy are at greater risk of toxicity compared with younger patients. Additional tools are needed to aid in management decisions for this population. The Cancer and Aging Research Group (CARG) chemotherapy toxicity calculator is one such tool, which stratifies older adults into high, intermediate, or low risk for chemotherapy toxicity (Hurria, A., Mohile, S., Tew, W. P., & et al. (2016). Validation of a prediction tool for chemotherapy toxicity in older adults with cancer. *Journal of Clinical Oncology*, *34*(20), 2366–2371. https://doi.org/10.1200/jco.2015.65.4327). This tool relies on a face-to-face encounter to ask questions, e.g. "How is your hearing?" or "Can you take your own medicines?" in addition to lab values such as hemoglobin and creatinine clearance. We modified the CARG chemo toxicity calculator to include data points which could be pulled from the electronic health record (EHR) without the need for a face-to-face encounter to assess for an association with emergency department (ED) visits and hospital admissions. **Methods:** Retrospective data analysis was conducted using the EHR of patients over age 65 diagnosed with a solid tumor from 1/1/2019 to 12/31/2020 who started chemotherapy. A modified CARG score was calculated using age, cancer type, number of drugs, hemoglobin, creatinine clearance, and falls within the past 6 months. The remaining items needed to calculate the complete CARG score were excluded since they were not accessible in the EHR. We assessed ED visits leading to admission, ED visits leading to discharge, direct admissions, and the total of all 3 visit types for all patients. **Results:** A modified CARG score was calculated for 763 patients. Multiple models were evaluated and negative binomial distribution was found to be the best fitted for our data. For every one unit increase in our calculated score the number of ED visits which lead to hospital admission increased by 6% (p-value = 0.0156). Additionally, there was a 5% increase in combined ED visits, ED visits leading to admission, and direct admissions for every one unit increase in risk score (p-value = 0.0063). ED visits that did not lead to admission were found not to have an association with the risk score (p-value= 0.1263). (Table) **Conclusions:** A modified CARG score using data obtained from patients' EHR had a statistically significant association with increased ER visits that resulted in hospital admission and with the total of ED visits leading to admission, ED visits leading to discharge, direct admissions. Using these outcomes as a surrogate for toxicity, we deduce that a simple tool could be used to predict chemotherapy toxicity in older adults. Research Sponsor: Geisinger Cancer Institute.

Outcomes	Incidence Rate Ratio for Risk Score (95% CI)	p value
ER Visits	1.04 (0.99, 1.10)	0.1263
ER Visits that Lead to Admission	1.06 (1.01, 1.11)	0.0156
Direct Admissions	1.05 (0.99, 1.12)	0.0899
Total Visits	1.05 (1.01, 1.09)	0.0063

12039 **Poster Session**

Improved overall survival of metastatic cancers in the United States across all age groups in the immunotherapy era: Implications for considering elderly patients (age ≥ 75) for immune checkpoint inhibitors (ICIs). *First Author: Yu-Wei Chen, Vanderbilt Ingram Cancer Center, Nashville, TN*

Background: ICIs have changed the treatment paradigm in many cancer histologies. Population-level data regarding the impact of ICIs on the contemporary US cancer patients is scarce. In addition, elderly patients were underrepresented in the landmark trials. **Methods:** Metastatic cancers (melanoma, lung cancer, kidney cancer, head and neck cancer, Hodgkin's lymphoma, and urothelial cancer) diagnosed between 2004-2018 were identified in the Surveillance, Epidemiology, and End Results (SEER) database. The year of the first FDA approved ICI in each cancer site was considered the commencement of the ICI era. The impact of metastatic cancers diagnosed in the ICI era was assessed in each age group (<65, 65-75, and ≥75) using multivariable Cox regression after adjustment for age, sex, race, household income and residence status (metropolitan vs non-metropolitan) **Results:** There were 363,191 patients with metastatic cancers included in the analysis [lung cancer: 68%, head and neck cancer: 14%, Hodgkin Lymphoma: 7%, kidney cancer: 7%, urothelial cancer: 3%, and melanoma: 2%): 60% were male and 73% were non-Hispanic White. The median age was 66 (interquartile range: 57-75). After baseline adjustments for sociodemographic factors, metastatic cancers diagnosed in the ICI era had improved overall survival except urothelial cancer (Table). Results of overall survival and cancer-specific survival were consistent across all age groups (<65, 65-75, and ≥75). Among patients with age ≥75, metastatic cancers diagnosed in the ICI era had improved overall survival in melanoma (AHR: 0.81, p-value<.0001), lung cancer (AHR:0.91, p-value<.0001), kidney cancer (AHR: 0.89, p-value: 0.0004), head and neck cancer (AHR:0.82, p-value<.0001), Hodgkin lymphoma (AHR: 0.75, p-value:0.003) but not in urothelial cancer. **Conclusions:** Metastatic cancers diagnosed in the ICI era had improved overall survival and cancer-specific survival including the subgroup of age ≥ 75. ICIs should not be withheld in elderly patients solely due to chronological age. Research Sponsor: U.S. National Institutes of Health.

The association between ICI era and overall survival in metastatic cancers.

		All-Cause Mortality (AHR, 95%)			
	Year of First FDA approved ICI indication	All Patients (N=363,191)	Age <65 (N=169,609, 47%)	65-75 (N=101,584, 28%)	>75 (N=91,998, 25%)
Melanoma	2011	0.75 (0.72-0.79)	0.71 (0.66-0.76)	0.81 (0.72-0.90)	0.81 (0.73-0.90)
Lung cancer	2015	0.88 (0.87-0.89)	0.86 (0.84-0.87)	0.88 (0.87-0.90)	0.91 (0.89-0.93)
Kidney cancer	2015	0.84 (0.81-0.87)	0.71 (0.66-0.76)	0.81 (0.76-0.87)	0.89 (0.83-0.95)
Head and Neck	2016	0.77 (0.74-0.79)	0.75 (0.72-0.80)	0.75 (0.70-0.81)	0.82 (0.75-0.89)
Hodgkin Lymphoma	2016	0.73 (0.66-0.81)	0.65 (0.55-0.76)	0.79 (0.66-0.96)	0.75 (0.63-0.91)
Urothelial cancer	2016	1.01 (0.95-1.07)	1.11 (1.00-1.23)	0.97 (0.88-1.08)	0.97 (0.89-1.07)

12040 **Poster Session**

Deficit Accumulation Frailty Index (DAFI) scores and acute myeloid leukemia outcomes. *First Author: Catherine Lai, University of Pennsylvania, Philadelphia, PA*

Background: Novel strategies are needed to assess frailty in the context of therapy decisions for older adults with acute myeloid leukemia (AML). Our objectives were to describe pre-treatment DAFI scores for older AML patients treated on clinical trials and explore their relationship with treatment outcomes. **Methods:** We conducted a exploratory analysis utilizing data from two clinical trials of adults aged ≥60 years with newly diagnosed AML (Alliance/CALGB 11001 [intensive therapy] and Alliance/CALGB 11002 [non-intensive therapy]). We included the subset of patients in each trial enrolled on geriatric assessment companion studies (Alliance/CALGB 361006, 361101). A DAFI score was calculated for each patient using 51 variables including demographic, geriatric assessment, and laboratory data derived from the geriatric assessment. Individuals with ≥90% items were included (consistent with other studies); DAFI scores ranged from 0 to 1 and were evaluated using established categories (0- <.2 [robust]; 0.2-<.35 [pre-frail]; 0.35+ [frail]) and as a continuous score. Associations between DAFI scores and toxicity and overall survival (OS) were evaluated with Fisher's exact-testing and Kaplan Meier/cox proportional hazards, respectively. **Results:** The median age was 68 years (range 61, 82) and 72 years (range 61, 92) for those getting intensive (N=31) and less intensive therapy (N= 75), respectively. Individuals in the intensive study had a median pre-treatment DAFI score of 0.15 (range 0.05, 0.31) and were all categorized as robust (75%) or pre-frail (25%). There was no significant difference in median OS (14.6 vs. 14.7 months) or non-hematological grade 3+ adverse events (AEs; 85% vs. 89%) between robust vs. pre-frail individuals in this trial, respectively. However, pre-frail adults experienced a trend towards greater grade 4 non-hematological toxicity than robust individuals (67% vs 26%, p=0.05). In the non-intensive trial, the median DAFI score was 0.24 (range 0.04, 0.48) and most individuals were pre-frail (49.3%) or frail (17.3%). Non-hematologic grade 3+ AEs did not vary by DAFI group, 88% robust, 95% pre-frail, and 77% frail (p=0.15). Median OS was 7.4, 10.8, and 6.3 months for robust, pre-frail, and frail respectively (p=0.17). Adjusting for age, each 0.1 increase in DAFI score was associated with increased mortality hazard (HR 1.8, 95% CI 1.0-3.2). **Conclusions:** DAFI score calculation provides a potential novel strategy for categorization of frailty in AML. In our assessment, higher DAFI scores were associated with toxicity during intensive induction and mortality in the less intensive setting. This method should be studied in larger samples randomized by treatment intensity. Support: UG1CA189823; Bayer Healthcare/Berlex (CALGB 11001); NCT01253070 (CALGB 11001). Clinical trial information: NCT01253070, NCT01420926. Research Sponsor: ALLIANCE studies.

12041 **Poster Session**

General practitioner contacts, hospitalizations, and nursing home transfers in older patients up to three years after new cancer diagnosis: Results from a large data linkage cohort study. *First Author: Victoria Depoorter, KU Leuven, Leuven, Belgium*

Background: Long-term outcomes after cancer diagnosis in older persons are largely unexplored because of limited follow-up in clinical studies. By linking clinical data with population-based data, studying long-term outcomes in large cohorts becomes feasible. The current study aims to explore long-term outcomes in the care trajectory of older patients with cancer and to assess their association with baseline geriatric screening and assessment (GS/GA) results. **Methods:** A large cohort study of older patients with a new cancer diagnosis was set up by linking clinical, cancer registry and administrative health data based on a unique patient identifier. Clinical data were derived from a previously performed prospective multicentric Belgian study (2009-2015). Patients aged ≥ 70 years were screened with G8 followed by GA in case of an abnormal result (≤14/17). Tumor characteristics and vital status were derived from cancer registry data and long-term outcomes (general practitioner (GP) contacts, hospitalizations and nursing home transfers) from administrative health data. In patients that survived at least 3 months since inclusion, outcomes were assessed from the day after inclusion until 3 years after. Event rates were calculated using person-time at risk to allow for varying follow-up time. Patients were censored 3 months before death to exclude influence of end-of-life care. **Results:** After data linkage, 6,391 older patients with a new cancer diagnosis were available for this analysis. The median age was 77 (range: 70–100) and 59.8% was female. Diagnoses included solid (92.8%) and hematologic malignancies (7.2%). In the patients with a solid tumor, breast, colorectal and lung cancer were the most common and 20.1% of patients had stage IV. 64.3% of patients had an abnormal baseline G8 score. During the 3 year follow-up, 2,602 (40.7%) of the included patients died. In these 3 years, 5,985 (95.2%) patients had at least one contact with a GP and 4,634 (72.5%) had at least one new hospital admission (event rates in Table 1). Of the 3,724 patients living independently at inclusion and still alive after 3 years, 281 (7.5%) had been transferred to a nursing home and of those, 240 (85.4%) patients had an abnormal baseline G8 score. **Conclusions:** Older patients with an abnormal baseline G8 score have more GP contacts, hospital admissions and nursing home transfers in the 3 years following a new cancer diagnosis compared to patients with normal baseline G8 score. Baseline G8 could help identify patients at risk for higher long-term healthcare utilization. Research Sponsor: Kom op tegen Kanker (Stand up to Cancer).

Event rate per person-year for GP contacts and hospitalizations.

	All pts (n = 6,391)	Pts with normal G8 score (> 14/17) (n = 2,281)	Pts with abnormal G8 score (≤ 14/17) (n = 4,110)
GP contacts (n = 101 missing)	10.96	8.95	12.47
Hospital admissions	0.91	0.72	1.06

GP = general practitioner, pts = patients.

12042 **Poster Session**

Functional decline in older breast cancer survivors treated with and without chemotherapy and non-cancer controls. *First Author: Jingran Ji, City of Hope National Medical Center, Duarte, CA*

Background: Although breast cancer and breast cancer chemotherapy (chemo) have been linked to accelerated functional decline, it is not well understood whether this decline is driven by cancer itself or the combination of cancer and chemo. Here, we compared the change in functional status over time in older breast cancer survivors treated with and without chemo and age-matched women without cancer. **Methods:** Women age ≥65 with non-metastatic breast cancer (n = 538; 441 treated with chemo and 97 without chemo) and n = 100 non-cancer controls were prospectively evaluated at two timepoints: ≤14 days pre-chemo (baseline) and ≤30 days post-chemo (or matched times for non-chemo and non-cancer controls). At each timepoint, functional status was measured using instrumental Activities of Daily Living (iADL) scores. The primary endpoint was the proportion of patients with a decline in functional status (Yes/No, yes defined as ≥2-point decrease [minimal meaningful difference] in iADL scores between timepoints). Baseline demographic, functional, and clinical characteristics were compared between survivors treated with and without chemo and non-cancer controls using *t* and chi-squared tests. Among the 441 women treated with chemo, univariate and multivariable logistic regression analyses were performed to determine baseline risk factors associated with chemo-induced functional decline. **Results:** 10% of older survivors treated with chemo experienced a clinically meaningful decline in function as compared to 3% in the non-chemo and 4% in non-cancer control groups (p = 0.017). Across the 3 groups, there were no differences in median age, race/ethnicity, education, number of comorbidities, or baseline functional status (iADL, ADL, Timed Up and Go [TUG]). Among the 441 older survivors treated with chemo, greater age, higher BMI, more comorbidity, lower ADL score, and longer TUG were significantly associated with functional decline univariately. After multivariable analyses, age ≥78 (26% declined, odds ratio [OR] = 3.67, 95% CI 1.60-8.43) and BMI > 30 (16% declined, OR = 2.11, 95% CI 1.02-4.38) remained significantly associated with functional decline. Patients who were both ≥78 years old and obese (BMI > 30) had the highest odds of developing functional decline post-chemo (41% declined, OR = 8.43, 95% CI 2.48-28.63). **Conclusions:** In this study, older breast cancer survivors treated with chemo had a 3-fold increased incidence of clinically meaningful decline in functional status as compared to age-matched survivors not treated with chemo and those without cancer. Although these findings need to be replicated in larger studies, our results raise the possibility that accelerated functional decline may be driven by cellular damage from cytotoxic chemo. Further research is warranted to understand the impact of cancer and its treatment on older adults' functional status and underlying aging processes. Clinical trial information: NCT01472094. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

12043 **Poster Session**

Validation of the Cancer and Aging Research Group (CARG) model to identify risks of chemotherapy toxicities in Asian older adults. *First Author: Jia Li Low, NUH, Singapore, Singapore*

Background: Older adults are at an increased risk of chemotherapy related toxicities. Identification of risk factors can facilitate oncologists in tailoring treatment, potentially mitigate the risk of chemotherapy toxicity and improve social economic outcomes. Tools like the Karnofsky Performance Status (KPS) and Geriatric Assessment (GA) are used in clinical practice to guide treatment decisions for older adults with cancer. The CARG model incorporating the GA and clinical variables was developed and validated to predict for grade 3-5 toxicities, although this has not yet been validated in Asians. **Methods:** Patients ≥70 years old with solid malignancies receiving chemotherapy at the National University Cancer Institute, Singapore were recruited between June 2017 and January 2018. The study aims to verify the application of the CARG model, KPS, GA and oncologists' estimate of toxicity in a multi-ethnic Asian population. The risks of chemotherapy toxicity were calculated using the CARG model (low risk: 0-5, medium risk: 6-9, high risk: ≥10). A GA including a physician rated KPS score (low risk: 90-100, medium risk:80, high risk: ≤70) and a timed up and go (TUG) test (low risk: ≤12s, high risk: > 12s) were performed for all patients. The attending oncologist (blinded to the CARG score) was asked to give an estimated likelihood (low/medium/high) of chemotoxicity. Chemotherapy related toxicities were captured by chart review based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The area under the receiver operating characteristic (ROC) curve and a univariate analysis of predictors of toxicity were calculated. **Results:** A total of 200 patients were included. Median age was 74 (range: 70-89). The ethnic makeup of the population consisted of Chinese (N = 177; 88.5%), Malay (N = 17; 8.5%), Indians (N = 4; 2%) and other ethnicities. Majority of patients were males (N = 110; 55%), had metastatic disease at diagnosis (N = 114; 57%) and had gastrointestinal cancers (N = 80; 40%). 75% (N = 150) had polychemotherapy and 55% (N = 110) received full dose chemotherapy. More than half of patients (68.5%) experienced G3-5 toxicities, with 65.5% requiring hospitalization. The CARG model predicted 22.5% of patients as low, 50.5% as medium and 27% as high risk of chemotoxicity. The area under ROC for the CARG model was 0.74 (95% CI, 0.67-0.82). A one-point increase in the CARG score was associated with a 15% increase in the odds of G3-5 toxicities. 84.5% of patients needed > 12s for the TUG test. The TUG score, KPS and oncologist's prediction of toxicity was predictive of an increased risk of G3-5 toxicities (p < 0.01). **Conclusions:** This study confirms the validity of the CARG predictive model in Asians and can streamline healthcare delivery in older adults. Development of a more robust predictive model incorporating the KPS and TUG into the CARG model could be considered. Research Sponsor: National Cancer Institute Singapore Centre Grant, Other Government Agency.

12044 **Poster Session**

Adherence to oral treatments in elderly patients with advanced prostate cancer: The ADHERE study, a prospective trial of the Meet-URO network. *First Author: Pasquale Rescigno, Candiolo Cancer Institute, FPO-IRCCS, Candiolo, Italy*

Background: Novel anti-androgen hormonal therapies (NAHTs) for advanced prostate cancer (PC) are mainly oral with an overall good toxicity profile and offer the convenience of home administration and reduced hospital footfalls. This imposes the burden of self-administration, often unsupervised, on a population of elderly patients overwhelmed by the assumption of many other concomitant medications. Therefore, lack of treatment adherence is becoming an increasingly social and health issue. **Methods:** In a prospective observational cohort study, metastatic castration-resistant PC (mCRPC) patients aged ≥70 years receiving abiraterone (ABI) or enzalutamide (ENZ) were enrolled in six Italian centres of the Meet-Uro network and monitored for their treatment adherence. Monitoring included pill counting, self-assessment questionnaire and clinical diaries at each clinical visit. Non-adherence rates were based on proportions of missed/prescribed pills ratios by pill counting as an overall estimate or the median of individual values. **Results:** Overall, 234 pts were recruited (median age: 78 years [73-82], 86 were treated with ABI and 148 with ENZ; 69% of the pts received NAHT in the pre-chemotherapy setting, while 24% in the post-chemo and 6% had the two treatments consecutively. Pts were monitored for adherence for a median time of seven cycles [IQR:4-12]. The two arms were well balanced for all baseline characteristics, besides steroids use (100% vs 9%, $p < 0.001$), as ABI requires steroids, and Charlson score, whose range was higher for ENZ pts than ABI pts (range 10-12 vs 8-11, $p = 0.028$). Overall, the percentage of non-adherence was higher for ABI than ENZ (5.2 vs 4.2 missed/prescribed pills, $p < 0.001$). After Bonferroni correction, geriatric G8 score correlated with non-adherence ($p = 0.004$, $r = 0.18$). Pts on ENZ tended to report missing pills more frequently than ABI pts, and the reason for non-adherence was forgetfulness (42% vs 17%, $p < 0.001$). A third of pts never completed the clinical diary given at each cycle. Overall survival (OS) within the study was 48.8 months. However, patients on ABI had a longer progression-free survival (PFS) compared to pts treated with ENZ (median PFS 28.4 [24.2-32.5] vs 23.1 [18.2-28.1] months, $p = 0.041$). **Conclusions:** Physicians tend to treat elderly and frailer people with ENZ. mCRPC patients on ENZ are more adherent to treatment, with forgetfulness being a potential barrier. Nevertheless, OS and PFS were consistent with those from ABI and ENZ pre-chemo registration studies, with ABI conferring a longer PFS in our study population. Research Sponsor: None.

12045 **Poster Session**

Early patient-reported outcomes are a promising predictive factor of cancer progress and outcome in older patients: The *EPROFECY* study. *First Author: Carole Helissey, Clinical Research Unit, Military Hospital Begin, Saint-Mandé, France*

Background: Contrary to commonly-held beliefs, older patients (OPs, aged 70 or more) in oncology are compliant with the use of a telemonitoring digital platform. Such a tool allows the medical team to gain detailed knowledge of the tolerance profile of patients, and help monitor and maintain their quality of life, which is a particularly important goal for older patients. The EPROFECY study assesses the predictive power of the patient health status in the first month of treatment, evaluated with the digital telemonitoring platform Cureety, on survival. **Methods:** This prospective study was conducted at the Military Hospital Bégin on OPs. Patients were allowed to respond to a symptomatology questionnaire based on CTCAE v.5.0, personalized to their pathology and treatment. An algorithm evaluated the patient status based on reported adverse events: correct (A), compromised (B), to be monitored (C) and critical state (D). For A/B (good health status), the patient received therapeutic advice to help manage each of the reported adverse events. For C/D (poor health status), the patient was invited to call the hospital. To assess the early tolerance of patience to their treatments, we determined the health status in the 1st month after initiation of treatment, which was classified as "Good health" (GH, majority of A/B reports) or "Poor health" (PH, majority of C/D reports). The primary endpoint was to assess if the first-month tolerance is a predictive factor of progression free-survival (PFS). The secondary endpoint was to assess if the first-month tolerance is a predictive factor of overall survival (OS). **Results:** Sixty-one patients were enrolled between July 1st, 2020 and September 30th, 2021. The median age was 78.0 years (range 70.0 – 99.0), with 81% presenting a metastatic stage, and the most represented cancer being prostate cancer. The median follow-up was 8.2 months. Overall, 2299 ePRO were completed, 89% (n= 2036) corresponding to a "correct" or a "compromised" state and only 11% (n=263) corresponding to a state "to be monitored" or "critical". Based on the first month of questionnaires, 62% of the patients were classified in the GH group, and 38% in the PH group. The PFS ratio at 6 months was 64.6 % in GH vs 23.4 % in PH (HR = 0.1980, 95% CI = 0.04431–0.8845, p = 0.0339). The OS ratio at 6 months was 100% in GH versus 95.5 % in PH (HR: 0.69, 95 % CI = 0.06 – 8.29, p = 0.77). **Conclusions:** This is the first study that assesses the use of PRO-based tolerance as a predictive factor of treatment response in older individuals. We demonstrated here a significant 80% reduction in the risk of progression in OPs that exhibited a good first-month tolerance. This suggests that e-PRO follow-up might be an effective predictor of response and a tool to treatment plan. Research Sponsor: None.

12046 **Poster Session**

New strategies for multimodal analgesia in patients with high-risk geriatric cancer in perioperative period. *First Author: Sergey V. Tumanyan, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation*

Background: Perioperative pain (POP) in high-risk geriatric patients with cancer (HRGCP) is an important issue. The purpose of this study was to optimize perioperative analgesia in HRGCP. **Methods:** This randomized study of the quality and effectiveness of perioperative analgesics included 115 HRGCP aged 64-88 years who underwent surgeries on the organs of the chest, abdomen and pelvis for various cancers. The patients were divided into 2 groups. Group 1 (n = 52): patient-controlled analgesia with morphine and nonsteroidal anti-inflammatory drugs (NSAIDs); group 2 (n = 63): ultrasound-guided bilateral transversus abdominis plane (TAP) block with ropivacaine. Intraoperative and perioperative analgesia was maintained with a continuous infusion of lidocaine, magnesium sulphate, microdoses of fentanyl and NSAIDs. Results and pain syndrome were assessed by monitoring the Efficacy Safety Score (ESS), personal and reactive anxiety, stress response (cortisol, insulin, lactate, glucose), rates of functional activity recovery, the need for opioid analgesics, frequency of postoperative nausea and vomiting (PONV). **Results:** Patients in group 2 showed a significant decrease in the perioperative need for opioid analgesics and significantly decreased POP. Analysis of variance of mean values revealed statistically lower scores of ESS, visual analogue scale and POP ($p < 0.05$) during the first 24 hours of perioperative period in group 2 compared with group 1. Patient-controlled analgesia showed analgesic effect in 88.5% ($p < 0.05$) cases. However, the effect was less pronounced, compared to multimodal analgesia, and did not reduce cognitive disorders. In group 2, opioid-sparing analgesic effect was 95.3% ($p < 0.05$). Multimodal analgesia reduced the stress response ($p < 0.05$) in perioperative period and did not cause cognitive dysfunction while reducing PONV episodes, unlike morphine. Despite the minimal doses of narcotic analgesics in group 2, multimodal analgesia provided safe analgesia and functional activity recovery in perioperative period with minimum negative effects of opioids. **Conclusions:** The strategy of multimodal analgesia based on a combination of intraoperative TAP block and infusions of lidocaine and microdoses of fentanyl can significantly improve the quality of analgesia in perioperative period. Research Sponsor: None.

12047 **Poster Session**

Locoregional therapy trends by frailty and life expectancy in older adults with T1N0 hormone receptor-positive breast cancer. *First Author: Christina Ahn Minami, Division of Breast Surgery, Department of Surgery, Brigham and Women's Hospital, Breast Oncology Program, Dana Farber/Brigham and Women's Cancer Center, Boston, MA*

Background: Women >70 years old with T1N0 hormone receptor-positive (HR+) breast cancer face complex locoregional therapy decisions, as breast surgery type, and omission of axillary surgery or radiation therapy (RT), do not impact overall survival. Although frailty status and life expectancy (LE) ideally factor into therapy decisions, their impact on decision-making is unclear. We sought to identify trends in, and factors associated with locoregional therapy type by frailty and LE, and to determine if therapy type was associated with cause of death. **Methods:** Women >70 years old with T1N0 HR+/HER2-negative breast cancer diagnosed 2010-2015 were identified in SEER-Medicare. Stratified by validated claims-based frailty (Kim et al) and LE (Tan et al) measures, trends in therapy (lumpectomy, lumpectomy + axillary surgery, lumpectomy + RT, mastectomy, lumpectomy + axillary surgery + RT, and mastectomy + axillary surgery, with the last two combinations deemed "more intense" therapy) were analyzed. Generalized linear mixed models were used to identify factors associated with therapy receipt (breast surgery type, axillary surgery, and RT) and, among the women who died in this cohort, to explore potential associations between local therapy received and cause of death. **Results:** Of the 16,188 women included, 21.8% were frail, 22.2% had a LE<5 years, but only 12.3% were both frail and had a LE<5 years. In frail women who had a LE < 5 years, more intense therapy regimens decreased significantly (lumpectomy + axillary surgery + RT: 27.5% to 17.3%, p<0.001; mastectomy + axillary surgery: 20.8% to 13.9%, p=0.02) over the study period. However, in 2015, 30% of frail women with a LE<5 years still underwent a more intense regimen. On multivariable analysis, frailty and LE<5 years were associated with a lower likelihood of axillary surgery (frailty: OR 0.65, 95% CI [0.57-0.73]; LE<5 years: OR 0.67, 95% CI [0.59-0.76]) and RT (frailty: OR 0.77, 95% CI [0.69-0.86]; LE<5 years: OR 0.73, 95% CI [0.65-0.83]), but not with breast surgery type. Of the 1868 women who died, 306 (16.4%) died of breast cancer and those undergoing more intense therapy were as likely to die of breast cancer vs other causes (Table). **Conclusions:** In older women with T1N0 HR+ disease, rates of more intense therapy are decreasing but 30% of frail women with a limited LE still underwent more intense therapy in the final study year. As therapy intensity does not affect breast cancer-specific mortality, appropriate de-escalation of locoregional therapy is needed. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

	OR for Breast Cancer-Specific Death vs Other Cause	95% CI
Lumpectomy + Axillary Surgery + RT	REF	REF
Lumpectomy + Axillary Surgery	0.52	**0.32-0.84**
Lumpectomy + RT	0.86	0.45-1.65
Lumpectomy	0.79	0.50-1.24
Mastectomy + Axillary Surgery	0.69	0.46-1.03
Mastectomy	0.68	0.30-1.54

Adjusted for frailty, LE, diagnostic year, race/ethnicity, income, SEER region, tumor grade, stage, histology.

12048 **Poster Session**

Predictive factors of toxicity of immune checkpoint inhibitors (ICI) in older patients with lung cancer: The ToxImmune study. *First Author: Carole Helissey, Clinical Research Unit, Military Hospital Begin, Saint-Mandé, France*

Background: Immunotherapy (Im) improved the survival of patients with lung cancer. It may be responsible for adverse events impacting these patients' quality of life. We have few data on the tolerance of older cancer patients (OP) to immunotherapy. The Toximmune study aims to describe the safety of older lung cancer patients to Im and identify clinical, biological and radiological markers that can help to predict immune-related adverse events for OP. **Methods:** All patients aged 60 years and older who had received at least one dose of ICI between June 2015 and December 2020 and diagnosed with lung cancer were included. We collected patients' baseline demographic characteristics, biological blood markers and imaging by PET-scanner. All adverse events (AEs) and immune-related AEs (irAEs) were recorded (CTCAE V.5.0). **Results:** 49 patients were included, median age was 71 (range 61-97). The incidence of grade 2 and grade 3-4 was 34% and 6% respectively. The main irAEs reported were: asthenia in 51% patients after 13.5 months median delay (grade ≥2 in 22%),musculoskeletal disorders in 45% after 21 months median delay (grade ≥2 in 10%), pneumonitis in 37% after 21 months median delay (grade ≥2 in 10%), and colitis in 35% after 21 months median delay (grade ≥2 in 6%). Female sex, primitive tumor SUV max < 5, number of metastases ≥ 3, prior systemic therapy > 1, PLR < 250 were significantly associated with a risk of toxicity in univariate analysis ($p < 0.05$) We developed the ToxImmune score (0, 1, or ≥2) to predict the risk of having a grade ≥2 adverse event by adding the following risk factors: Primitive Tumor SUV < 5 = 1, Number of metastases ≥3 = 1, And L1 = 0 vs > L1 = 1. The incidence of grade ≥2 adverse events was 31%, 35% and 86% with ToxImmune scores 0, 1 and 2 respectively ($p = 0.032$). Median overall survival times (OS) & progression-free survival (PFS) were 21.8 & 21 months, 15.1 & 6.6 months, and 9.8 & 2.1 months for ToxImmune scores 0, 1 and ≥ 2 respectively ($p = 0.06$ & $p = 0.001$). There was significant association between the ToxImmune score and the risk of "progressive disease" at the first assessment of the disease: 16% for score = 0, 48% for score = 1, and 71% for score = 2, ($p = 0.01$). **Conclusions:** The quality of life is our goal for OP care. The ToxImmune score, which is based on objective clinical parameters, identifies OP with a significant higher risk of severe adverse events. Also, this score was significantly associated with patients' PFS risk of developing rapid tumor progression. It could be used in clinical practice to personalize toxicity surveillance in OP treated for lung cancer with immunotherapy. This score will be validated in larger prospective cohorts. Research Sponsor: None.

12049 **Poster Session**

Geriatric assessment (GA) and the influence on the variability of treatment recommendations for elderly patients (pts) with gastrointestinal (GI) tumors. *First Author: Moritz Buettelmann, Technical University Carl Gustav Carus, Dresden, Germany*

Background: GA is recommended to guide therapy for elderly cancer pts. To assess whether GA results influence the recommended treatment and the inter-oncologist variability of treatment recommendations, we conducted a case-vignette-based study in medical oncologists (MOs). **Methods:** MOs were asked to give medical treatment recommendations for GI cancer pts in three steps: (1) based on tumor findings alone to simulate the guideline recommendation for a "50-year-old standard patient (pat.) without comorbidities", (2) for the same tumor situation in an elderly pat. according to the medical history, comorbidities, lab values and a short video simulating the clinical consultation situation and (3) after in addition the results of a full GA were disclosed (Barthel index, Cumulative Illness Rating Scale, G8, Geriatric Depression Scale, Mini Mental Status Examination, Mini-Nutritional-Assessment [MNA], Time Get Up and Go, EORTC-QLQ30 and stair climb test - each with short interpretation aid). Each MO voted for 2-4 randomly allocated pts out of a pool of 10 pts with mean age 78.5 years. A slider (like a visual analogue scale) was used to express the grade of recommendation for several treatment options per patient. The means and variances for each treatment option were calculated and compared for analysis. **Results:** Seventy German MOs had given 164 treatment recommendations that were substantially different for elderly compared to younger pts. The recommendations had a significantly higher variance for elderly pts than for the "standard" pts ($p < 0.0001$) indicating a lower inter-oncologist agreement regarding the treatment recommendations in elderly pts. MOs with > 6 years working experience as specialist had no lower variance in their recommendations. There was a non-significant trend towards a lower variance if the MOs were based at outpatient units of hospitals (compared to MOs working with in-patients or as private oncologists) and for MOs working at larger hospitals (> 800 beds) compared to those based at smaller ones. The knowledge on the full GA results had marginal influence on the treatment recommendations itself or its variance, only ($p = 0.92$). In the survey, the geriatric tools were rated more than two times higher as being meaningful (53%) and useful (49%) than they were used in clinical practice (19%). The most used tool in the routine care for geriatric pts was the MNA (30%). **Conclusions:** There is a large variability regarding the "optimal" treatment in geriatric pts without meaningful improvement with larger working experience. Although the recommended therapeutic regime varied in elderly pts and the MOs rated the GA results as "useful", the GA results did not influence the individual recommendations or its variance, and GA is rarely used in daily practice indicating that more research on an effective implementation into the clinical practice is needed. Research Sponsor: None.

12050 **Poster Session**

Factors associated with the evaluation of geriatric assessment (GA) domains by oncology specialists in Mexico. *First Author: Haydee Cristina Verduzco-Aguirre, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, DF, Mexico*

Background: Use of GA by oncology specialists is low in Mexico, with some of the domains of the GA more frequently assessed than others in everyday practice. We aimed to explore factors associated to the evaluation of individual GA domains by Mexican cancer care providers. **Methods:** Secondary analysis of a mixed-methods study which consisted of an online cross-sectional survey of Mexican oncology specialists and follow-up interviews on the use of GA in cancer care. We performed multiple logistic regression analyses with frequency of evaluation of specific GA domains as the dependent variable (dichotomized as never/sometimes vs most of the time/always). Independent variables included age, gender, medical specialty, and practice size of the survey respondent, presence of a geriatrician in main practice site, and perceived confidence in managing common situations in older adults relevant for each GA domain (dichotomized as not at all/mildly vs very/completely). A p-value of < 0.05 was considered significant in each model. **Results:** Of 196 survey respondents, 62% were male, 50% surgical oncologists, 51% took care of > 10 patients per day, and 61.7% had access to a geriatrician at their main practice site. Frequently (most of the time/always) evaluated domains included: comorbidities (94.4%), daily function (72.9%), nutrition (67.3%), cognition (54.1%), depression (42.9%) and falls (42.3%). Self-perceived confidence in managing dementia (OR 2.72; 95% CI 1.42-5.51, $p = 0.008$) and being a surgical oncologist (OR 2.80; 95% CI 1.29-5.72, $p = 0.003$) were associated with increased evaluation of cognition. For nutrition, only self-perceived confidence in nutritional evaluation was associated (OR 3.86; 95% CI 2.0-7.46, $p < 0.001$). For comorbidities, self-perceived confidence in managing osteoporosis (OR 5.61; 95% CI 1.03-30.4, $p = 0.046$). For falls, significant factors included age (OR 1.04; 95% CI 1.01-1.07, $p = 0.004$), practice size (OR 0.46; 95% CI 0.23-0.91, $p = 0.026$), and self-perceived confidence in evaluation and prevention of falls (OR 6.31; 95% CI 3.19-12.46, $p < 0.001$). Age (OR 1.03; 95% CI 1.01-1.06, $p = 0.011$) and self-perceived confidence in managing depression (OR 2.52; 95% CI 1.33-4.78, $p = 0.005$) were associated with evaluation of depression. For daily function, no variables were significantly associated. Follow-up interviews showed quality and appropriateness of evaluations may not be ideal, such as asking only about orientation and level of consciousness when evaluating cognition. **Conclusions:** Self-perceived confidence in evaluating and managing common situations in older adults is associated with the evaluation of GA domains as part of everyday practice among cancer care providers in Mexico. This analysis supports the use of educational interventions to boost knowledge and confidence regarding the proper use of validated GA tools among oncology specialists. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

12051 **Poster Session**

Nurse navigator–initiated geriatric assessments in hematology/oncology clinics. *First Author: John L. Shaia, Permanente Medical Group, San Francisco, CA*

Background: As the number of older adults with cancer continues to grow, there is an urgent and unmet need to implement geriatric assessments and toxicity screening tools (G8 and CARG toxicity tool) for patients 65 and older with a cancer diagnosis in real-world settings. Studies of these tools show completion rates of 20-35% when administered by a physician. To determine if nurse navigators could increase completion rates, we implemented a pilot in seven community cancer centers within an integrated health system. **Methods:** A pilot project of G8 and CARG toxicity tool implementation was completed at seven community cancer centers from May 1,2021 to December 31,2021 in patients age ≥ 65 years, with solid or malignant hematologic cancer diagnosis. G8 was administered at seven sites and CARG was assessed in addition to G8 on solid tumor patients undergoing chemotherapy at four of the seven sites. Referrals to nutrition, audiology, physical therapy, psychiatry, and neurology were sent by nurse navigators based on assessment results. **Results:** The total number of eligible patients for G8 was 1372, with 1082 (78.9 %) successfully completing assessment, and the total number of eligible patients for CARG toxicity tool was 563 with 516 (91.6%) successfully completing assessment. The median age of patients completing assessment was 74 years old (range 65-100) and 52% were female. The cohort included Asian / Pacific Islanders (23%), Black (15%), Hispanic White (8%), and Non-Hispanic Whites (51%). Most common cancers included genitourinary cancer (18%), breast cancer (17%), upper GI cancer (15%), and thoracic cancer (13%). The assessments resulted in referrals to multiple services including nutrition (193 referrals), audiology (30), physical therapy (18), psychiatry (5), and neurology (5). **Conclusions:** Nurse navigators can successfully implement G8 and CARG toxicity tool in hematology-oncology clinics in a broad range of cancer types at a high rate with resultant referrals to multiple supportive services in real-world settings. Research Sponsor: None.

12052 **Poster Session**

Remote geriatric assessment program for older patients starting new chemotherapy treatment in Brazil. *First Author: Cristiane Decat Bergerot, Centro de Cancer de Brasilia, Instituto Unity de Ensino e Pesquisa, Brasilia, Brazil*

Background: Older cancer patients in developing countries face considerable challenges in obtaining access to specialized medical attention, often due to a lack of human resources and healthcare infrastructure. This study sought to explore the benefit of a remote, validated geriatric assessment (GA) program for older patients starting chemotherapy in Brazil. **Methods:** Older adults (65+ years) beginning a new chemotherapy treatment regimen in Brazil were recruited. Through telehealth, patients were assessed with GA before starting chemotherapy treatment for any type of solid cancer and at a follow-up visit (3 months after enrollment). GA results were discussed by a multidisciplinary team (e.g., geriatrician, psychologist, nutritionist) and recommendations were determined. Outcome measures included chemo toxicity scores (CARG, scale 0-19), physical symptoms (FACT-G, scale 0-108) and activities of daily living (IADL, scale 0-5 for men and 0-8 for women, or scale 0-1 for IADL ratio). Descriptive statistics were generated, and paired t-tests were used to evaluate the change in these measures over time. **Results:** A total of 51 older patients from 5 different Brazilian states (Amazonas, Distrito Federal, Espirito Santo, Pernambuco and Rio Grande do Sul) have been enrolled to date. The mean distance from a patients' home to their place of cancer treatment was 21 miles (range: 3-101 miles). Participants had a mean age of 76.5 years (SD = 7.6) and were predominantly female (57%), white (57%), married (61%), and had a high school degree or more (65%). Patients were mostly diagnosed with gastrointestinal (39%) or gynecological (20%) cancers; 55% of patients were diagnosed with a stage IV disease. The majority of patients (80%) were referred to appropriate remote services based on the GA; including geriatricians (41%), nutritionists (39%) and/or psychologist (16%). At the time of abstract submission, data from 34 complete cases were available for longitudinal analysis, in which we observed a decrease in chemo toxicity scores (M_1= 6.65, M_2= 5.88, p = 0.035) and an improvement in FACTG (M_1= 92.94, M_2= 98.53, p < 0.001). The improvement in IADL ratio was not significant (M_1= 0.79, M_2= 0.85, p = 0.069). **Conclusions:** This novel, ongoing study is, to our knowledge, the first to implement a remote GA program in Brazil. Our preliminary findings suggest that a remote GA program, with appropriate referrals to specialists, may increase the reach of supportive services and improve cancer care in developing countries. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

12053 **Poster Session**

Association of polypharmacy and potential drug-drug interactions with adverse outcomes in older adults with advanced cancer receiving systemic treatment. *First Author: Mostafa Refaat Mohamed, University of Rochester James Wilmot Cancer Institute, Rochester, NY*

Background: Polypharmacy (PP) is common in older adults starting cancer treatment and associated with increased risk of potential drug-drug interactions (PDI). PP and PDI may affect treatment-related outcomes in older patients. This study evaluates the association of PP and PDI with systemic treatment adverse outcomes in older adults with advanced cancer. **Methods:** This secondary analysis of prospectively collected data from the GAP 70+ Trial (NCT02054741; PI: Mohile) enrolled patients aged 70+ with advanced (i.e. incurable) cancer; had ≥1 geriatric assessment domain impairment; and planned to start a new chemotherapy regimen or another regimen with high risk of toxicity. PP was assessed prior to initiation of treatment and defined as concurrent use of ≥8 medications (meds). PDI among all drugs were reviewed prior to initiation of treatment using Lexi-Interact® Online with category D and X considered "major PDI". Study outcomes were assessed within 3 months of treatment initiation and included: 1) total number of Grade ≥2 toxicities according to National Cancer Institute Common Toxicity Criteria; 2) total number of Grade ≥3 toxicities; and 3) early treatment discontinuation due to toxicity. Multivariable linear and logistic regression models were used to examine the association of PP and PDI with treatment adverse-outcomes adjusted for age, gender, cancer type, comorbidity, physical function, social support, and study arm. **Results:** Among 718 participants, the mean age was 77 (range 70-96); 43% were females; and 57% had lung or gastrointestinal cancers. The median number of meds was 5 (range 0-24); 28% received ≥8 concurrent meds; and 25% had ≥1 major PDI. The mean number of Grade ≥2 toxicities for patients with PP was 9.8 versus 7.7 in patients without PP (adjusted β=1.87, standard error [SE]=0.71, P<0.01). The mean number of Grade ≥3 toxicities for patients with PP was 2.9 versus 2.2 in patients without PP (adjusted β=0.59, SE=0.29, P=0.04). Patients with ≥1 major PDI had 59% higher odds of early treatment discontinuation versus those without major PDI (adjusted odds ratio 1.59, 95% confidence interval=1.03-2.46, P=0.03). There was no significant association between PP and early treatment discontinuation. Major PDI were not significantly associated with toxicity (Ps>0.05). **Conclusions:** In a cohort of vulnerable older adults with advanced cancer, PP and PDI are associated with increased risk of systemic treatment adverse outcomes. Providing meaningful screening and interventional tools to optimize medication use may improve treatment outcomes in these patients. Funding:UG1-CA18996, U01CA233167. Research Sponsor: U.S. National Institutes of Health.

12054 **Poster Session**

Prevalence of frailty for middle-aged and older adults starting a new line of systemic cancer treatment: Is age just a number? *First Author: Mackenzi Pergolotti, The University of North Carolina at Chapel Hill, Chapel Hill, NC*

Background: Frailty is associated with adverse outcomes and increased risk of mortality for older adults (>60 years) with cancer. Geriatric assessment (GA) has gained popularity in routine cancer care as a clinical tool to screen for frailty in older adults starting a new line of cancer treatment, and to guide clinical decision making during systemic therapy. Emerging research indicates GA may also be useful to identify frailty in middle-aged adults (40-60 years) with cancer, but more research is needed. In this study, we used GA data to compare the prevalence of frailty between middle-aged and older adults starting a new line of systemic cancer treatment. **Methods:** Participants included adult patients with cancer due to begin a new line of systemic therapy at a multi-office community-based oncology private practice and enrolled in a clinical trial (NCT04852575). At baseline, participants completed an online version of the Cancer and Aging Resilience Evaluation (CARE) — a patient-reported GA adapted from the Cancer and Aging Research Group. Frailty score was constructed using a 44-item deficit accumulation method and categorized as frail (>0.35), pre-frail (0.2-0.35) or robust (0-0.2) using published cutoffs. We grouped participants by age, middle-aged (40-60 years) or older-aged (>60 years), then used independent t-test and chi-squared statistic to compare frailty scores (continuous) prevalence of frailty (categorical) between groups. Hypothesis testing was two sided and the level of significance was 0.05. **Results:** Participants (n=96) were predominantly female (62%), Caucasian (68%) and beginning first line systemic therapy (69%) for either newly diagnosed cancer or new recurrence of disease; median time since diagnosis was 1 month. Common cancer types included: breast (34%), gastrointestinal (23%), hematologic (15%) and lung (12%). Disease stage was predominantly stage 3 (28%) or stage 4 (38%). When comparing middle-aged (n=31, M_{age} = 54.74 ± 4.79, range = 41.23 – 59.98 years) vs. older adult -groups (n=65, M_{age} = 70.27 ± 5.91, range = 60.64 – 84.29 years), there was no significant difference in mean frailty score (p = 0.22) or the proportion categorized as frail vs. pre-frail vs. robust (p = 0.32); see Table. Stage of disease and prevalence of common cancer types was similar between age groups (p>.05). **Conclusions:** In our cohort, middle and older aged patients who completed patient-report GA had similar prevalence of frailty before starting systemic therapy. Using the GA as a functional-age assessment to detect frailty for adults of varied ages could allow for earlier intervention aimed at impacting tolerance to therapy. Clinical trial information: NCT04852575. Research Sponsor: None.

Frailty scores and categorization for middle- vs. older-aged.

	Frailty score, *M* ± SD	% Frail	% Pre-frail	% Robust	Between-group difference
Middle-aged	0.22 ± 0.10 (0.07 – 0.54)	8.2%	36.7%	55.1%	p>.05
Older adult	0.24 ± 0.10 (0.13 – 0.59)	14.3%	40.8%	44.9%	

12055 **Poster Session**

Using G8 and carg toxicity score to predict emergency room (ER) visits, hospitalizations, and mortality in older patients with newly diagnosed cancer. *First Author: Amit Arora, Kaiser Permanente, Fremont, CA*

Background: ASCO and NCCN guidelines recommends Geriatric Screening (G8) and CARG chemotherapy toxicity tool assessment for all older patient before receiving chemotherapy as high risk G8 (< 14) and CARG (≥10) are associated with increased chemotherapy toxicities. We conducted a pilot to understand predictors of high risk G8/CARG and if high risk G8/CARG can predict ER/hospitalization and mortality in community-based Oncology clinics in Kaiser Permanente Northern California. **Methods:** G8 and CARG were administered to all patients ≥65 years with newly diagnosed cancer from 5/1/21 to 12/31/21. Patients were followed for at least 30 days after assessment for ER/hospitalization and mortality. The median follow-up days from referral to ER/hospitalization was 96 days (range 0-273 days). Chi-Square tests were applied for G8/CARG risk category with demographic and utilization variables. Cox proportional-hazards models were performed to see the association between G8/CARG score and days from referral to ER/hospitalization, and days from referral to death, adjusted for age, sex, race, and cancer type. **Results:** During this pilot 1082 patients (52% female) completed G8, and 516 patients (57% female) completed CARG. Percentage of patients with high risk G8/CARG increased with each decade (G8: < 70 yrs (58%), 70-79 (63%), 80-89 (90%), ≥ 90 (100%); p < 0.001); (CARG: < 70 yrs (19%), 70-79 (43%), 80-89 (65%), 90 and above (81%); p < 0.001). More men than women had high risk CARG (48% vs. 39%, p = 0.012). Ethnicity was not associated with high risk G8 / CARG. Upper GI cancers (UGI) were associated with highest proportion of patients with high risk G8 (88%) and CARG (58%) whereas breast cancer (BC) had the lowest proportion of patients with high risk G8 (46%) and CARG (14%); p < 0.001. In the adjusted G8 model for ER/hospitalization, high risk G8 vs low risk (HR 1.58, CI 1.23-2.03, p = 0.0003) was related to ER/hospitalization. In the adjusted CARG model for ER/ hospitalization, high risk CARG vs low risk (HR 2.42, CI 1.37-4.29, p = 0.0024) and medium risk CARG vs low risk (HR 2.17, CI 1.23-3.83, p = 0.0074) were related to ER/hospitalization. In the adjusted G8 model for mortality, high risk G8 vs low risk (HR 4.52, CI 2.28-8.97, p < 0.0001) were related to mortality. In the adjusted CARG model for mortality, high risk CARG vs low risk (HR 3.92, CI 1.21-12.74, p = 0.023) and medium risk CARG vs low risk (HR 1.59, CI 0.48-5.33, p = 0.45) were related to mortality. **Conclusions:** This community-based pilot shows that increasing age is associated with high risk G8 / CARG. G8 and CARG assessment at the time of initial cancer diagnosis can predict early ER/hospitalization and mortality in older adults with cancer and should be included as a part of initial assessment. Research Sponsor: None.

12056 **Poster Session**

Remote symptom monitoring (RSM) during treatment for metastatic prostate cancer (mPC) in older men: Feasibility and efficacy. *First Author: Shabbir M.H. Alibhai, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Emerging data support multiple benefits of RSM during chemotherapy to improve outcomes. These studies do not focus on older adults and do not include non-chemotherapy strategies. mPC represents a major burden in older men. Although both chemotherapy and androgen receptor axis-targeted therapies (ARATs) prolong survival, toxicities are substantial and increased in older men. Understanding the feasibility of RSM and key symptoms experienced by men with mPC on treatment is crucial to designing appropriate supportive care interventions. We aimed to assess RSM feasibility and understand key symptoms during treatment with chemotherapy or an ARAT among older men. **Methods:** Older adults aged 65+ starting chemotherapy, an ARAT, or Radium-223 for mPC were enrolled in a prospective observational multicentre study. Participants completed the Edmonton Symptom Assessment Scale (ESAS) on weekdays online or by phone. Weekly detailed questionnaires assessed mood, anxiety, fatigue, insomnia, and pain. Notifications were sent to the clinical oncology team with severe symptoms (ESAS 7 or higher). Study duration was the first treatment cycle (~3-4 weeks). Feasibility data were analyzed descriptively. Linear mixed effects models examined symptoms over time and by cohort. Clinician responses were assessed descriptively. **Results:** A total of 90 men were included (mean age 76.5y, 48% ARAT, 38% chemotherapy, and 14% Radium-223, 42% frail by Vulnerable Elders Survey-13 cutoff of 3+). Approximately half the patients preferred phone-based RSM. Patients provided RSM responses in 1,874 of approximately 2,000 (94%) instances. In the combined cohort, the most common symptoms of moderate to severe intensity (ESAS 4 or higher) occurring at least once were poor well-being (66%), fatigue (62%), reduced appetite (56%), insomnia (54%), and pain (46%). Symptom patterns were similar between chemotherapy and ARAT groups. Moderate to severe symptoms were more common and lasted longer among frail than non-frail men. Symptoms tended to remain stable or improve over the course of 3-4 weeks of RSM. 89% of participants were satisfied or very satisfied with RSM, although daily reporting was reported by several as burdensome. 45% had severe symptoms from RSM leading to informing the oncology care team, 79% of whom were followed up by a nurse or physician, and 12% of treatments were modified. **Conclusions:** RSM is feasible, acceptable to older adults, and identifies clinically relevant symptoms, but accommodation needs to be made for phone and the optimal frequency of RSM needs to be established. Poor well-being, fatigue, reduced appetite, and insomnia occurred in over half of participants. Longer-term follow up will be important. Research Sponsor: Prostate Cancer Canada.

12057 **Poster Session**

Using CT-based body composition metrics and frailty index in predicting survival among older adults with cancer. *First Author: Smith Giri, University of Alabama at Birmingham, Birmingham, AL*

Background: Older adults with cancer are at an increased risk of treatment related toxicities and excess mortality during cancer treatment. While altered body composition and frailty are associated with worse survival among older adults with cancer, no prior study has examined their combined influence on survival prediction. **Methods:** Prospective study of older adults (≥60 years) undergoing geriatric assessment (GA) at initial visit with a medical oncologist at UAB from 9/2017-07/2021 with available abdominal computed tomography (CT) within 60 days of GA. Using multi-slice CT images from T12 to L5 level, volumetric skeletal muscle (SMV), visceral (VATV) and subcutaneous (SATV) adipose tissues, and skeletal muscle density (SMD), were derived. Sex-specific z-scores for each measure were determined. A 44-item frailty index was obtained, using the deficit accumulation model. Overall survival (OS) was defined as time from GA to death or last follow-up (11/8/2021). Kaplan-Meier estimates of survival rates were compared using log-rank statistics. Multivariable cox regression models were used to predict OS in a random sub-sample (1:1 split of training:validation set), sequentially adding frailty and each body composition measure and assessing improvement with likelihood ratio tests and Harrel's C statistic. **Results:** 815 patients were included (median age 68 years, 61% men, and 75% non-Hispanic Whites. 73% had gastrointestinal malignancies (stage III, 25%, stage, IV 48%). 32% were frail, 31% pre-frail. There was a weak negative correlation between height-adjusted SMV and frailty (r = -0.16), particularly among men (r -0.24). Over a median follow-up of 25.7 months (range 0.3-49.6 months), 268 patients (33%) died. The 2-year survival rate was 75.9%, 68.5% and 52.2% among robust, pre-frail and frail (log-rank p < .001), respectively. In multivariable models adjusted for age, sex, race, cancer type and cancer stage, being frail (vs robust) (Hazards Ratio, HR = 2.32; 95%CI: 1.69-3.2; $p < .001$) and higher skeletal muscle volume (HR = 0.85; 95%CI: 0.72-0.99; $p = 0.04$, per SD increment) were independently associated with OS. Adding body composition and frailty to clinical variables led to significant improvement in prediction (Harrel's C increased from 0.69 to 0.74). In the validation set, discrimination was similar (Harrel's C = 0.72) and plots suggested good model calibration. **Conclusions:** CT-based body composition metrics and frailty are independent predictors of OS among older adults with cancer and improve survival prediction compared to routine clinical risk factors. Research Sponsor: None.

12058 **Poster Session**

Complementary and alternative medicine use and recommendations for discontinuation of supplements in an integrative oncology clinic. *First Author: Stacy D. D'Andre, Mayo Clinic, Rochester, MN*

Background: It is well established that many patients with cancer are taking dietary supplements (DS) and alternative medicines and often do not disclose such to their care teams. There is potential for harm in several ways: 1) interactions with their medications that may increase side effects, 2) interactions with their treatment that may lead to decreased efficacy, 3) direct toxicity from the supplement 4) financial toxicity. We have recently started a new Integrative Oncology service to help counsel patients about improving lifestyle factors and assist patients with safe and evidence-based integrative treatments and supplements. **Methods:** Patient data (N=100) were collected prospectively from an Integrative Oncology Clinic. The number and type of DS were documented. Using the Natural Medicines Database (NMD), we determined whether supplements interacted with the patients' other medications or cancer therapies. We calculated the percentage of patients in which a recommendation for discontinuation of DS was recommended, along with the supporting reasons. We calculated the most common DS being taken and other alternative therapies beyond supplements. **Results:** Ninety-one percent of patients took DS, with an average of 5.5 per patient (range 0-20). The most common DS patients reported taking (%): Vit D (52), Vit C (41), Multivitamin (34), probiotic (27), B Vitamins (26), Ca (20), zinc (20), fish oil (18), cannabis (18), mushrooms (18), turmeric (17), magnesium (15), melatonin (14), biotin (11), coq10 (7), iron (8), VIT E (5), and glucosamine (5). Eighty-nine percent of patients using DS were on active cancer therapy. In thirty-five percent of patients, we recommended stopping some of their DS or other therapies. Number of patients using alternative therapies beyond DS: IV Vitamin C (5), Rick Simpson oil (high dose THC) (4), extreme diets (4), mistletoe (2), re-purposed meds (2); and one each was using hyperbaric O2, ozone, homeopathic, ayurvedic, insulin-potentiated chemo, miracle mineral cure, chelation, low dose naltrexone **Conclusions:** Cancer patients both on and off active treatment are using large numbers of DS with potential for adverse effects and/or decreasing efficacy of treatments. This study highlights the prevalence of DS and alternative medicine usage in cancer patients referred to an integrative oncology clinic and demonstrates the need for counseling about safe supplement use; in 35% of patients, discontinuation of DS was recommended. Research Sponsor: None.

Reasons for recommending discontinuation of supplements.

Reason for Recommending D/C supplement	%
Potential for toxicity (ex. bleeding, known toxicity, excess vitamins)	46
Potential to decrease the efficacy of treatment (ex. antioxidants, excess B12, iron)	37
Interaction with medications or cancer treatment (per NMD)	17

12059 **Poster Session**

Impact of circuit, interval-based exercise on insulin resistance and adiponectin among minority cancer survivors. *First Author: Cameron N. Christopher, Dana-Farber Cancer Institute, Boston, MA*

Background: Hispanic and Black adults have a heightened risk of metabolic syndrome compared to non-Hispanic white adults, increasing the risk of cardiovascular disease, diabetes, and co-morbid outcomes. Further, Hispanic and Black adults are more likely to be sedentary and obese than non-Hispanic white adults, leading to an increased risk of insulin resistance and poor metabolic health. Exercise improves cardiometabolic health, including insulin sensitivity and adiponectin, however few studies have focused on minority cancer survivors. The aim of our (NCT03284346) was to determine whether a 4-month circuit-based aerobic and resistance exercise intervention can improve insulin resistance and adiponectin levels in breast, prostate, and colorectal Hispanic and Black cancer survivors. **Methods:** Overweight or obese (BMI > 25.0 kg/m2), sedentary breast, prostate or colorectal cancer survivors who self-identified as Hispanic or Black were randomized to exercise (n = 30) or usual care (n = 10). Survivors in the 4-month supervised exercise intervention participated in a thrice weekly, circuit, interval-based moderate-vigorous aerobic (65-85% of VO_{2max}) and resistance (65-85% of 1-repetition maximum). Insulin resistance, assessed by Homeostasis Model of Assessment (HOMA-IR), and adiponectin levels were collected at baseline and post-intervention from fasting blood sample collection. Repeated-measures analysis of variance and t-tests were performed to assess within- and between-group differences. **Results:** The study sample was 66 ± 10.4 years old, Hispanic (55%), Black (45%), overweight (78%), and female (60%). Adherence to the intervention was 90% and post-intervention outcome measures were available on 100% of participants. Post-intervention, insulin resistance (within group mean difference: -3.2, p < 0.01; between group mean difference: -4.5, p < 0.01) and adiponectin levels (6.1 ug/mg, p < 0.01; 8.6 ug/mg, p < 0.01) significantly improved in the exercise group when compared to baseline and to usual care, respectively. **Conclusions:** A circuit, interval-based aerobic and resistance exercise intervention improved insulin resistance and adiponectin levels in breast, prostate, and colorectal minority cancer survivors. Accessible exercise interventions for minority cancer survivors may be effective to mitigate metabolic dysregulation and co-morbid conditions in survivorship and support cardiometabolic health. Clinical trial information: NCT03284346. Research Sponsor: Donations to the Dieli-Conwright Laboratory (patients donated money who had participated in previous studies).

12060 **Poster Session**

Symptom monitoring with patient-reported outcomes using a web app with alerting algorithms among patients with lung cancer (SYMPRO-Lung). *First Author: Annemarie Becker, Amsterdam University Medical Centers, Amsterdam, Netherlands*

Background: The use of patient reported outcomes (PROs) to monitor symptoms during and after cancer treatment can improve symptom management, health-related quality of life (HRQoL), and overall survival, especially when linked to an alert system. Previous studies used alerts to the health care provider (HCP), but will this also work when patients receive the alerts? The aim is to compare a reactive (patient receives alert) and an active (HCP receives alert) method of PRO symptom monitoring on symptom incidence and management during the first 15 weeks of treatment. **Methods:** SYMPRO-Lung is a Dutch multicenter stepped wedge RCT performed among lung cancer (LC) patients to monitor symptoms, using a PRO-CTCAE LC subset . The NCI scoring algorithm assessed the symptom severity. If symptoms exceeded a predefined threshold an alert was sent by email to the HCP (active arm) or to the patient (reactive arm). Differences between both study arms in baseline characteristics, symptom incidence and management, were assessed using chi-square tests. **Results:** In total, 244 patients (active arm n = 155, 64%, reactive arm n = 89, 37%) completed 2412 symptom checklists during the first 15 weeks of treatment, with a mean of 10 per patient (pp) (SD 4.3). A total of 673 alerts (28%) were triggered, with a mean of 3 (SD 2.1) pp in both arms. The top 3 symptoms that caused the app to send an alert were fatigue (n = 231, 19%), pain (n = 188, 16%), and constipation (n = 144, 12%). Decreased appetite, diarrhea, and nausea were significantly higher in the reactive arm compared to the active arm (see table). For 313 alerts (74%), telephone contact with a HCP was the only intervention needed. 57 Alerts (13%) were discussed during a planned outpatient's consultation in the week of the alert. For 39 alerts (9%) the patients were referred to another specialty (see table). However, 'no need to follow-up' (FU) was requested after 237 alerts (35%). For all symptoms, the no FU request was significantly higher in the reactive arm (n = 135, 32% vs n = 102, 40%), compared to the active arm (p-values between 0.02 and < 0.001). **Conclusions:** In both arms an average of 3 alerts pp were triggered. In the reactive arm, significantly more patients chose not to contact their HCP compared to the active arm. Future research needs to unravel the underlying mechanisms and the potential consequences of this observed difference between study arms. Clinical trial information: Trial NL7897. Research Sponsor: Roche, Other Foundation.

No. of symptoms that caused an alert with a sign. difference	Total n (%)	Active n (%)	Reactive n (%)	*p*-Value
Decreased appetite	108 (8.9)	57 (7.8)	51 (10.5)	.025
Diarrhea	79 (6.5)	39 (5.3)	40 (8.2)	.011
Nausea	64 (5.3)	29 (4.0)	35 (7.2)	.003
Interventions taken in direct response to alerts				< .001
Telephone contact	313 (73.5)	233 (85.0)	80 (52.6)	
Discussed during a planned consultation	57 (13.4)	10 (3.6)	47 (30.9)	
Referral to another specialty	39 (9.2)	22 (8.0)	17 (11.2)	
Extra consultation scheduled	17 (4.0)	9 (3.3)	8 (5.3)	

12061 **Poster Session**

Evaluation of social connectedness, loneliness, and anxiety among cancer survivors during the 2020-2021 winter surge of COVID-19 pandemic. *First Author: Hermine Poghosyan, Cancer Outcomes, Public Policy, and Effectiveness Research (COPPER) Center, Yale University, New Haven, CT*

Background: Limited research is available about cancer survivors' level of stress, social connectedness and loneliness during the COVID-19 that can put them at increased risk for poor physical and mental health. We estimated relative decreased rate of social connectedness and increased rates of loneliness/sadness and stress/anxiety among cancer survivors during the 2020-2021 winter surge of COVID-19 and investigated whether decreased social connectedness is associated with increased feelings of loneliness/sadness and stress/anxiety. **Methods:** This cross-sectional study used data from Medicare Current Beneficiary Survey COVID-19 Winter 2021 Supplement, nationally representative phone survey of Medicare beneficiaries living in community, conducted in March-April 2021. We included 1,836 respondents who self-reported cancer history (other than skin cancer). Outcomes were self-reported feelings of loneliness/sadness and stress/anxiety over the past 4 months. The independent variable was social connectedness defined as feeling less socially connected to family/friends over the past 4 months. We used weighted descriptive statistics and multivariable logistic regression adjusting for self-reported socio-demographics (age, sex, race, income), region, metropolitan residency, Medicaid eligibility, living alone, depression, having access to internet and health care. We applied sample weights to account for complex survey design with results generalizable to 9.5 million cancer survivors. **Results:** Out of 9505626 cancer survivors, 6.8% self-reported as Black, 7.1% Hispanic, 80.4% White, 59% women, 42.7% reported decreased social connectedness, 20.3% increased feeling of loneliness/sadness, and 40.0% increased feeling of stress/anxiety in the past 4 months. Women had higher rates of reporting increased feelings of loneliness/sadness (12.0% vs. 26.1%, P = < .001), stress/anxiety (30.0% vs. 46.6%, P = < .001), and decreased social connectedness (38.7% vs. 45.5% P = .028) than men in the past 4 months. Among self-reported racial and ethnic groups, Hispanics had the highest rates of reporting increased feelings of loneliness/sadness (31.2% vs. 20.5% of Whites vs. 10.2% of Blacks, P = .008) and stress/anxiety (54.0% vs. 39.4% of Whites vs. 31.2% of Blacks, P = .034). No statistically significant difference was found in social connectedness by self-reported race and ethnicity. Survivors who reported decreased social connectedness had higher odds of feeling more lonely/sad (adjusted OR = 3.67, 95%CI 2.85-4.72, P = < .001) and more stressed/anxious (adjusted OR = 2.63, 95%CI 2.1- 3.26, p = < .001) over the past 4 months. **Conclusions:** Increased feelings of loneliness/sadness and anxiety/stress in the past 4 months were prevalent among cancer survivors. Also, almost half of them reported decreased social connectedness at the end of the second year of COVID-19. Research Sponsor: None.

12062 **Poster Session**

Prevalence of pain symptoms among U.S. adult cancer survivors. *First Author: Xinwen Hu, Washington University School of Medicine, St. Louis, MO*

Background: Pain symptoms are common in cancer survivors. The life expectancy of US cancer survivors continues to raise. To date, the comprehensive pattern of pain symptoms in US cancer survivors by cancer history remains unknown. **Methods:** Data on pain symptoms and correlates were derived from a nationally representative sample of cancer survivors (n = 55,716, weighted population = 17,352,886) in the 1997-2018 National Health Interview Survey. Individuals who answered "yes" to the questions "During the past three months, did you have headache/facial/neck/low back pain/low back pain radiating to the leg" were considered as having pain symptoms at respective anatomical regions. The US national prevalence of pain overall and by anatomical regions were estimated. Correlates of pain symptoms were examined using multivariable logistic regression. **Results:** The prevalence of overall pain symptoms was persistently high (48.5%, 95% CI: 48.0-49.0) in cancer survivors from 1997-2018 (P for trend = .58), driven by low back (37.6%, 95% CI: 37.1-38.0) and neck pain (20.9%, 95% CI: 20.5-21.3), and was leading in survivors of bone (63.1%, 95% CI: 57.9-68.4), soft tissue (58.1%, 95% CI: 50.6-65.6), and brain (58.2%, 95% CI: 52.3-64.0) cancers. Considerable pain symptoms were reported by survivors of commonly diagnosed cancers: lung (48.5%), breast (46.7%), colon (52.2%) and prostate (38.4%) cancers. The prevalence of pain is higher in females (52.9%) than males (42.6%) across all anatomical regions (OR, 1.50 [95% CI, 1.38-1.63]), particularly headache (19.8% vs. 8.6%) and facial pain (8.6% vs. 3.9%). Of note, females with reproductive system cancers, cervical (66.3%), uterine (60.0%) and ovarian (59.4%) cancers, have a higher prevalence in all types of pain than those with other cancers. Cancer survivors aged ≥65 years were less likely to report pain symptoms than younger survivors (OR, 0.71 [95% CI, 0.64-0.79]). Despite no racial disparity in the prevalence of overall pain, Non-Hispanic Blacks (18.6%, 95% CI: 17.2-20.0) and Hispanics (21.2%, 95% CI: 19.5-22.9) were more likely to report headache than Non-Hispanic Whites (14.4%, 95% CI: 14.0-14.8). A higher prevalence of pain symptoms was consistently observed in cancer survivors with low income, smoking history, low physical activity levels, diabetes, and cardiovascular diseases (all $P < .05$). Age at cancer diagnosis (P for trend < .001), but not the time since, affected pain symptoms. Cancer survivors diagnosed at age 0-14 (53.0%, 95% CI: 49.1-56.9) and 15-39 years (58.6%, 95% CI: 57.5-59.7) had a significantly higher prevalence of pain across all anatomical regions than those at ≥40 years (45.5%, 95% CI: 44.9-46.1). **Conclusions:** Half of US cancer survivors experienced pain symptoms, driven by low back and neck pain. Higher prevalence of pain was noted in cancer survivors with younger age, female sex, low income and suboptimal lifestyle behaviors, calling for adequate pain management in cancer survivorship. Research Sponsor: None.

12063 **Poster Session**

Sacubitril-valsartan improves longitudinal strain and ejection fraction in preclinical models treated with anthracyclines through NLRP3, MyD88 pathways resulting in a reduction of myocardial IL-1β, IL-6, TNF-α and growth factors. *First Author: Nicola Maurea, Istituto Nazionale per lo Studio e la Cura dei Tumori "Fondazione G. Pascale"-IRCCS, Naples, Division of Cardiology, Naples, Italy*

Background: Doxorubicin-mediated adverse cardiovascular events are among the leading causes of morbidity and mortality in breast cancer patients. Sacubitril-valsartan (LCZ 696) is a combination drug, made up of neprilysin inhibitor sacubitril and angiotensin II receptor blocker valsartan, used for the treatment of heart failure in patients with a reduced ejection fraction. We hypothesized that LCZ 696, administered during doxorubicin, could improve cardiac function and cardiac inflammation in preclinical models. **Methods:** Human fetal cardiomyocytes (HFC cell line) were exposed to subclinical concentration of doxorubicin (200 nM) alone or in combination with LCZ-696 (100 mM) for 72 h. After the incubation period, we performed the following tests: cell viability, apoptosis and necrosis; expression of malondialdehyde and 4-hydroxynonenal and concentration of intracellular Ca2+. Moreover, pro-inflammatory studied were also performed (activation of NLRP3 inflammasome; expression of TLR4/MyD88; mTORC1 Fox01/3a; NF-κB). C57Bl/6 mice were untreated (Sham, n = 6) or treated for 10 days with doxorubicin i.p at 2.17 mg/kg (DOXO, n = 6), LCZ-696 at 60 mg/kg (LCZ, n = 6) or doxorubicin combined to LCZ-696 (DOXO-LCZ, n = 6). Ejection fraction, radial and longitudinal strain were analyzed through transthoracic echocardiography (Vevo 2100). Cardiac tissue expression of NLRP3 inflammasome, Myd88, NF-kB and 13 chemokines (IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-10, IL-12, IL17-α, IL-18, IFN-γ, TNF-α, G-CSF, and GM-CSF) were quantified. **Results:** LCZ-696 exerts cardioprotective effects, enhancing cell viability of 48-54.6% compared to only doxorubicin-treated cells (p < 0,001 for all); LCZ 696 decreased NLRP3, MyD88 and NF-kB expression in cardiac cells. In preclinical study, LCZ 696 improved significantly the EF and prevented the reduction of radial and longitudinal strain after 10 days of treatment with doxorubicin. A reduced expression of NLRP3, MyD88 and NF-kB in cardiac tissues was seen in DOXO-LCZ group compared to DOXO mice (p < 0.001). Cardiac expression of IL-1β, IL-6, TNF-α, G-CSF and GM-CSF were significantly reduced after treatment with LCZ-696 indicating anti-inflammatory properties. **Conclusions:** LCZ-696 exerts direct beneficial effects in cardiomyocytes exposed to doxorubicin. In preclinical models, LCZ-696 reduced inflammation and cytokine expression involved in doxorubicin-mediated cardiotoxicity. Research Sponsor: Ricerca Corrente.

12064 **Poster Session**

Performance of the 2021 CKD-EPI equations without a race coefficient in a multi-racial population of adults with solid tumors: A prospective cross-sectional study. *First Author: Veronica Torres Costa E Silva, Instituto do Cancer do Estado de São Paulo, São Paulo, Brazil*

Background: We previously showed that estimated glomerular filtration rate (eGFR) based on serum creatinine (Scr)(eGFRcr) using the 2009 CKD-EPI equation performed better than Cockroft-Gault equation (CG) in solid tumor patients in Brazil (Onco-GFR Study). In that study, eGFR based on Scr and cystatin C (Scys)(eGFRcr-cys) using the 2012 CKD-EPI was the most accurate equation and suitable for use as a confirmatory test. The CKD-EPI 2009 eGFRcr and 2012 eGFRcr-cys equations include a term for race (Black vs. non-Black). The 2021 CKD-EPI eGFRcr and eGFRcr-cys equations do not include race and are now recommended in the US, but have not been assessed in a multi-racial population or in cancer patients. The aim of this study is to evaluate the performance of the 2021 CKD-EPI equations in the Onco-GFR Study. **Methods:** Measured GFR (mGFR) was determined using the plasma clearance of ^{51}Cr-EDTA. Scr and Scys assays were traceable to international standards. **Results:** A group of 1,200 patients recruited between April 2015 and September 2017 were included for analysis. Patients were 58.8±13.2 years, 50.8% male. Race distribution was Black participants 12.8% and non-Black participants 81.2%. Mean (SD) mGFR was 78.5±21.7 ml/min/1.73 m^2. For eGFRcr, the overestimation of mGFR was larger for the 2021 vs. 2009 equation -10.0 vs. 8.1 ml/min/1.73m^2, resulting in lesser accuracy 1-P30 of 22.3 vs. 19.1, but still more accurate than CG equation (1-P30 of 24.9, P = 0.05). For eGFRcr-cys, the overestimation of mGFR was larger for the 2021 vs. 2012 equation (-4.1 vs. -2.0 ml/min/1.73m^2). eGFRcr-cys using the 2021 equation was more accurate than eGFRcr using the 2021 equation and eGFRcys using the 2012 equation (1-P30 9.8 vs. 22.3 and 12.3, p-values < 0.001 and 0.01, respectively) (Table). **Conclusions:** 2021 CKD-EPI eGFRcr equation race performed better than CG. 2021 CKD-EPI eGFRcr-cys performed better than 2021 eGFRcr and 2012 eGFRcys equations. Removing race from eGFR equations represents an advance and should be incorporated in cancer care. Research Sponsor: Fundação de Amparo à Pesquisa do Estado de São Paulo.

Filtration marker (eGFR)	Equation and Year	Median bias (eGFR - mGFR) (ml/min/1.73 m2)	Precision IQR (ml/min/1.73 m2)	Accuracy (1-P_{30}) (%)	RMSE
Creatinine (eGFRcr)	CG 1976	-8.1 (-9.4 to -6.7)	24.2 (22.4 – 25.8)	24.9 (22.4 – 27.3)	0.239 (0.229 – 0.249)
Creatinine (eGFRcr)	CKD-EPI 2009	-8.1 (-8.9 to -7.1)	18.4 (17.1 – 19.6)	19.1 (16.8 – 21.2)	0.206 (0.197-0.215)
Creatinine (eGFRcr)	CKD-EPI 2021	-10.0 (-10.7 to -8.8)	18.2 (17.0 – 19.6)	22.3 (19.8 – 24.4)	0.220 (0.211 – 0.230)
Cystatin C (eGFRcys)	CKD-EPI 2012	4.6 (3.7 to 5.5)	17.5 (16.3 – 19.2)	12.3 (10.3 – 14.3)	0.215 (0.204 – 0.225)
Creatinine-Cystatin C (eGFRcr-cys)	CKD-EPI 2012	-2.0 (-2.6 to -1.1)	15.9 (14.7 – 16.8)	7.8 (6.3 – 9.4)	0.165 (0.157 – 0.172)
Creatinine-Cystatin C (eGFRcr-cys)	CKD-EPI 2021	-4.1(-4.8 to -3.3)	15.7 (14.6 – 17.1)	9.8 (8.0 – 11.4)	0.171 (0.163 – 0.179)

LBA12065 **Poster Session**

Humoral and cellular immune response to Sars-CoV-2 wild-type and variants of concern following 3-dose vaccination in a large cohort of adults with cancer: The SerOzNET study. *First Author: Eva Segelov, Monash Health, Melbourne, Australia*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

12066 **Poster Session**

Development of breast cancer after thyroid cancer and trends over time. *First Author: Kriti Ahuja, John H. Stroger, Jr. Hospital of Cook County, Chicago, IL*

Background: Thyroid cancer occurs early in adulthood and is thrice as common in women. Further, 1 of 8 women in the U.S develop breast cancer, usually later in life. We are studying the development of breast cancer after thyroid cancer in women within the US. **Methods:** The Incidence – SEER Research Data, 18 registries, Nov 2020 Sub (2000-2018) database was queried with SEER*Stat 8.3.9.2 for thyroid cancer in females and subsequent breast cancer. Further, the MP-SIR function of SEER*Stat 8.3.9.2 was applied to evaluate the Incidence – SEER Research Data, 18 Registries (excl AK), Nov 2020 Sub (2000-2018) for risk of developing breast cancer after thyroid cancer in females in terms of SIR (Standardized Incidence Ratio) and Excess Risk, stratified by age categories. **Results:** From 2000 to 2018, 151654 cases of thyroid cancer were diagnosed in 150787 women, most of which were papillary adenocarcinoma, NOS (50.2%) and papillary carcinoma, follicular variant (26.8%). About 64% cases occurred in Non-Hispanic Whites (NHW) and 60% of all cases developed from ages 30 to 60 (~ 20% per decade). There was a considerable rise in incidence over the years, from > 4000 cases in year 2000 to > 9500 cases in 2018, with percentage change (PC) of 122.3%, and Annual Percentage change (APC) of 4.6% (CI 3.6-5.7, p < 0.05) across all age groups, highest in 60-69 age group (APC 7.5; CI 6-9.1, p < 0.05). At follow-up, 3300 cases of primary breast cancer were diagnosed in 3062 women of the above population. Infiltrating duct carcinoma, NOS constituted 70.5% cases, followed by lobular carcinoma, NOS at 10%. About 4 out of 5 breast tumors were ER positive (82.6%). NHW constituted > 70% cases and >50% cases occurred in age group 50-69 (approximately 25% per decade). We found an overall increasing trend in frequency of breast cancer after thyroid cancer with APC 14.1 (CI 11.9-16.3, p < 0.05). MP-SIR function in Incidence – SEER Research Data, 18 Registries (excl AK), Nov 2020 Sub (2000-2018) indicated that 3005 women developed breast cancer after thyroid cancer (consistent with the above data as it has latency criteria of 2 months and excludes AK). Overall, an increased risk of developing breast cancer after thyroid cancer was found, with SIR 1.21 (CI 1.16-1.25, p < 0.05) and Excess risk 4.88 across all age categories, highest at 1 year following diagnosis of thyroid cancer with SIR 1.29 (CI 1.15-1.44, p < 0.05) and excess risk 5.91. Among different age categories, SIR was highest for ages ≥70 at 1.32 (CI 1.2-1.45, p < 0.05) with excess risk 13.45. **Conclusions:** Women with thyroid cancer are at increased risk for subsequent primary breast cancers (usually ER+), with an overall increasing trend from 2000 to 2018. As we continue to make progress in the diagnosis and treatment of thyroid cancer in women, it is important to be cognizant of their increased risk for developing a subsequent primary and possible significance in terms of breast cancer screening. Research Sponsor: None.

12067 **Poster Session**

Retrospective analysis of healthcare disparities in Philadelphia chromosome-positive ALL: A single-institution experience of a large metropolitan area. *First Author: Ian Michael Bouligny, VCU Massey Cancer Center, Richmond, VA*

Background: Philadelphia chromosome-positive (Ph+) ALL is an aggressive hematological neoplasm with a dismal prognosis. Hematopoietic stem cell transplant (HSCT) remains the standard of care for those reaching complete remission due to high relapse rates with conventional therapy alone. We have previously demonstrated findings concerning for imbalanced outcomes among racial groups in AML. In the era of TKIs targeting BCR-ABL1 in combination with conventional therapy, it is unclear whether trends noted in AML are also seen in Ph+ ALL. Thus, the purpose of this study was to investigate the impact of healthcare disparities on outcomes in Ph+ ALL with regards to access to care, response rates, toxicities, and overall outcomes. **Methods:** We retrospectively analyzed 59 patients with Ph+ B-ALL treated at our institution with TKIs +/- chemoimmunotherapy during January 2015 to January 2021. Baseline patient demographics were obtained, including insurance type, performance status at diagnosis, cytogenetic and molecular profiling, dates and doses of induction, toxicity, response, MRD analysis, and HSCT access and outcomes. Race was determined by patient self-report as recorded in the electronic medical record. **Results:** We divided 58 patients (one excluded as race was unknown) into two cohorts: 23 (39.7%) patients that identified as minorities, including African American, Hispanic/Latino, and Asian, and 35 (60.3%) identifying as White. There were no differences in baseline characteristics including age (p = .367), sex (p = .788), ECOG at diagnosis (p = .438), Charlson Comorbidity Index scores (p = .551), or presence of additional poor-prognostic mutations (p > .999). Despite this, minorities were significantly more likely to be treated with lower-intensity regimens compared to non-minorities (p = .022). Achievement of CR by MRD was approaching statistical significance favoring the non-minority cohort (60.0% versus 27.3%, p = .055). Receipt of HSCT numerically favored the non-minority cohort, approaching statistical significance (54.3% versus 26.1%, p = .056). At a median follow-up time of 3.3 y., the median OS was not reached between the two groups and there was no difference in survival between the two groups (p = .662). **Conclusions:** Despite similar patient-related characteristics, minority populations are more likely to be treated with lower-intensity strategies, concerning for bias in regimen selection. Achievement of CR by MRD and receipt of HSCT appeared to be numerically lower in the minority cohort. While there appeared to be no difference between the two cohorts with regards to survival during the follow-up period, it is unclear if this would be maintained with longer follow-up. These findings highlight the need for ongoing vigilance regarding physician biases and increasing the need for improving access to curative treatment for all patients. Research Sponsor: None.

LBA12068 **Poster Session**

Patient-reported toxicity and quality of life following Sars-CoV-2 vaccination in adults and children with cancer. *First Author: Amy Body, Monash Health, Clayton, VIC, Australia*

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*.

12069 **Poster Session**

Lymphedema therapy referral is associated with improved understanding of lymphedema prevention among breast cancer survivors. *First Author: Madelyn Klugman, NewYork Presbyterian-Weill Cornell, New York, NY*

Background: Lymphedema is common among breast cancer survivors (BCS) and negatively affects quality of life. There are modifiable factors to reduce lymphedema risk and exacerbation; it is unknown how aware survivors are of these factors. We hypothesized referral to lymphedema therapy (LT) to be associated with improved lymphedema knowledge. **Methods:** BCS were approached during follow-up visits at an NCI-designated cancer center between 2014-2015 and asked to complete an anonymous survey. Eligibility criteria: age ≥18, English-speaking, > 6 months post-surgery, no cancer recurrence, no prior or subsequent second cancer. Surveys included 10 true/false questions to assess beliefs of common lymphedema misconceptions and questions about sociodemographics, cancer treatment, and prior LT referral. Charts were reviewed to determine history of axillary lymph node dissection (ALND) or sentinel node biopsy (SLNB). Multivariable logistic regression assessed the relationship between prior LT referral and correctly answering questions about lymphedema misconceptions. **Results:** Of 209 participants, 67% identified as non-Latinx white, 13% Black, 10% Latinx and 8% Asian. 53 (25%) had been referred to LT. Those who had SLNB were less frequently referred to LT [15 (14%)] than those who had ALND [38 (39%)]. There were 5 lymphedema knowledge questions with < 80% correct responses (Table). Those previously referred to LT more often correctly answered the questions about weight gain and using the arm on an airplane than those not referred (chi-2: $p < 0.01$ and $p < 0.01$), but they were less likely to answer correctly about carrying > 10 lbs or strenuous activity at work ($p < 0.01$ and $p = 0.02$, respectively) (Table). These associations remained in multivariable analyses, other than strenuous work activity (Table). **Conclusions:** We identified several misconceptions regarding lymphedema among BCS. LT referral is a potential opportunity to debunk common misunderstandings regarding lymphedema risk reduction; providers should have a low threshold to refer patients. Lymphedema therapists teach progressive exercise strategies, which may have inadvertently caused participants to think they should avoid carrying objects > 10 lbs. Research Sponsor: American Cancer Society, Conquer Cancer Foundation of the American Society of Clinical Oncology, U.S. National Institutes of Health.

Multivariable analysis* of lymphedema therapy referral with correctly answering lymphedema questions.

Question (answer)	% correct	% correct (referred to LT)	% correct (not referred)	Odds ratio	95% confidence interval
Avoid using arm on affected side for strenuous activity at work (F)	48	33	52	0.52	0.24-1.11
Avoid using arm on affected side to carry > 10lbs (F)	49	32	54	0.37	0.17-0.80
Weight gain can increase risk of lymphedema (T)	55	73	49	3.63	1.66-7.96
Exercise arm on airplane (T)	63	80	58	2.65	1.15-6.13
Avoid using arm on affected side to lift weights (F)	75	76	74	0.85	0.36-2.01

*Adjusted for age, race/ethnicity, education, axillary surgery (ALND vs. SLNB), radiation therapy.

12070 **Poster Session**

Cardiovascular disease in testicular cancer survivors: Identification of risk factors and impact on quality of life. *First Author: Sjoukje Lubberts, Department of Medical Oncology, University Medical Center Groningen, Groningen, Netherlands*

Background: Testicular cancer (TC) treatment has been associated with cardiovascular disease (CVD) development. To facilitate development of preventive strategies, this study assessed risk factors associated with CVD in TC survivors. **Methods:** Incidence of coronary artery disease, myocardial infarction and heart failure was assessed in a multicenter cohort comprising 4,748 TC survivors treated at ages of 12-50 years between 1976-2007. Patients who developed CVD and a random sample from the cohort received a questionnaire on cardiovascular risk factors (CVRF) and quality of life (QoL, measured with SF-36). A subgroup (n=304) of responders in the cohort additionally underwent clinical evaluation of CVRF. **Results:** After a median follow-up of 16 years, 272 patients developed CVD. Compared to orchidectomy only, platinum-based chemotherapy was associated with increased CVD risk (Hazard Ratio (HR) 1.8, 95% Confidence Interval(CI) 1.3-2.5). CVD risk was increased among patients who were obese or a smoker at diagnosis (HR 4.7, 95%CI 2.4-9.3 and HR 1.5, 95%CI 1.1-2.2, respectively) and patients with Raynaud's phenomenon (HR 1.9, 95%CI 1.1-3.6) or a family history of CVD (HR 2.7, 95%CI 1.6-4.5). TC survivors with CVD reported inferior QoL on physical domains (table). In TC survivors who underwent clinical evaluation for CVRF (median age at assessment 51 years), 86% had dyslipidemia, 50% hypertension and 35% metabolic syndrome, irrespective of treatment. **Conclusions:** TC survivors treated with platinum-based chemotherapy, who were obese or smoking at diagnosis, had family history of CVD and who developed Raynaud's phenomenon are at risk to develop CVD, which affects QoL. Many TC survivors carry undetected CVRF. We advocate early lifestyle adjustments and lifelong follow-up with low-threshold treatment of CVRF, especially in obese and smoking patients treated with platinum-based chemotherapy. Research Sponsor: Dutch Cancer Society.

Quality of life in TC survivors with or without CVD. (The SF-36 scale scores are presented as mean with standard error. *:corrected for age at completion of questionnaire, using linear regression.)

	Patients with CVD (n=120)	Cohort patients without CVD (n=417)	P*
Physical functioning	72 (2.3)	89 (0.9)	**<.001**
Social functioning	82 (2.1)	87 (1.0)	.06
Role limitations due to physical health	70 (3.7)	85 (1.5)	**.001**
Role limitations due to emotional health	83 (3.1)	88 (1.5)	.15
Mental health	77 (1.7)	79 (0.8)	.11
Energy and vitality	62 (2.1)	68 (1.0)	**.002**
Bodily pain	80 (2.0)	88 (1.0)	**.028**
General health	54 (2.1)	68 (1.0)	**<.001**

12071 **Poster Session**

Time for paying attention to fluoropyrimidine-associated cardiotoxicity: A pooled data analysis for epidemiology based on 60537 cases. *First Author: Yajie Lu, Xijing Hospital, Air Force Medical University of PLA, Xi'an, China*

Background: With the rise of cardio-oncology discipline, treatment-related cardiotoxicity has become a growing concern. However, fluoropyrimidine induced cardiotoxicity has been underestimated for a long time. The aim of this study was to comprehensively investigate the incidence and profiles of the cardiotoxicity associated with fluoropyrimidine using a pooled data meta-analysis. **Methods:** A systematic literature review was performed using PubMed, Embase, Medline, Web of Science, Cochrane library databases and clinical trials on studies published between the establishment of each database and March 31, 2021, investigating fluoropyrimidine associated cardiotoxicity (FAC). The main outcome was pooled incidence of FAC, and the secondary outcome were specific treatment-related cardiac AEs. Random-effects or fixed-effects modeling was used for analyses according to the heterogeneity assessed by Cochran's Q test. Subgroup analysis and meta-regression were conducted to explore the source of heterogeneity, and the incidence of FAC was compared among different clinical characteristics. The protocol was registered in PROSPERO (No. CRD42021282155). **Results:** Two hundred and six studies involving 60537 patients were included in this meta-analysis, covering 31 countries or regions in the world. The pooled incidence of FAC was 5.18% (95% CI 4.32%-6.10%) for all grade and 1.5% (95% CI 1.09%-1.96%) for grade 3 or higher. A total of 0.29% of patients died from severe cardiotoxicity. Cardiac ischemia and arrhythmia were the two most common cardiac AEs, occurring in 2.31% (95% CI 1.70%-3.00%) and 1.69% (95% CI 1.08%-2.42%) of patients, respectively. ECG alterations occurred in 5.85% (95% CI 3.4%-8.9%) of patients, indicating asymptomatic ECG alterations in a subset of the population. The incidence of cardiotoxicity varied among different regions, gender, cancer types and treatment regimens. Studies conducted in Asia outlined a significant higher pooled incidence of FAC than in Europe ($\chi 2 = 4.47$, $p = 0.03$) and America ($\chi 2 = 4.49$, $p = 0.03$). Female population had a lower pooled incidence than general population ($\chi 2 = 9.90$, $p = 0.01$). The highest pooled incidence was observed in esophagus cancer (10.53%, 95% CI 5.8%-16.35%), and the lowest occurred in breast cancer (3.66%, 95% CI 2.4%-5.12%). In addition, combination therapy, high cumulative dose, anthracycline addition, and pre-existing cardiac disorder significantly increased the risk of FAC ($p < 0.05$). No obvious publication bias was detected by funnel plots and Egger's test ($p < 0.05$), and the stability of our results was confirmed by the sensitivity analysis. **Conclusions:** FAC is not a rare condition during treatment containing fluoropyrimidines. Our results provide comprehensive global data on epidemiology of FAC, potentially representing an important reference on cancer management in clinical practice. Research Sponsor: None.

12072 **Poster Session**

Randomized trial of atorvastatin during and following receipt of doxorubicin for breast cancer and lymphoma (WF-98213). *First Author: William Gregory Hundley, Virginia Commonwealth University, Richmond, VA*

Background: Statins taken for cardiovascular (CV) indications by breast cancer (BC) and lymphoma survivors during doxorubicin (DOX) treatment may attenuate left ventricular ejection fraction (LVEF) decline, but statin impact among these survivors with no CV indications is unknown. **Methods:** In 279 patients from 31 cancer centers, we conducted a double blind, placebo-controlled, 24-month randomized trial of 40mg/day atorvastatin among those receiving DOX for BC or lymphoma. At pretreatment, six and 24 months after initiating DOX for BC or lymphoma, we assessed LV volumes, strain, mass, and LVEF (via cardiac magnetic resonance), cognitive function and serum markers of inflammation. Using a linear model adjusted for pretreatment measures, our primary analysis assessed change in LVEF over time by randomization group. **Results:** Participants were aged 49±12 years; 92% women, 83% white race. The mean pooled LVEF decline from pretreatment to 24 months was 62.2±6.0% to 57.6±6.3% ($p < 0.001$). Adjusting for pretreatment LVEF, 24-month declines in LVEF averaged 3.5±0.5% and 3.3±0.5% respectively for placebo vs statins ($p = 0.83$). Both randomized groups were similar for: incidence of > 10% change in LVEF, LV strain, LV mass, cognition and inflammation biomarkers, including among those > 90% study drug compliant ($p > 0.05$ for all). **Conclusions:** In BC and lymphoma survivors with no existing indication for statin therapy, prospective statin administration does not appear to impact LVEF declines two years after doxorubicin. Clinical trial information: NCT01988571. Research Sponsor: U.S. National Institutes of Health.

Measure	Group	Baseline	6 Month	24 Month	p-value, Change from Baseline to 24 Month
Ejection Fraction (%)	Statin	62.6 (61.5 – 63.8)	57.5 (56.3 – 58.7)	57.8 (56.5 – 59.1)	p < 0.001
	Placebo	61.8 (60.6 – 63.0)	57.5 (56.4 – 58.7)	57.4 (56.1 – 58.6	
Left Ventricular End Diastolic Volume Index (ml/m^2)	Statin	67.5 (65.1 – 70.0)	67.9 (65.4 – 70.4)	66.5 (63.9 – 69.1)	p = 0.81
	Placebo	67.0 (64.5 – 69.6)	66.4 (63.9 – 68.9)	67.0 (64.4 – 69.5)	
Left Ventricular End Systolic Volume Index (ml/m^2)	Statin	25.3 (24.0 – 26.6)	28.9 (27.6 – 30.2)	28.0 (26.6 – 29.5)	p < 0.001
	Placebo	25.7 (24.3 – 27.0)	28.2 (26.9 – 29.5)	28.7 (27.4 – 30.1)	
Left Ventricular Mean Circumferential Strain (ε_f)	Statin	-21.0 (-21.8 – -20.2)	-18.5 (-19.3 – -17.7)	-18.2 (-19.1 – -17.3)	p < 0.001
	Placebo	-19.5 (-20.3 – -18.7)	-17.7 (-18.5 – -16.9)	-17.6 (-18.5 – -16.7)	

Baseline, 6 month, 24 month values = Mean (Confidence Interval); $p < 0.05$ statistically significant. Statin vs. placebo comparisons at each timepoint were not significant.

12073 **Poster Session**

Analysis of incidence/mortality/cost for thrombotic events in hospitalized patients with lung cancer using the National Inpatient Sample database. *First Author: Kuldeepsinh Atodaria, Abington Jefferson Health, Abington, PA*

Background: Thrombotic events are a common complication of lung cancer. We performed a retrospective analysis of an inpatient adult population (age ≥18) using the National Inpatient Sample (NIS) database from the years 2003-2014. **Methods:** The analysis was performed on the NIS database, using IBM SPSS Statistics 28.0.0.0 software. The cases for lung cancer were selected based on ICD-9(International Classification of Disease) codes for lung cancer. The cases were weighted by Weight to discharges in the universe. These cases were checked for a diagnosis of acute lower extremity Deep Vein thrombosis (DVT) and acute Pulmonary Embolism (PE) again using ICD-9 codes. Chi square tests were utilized to check the significance of association between mortality and DVT/PE. Independent T-tests were utilized to check the association of cost of hospitalization and length of stay with DVT/PE. **Results:** There were a total of 4,940,262 cases (53.0% male) of lung cancer from the years 2003-2014. 112,569 (2.3%) cases had a diagnosis of acute lower extremity DVT, and 164,208 (3.3%) cases had a diagnosis of acute PE. Overall, death for lung cancer cases was 516,070(10.5%). Death rate in patients with DVT was 12.4%(frequency = 13,943). DVT and death during hospitalization were positively associated, X^2 (1, N = 4,936,702) = 578.792, $p < .001$. Rate of death for PE was 15.5% (25,360). PE and death during hospitalization were positively associated as well, X^2 (1, N = 4,936,702) = 4540.012, p .000. DVT was associated with a prolonged length of stay (M = 8.66 days, SD = 8.8.624), compared to cases without DVT (M = 6.42 days, SD = 6.42), t(4,940,122) = 115.02, p = .000. DVT was also associated with increased total charges of hospitalization (M = $ 62,950, SD = 85,105), compared to cases without DVT (M = $ 41,764, SD = 55,410), t(4,864,517) = 124.09, p = .000. PE was associated with a prolonged length of stay (M = 8.01 days, SD = 8.13), compared to cases without PE (M = 6.42 days, SD = 6.41), t(4,940,122) = 97.89, p = .000. PE was also associated with increased total charges of hospitalization (M = $ 56,161, SD = 76,585), compared to cases without PE (M = $ 41,772, SD = 55,468), t(4,864,517) = 100.85, p = .000. **Conclusions:** DVT and PE are common complications of Lung Cancer. They are associated with increased mortality in these patients. DVT increases the mean LOS by 2.24 days, and mean charges by $21,186. PE increases the mean LOS by 1.59 days, and the mean charges by $14,389. Prevention of DVT and PE could help bring down the mortality, LOS and charges of hospitalization. This data provides support to the usage of prophylactic anticoagulation in patients with lung cancer as shown in recent trails with Direct Acting Oral Anticoagulants(DOACs), and further study of DVT/PE in Lung cancer patients would be warranted. Research Sponsor: None.

12074 **Poster Session**

The association of early integrated rehabilitation and moderate or severe fatigue in 600 patients with breast cancer: A comparison between the intervention group and control group in a prospective study. *First Author: Nikola Besic, Institute of Oncology Ljubljana, Ljubljana, Slovenia*

Background: Fatigue after breast cancer treatment is a major health problem that is very difficult to treat. Our aim was to determine whether the early introduction of focused rehabilitation from the start of the cancer treatment is associated with the frequency of fatigue in breast cancer patients. **Methods:** The subjects of our prospective study were 600 female breast cancer patients (26-65 (mean 52) years of age), who participated in the pilot study on the individualized integrated rehabilitation of breast cancer patients in 2019-2022 and were followed for at least six months. The control group included 300 patients and the intervention group 300 patients. The patients completed three questionnaires (EORTC QLQ - C30, B23 and NCCN): before and six months after the beginning of cancer treatment. The control group obtained the same rehabilitation as was offered to all breast cancer patients in our hospital before the start of our study. The multidisciplinary rehabilitation team reviewed the documentation of all the patients from the intervention group before six months after the beginning of treatment and recommended appropriate interventions according to the patient's problems. The integrated rehabilitation coordinator referred patients for additional treatments in compliance with the institute's new clinical pathway (psychologist, general practitioner, nutritional treatment, physical rehabilitation, kinesiologist-guided online exercises, gynaecologist, analgesia, vocational rehabilitation). Data on the patients' demographics, disease extent, cancer treatment and complaints reported in questionnaires were collected. This data and the frequency of fatigue six months after the beginning of treatment in both groups of patients were analysed using the chi-square and ANOVA test. **Results:** There were no differences between the control and the intervention group of patients in terms of age, education, disease extent, surgical procedures, systemic cancer treatment, or radiotherapy. There were no differences between the groups in the prevalence of fatigue before the start of treatment. Before the cancer treatment, 50% of the patients in both groups reported fatigue, while moderate or severe fatigue was reported in the intervention and control groups in 9% and 10% ($p = 0.69$), respectively. Six months after the beginning of cancer treatment, fatigue was reported in the intervention and control groups in 66% and 70% ($p = 0.38$), respectively. However, moderate or severe fatigue were reported in the intervention and control groups in 17% and 26% ($p = 0.02$), respectively. **Conclusions:** Early integrated rehabilitation is associated with a lower prevalence of moderate or severe fatigue in breast cancer patients in comparison to the control group six months after the beginning of cancer treatment. Research Sponsor: Grant V3-1906.

12075 **Poster Session**

Racial differences in cardiovascular disease mortality among cancer survivors. *First Author: Hyuna Sung, American Cancer Society, Atlanta, GA*

Background: Cancer survivors have an elevated risk of death from cardiovascular disease (CVD). Whether the risk differs by race/ethnicity and cancer type has not been fully explored in the U.S. **Methods:** Data from survivors of top 23 cancers diagnosed at ages 20 to 64 years during 2000-2018 were obtained from 17 Surveillance, Epidemiology, and End Results registries. Risks for CVD death among survivors relative to the general population were calculated using standardized mortality ratios (SMRs) in each racial/ethnic group: Non-Hispanic White (NHW), Non-Hispanic Black (NHB), Hispanic, Non-Hispanic Asian or Pacific Islander (API), and Non-Hispanic American Indian (AI). Among survivors, the risks were compared by race/ethnicity using cause-specific proportional hazards models for competing risks, controlling for year of diagnosis, age at diagnosis, sex, stage (when appropriate), and the first course of treatment receipt (surgery, radiotherapy, chemotherapy). **Results:** Among 2,806,515 survivors (NHW, 68%; NHB, 13%; Hispanic, 12%; API, 7%; AI, 0.5%), 57,883 CVD deaths occurred during 6.4 person-years of mean follow-up (32 per 10,000). Cancer survivors overall were at increased risk of CVD death compared to their general population counterpart with an SMR of 1.76 among API (95% CI = 1.69-1.84; 8.7 excess deaths per 10,000), 1.49 among AI (95% CI = 1.33-1.68; 11.9 excess deaths per 10,000), 1.46 among Hispanic (95% CI = 1.41-1.50; 7.4 excess deaths per 10,000), 1.30 among NHB (95% CI = 1281-1.33; 14.9 excess deaths per 10,000), and 1.13 among NHW (95% CI = 1.12-1.14; 3.4 excess deaths per 10,000) survivors. Compared with NHW survivors, the adjusted hazard of CVD death was statistically significantly higher among NHB survivors for 23/23 cancers and among AI survivors for 9/18 cancers but was statistically significantly lower among Hispanic survivors for 5/23 cancers and among API survivors for 10/23 cancers, with no significant difference otherwise. The highest hazards ratios (HRs) were among NHB survivors of melanoma (HR = 3.19, 95% CI = 2.11-4.83); breast (HR = 2.73, 95% CI = 2.57-2.89); pancreatic (HR = 2.63, 95% CI = 2.19-3.16); and testicular (HR = 2.59, 95% CI = 1.62-4.14) cancers, whereas the lowest HRs were among API survivors of head and neck (HR = 0.53, 95% CI = 0.44-0.63) and cervical (HR = 0.57, 95% CI = 0.41-0.80) cancers and Hispanic survivors of cervical cancer (HR = 0.59, 95% CI = 0.46-0.75). **Conclusions:** The risk of CVD death differs considerably among cancer survivors by race/ethnicity and cancer types, highlighting the need for targeted prevention and surveillance in primary care. Future studies are needed to identify factors that contribute to this variation in order to inform efforts towards mitigating risk. Research Sponsor: None.

12076 **Poster Session**

SNP-SNP interactions and a 4-locus model for prediction the risk of anthracycline-mediated cardiotoxicity in patients with breast cancer. *First Author: Dmitry Yu. Gvaldin, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation*

Background: Numerous pharmacogenetic studies have identified genetic polymorphisms (SNPs) associated with an increased risk of anthracycline-mediated cardiotoxicity (AMC). The purpose was to search for SNP-SNP interactions associated with the risk of cardiotoxic manifestations caused by anthracycline therapy in breast cancer patients. **Methods:** The study included 256 Caucasian patients (median age - 55 years) with a diagnosis of breast cancer with normal cardiovascular system parameters at baseline, who were treated with anthracyclines in 2019-2020. For SNP genotyping of c.4544G > A rs8187710 (ABCC2), c.1744C > T rs11549465 (*HIF1A*), g.22125504G > C rs1333049 (*CDKN2A/B*) and c.214T > C rs4673 (*CYBA*). DNA was extracted from blood by using DNA-sorb-B (AmpliSens, Russia). HRM-PCR was performed on a CFX96 amplifier (Bio-Rad, USA). The presence of polymorphism was confirmed by the Sanger method on a Genetic Analyzer 3500 (ABI, USA). **Results:** During the follow-up period 21 (8.2%) patients developed signs of subacute (changes developed within several weeks after the last course of therapy) or early chronic anthracycline mediated cardiotoxicity (changes developed within a year after completion of anthracycline therapy). Using the multifactorial dimension reduction method. We obtained a 4-locus model of SNP-SNP interactions c.4544G > A rs8187710 (*ABCC2*) x g.22125504G > C rs1333049 (*CDKN2A/B*) x c.214T > C rs4673 (*CYBA*) x g.23708527G > A rs28714259 which has high prognostic properties. The specificity of the test based on the 4-locus model was 68%, the sensitivity was 100%, and the overall accuracy was 71%. The results of the analysis of SNP-SNP interactions indicate the greatest contribution of rs4673 and rs28714259 to the predisposition to AMC. The first ones yet into antagonistic interactions with rs28714259, rs1333049 and rs11549465, the second with rs8187710, rs11549465 and rs4673. On the contrary rs11549465 and rs1333049 contribute to a synergistic effect. **Conclusions:** The 4-locus model discovered in this study can form the basis of prognostic tests that predict early the risks of developing AMC in cancer patients, which in the future allow to personalize and select the most optimal treatment regimen. Research Sponsor: None.

12077 **Poster Session**

Polymorphism rs4673 and plasma paraoxonase 1 level for prediction and early diagnosis of anthracycline-mediated cardiotoxicity in patients with breast cancer. *First Author: Dmitry Yu. Gvaldin, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation*

Background: Anthracyclines are highly effective chemotherapeutic agents, used for a wide variety of malignancies. Despite their antitumor efficacy there is a risk of cardiotoxic manifestations that reduce the time and quality of life of patients. The purpose was to study the effectiveness of molecular genetic tests based on rs4673 *CYBA* genotyping (c.242C > T) and measurement of plasma paraoxonase 1 (PON1) level in patients with breast cancer (BC) for predicting and diagnosing anthracycline-mediated cardiotoxicity (AMC). **Methods:** The study included 256 Caucasian patients (median age - 55 years) with a diagnosis of breast cancer normal cardiovascular system parameters at baseline, who were treated with anthracyclines in 2019-2020. For rs4673 genotyping, DNA was extracted from the blood by using DNA-sorb-B (AmpliSens, Russia). HRM-PCR was performed on a CFX96 amplifier (Bio-Rad, USA). The presence of polymorphism was confirmed by the Sanger method on a Genetic Analyzer 3500 (ABI, USA). The concentration of PON1 in blood plasma was measured at baseline and after 4 course of chemotherapy with anthracyclines using ELISA kits (Cloud-Clone Corp., China/USA). **Results:** During the follow-up period 21 (8.2%) patients developed signs of subacute (changes developed within several weeks after the last course of therapy) or early chronic AMC (changes developed within a year after completion of anthracycline therapy). In the group of patients without AMC the frequency of the minor allele rs4673 (c.214C > T *CYBA*) was 0.38, the frequency of genotypes C/C was 0.4, C/T - 0.43, and T/T - 0.17. The risk of AMC increased by 6.49 times in the presence of the rs4673 polymorphic allele (p = 0.002). The area under the ROC curve of the test based on rs4673 genotyping was 71.9%. The concentration of PON1 after the 4 courses of chemotherapy increased by 19.57% in the group of patients without cardiotoxic manifestations (p = 0.018) and in the group of patients with AMC by 20.23% (p = 0.007) as compared to the initial level. Besides, after 4 courses of chemotherapy the PON1 level was higher in patients with AMC by 25.08% (p = 0.026) than in patients without cardiovascular complications. The sensitivity of the test based on the measurement of the PON1 level in the blood plasma after 4 courses of chemotherapy was 100%, the specificity was 70.8% with a cut-off value of 2.9 ng/ml. **Conclusions:** This study has showed that genotyping of patients for the rs4673 polymorphism allows pre-stratification of the risk group white determination of the PON1 level in blood plasma after 4 courses of chemotherapy gives the opportunity to identify patients with AMC and promptly correct the chosen treatment. Research Sponsor: None.

12078 **Poster Session**

CT scan versus bioelectrical impedance spectrometry sarcopenia assessment to predict chemotherapy toxicity in early breast cancer. *First Author: Gabriel Aleixo, Cleveland Clinic Foundation, Cleveland, OH*

Background: There is growing literature on the impact of the progressive loss of skeletal muscle known as sarcopenia in women with early breast cancer (EBC). Imaging techniques such as Computed Tomography (CT) scans are the most studied methods to detect sarcopenia in patients with cancer; however, most patients with EBC do not require routine CT scans. Bioelectrical impedance spectrometry (BIS) is a method that does not expose patients to radiation and provides measurements to assess sarcopenia instantaneously. The extent to which BIS-assessed sarcopenia correlates with CT-assessed sarcopenia is uncertain. It is also unclear whether sarcopenia detected with either method can be associated with chemotherapy tolerance To address these questions, we evaluated the correlation between CT and BIS sarcopenia and associations of sarcopenia by each method with chemotherapy related outcomes in patients with EBC. **Methods:** This retrospective study identified patients with EBC who received chemotherapy (ACT, TC, TH, THP), underwent BIS analyses (ImpediMed) at any point between diagnosis and treatment completion and also received a CT abdomen including L3 level. Axial CT L3 segments were analyzed using Slice-O-Matic software. CT L3, and BIS generated the Skeletal Muscle (SM). Skeletal Muscle Index (SMI) was then calculated to assess for sarcopenia: BIS SMI= (SM in kg)/ (patient height, m2) and CT L3 SMI (SM cm2/ height m2). Patients were divided into normal SMI, and sarcopenia (if BIS was used SMI <6.75 kg/m2 and if CT SMI <40 cm2/m2). Patient medical records were reviewed for patient characteristics, grade 3 and 4 toxicity, including neuropathy symptoms, chemotherapy dose reductions, early treatment discontinuation or need for hospitalization during chemotherapy treatment. Spearman's rank coefficient was used to assess the correlation between CT SMI and BIS SMI. Multivariable logistic regression was used to associate sarcopenia with outcomes, controlling for age and BMI. **Results:** 361 patients received chemotherapy, underwent BIS; of those 171 had L3 CT scans. The correlation between L3 CT SMI and BIS SMI was r= 0.64 p<0.0001. In the multivariable model, sarcopenia assessed by L3 CT scan was associated with chemotherapy dose reduction (CI 0.04-0.60 p=0.01) and neuropathy (CI 0.10-0.95 P=0.04) but not with grade 3 or 4 chemotherapy toxicity (CI 0.13-1.09 p=0.07), early treatment discontinuation (p=0.3) or hospitalization (p=0.60). Sarcopenia assessed by BIS was associated with grade 3 or 4 chemotherapy toxicity (CI 0.2-0.83 p=0.01), neuropathy (CI 0.1-0.51 p=0.0003), early treatment discontinuation (OR 0.26 CI 0.11-0.80 p=0.001), and hospitalization (CI 0.12-0.68 p=0.004). **Conclusions:** There is a strong correlation between L3 CT scan and BIS screened sarcopenia in patients with EBC. Sarcopenia detected with either CT L3 or BIS is associated with worse chemotherapy tolerance. Research Sponsor: HONORS award from American Society of Hematology.

12079 **Poster Session**

Change in telomere length and cardiovascular risk in testicular cancer survivors. *First Author: Ellen L.D. Volders, Department of Medical Oncology, University Medical Center Groningen, Groningen, Netherlands*

Background: Testicular cancer (TC) survivors cured with chemotherapy (CT) are prone to develop cardiovascular events, as part of an early aging phenotype. Telomere shortening could be a mechanism contributing to these events and their risk factors. **Methods:** In a prospectively followed cohort of patients with disseminated TC who received cisplatin containing CT (Lubberts et al., Eur J Cancer 2016), mean absolute leukocyte telomere length (TL) was measured using qPCR before and one year after start of cisplatin containing CT. Cardiovascular risk factors, including development of the metabolic syndrome (according to the NCEP ATP III definition) and hypogonadism (LH >10 U/L or testosterone < 10 nmol/L or use of testosterone suppletion), were assessed before and up to 5 years after CT. Shortening of TL was defined as a decrease of >33% after one year compared to baseline; short TL was defined as <5 kilobase (kb) pair (=P25). Data are presented as median (range). For comparisons, a Mann-Whitney U or Chi-Square test was applied. **Results:** 55 out of 73 patients of the initial cohort were evaluable for this analysis. CT regimens consisted of 3xBEP (n=41), 4x BEP (n=11), 4xEP (n=3). At baseline, patients with a BMI > 30 kg/m2 (n=12) had a shorter TL (4.9 (2.2-13.4) vs. 6.3 kb (3.1-12.9), p= .045); there was no difference in age. For the whole group, TL did not change one year after CT compared to baseline (5.7 (2.2-13.4) vs. 5.8 kb (1.6-19.2), p=.335). Patients with TL shortening after 1 year (n=7) showed a significant increase in diastolic blood pressure (p=.007) and triglycerides (p=.003), compared to those with unchanged TL (table). TL shortening after 1 year or short TL at baseline (n=7+11) are not significant predictors for newly developed metabolic syndrome (25 vs. 21%; p=.777), nor hypogonadism (38 vs. 17%; p=.120) after 5 years, compared to the others. **Conclusions:** A small subset of TC patients treated with cisplatin containing CT showed shortening of TL 1 year after treatment. This shortening is associated with a rise in diastolic blood pressure and triglycerides. Short or shortening of telomeres are not predictive for development of the metabolic syndrome or hypogonadism. Research Sponsor: Dutch Cancer Society.

Changes in cardiovascular risk factors over 1 year.

	Patients with unchanged TL over 1 year (N = 48) Median (range)			Patients with shortened TL over 1 year (N = 7) Median (range)			
	Baseline	+1 year	Δ	Baseline	+1 year	Δ	p*
Age (years)	30.5 (18 – 46)			27.0 (21 – 38)			
BMI (mg/m2)	25.1 (18.2 – 37.7)	25.4 (20.3 – 42.3)	0.4 (-4.1 – 6.6)	23.9 (22.5 – 42.4)	25.0 (22.6 – 46.4)	2.0 (-1.2 – 4.3)	.084
Systolic BP (mmHg)	130 (118 – 160)	120 (100 – 150)	-10 (-31 – 10)	130 (130 – 145)	130 (115 – 140)	-5 (-20 – 10)	.412
Diastolic BP (mmHg)	80 (67 – 99)	76 (60 – 90)	-5 (-25 – 20)	80 (70 – 95)	90 (80 – 100)	5 (-5 – 25)	**.007**
Triglycerides (mmol/L)	1.18 (0.57 – 3.87)	1.29 (0.52 – 4.78)	0.04 (-1.70 – 1.75)	0.86 (0.72 – 1.68)	2.28 (0.86 – 3.50)	1.20 (0.14 – 1.82)	**.003**

BP: Blood pressure.*Δ of unchanged TL group vs. Δ shortened TL group.

12080 **Poster Session**

Impact of adverse health outcomes (AHOs) on self-reported physical and mental health in U.S. testicular cancer survivors (TCS). *First Author: Paul C. Dinh, Indiana University School of Medicine, Indianapolis, IN*

Background: No study has systematically evaluated the impact of AHOs on PROMIS-validated measures of physical and mental health in TCS. Patient-reported outcomes are increasingly recognized as crucial in TCS follow-up, given their young age at diagnosis and high cure rates. **Methods:** Eligible TCS (age < 60 yr at diagnosis, given first-line cisplatin-based chemotherapy (CHEM)) completed comprehensive health surveys, prescription drug usage, and PROMIS global physical health and global mental health measures. PROMIS scores were compared to US subpopulation norms for similar-age men. 2017-2018 NHANES data were compared with select survey responses. Linear regression examined the relationship between individual AHOs (pain, obesity, cisplatin-induced peripheral neuropathy (CIPN)), cisplatin-related AHOs (CIPN, hearing loss, vertigo, tinnitus, renal disease), cardiovascular (CVD) AHOs (7 AHO), and all AHOs taken together (24 AHOs), with PROMIS global physical and mental health measures. Regression models were adjusted for age, cisplatin dose, time since CHEM, education, income, smoking, and alcohol. **Results:** Among 213 TCS (median age at evaluation: 46 yr; IQR: 38-52 yr; median time since CHEM completion: 10.6 yr; IQR: 6.8-16.6 yr), the most common AHOs were tinnitus (60%), self-reported hearing loss (60%), CIPN (55%), and Raynaud Phenomenon (43%). The median number of AHOs was 5 (IQR: 3-7), and 12% of TCS had ≥10 AHOs. Only 1.4% of TCS had no AHOs. Compared to NHANES men without cancer, controlling for age, education, and race, fewer TCS currently smoked (3% vs. 22%; P< .001) and fewer were obese (31% vs. 43%, P= .026) but alcohol intake was comparable. However, TCS had significantly lower physical (mean: 48.5 vs. 51.2, P< .001) and mental health (mean: 48.4 vs. 50.8, P< .001) than US men. Increasing numbers of AHOs were significantly associated with decreasing physical (P< .001) and mental health (P< .001) after adjustment. The magnitude of effect was strongest for the number of cisplatin-related AHOs with both physical (β: -1.3; 95% CI: -1.9, -0.7; P< .001) and mental health (β: -1.3; 95% CI: -2.1, -0.4; P= .003) after adjustment. In individual AHO adjusted models, CIPN (β: -1.8; 95% CI: -3.3, -0.4), pain (β: -5.0; 95% CI: -6.8, -3.2) and obesity (β: -2.7; 95% CI: -4.3, -1.1) were significantly associated with decreased physical health. Only pain (β: -5.9; 95% CI: -8.4, -3.4) and CIPN (β: -2.0; 95% CI: -4.0, -0.1), but not obesity, were associated with decreased mental health. **Conclusions:** At a median of 11 years after CHEM completion, 50% of TCS have ≥5 AHOs, and over 1 in 10 have ≥10 AHOs. AHO following cisplatin chemotherapy have major deleterious impacts on patient-reported measures of physical and mental health. Future survivorship research should focus on developing preventive and interventional strategies to care for TCS most vulnerable for impaired physical and mental health after CHEM. Research Sponsor: U.S. National Institutes of Health.

12081 **Poster Session**

Effects of exercise during adjuvant chemotherapy for breast cancer on long-term cardiotoxicity. *First Author: Willeke Naaktgeboren, UMC Utrecht, Utrecht, Netherlands*

Background: A common conception is that exercise training is cardioprotective for patients with breast cancer receiving adjuvant chemotherapy, but evidence to support this assertion is limited. This study aims to evaluate the effect of exercise training during adjuvant chemotherapy for breast cancer on long-term structural and functional cardiac outcomes. **Methods:** This is a follow-up study of two previously performed randomized studies in breast cancer patients; the PACT (N = 204) and PACES (N = 230) study. Cardiac outcomes, including extracellular volume fraction (ECV), left ventricular ejection fraction (LVEF) on cardiac MRI and global longitudinal strain (GLS) on echocardiography, were evaluated in patients allocated to moderate-to high-intensity exercise and non-exercise controls using linear and logistic regression models, adjusted for relevant confounders. Additionally, we explored the influence of self-reported PA during chemotherapy on cardiac outcomes, regardless of treatment allocation. **Results:** In total, 185 breast cancer survivors were included (mean age 58.9±7.8 years, mean time since treatment 8.5±1.1 years). Mean ECV was 25.3±2.5 in the control group and 24.6±2.8 in the exercise group. Mean LVEF was borderline normal in both (54.6±4.9 and 53.0±7.8) with an LVEF < 50% of 17.1% and 27.8% in control and exercise group, respectively. Compared to control, no significant effect of exercise during chemotherapy on ECV (β = -0.61, 95%CI: -1.55;0.32) or on abnormal ECV (OR = 0.80, 95%CI: 0.26;2.45) was found. Native T1 was statistically significantly lower in the exercise group compared to control (β = -16.75%CI: -31.5 ;-1.93). The odds of having an abnormal native T1 appeared lower in the exercise group (OR 0.58, 95%CI: 0.28;1.17). We found no benefit of exercise for LVEF or GLS (β = -1.82, 95%CI: -4.06;0.42 and β = 0.21, 95%CI: -0.87;1.28), nor on the likelihood of having an abnormal LVEF or GLS (OR = 1.78, 95%CI: 0.79;4.16); OR = 1.21, 95%CI: 0.56;2.63), respectively. Higher self-reported physical activity levels during chemotherapy tended to be associated with better cardiac outcomes. **Conclusions:** Exercise training during chemotherapy was not associated with long-term cardioprotection in patients with early-stage breast cancer. The high prevalence of cardiac abnormalities years post-chemotherapy suggests the need to include cardiac assessment in long-term follow-up programs for breast cancer survivors and calls for more research on cardioprotective measures during adjuvant chemotherapy, including alternative exercise dosing regimens and pharmacological adjuncts. Clinical trial information: NTR7247. Research Sponsor: KWF/Alpe, 10325 / 2016-1.

12082 **Poster Session**

Thromboembolism (TE) and association with survival in patients (pts) with melanoma receiving chemo– or immunotherapy. *First Author: Tamara A. Sussman, Dana-Farber Cancer Institute, Boston, MA*

Background: Emerging reports suggest high rates of venous thromboembolism (VTE) and arterial thromboembolism (ATE) with immune checkpoint inhibitors (ICI) in pts with melanoma, but it is unclear whether these are truly increased compared to older systemic therapy approaches. We assessed the incidence of TE in melanoma pts on ICI, cytokine therapy (CY), and chemotherapy (chemo), and evaluated its impact on survival. **Methods:** We conducted a cohort study using the SEER-Medicare database to evaluate rates of TE in pts with melanoma treated from 2008-2019 with ICI (ipilimumab, nivolumab, pembrolizumab), CY (IL2, IFN), and/or chemo (antineoplastic agents, BRAF/MEK inhibitors) within two years of treatment initiation. TE including VTE events of deep venous thrombosis, pulmonary embolism, and ATE of MI, ischemic stroke, and transient ischemic attack were identified by at least two outpatient claims or one inpatient claim. Overall survival (OS) from treatment start was analyzed by time-varying Cox analysis. **Results:** The cohort comprised 13,124 pts with median age 75 (24-101) years and 68% male. Of these, 14.8% received ICI, 48.9% chemo, 1.7% CY, 31.8% chemo+ICI, and 2.8% chemo+CY. At treatment start, comorbidities included 72% of pts with hypertension, 33% cerebrovascular disease, 17% atrial fibrillation, 7.3% history of VTE, and 13.0% history of ATE. Overall, 11.4% were on anticoagulation and 5.2% on antiplatelet agents. Incidence rates of ATE and VTE after treatment start are shown (Table). VTE was highest at 3 months after starting therapy with 19.6 events per 100 person-years in those receiving chemo+ICI, 17.1 events with chemo, 15.4 events with ICI, 10.1 events with chemo+CY, and 7.7 events with CY. In multivariable analysis, VTE and ATE were associated with worse OS compared to patients without (HR 2.77 [95%CI, 2.50-3.08], and HR 2.53 [95%CI, 2.23-2.86], respectively). **Conclusions:** Systemic therapy with ICI and chemo, especially when exposed to both sequentially or concurrently, demonstrates a high incidence of TE in pts with melanoma. TE is associated with substantial worsening of survival. TE rates are not substantially increased with ICI in comparison to chemo. Further studies are needed to identify benefit of thromboprophylaxis. Research Sponsor: Sondra and Stephen Hardis Endowed Chair to Dr Khorana.

Incidence rate (100 person-years).

	ICI		Chemo		CY		Chemo+ICI		Chemo+CY	
	VTE	ATE	VTE	ATE	VTE	ATE	VTE	ATE	VTE	ATE
3 months	15.4	7.7	17.1	9.7	7.7	7.7	19.6	10.1	10.1	10.0
6	13.8	7.0	14.5	8.8	7.4	9.0	16.0	9.1	7.0	8.4
9	12.4	6.9	12.6	8.0	5.8	6.9	14.4	8.7	6.4	7.3
12	11.1	6.4	11.1	7.4	6.2	6.7	12.8	8.4	5.0	5.7
24	8.9	5.7	8.9	6.4	3.8	5.1	9.6	6.7	4.0	4.3

12083 **Poster Session**

Adverse health outcomes (AHO) in testis cancer survivors (TCS) following high-dose chemotherapy (HDCT) and autologous stem cell transplant. *First Author: Meagan Elizabeth Miller, Indiana University School of Medicine, Indianapolis, IN*

Background: Patients with relapsed/refractory germ cell tumors are often cured with tandem platinum-based HDCT followed by autologous stem cell transplant in the ≥2nd line treatment setting. A comprehensive assessment of long-term AHO (adverse health outcomes) in TCS cured with HDCT has not been previously described. **Methods:** Testis cancer survivors (TCS) at least 1 year after HDCT and treated at Indiana University were eligible. TCS were asked to complete a comprehensive, well validated survey regarding 19 different AHO. TCS demographics, disease characteristics, treatment received, and AHO were collected. **Results:** From 2/2021-1/2022, 118 eligible TCS were invited. 70 TCS completed the survey (59.3% completion rate). TCS received HDCT followed by autologous stem cell transplant in the 2nd (91.4%), 3rd (7.1%) or 4th line (1.4%) setting. At the time of survey completion, 93% of respondents were at least two years from HDCT (range 1.6-16.2 y) with a median age of 42 y (range 24.8-66.6 y). Median age at the time of original germ cell tumor diagnosis was 32 y (range 17.4-56.8 y). TCS reported a median of 3 AHO with 37% of participants reporting 5 or more AHO. 90% of participants reported tinnitus, 91% experienced hearing impairment, and 52% required the use of hearing aids. Additionally, 46% TCS noted peripheral neuropathy and 26% reported problems with balance/vertigo/dizziness. Prevalence of kidney disease was 10%, and 24% TCS experienced erectile dysfunction. In regards to physical activity, 47% of participants were not participating in vigorous physical activity (defined as > 6 mets/week). 16% TCS reported use of medications to treat anxiety and/or depression, and 19% required testosterone replacement therapy. The prevalence of hypertension, coronary artery disease, Raynaud phenomenon, hypercholesterolemia, diabetes, and thyroid disease were 13%, 1%, 17%, 12%, 4%, and 6% respectively. **Conclusions:** Despite the high cure rate of HDCT, TCS report a substantial burden of morbidity with the majority experiencing ototoxicity, and with half of the TCS requiring hearing aids. Special attention to these AHO and efforts to develop ototoxicity prevention approaches are urgently needed for this patient population. Research Sponsor: None.

12084 **Poster Session**

Impact of anti-HER2 therapy alone and in association with weekly paclitaxel on the ovarian reserve of young women with HER2-positive early breast cancer: Biomarker analysis of the NeoALTTO trial. *First Author: Matteo Lambertini, IRCCS Ospedale Policlinico San Martino-University of Genova, Genoa, Italy*

Background: The potential gonadotoxicity of anti-HER2 agents remains largely unknown and limited conflicting evidence exists for taxanes. Anti-Mullerian hormone (AMH) is an established biomarker of ovarian reserve; its measurement during systemic therapies may aid in indicating gonadotoxicity, in the diagnosis and prediction of primary ovarian insufficiency (POI). The present analysis explored for the first time the impact of anti-HER2 therapy alone and then combined with weekly paclitaxel on ovarian reserve measured by AMH levels in breast cancer (BC) patients not previously exposed to anthracycline and cyclophosphamide. **Methods:** This biomarker analysis of the NeoALTTO (NCT00553358) randomized phase III neoadjuvant trial included premenopausal women aged ≤45 years at diagnosis of HER2-positive early BC with available frozen serum samples at baseline (i.e. before administering any anticancer treatment), at week 2 (i.e. "biological window" of anti-HER2 therapy alone) and/or at the time of surgery (i.e. after completion of paclitaxel plus anti-HER2 therapy and before starting adjuvant chemotherapy). Central AMH testing was performed with the Roche Elecsysâ AMH Plus assay (LoD = 0.01 ng/ml). AMH levels during anti-HER2 therapy alone and then combined with paclitaxel were assessed as a measure of treatment acute gonadotoxicity. The impact of different anti-HER2 agents, patients' age, and baseline AMH levels on treatment gonadotoxicity were also investigated. **Results:** The present analysis included 130 patients with a median age of 38 years (IQR: 33-42 years). AMH values at the 3 time points differed significantly from each other ($p < 0.001$). At baseline, median AMH levels were 1.29 ng/mL (IQR 0.56 – 2.62 ng/mL). At week 2, a small but significant reduction in AMH levels was observed (median value: 1.10 ng/mL, IQR 0.45 – 2.09 ng/mL, $p < 0.001$). At surgery, there was a larger significant decline in AMH levels (median value: 0.01 ng/mL, IQR 0.01 – 0.03 ng/mL, $p < 0.001$). There was no significant difference between treatment arms (trastuzumab vs. lapatinib vs. trastuzumab plus lapatinib) in the degree of reduction in AMH levels at week 2 ($p = 0.763$) and at surgery ($p = 0.700$). Age and pre-treatment ovarian reserve had a major influence on treatment-induced gonadotoxicity risk, with older age and lower AMH levels at diagnosis being associated with a greater negative impact. **Conclusions:** This biomarker analysis of the NeoALTTO trial showed for the first time that anti-HER2 therapies alone had limited gonadotoxicity but the addition of weekly paclitaxel resulted in marked AMH decline which likely has implications for subsequent ovarian function and fertility. These data highlight the importance of oncofertility counselling among all premenopausal women with HER2-positive BC receiving systemic anticancer treatments. Clinical trial information: NCT00553358. Research Sponsor: AIRC, 5x1000 Italian Ministry of Health.

12085 **Poster Session**

Open-label, phase 2 study of roxadustat for treatment of anemia in patients receiving chemotherapy for non-myeloid malignancies. *First Author: John A. Glaspy, University of California Los Angeles School of Medicine, Los Angeles, CA*

Background: Anemia is prevalent in patients (pts) receiving myelosuppressive chemotherapy (> 60%) and exacerbated by repeated treatment cycles due to cytotoxic agent accumulation. Chemotherapy-induced anemia (CIA) management options are suboptimal. We evaluated the efficacy and safety of roxadustat in pts with anemia receiving myelosuppressive chemotherapy. **Methods:** This open-label, single-arm, proof-of-concept Phase 2 study included pts with mostly advanced, non-myeloid malignancies and CIA (hemoglobin [Hb] ≤10 g/dL) who had not received red blood cell (RBC) transfusion or erythropoietin-stimulating agents within 4 weeks of enrollment. Patients were treated with oral roxadustat for ≤16 weeks. The primary efficacy endpoint was maximum mean change in Hb within 16 weeks of baseline without RBC transfusion in pts who had received ≥1 dose of roxadustat and who had a baseline and ≥1 post-dose Hb assessment. Hb response and safety data were preliminarily assessed in pts receiving a starting dose of 2.0 mg/kg thrice weekly (TIW) for 4 weeks: doses of 100, 150, and 200 mg were given to pts weighing < 70, 70–100, and > 100 kg, respectively. Following a review of data from these pts, dose was increased to 2.5 mg/kg—150, 200, and 250 mg TIW to pts weighing < 70, 70–100, and > 100 kg, respectively—and adjusted every 4 weeks from Week 5 based on Hb response. **Results:** Patients were assigned to 2.0 mg/kg (n = 31) and 2.5 mg/kg (n = 61) starting doses, and 89 were assessed for efficacy. The maximum mean Hb change from baseline without RBC transfusion was 2.47±1.51 g/dL and 2.52±1.54 g/dL in the 2.0 mg/kg and 2.5 mg/kg cohorts, respectively. Hb increased by ≥1.5 g/dL in 73% of pts and ≥2.0 g/dL in 61% of pts. Median time to ≥2.0 g/dL Hb increase was 71.0 days. Both cohorts had higher proportions of pts with a Hb increase of ≥1, ≥1.5, or ≥2 g/dL at Week 16 compared with baseline. Median time to ≥1 and ≥2 g/dL Hb increase was shorter in pts who started on 2.5 mg/kg compared with 2.0 mg/kg doses (≥1 g/dL: 30 vs 44; ≥2 g/dL 57 vs 105, respectively). Fewer pts required an RBC transfusion (Week 5 to end of treatment) when starting on 2.5 mg/kg compared with 2.0 mg/kg doses (10.2% vs 20.0%). Subgroup analyses based on major tumor and baseline chemotherapy types demonstrated efficacy of roxadustat at both starting doses. The overall safety profile observed was consistent with the patient population under study. Overall, 92% of pts experienced an adverse event (AE). Most AEs were consistent with the underlying malignancies and chemotherapy regimens used. The incidence of deep vein thrombosis was 15.2% (n = 14) and pulmonary embolism was 9.8% (n = 9). There were 17 deaths (18.5%) during the study; none were attributed to roxadustat, and most were associated with disease progression. **Conclusions:** Roxadustat increased Hb in CIA regardless of tumor type and chemotherapy regimen. These data support additional clinical study. Clinical trial information: NCT04076943. Research Sponsor: FibroGen, Inc.

12086 **Poster Session**

Cancer diagnosis, cancer treatment, and association with cardiovascular disease in older adults: Results from ASPREE. *First Author: Jaidyn Muhandiramge, School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia*

Background: New treatments and early detection measures have led to declines in cancer mortality rates and a growing population of cancer survivors at risk of short- and long-term effects of cancer and cancer treatment (C&CT), including cardiovascular disease (CVD). Although shared risk factors may contribute, several C&CT-related mechanisms including inflammation, treatment-related cardiotoxicity, and coagulation disorders may play a role. There are several studies exploring the link between C&CT and CVD; however, many do not examine risk stratified by cancer type or disease extent, nor investigate the impact of different treatment modalities. **Methods:** This analysis utilized data from the ASPirin in Reducing Events in the Elderly (ASPREE) trial, an international, multi-center, double-blinded randomized controlled trial that investigated the benefits and risks of aspirin in healthy older people. Multivariate time-dependent Cox regression models (adjusted for clinically significant factors including age, gender, smoking, and metabolic disease) were used to investigate the impact of C&CT on myocardial infarction, stroke, hospitalization for heart failure, and a composite endpoint combining these. Crude incidence rates were estimated using a competing risks regression model. Subgroup analysis was performed by metastatic status, cancer type, and treatment modality. **Results:** Of the 19,114 ASPREE participants (56% female; median age 75.1 years; median follow up 4.7 years), 1,933 received a post-randomisation cancer diagnosis. Participants with cancer had a greater rate and risk of CVD than those without cancer (15.3 per 1000 person-years (/1000pyrs] vs 10.5/1000pyrs, respectively; Hazard Ratio [HR] = 1.70, 95% Confidence Interval [CI] 1.32-2.10). The greatest increase in risk was seen for hospitalization for heart failure (HR 2.00, 1.18-3.38, 95% CI 1.18-3.38), although increases in risk were also seen for myocardial infarction, all-stroke, and ischaemic stroke. In subgroup analysis by cancer type, blood cancer (HR 2.33, 95% CI 1.25-4.36), lung cancer (HR 2.76, 95% CI 1.23-6.19), and melanoma (HR 1.97, 95% CI 1.02-3.82) were associated with an increased risk of composite CVD. 'Any cancer treatment' conferred increased risk of hospitalisation for heart failure (HR 1.78, 95% CI 1.15-2.75), although individual treatment modalities, including cytotoxic chemotherapy, targeted therapy, and radiotherapy conferred increased risks of various cardiovascular outcomes. **Conclusions:** Our findings indicate that both cancer and anti-cancer treatment confer risk for CVD in the elderly, the magnitude of which varied depending on cancer type and treatment modality. Given the implications of cardiovascular events for quality of life and mortality, these results support the integration of CVD screening and management into routine care for cancer survivors. Research Sponsor: U.S. National Institutes of Health, National Health and Medical Research Council of Australia, Monash University, Victorian Cancer Agency.

12087 **Poster Session**

Trajectory of aging following diagnosis of cancer. *First Author: Morgan Simons, NYU Grossman School of Medicine, New York, NY*

Background: Aging is a nebulous concept with several definitions, but they all generally include physical and cognitive decline in function as a key component. We hypothesized that following cancer diagnosis, patients decline in physical and cognitive function would correspond with accelerated and/or accentuated aging trajectories. The magnitude of the functional changes could inform strategies to minimize impact of cancer diagnosis on trajectory of aging. **Methods:** We analyzed 32,935 participants >50 years enrolled between 1995-2018 in the Health and Retirement Study (HRS), a population-based, biennial longitudinal health interview survey of older adults in the United States. We assessed the changes in physical and cognitive function among cancer patients controlling for their pre-cancer trajectories and comparing it with aged population with no cancer diagnosis as control. The primary outcomes were change in physical function (Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL): range 0–11) and global cognitive function (Telephone Interview for Cognitive Status (TICS): range 0–27). The secondary outcome was change in self-rated health (SRH: range 1-5). We estimated the effect of acute change based on the immediate post-cancer outcome measurements compared to the trajectories before cancer; and the long-term effect as the per-year change in outcome decline post cancer compared to aging of cancer-free respondents adjusting covariates by linear mixed models. **Results:** 5,101 developed incident cancer: 1,514 in the 50-64 age group, 1,901 in the 65-74 age group, and 1,686 in the 75+ age group. 27,834 participants were cancer-free throughout. Cancer was associated with acute declines in physical function (0.06 [0.01– 0.10] and 0.25 [0.14– 0.36] points), cognitive function (0.22 [0.04–0.39] and 0.24 [0.01– 0.46] points), and SRH (0.19 [0.14–0.23] and 0.22 [0.12–0.33] points) for age of onset groups 50- and 75+ respectively. Moreover, participants with cancer demonstrated accelerated decline in physical function (0.02 [0.01–0.03], and 0.06 [0.05–0.07] points per year faster for 50-74 and 75+ age-of-onset groups respectively) compared to cancer-free participants, but not in cognitive and SRH. Lung, colorectal & breast cancer were associated with the highest acute and accelerated decline in functions, while prostate cancer was associated with moderate and insignificant decline. **Conclusions:** Using 24 years of nationally representative longitudinal data, this study provides, for the first time, evidence for the heterogeneous aging trajectories of cancer patients across varying age-of-onset and cancer types. Our results supported an accelerated aging trajectory of physical function with increased acceleration with increasing age-of-onset compared to the non-cancer population. It also provides evidence for accentuated aging trajectories of cognitive function and self-rated health. Research Sponsor: None.

12088 **Poster Session**

Associations between DNA methylation age and chronic health conditions in survivors of childhood leukemia and CNS tumor. *First Author: Maria Monica Gramatges, Baylor College of Medicine and Dan L. Duncan Comprehensive Cancer Center, Houston, TX*

Background: Survivors of childhood cancer are at risk for treatment related morbidities, including an early onset of chronic health conditions (CHC). Survivors are at risk for epigenetic age acceleration (EAA), i.e. when DNA methylation (DNAm)-predicted age exceeds chronologic age. EAA has been associated with treatment exposures and incidence of cardiometabolic, pulmonary, and neurologic CHC. We characterized the burden of CHCs in survivors of acute lymphoblastic leukemia (ALL) and central nervous system (CNS) tumors, two of the most common childhood cancers, and determined the association between EAA, cancer diagnosis, and burden of CHC. **Methods:** We included survivors of CNS tumor or ALL diagnosed at Texas Children's Hospital (TCH) between 1992-2013, who were seen at least once in the TCH Long-Term Survivor Clinic. Demographics, diagnosis, treatment data and date of onset and type of CHC were abstracted from the electronic health record. All CHCs required subspecialty care, were present for at least 1 year, and were classified by system into one of 8 categories. Germline samples were obtained at an average of 10.5 years after diagnosis, and at an average age of 15.9 years of age. Samples were analyzed by Illumina MethylationEPIC BeadChip array on an iScan System in the Baylor College of Medicine (BCM) Laboratory for Translational Genomics. Methylation data were processed using *minfi*, normalized with *noob*, and EAA estimated using the Horvath calculator. The relationship between EAA, diagnosis, and CHCs was determined by multivariable linear regression. **Results:** Endocrine (65%), neuropsychiatric (78%), and sensory/motor (73%) CHCs were common in the CNS tumor group (n = 77). Metabolic (22%) and neuropsychiatric (59%) CHCs were common in the ALL group (n = 268). Survivors of CNS tumor had an earlier time of CHC onset, were more likely to have endocrine and sensory motor outcomes, and less likely to have metabolic outcomes vs. ALL survivors. On average, both survivor groups had EAA: 3.3 years (range: -12.2-15.5 years) for 138 ALL survivors and 4.4 years (range: -0.9-10.9 years) for 38 CNS tumor survivors, but EAA did not differ between diagnoses after adjustment for RT (p = 0.75). For CNS tumor survivors, EAA was 0.8 years greater for each system affected by CHC (beta = 0.8, p = 0.043) after adjustment for RT. For ALL survivors, EAA was not associated with CHCs (p = 0.33), but was associated with RT (p = 0.007). **Conclusions:** CHCs are prevalent in survivors of childhood ALL and CNS tumors, with patterns that differ by cancer diagnosis. In this cohort of relatively young 5 year + survivors of ALL and CNS tumor, all survivors had similar EAA but demonstrated cancer diagnosis-specific differences in associations between EAA, RT and burden of CHC. Research Sponsor: Hyundai Hope on Wheels Scholar of Hope Award.

12089 **Poster Session**

Association of metabolic risk factors with breast cancer survival in a population-based cohort. *First Author: Elizabeth Feliciano, Kaiser Permanente Division of Research, Oakland, CA*

Background: Metabolic abnormalities may impact breast cancer prognosis, but research has been limited by small samples and assessment of laboratory values at a single time point, often prior to cancer diagnosis and treatment. In a population based cohort, we utilized time-updated laboratory values and adjusted for cancer treatment to assess the association between metabolic risk factors (glucose, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides) and breast cancer survival. **Methods:** 13,434 women diagnosed with stage I-III breast cancer from 2005-15 at Kaiser Permanente were included. All outpatient fasting glucose, HDL, LDL, and triglyceride values from diagnosis through 2019 or death were extracted from electronic medical records. Lab values were updated a median of 5 times between 1-7 years post-diagnosis. Risk of breast cancer-specific mortality was evaluated with Cox proportional hazards models adjusted for metabolic labs, demographics, body mass index, and diabetes, and then for dyslipidemia and anti-hypertensive medications, tumor characteristics (stage, ER and HER2 receptor status) and cancer treatment (use of chemotherapy, and tamoxifen v. aromatase inhibitors). **Results:** Mean (SD) age at diagnosis was 62.3 (11.8) years. Over median follow-up of 9 years, 2,876 patients died (1,080 of breast cancer). Patients with low HDL (≤45 vs. >45 mg/dL) had higher breast cancer-specific mortality (HR, 1.87; 95% CI, 1.62-2.16); high levels of glucose, triglycerides, and LDL were not associated. The increased risk associated with low HDL persisted after adjusting for tumor characteristics, cancer treatment, and medications. **Conclusions:** Low HDL evaluated over time after cancer diagnosis is associated with higher breast cancer mortality independent of cancer treatments and changes in other metabolic risk factors. Cholesterol may play a role in breast cancer due to its role in cell membrane structure, signaling pathways, and steroid hormone synthesis. Future studies should address whether pharmacologic or lifestyle treatment of lipids after breast cancer diagnosis can optimize survival outcomes. Research Sponsor: U.S. National Institutes of Health.

Time-updated Cox model: Breast cancer mortality.

	Model 1*			Model 2**		
Characteristic	**HR[1]**	**95% CI[1]**	**p-value**	**HR[1]**	**95% CI[1]**	**p-value**
Glucose[2]						
High (>99 mg/dL)	1.14	0.99, 1.31	0.066	1.11	0.96, 1.28	0.2
HDL[2]						
Low (≤45 mg/dL)	1.87	1.62, 2.16	<0.001	1.72	1.49, 1.99	<0.001
LDL[2]						
High (≥129 mg/dL)	1.11	0.96, 1.27	0.2	1.11	0.96, 1.27	0.2
Triglycerides[2]						
High (≥199 mg/dL)	0.94	0.78, 1.13	0.5	0.96	0.80, 1.16	0.7

*Model 1 adjusts for age at diagnosis, race/ethnicity, body mass index, and diabetes.
**Model 2: adds stage, ER status, HER2 status, chemotherapy, tamoxifen, aromatase inhibitor, anti-hypertensive medication, dyslipidemia medication.
[1]HR = Hazard Ratio, CI = Confidence Interval.
[2]Reference category = normal.

12090 **Poster Session**

Quantification of methylation-specific cardiomyocyte cell-free DNA as an early marker of cardiotoxicity in patients with breast cancer receiving anthracyclines and trastuzumab. *First Author: Zachary Ray Moore, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: There is currently no way to reliably predict which patients undergoing therapy for breast cancer will develop cardiotoxicity. An early biomarker of cardiotoxicity could provide opportunity for intervention prior to the appearance of gross abnormalities on echocardiogram (ECHO). A droplet digital PCR (ddPCR) assay for circulating cell-free DNA (cfDNA) can detect cfDNA released from dying cardiomyocytes with high sensitivity by differentiating cfDNA of cardiomyocyte origin based on the pattern of methylation specific to the cell type. Circulating cfDNA of cardiac origin was tested as an early biomarker of toxicity in patients who underwent breast cancer treatment while closely monitoring cardiac function in a prospective clinical trial. **Methods:** A cardiomyocyte methylation-specific quantitative ddPCR assay was tested in plasma samples from 29 patients who were part of a larger prospectively enrolled cohort of women who received anthracyclines and trastuzumab for HER2-positive breast cancer. Blood samples were tested from prior to doxorubicin and cyclophosphamide (AC) chemotherapy, two months later after completing AC and prior to trastuzumab, and every 3 months to 12 months post-treatment. Patients were assessed for clinical cardiotoxicity, defined as heart failure (NYHA class III/IV) or significant EF decline (> = 10% to below 53% or > = 16%) until completion of cancer therapy. The maximum detected level of cardiac cfDNA (copies per 500 μL plasma) was compared between those who experienced cardiotoxicity and those who did not by two-sided T-tests. Results are reported as mean +/- standard deviation. **Results:** At baseline, cardiac cfDNA levels were low (mean 1.1 +/- 2.4 copies). Of 29 patients, five developed clinical cardiotoxicity. The maximum number of cfDNA copies at any time point was elevated in patients who experienced cardiotoxicity compared to those who did not (mean of 20.6 +/- 7.3 copies versus 9.3 +/- 9.8 copies, p = 0.0216). Of the patients with cardiotoxicity, elevated cfDNA of greater than 10 copies was detected an average of 3.6 +/- 2.5 months prior to the onset of clinical cardiotoxicity. **Conclusions:** Methylation specific cardiac cfDNA shows promise as an early indicator of cardiotoxicity in patients treated with anthracyclines in this pilot study. A previously reported analysis in the levels of seven other biomarkers including high-sensitivity troponin I and NT-proBNP pre- versus post-treatment in the full cohort of 80 patients did not show any statistically significant associations with the development of cardiotoxicity, suggesting that cardiac cfDNA may be uniquely informative. Clinical trial information: NCT02177175. Research Sponsor: Chanel Endowment for Survivorship Research Grant, MSKCC Imaging and Radiation Sciences Program.

12091 **Poster Session**

Racial disparity in breast cancer survivorship: Results of a qualitative research study to identify themes from a series national healthcare provider live virtual forums. *First Author: Jill M. Binkley, TurningPoint Breast Cancer Rehabilitation, Atlanta, GA*

Background: Significant disparity exists in the diagnosis, treatment, and survivorship outcomes among Black breast cancer (BC) survivors. Unmet physical and emotional needs in BC survivors are well documented, but there is mounting evidence that Black BC survivors have more significant survivorship issues and a greater burden of illness than White counterparts. Barriers to rehabilitation and recovery care exist for all BC survivors; however, they are magnified in Black BC survivors due to systemic racism, healthcare provider bias and discrimination, lack of culturally relevant care models, and socio-economic barriers. There is limited literature on lived personal and professional experiences of racial disparity in BC survivorship. **Methods:** The purpose of this qualitative research was to document patient, clinician and researchers' perceptions surrounding contributing factors, lived experiences, and potential solutions to racial disparity in BC survivorship against the contextual background of reported inequities. A narrative approach was utilized to identify themes from a series of four virtual healthcare provider forums that explored lived personal and professional experiences, issues and potential solutions surrounding racial disparity in BC survivorship from October 2020-September 2021. The forums included perspectives of patients, healthcare providers, researchers, and stakeholders in the BC field. The total live and online views for all four forums was 2,093. An independent thematic analysis was performed by the investigators, all of whom have emic perspectives with respect to race and/or breast cancer. **Results:** Three main themes were independently identified by study investigators: 1. societal and cultural contributing factors contributing to racial disparity in BC survivorship, 2. contribution of healthcare providers and systems to racial disparity in BC survivorship and 3. models of care and research considerations that would reduce racial disparity. These themes were widely echoed by forum participants throughout the series. With respect to solutions, widespread implementation of navigation models and the *Prospective Model of Rehabilitation for Women with Breast Cancer* that address physical and psychosocial treatment side effects would reduce disparity. The importance of the inclusion of voices of Black BC survivors in community-based participatory research aimed at reducing survivorship disparity is critical. **Conclusions:** The findings provide compelling documentation of lived personal and professional experiences of racial disparity in BC survivorship. These issues have been described in the literature for nearly two decades. Potential solutions exist and must be enacted immediately to ensure equitable survivorship outcomes for Black individuals following a BC diagnosis. Research Sponsor: TurningPoint Breast Cancer Rehabilitation and Emory University, Atlanta.

12092 **Poster Session**

Long-term outcomes of adrenal insufficiency (AI) due to anti–PD(L)-1 immune checkpoint inhibitors (ICI) among patients with cancer. *First Author: Ben Nguyen, SUNY Downstate Medical Center, Brooklyn, NY*

Background: Endocrine immune-related adverse events (irAEs) to anti-PD-(L)1 ICI, including hypophysitis, autoimmune insulin-dependent diabetes mellites (ICI-DM), and primary adrenal insufficiency (AI), are rare but often associated with long term co-morbidities. AI from anti-PD-(L)1 ICI without CTLA-4 blockade is not well characterized in the literature. Long term outcomes for AI including need for replacement steroids and cortisol levels are unknown. **Methods:** We performed a single center retrospective analysis of patients treated with ICI including anti-programmed cell death protein-1 (Anti-PD-1: nivolumab or pembrolizumab), anti-programmed death-ligand-1 (anti-PD-L1: atezolizumab or cemiplimab) and diagnosed with ICI induced AI by a board-certified endocrinologist from 1/1/2011 to 12/31/2021. Patients treated with anti-CTLA-4 based therapy were not included. Patient baseline characteristics, presenting symptoms at the time of AI diagnosis, and treatment with corticosteroids were obtained by chart review. Baseline labs were collected at the time of AI and during routine patient follow-up. Descriptive statistics are reported for the cohort. **Results:** Twenty-nine patients were identified, 27 diagnosed with secondary and 2 diagnosed with primary AI. The median age was 63 (range 39-84), 18 (62%) males and 11 (38%) females, 14 (48%) receiving anti-PD(L)-1 monotherapy and 22 receiving anti-PD(L)-1 combination therapy either with chemotherapy (7, 24%), targeted therapy (6, 21%) or other/investigational therapy (2, 7%). The common tumor types were 6 renal cell carcinoma, 4 urothelial carcinoma, 4 melanoma, 15 others. The common presenting symptoms were 26 (90%) with fatigue,16 (55%) weakness, 11 (38%) nausea/vomiting, 4 (14%) headaches and 2 (7%) arthralgias. The common concomitant irAEs were 16 (55%) hypothyroidism, 8 (28%) acute kidney injury, 7 (24%) colitis, 6 (21%) joint pain, 3 (10%) pneumonitis & dermatitis. Eleven (38%) patients were treated with high dose steroids. Median follow-up time for survivors in the cohort was 24 months (range 7-68). Median cortisol level at time of AI diagnosis was 1.1 (IQR 0.9, 2.7; n = 27) and 1.8 (IQR 0.6, 6.4; n = 10) at last follow-up (median lab follow-up 39 months, range 29-58); 7 of 10 patients with available data had cortisol < 5.0 at last follow-up. For secondary AI patients, median ACTH at time of diagnosis was 2.3 (IQR 2.0, 5.0; n = 21) and 2.0 (IQR 2.0, 7.2; n = 7) at last follow-up. Twenty-two of 23 patients with available data continued replacement steroids at last follow-up. **Conclusions:** AI associated with anti-PD(L)-1 ICI is primarily secondary. Cortisol and ACTH levels remain low even during long-term follow-up. Most patients need long-term replacement steroids. Systemic and comprehensive follow-up for patients who develop AI due to anti-PD(L)-1 ICI is needed to confirm these findings. Research Sponsor: None.

12093 **Poster Session**

Hair Safe Study: Effects of scalp cooling on hair preservation and hair regrowth in breast cancer therapy—A prospective interventional study. *First Author: Christine Brunner, Department of Obstetrics and Gynecology, Medical University of Innsbruck, Innsbruck, Austria*

Background: Chemotherapy (CT) is a frequent and well established treatment in women with breast and gynecological tumors. Alopecia is one of the most common side effects of CT seriously impairing patient quality of life and body image. While other CT associated side effects can be controlled by supportive treatment strategy, adequate preventive measures for alopecia have been lacking. New evidence supports the efficacy of scalp cooling for alopecia prevention during CT. The aim of this study was to investigate preventive scalp cooling (SC) for chemotherapy-induced-alopecia in breast cancer patients undergoing standard adjuvant or palliative chemotherapy. We also analysed the impact of SC on hair regrowth after chemotherapy-induced-alopecia. **Methods:** This was a non-randomized, 2-arm interventional study conducted at the Department of Obstetrics and Gynecology, Medical University Innsbruck. Breast cancer patients receiving any chemotherapy associated with alopecia (i.e. taxane or anthracycline-based chemotherapy) were allocated either to an intervention group receiving SC or to a control group (no SC). SC during chemotherapy was applied by the Paxman scalp cooling system. The primary endpoint was hair preservation (HP) which was assessed by experts and patients using the CTCAE score and analysed during and after completion of chemotherapy. The secondary endpoint was hair regrowth (HR) after 3 and 6 to 9 months post chemotherapy. **Results:** The study population included 128 patients. The majority, namely 88 (69%) patients were assigned to the intervention group (CAP) and received SC, 40 patients were allocated to the control group (NCAP). HP was significantly higher in the group receiving SC than in the NCAP by patients' self-evaluation (24% vs. 0%; P = 0.001) and experts' assessment (72% vs. 0%, P ≤ 0.001). HR was comparable between both groups. Using the patients' evaluation 50% of patients with taxane monotherapy had a grade 1 alopecia compared to 17% of patients with an anthracycline-taxane CT (50% vs 17%, P = 0.018). Drop-out rate was 13% in CAP and 5% in NCAP group. Main reasons for drop-out were hair loss and patients' requests. **Conclusions:** Our study demonstrates that SCsignificantly reduced or avoided chemotherapy-induced-alopecia in breast cancer patients undergoing chemotherapy, especially in patients who received taxane-monotherapy. SC was a safe procedure without severe adverse events. Therefore, SC can be highly beneficial for patients receiving specific chemotherapy and the option should be made available to as many patients as possible. No significant effect was noted regarding regrowth after chemotherapy in the SC group. Research Sponsor: None.

12094 **Poster Session**

Predictive value of baseline patient-rated treatment bother for early anastrozole discontinuation in a racially diverse cohort: Results from ECOG-ACRIN E1Z11. *First Author: Fengmin Zhao, Dana–Farber Cancer Institute, Malden, MA*

Background: The Functional Assessment of Cancer Therapy patient-reported outcomes (PRO) item GP5 ("I am bothered by side effects of treatment") estimates treatment tolerability. We aimed to extend our previous finding that GP5 predicts early aromatase inhibitor (AI) discontinuation (E1Z03, 96% White) in the racially diverse E1Z11 trial cohort. **Methods:** E1Z11 was coordinated by the ECOG-ACRIN NCI Community Oncology Research Program (NCORP) Research Base. Postmenopausal women initiating anastrozole per clinical care for ER+ stage I-III breast cancer with a pain score 0-3/10 and no rheumatologic comorbidities were eligible. Accrual of a racially diverse cohort of 1,000 women, including Black and Asian women, was planned. GP5 was administered prior to initiating anastrozole (trial baseline) and at 3, 6, 9 and 12 months. GP5 was scored on a 5-point Likert scale from 0 (not at all) to 4 (very much) and dichotomized as no/little treatment bother (0/1) or moderate/high treatment bother (2-4), consistent with previous analyses. A univariate Cox proportional hazards model estimated baseline GP5's association with treatment duration via hazard ratio (HR). Early treatment discontinuation status was defined as treatment duration < 12 months with discontinuation not attributed to disease progression or death (n = 4), consistent with previous analyses. **Results:** 1,046 women enrolled from 6/2013-10/2018 (640 White, 201 Black, 205 Asian), including 590 (56%) from NCORP Community or Minority/Underserved Sites. Approximately 10% (100/987 with GP5 data) reported moderate/high treatment bother prior to initiating anastrozole. Anastrozole discontinuation rate at 1-year was 26.2% overall; it was lower among women with no/little treatment bother (25.7%, GP5 = 0-1) compared to moderate/high treatment bother prior to initiating anastrozole (34.7%, GP5 = 2-4; HR = 1.50, 95% confidence interval [CI]:1.04-2.15, p = 0.027). Subgroup analyses by racial cohort showed a similar predictive effect of GP5 in the White (n = 606, HR = 1.76, 95% CI: 1.12-2.77, p = 0.014) and Black (n = 184, HR = 1.85, 95% CI: 0.92-3.71, p = 0.079) cohorts, but not in the Asian cohort (n = 197, HR = 0.40, 95% CI: 0.10-1.62, p = 0.20). **Conclusions:** Moderate/high treatment bother prior to starting anastrozole was observed in 10% of patients and associated with a higher risk of early discontinuation, except in Asian patients. Our findings support the presence of a treatment tolerability threshold which can be compromised by pre-treatment burden. Treatment tolerability may also be influenced by cultural and genetic factors, which will be explored in further analysis of genetic and PRO data. Clinical trial information: NCT01824836. Research Sponsor: U.S. National Institutes of Health.

12095 **Poster Session**

Associations between diet quality and chronic health conditions (CHCs) in adult survivors of childhood cancer in the St. Jude Lifetime Cohort Study (SJLIFE). *First Author: Emily R Finch, St. Jude Children's Research Hospital, Memphis, TN*

Background: Survivors of childhood cancer are at increased risk for early development of CHCs, including metabolic syndrome (MetS), low bone mineral density (LBMD), and gastrointestinal (GI) disease. Dietary modification is often recommended for prevention and/or treatment of these CHCs in non-cancer populations. However, associations between diet quality and severity of CHCs in adult survivors of childhood cancer are not well known. **Methods:** Adult survivors (≥10 years post-diagnosis) of childhood cancer who completed a clinical evaluation and Block Food Frequency Questionnaire were included. Diet quality was estimated using the Mediterranean diet score (aMED), with scores ranging from 0 to 9 (increased scores represent higher adherence to diet). CHCs were graded (modified CTCAE) and classified as "low" (grade ≤1 for LBMD and GI; grade ≤2 for MetS) or "high" (grade 2-4 for LBMD and GI; grade 3-4 for MetS). A multivariable linear regression model was used to estimate the mean aMED score by "low" or "high" disease category, with adjustment for age at evaluation, sex, race, education, total energy intake, adjusted BMI, physical activity, smoking, and alcohol consumption. **Results:** 2,822 survivors of childhood cancer (52.4% male, 83.1% non-Hispanic white) were included. The most prevalent diagnosis was acute lymphoblastic leukemia (34.1%). Time from primary diagnosis was 24.2±8.5 years and age at recruitment was 32.5±8.7 years. Lower adherence to aMED diet was associated with "high" MetS and LBMD, but not GI disease. See the Table for aMED multivariate-adjusted diet quality scores by CHC. **Conclusions:** In this cross-sectional analysis, MetS and LBMD were associated with poor adherence to the aMED diet. Although longitudinal investigation of associations between diet quality and CHCs in survivors of childhood cancer are needed to determine causal association between diet quality and CHCs in childhood cancer survivors, dietary interventions in early or late cancer survivors may help prevent development or progression of specific treatment related chronic conditions. Research Sponsor: U.S. National Institutes of Health, American Lebanese Syrian Associated Charities.

Multivariate-adjusted aMED diet quality scores by dichotomized CHC category in adult survivors of childhood cancer.

Chronic Health Conditions	Low Disease Category Adjusted Mean Diet Score (95% CI)	High Disease Category Adjusted Mean Diet Score (95% CI)	p-value
MetS	4.21 (4.13-4.30)	4.07 (3.94-4.20)	***0.002***
LBMD	4.22 (4.12-4.25)	3.98 (3.77-4.19)	***<0.0001***
GI	4.17 (4.09-4.24)	4.16 (4.03-4.30)	0.82

12096 **Poster Session**

Physical performance limitations and participation restrictions among cancer survivors: A population-based study from NHANES data 2015-2018. *First Author: Samantha A. Myers, University of British Columbia, Vancouver, BC, Canada*

Background: Anti-cancer therapies have improved survival outcomes in cancer survivors; however, therapy-related toxicities may impact organ structure and function and interfere with physical performance and participation in life roles. This analysis aimed to estimate the prevalence of physical performance limitations (PL) and participation restrictions (PR) among recent (< 5 years since diagnosis), and long-term (≥ 5 years) cancer survivors. **Methods:** Data from the 2015-2018 National Health and Nutrition Examination Survey (NHANES) were analyzed using multivariable logistic regression, accounting for age, sex, race, and income, and incorporating survey sampling methodology. Odds ratios compared proportions of PL and PR among 663 (weighted population estimate 14,319,219) recent and 341 (weighted population estimate 7,261,088) long-term survivors, and 10,284 (weighted population estimate 215,042,155) persons with no reported cancer history. Two-sided two sample z-tests were used to compare proportions to a previous publication of data from 1999-2002 NHANES data. **Results:** Physical performance limitations were 1.5-1.7 times (63% vs 29%) and PR 1.5-1.6 times (38% vs 18%) more prevalent in cancer survivors than in those with no cancer history. Long-term cancer diagnosis was associated with increased prevalence of PL and PR, particularly in survivors aged 20-39 years. Proportions increased by 7% for PL and by 10% for PR compared to 1999-2002 values (p-values <0.001). **Conclusions:** Over 60% of cancer survivors reported PL and nearly 40% reported PR. Despite an interim increase in evidence of the benefits of exercise to manage therapy-related toxicities, these values are a significant increase when compared to 1999-2002 NHANES data. Targeted education for providers and exercise interventions aimed to improve physical function and performance in early cancer survivors should be considered to address the physical sequelae from anti-cancer therapies. Research Sponsor: None.

Associations between age, cancer history and physical performance limitations (PL) and participation restrictions (PR) reported among adult participants in NHANES 2015-2018.

	No Cancer PL	< 5 yr survivor PL	5 + yr survivor PL	No Cancer PR	< 5 yr survivor PR	5 + yr survivor PR
Age (years)	% (SE%)	% (SE)	% (SE)	% (SE%)	% (SE)	% (SE)
20-39	10.6 (0.7)	26.7 (10.2)	58.9 (14.7)	9.0 (0.8)	20.0 (6.7)	49.5 (15.4)
40-49	15.5 (1.5)	29.1 (9.3)	22.1 (8.6)	11.6 (1.3)	19.5 (6.2)	14.6 (7.4)
50-59	29.4 (1.6)	42.3 (6.8)	41.2 (9.5)	20.6 (1.4)	38.2 (7.4)	32.4 (8.6)
60-69	60.0 (3.0)	70.0 (6.4)	53.4 (11.8)	28.5 (1.9)	34.3 (4.6)	28.9 (8.5)
70+	77.5 (1.4)	81.4 (2.2)	82.9 (3.6)	45.3 (1.6)	48.9 (3.0)	48.7 (6.3)

Presented as percentage (%) and standard error percent (SE%).

12097 **Poster Session**

The safety and efficacy of psilocybin therapy in patients with cancer and major depressive disorder. *First Author: Manish Agrawal, Associates in Oncology, Rockville, MD*

Background: More than 17 million people in the U.S. live with cancer and up to 25% of them have major depression. Depression leads to lower treatment adherence, reduced quality of life, and higher rates of mortality in cancer. Yet, interventions used to treat depression in patients with cancer have limited success. Prior trials using psilocybin to treat anxiety and depression associated with cancer suggested improvements in psychological distress. However, treatment in a homogenous psychiatric sample has yet to be investigated. Further, psilocybin has not been given in groups, and in a setting conducive to the "whole person" approach to treatment. This trial built upon previous studies and tested the safety, feasibility, and efficacy of psilocybin therapy in cancer patients diagnosed with major depressive disorder (MDD), with the novel use of group treatment in a cancer center setting. **Methods:** Phase II, single-center, open label trial, where 30 patients received a dose of 25 mg of psilocybin. Inclusion criteria: 1) age ≥ 18 years, 2) met criteria for MDD, 3) a Hamilton Depression Rating Scale score ≥ 18 at baseline, 4) diagnosis of a malignant neoplasm. Patients who had curative treatment for cancer as well as those with advanced metastatic disease were included. Patients were divided into cohorts and they received 1 group preparation session, simultaneous administration of psilocybin, and 2 group integration sessions. Therapeutic care was also provided before, during, and after the session using the 1:1 model of psychological support. The primary outcome measures for safety were adverse events, vital signs, ECGs, blood tests, and suicidality scores (C-SSRS). The secondary and exploratory outcome measures consisted of 15 assessments conducted at baseline and post-treatment at day 1, week 1, week 3, and week 8 to determine the efficacy of treatment. **Results:** A total of 30 patients were enrolled over the course of only 8 months with an attrition rate of 0%. All completed the trial with no serious adverse events. Beyond high tolerability of the treatment, we also found a clinically meaningful change in depressive symptoms. After a single administration of psilocybin therapy, the average score on the Montgomery Asberg Depression Rating Scale (MADRS) dropped by 19.1 points (95% CI, 22.3 to 16.0, p < 0.0001). A sustained response rate (a decrease of ≥ 50% in the MADRS score from baseline to week 8) was seen by 24 patients. 50% of patients showed complete remission of depression symptoms (a MADRS score < 10) one week after treatment, which was sustained for up to 8 weeks. **Conclusions:** This study adds to the growing body of psilocybin research with promising results showing the safety, feasibility, and efficacy of simultaneous psilocybin treatment in patients with cancer with MDD. The value of group support for patients with cancer was also explored, with implications for increased scalability of psilocybin therapy in real-world settings. Clinical trial information: NCT04593563. Research Sponsor: COMPASS Pathways.

12099 **Poster Session**

An open-label, randomized, controlled trial to evaluate the efficacy of antihistamine premedication and infusion prolongation in prevention of hypersensitivity reaction to oxaliplatin. *First Author: Chalita Lagampan, Division of Medical Oncology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand*

Background: Hypersensitivity reaction (HSR) is a common toxicity in patients receiving repeated oxaliplatin. Oxaliplatin induced HSR could be severe and results in treatment discontinuation. There is no standard recommendation for prevention of oxaliplatin induced HSR. **Methods:** We conducted a prospective, single center, open-label, randomized controlled trial comparing the standard premedication and 2-hour infusion protocol to the additional antihistamine premedication, intravenous chlorpheniramine, and 3-hour infusion protocol. After three months of chemotherapy, the randomization was done at 5thand 7th cycles of 3-week and 2-week oxaliplatin based regimens, respectively. The primary endpoint was the incidence of HSR. **Results:** From July 2020 to March 2021, a total of 160 patients underwent randomization (80 patients in both intervention and control groups). After 11 months follow-up, all patients had completed planned treatment cycles. HSRs occurred in 1 (1.3 %) and 10 (12.5%) patients in intervention and control groups, respectively, p = 0.005). There were 6 (7.5%) patients with more than grade 1 HSRs in control groups, but none in intervention group. In the intervention group, one patient with HSR experienced grade 1 erythema and palpitation. There is no report of significant adverse event from anti-histamine premedication or oxaliplatin infusion prolongation. **Conclusions:** Additional antihistamine premedication and infusion prolongation started in 2nd half of treatment course can significantly reduced HSR incidence in patients receiving oxaliplatin. Clinical trial information: TCTR20210506001. Research Sponsor: None.

12100 **Poster Session**

Interim analysis of a single-center, single-arm, prospective phase 2 study to evaluate the efficacy and safety of benralizumab for alpelisib rash in metastatic PIK3CA-mutant, hormone receptor–positive breast cancer. *First Author: Mario E. Lacouture, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Rash associated with increased peripheral eosinophils develops in approximately 50% of metastatic breast cancer patients receiving alpelisib. Antihistamines and corticosteroids have limited benefit. Refractory rash may lead to decreased dose intensity and affect clinical outcome. Benralizumab is an anti-IL-5Rα chimeric monoclonal antibody that depletes peripheral eosinophils and has demonstrated benefit in eosinophilic asthma and hypereosinophilic syndrome. We investigate the efficacy and safety of benralizumab for the treatment of alpelisib rash. **Methods:** We performed a single-center, single-arm, prospective phase 2 study to evaluate the efficacy and safety of benralizumab in cancer patients who developed CTCAE grade 2/3 skin events resulting from immunotherapy or targeted therapies with absolute blood eosinophil counts of ≥300/mcl. While remaining on culprit drugs, patients were treated with benralizumab 30mg once every 4 weeks for the first 3 doses followed by once every 8 weeks for 3 additional doses (approved dosing for eosinophilic asthma). Primary endpoint was clinical response measured as reduction in CTCAE grade 2/3 skin event to grade ≤1 by week 4. Secondary endpoints were patient quality of life (QoL) measured by skindex16, safety data, need for supportive oral corticosteroids, and changes in cytokines and eosinophil biomarkers. This interim analysis focuses on patients with PIK3CA-mutant metastatic breast cancer receiving alpelisib. **Results:** Between September 16th 2020 and January 1st 2022, we enrolled 10 metastatic breast cancer patients with grade 2/3 rash attributed to alpelisib (5 pts with G3). All patients had a reduction of rash to grade ≤1 (n = 10, p < 0.0001), and a decrease in peripheral absolute eosinophils (mean 500/mcl to 0, p < 0.0001). Of these, 6 patients had been on prophylactic oral antihistamines and 2 had oral steroid coadministration. QoL significantly improved (Skindex16 mean score 58 to 16, p = 0.0001) and eosinophils in skin histology decreased per HPF (mean 6.25 to 0.25, n = 8, p = 0.2) by week 4. An increase in IL-5 > 600% and reduction IL-6 and TNF-α > 50% were reported by week 4 and 8. Grade 1/2 mucositis in 4 patients were reported as adverse events. **Conclusions:** Our findings suggest that benralizumab is safe and effective for the treatment of grade 2/3 rash with eosinophilia related to alpelisib in patients with breast cancer. A reduction in rash severity was evidenced in all patients, along with improved QoL. Larger controlled studies are in development to evaluate the efficacy of benralizumab for the prevention of alpelisib rash. Clinical trial information: NCT04552288. Research Sponsor: U.S. National Institutes of Health.

12101 **Poster Session**

Racial differences in interest and use of integrative medicine among patients with breast cancer. *First Author: Jori Sheade, University of Chicago Medical Center, Chicago, IL*

Background: Breast cancer treatment can be associated with side effects (SEs) that negatively impact quality of life. While some SEs can be treated with medications, such interventions come with additional SEs. Acupuncture, massage, meditation, music therapy and yoga have received ASCO endorsement for the management of therapy-related SEs. Many patients are interested in integrative services, but little is known about racial differences in interest and use of integrative services among patients with breast cancer. **Methods:** Breast cancer patients enrolled in the Chicago Multiethnic Epidemiologic Cohort study were sent a survey regarding their interest and use of five integrative services: acupuncture, massage, meditation, music therapy and yoga. Participants were asked how interested they would be in these services if offered, using a five-point Likert scale. Prior use was self-reported. Proportional odds were modeled for "interest" and binary logistic regression was modeled for "self-reported use." Adjusted odds ratios (aOR) and 95% confidence intervals (CI) were calculated, controlling for age, education, marital status, household income, insurance, Carlson comorbidity index, molecular subtype and stage. **Results:** 1,300 patients responded to the survey, 928 White and 285 Black. Compared with White patients in this cohort, Black patients were less educated, had a lower household income, were more likely enrolled in Medicaid/Medicare, and had a greater Carlson comorbidity index. Over 97% of patients had stage 0-III breast cancer. While there was no difference in interest in acupuncture between Black and White patients (aOR 1.1, 95% CI 0.8-1.7), Black patients were significantly more interested in the use of massage (aOR 1.9, 95% CI 1.3-2.8), meditation (aOR 2.0, 95% CI 1.4-3.0), music therapy (aOR 2.7, 95% CI 1.8-4.0) and yoga (aOR 2.1, 95% CI 1.4-3.1). Black patients were significantly less likely than Whites to report acupuncture use (aOR 0.5, 95% CI 0.3-0.8); but there were no racial differences in self-reported use of massage (aOR 0.8, 95% CI 0.5-1.3), meditation (aOR 0.8, 95% CI 0.5-1.4), music therapy (aOR 1.7, 95% CI 0.8-3.3) and yoga (aOR 0.7, 95% CI 0.4-1.2). **Conclusions:** Black patients with breast cancer expressed more interest in integrative services than their White counterparts; there were no racial differences in self-reported use of integrative services except an increased use of acupuncture among White patients. A breast program focused on equity should provide access to these resources for all patients. Interest and self-reported use of integrative services among patients with breast cancer, by race. Research Sponsor: None.

	Interested or very interested		Self-reported use	
	White (n=928), %	Black (n=285), %	White (n=928), %	Black (n=285), %
Acupuncture	42.3	49.2	29.5	14.7
Therapeutic massage	59.5	74.0	42.9	37.5
Meditation	43.1	60.7	18.8	17.5
Music therapy	35.8	56.2	6.6	11.2
Yoga	45.5	62.7	20.8	13.0

12102 **Poster Session**

Race differences in patient-reported symptoms and adherence to adjuvant endocrine therapy among women with early-stage, hormone receptor-positive breast cancer. *First Author: Xin Hu, Emory University, Rollins School of Public Health, Atlanta, GA*

Background: Low rates of adherence to adjuvant endocrine therapy (AET) is a significant clinical problem. Symptom burden is a key barrier to adherence, but less is known about how changes in symptom burden affects adherence. Moreover, whether higher symptom burden in racial minorities explains their lower rates of adherence, has been relatively unexamined. We used longitudinal data to address these gaps in knowledge. **Methods:** Using electronic medical records linked with patient-reported data, Medicare and Medicaid claims, we identified women with early-stage, hormone receptor-positive breast cancer who initiated AET from a large cancer center in 08/2007-12/2015, had continuous insurance coverage and ≥1 symptom report before and during AET. Patient-reported symptoms were collected using a tablet-based platform [ConcertAI]. A total of 49 physical symptoms and 11 mental health symptoms were evaluated and classified into 7 physical and 2 mental clusters based on previous literature and clinical expertise. For each cluster, we counted the number of symptoms with moderate severity (≥3 points) at baseline, and with ≥3-point increase during 1-year follow-up. Adherence was defined as the percent of days covered by AET during the 1-year follow-up. We compared Black and White patients' symptoms at baseline and changes during the therapy, and conducted multivariable regression for patients' adherence adjusting for race, symptom measures, sociodemographic and clinical characteristics. **Results:** Black women (n = 168) were diagnosed at a younger age, with more advanced stage, and lived in areas with lower socioeconomic status than White women (n = 391, $p < .05$). Adherence to AET in the first year was 78.8% for Black and 82.3% for White women ($p = .16$). Black women experienced higher severity in most symptom clusters at baseline and during the follow-up than White women ($p < .05$). Neuropsychologic, Vasomotor, Musculoskeletal, Cardiorespiratory, Distress and Despair symptom clusters both at baseline and their increases during the follow-up were associated with 1.2 to 2.6 percentage points (ppt, $p < .05$) decreases in adherence. This means, each additional count of moderate severity symptoms in these clusters would decrease 4 to 9 days on AET. After adjusting for distress and despair symptoms, Black women had a 6.5 ppt higher adherence rate than White ($p < .05$). **Conclusions:** Black women had higher symptom burden at baseline and during the first year of AET. Both physical and mental health symptoms at baseline and the changes during therapy were associated with lower adherence. However, Black women had non-significantly lower rates of adherence despite the higher symptom burden due to unmeasured factors that offset the impact of symptom severity. Better symptom management could improve AET adherence and potentially reduce racial disparities in cancer outcomes. Research Sponsor: U.S. National Institutes of Health.

12103 **Poster Session**

Efficacy and safety of dexamethasone-based mouthwash to prevent chemotherapy-induced stomatitis in women with breast cancer: A multicenter, open-label, randomized phase II study. *First Author: Shigeto Maeda, National Hospital Organization Nagasaki Medical Center, Omura, Japan*

Background: Stomatitis, a frequent adverse event in patients undergoing chemotherapy, can lead to pain, ulcers, bleeding, and malnutrition due to reduced oral intake, which not only deteriorates quality of life but may also result in dose reduction or interruption of chemotherapy. However, there is currently no standard approach for preventing chemotherapy-induced stomatitis. Therefore, this study aimed to assess the efficacy and safety of a dexamethasone-based mouthwash for preventing chemotherapy-induced stomatitis in patients with early breast cancer. **Methods:** We conducted a multicenter, randomized, controlled phase II trial. Patients with early-stage breast cancer scheduled for epirubicin and cyclophosphamide (EC) or docetaxel and cyclophosphamide (TC) therapies were allocated in a 1:1 ratio to the intervention and control groups. The sample size was set to 120 cases based on the following assumptions: stomatitis incidence of 50% in the control group and 30% in the intervention group, alpha error of 0.2, one-sided power of 0.9, and dropout proportion of 10%. The intervention group received chemotherapy, oral care, and a dexamethasone-based mouthwash (10 mL, 0.1 mg/mL; swish for 2 min and spit, 4 times daily for 9 weeks), and the control group received chemotherapy and oral care. The primary endpoint was the incidence of stomatitis that was compared between the two groups. **Results:** There were 60 patients in the control group and 61 in the intervention group. One patient in the control group and two in the study group withdrew consent; one patient in the control group was excluded because of discontinuation of the first cycle of chemotherapy and unavailability of data related to the incidence of stomatitis. Finally, the data of 58 patients in the control group and 59 in the intervention group were analyzed. There were no differences in age and chemotherapy regimens between the groups. The incidence of stomatitis was 55% in the control group and 38% in the intervention group (risk ratio 0.68; 80% confidence interval, 0.52 – 0.88; p = 0.052). The grade of stomatitis (0/1/2/3) was significantly lower in the study group (intervention group vs. control group: 37/13/7/2 vs. 26/16/7/9, p = 0.03). There were no differences in the duration of stomatitis between the groups. Moreover, the percentage of patients who adhered to the mouthwash regimen was 87% (range, 14% – 100%). There were no significant differences in the occurrence of other adverse events between the groups, and only one case of oral candidiasis was observed in the intervention group. **Conclusions:** Dexamethasone-based mouthwash safely reduced the incidence and severity of stomatitis in patients receiving chemotherapy (EC/TC) for early breast cancer. Clinical trial information: UMIN000030489. Research Sponsor: None.

12104 **Poster Session**

Efficacy of olanzapine, netupitant, and palonosetron in controlling nausea and vomiting associated with highly emetogenic chemotherapy in patients with breast cancer (OLNEPA). *First Author: Camilla Vieira de Reboucas, Faculdade de Medicina do ABC, Santo André, Brazil*

Background: Chemotherapy induced nausea and vomiting (CINV) is a highly prevalent adverse event[1,2] that can result in decreased quality of life, dose reduction and interruptions of treatment.[3] Four drug protocol including Olanzapine, 5-hydroxytryptamine type 3 receptor (5HT3) antagonist, a neurokinin 1 receptor (NK1) antagonist and dexamethasone is the current standard of care for highly emetogenic chemotherapy (HEC) [2,4-6]. Corticosteroids are associated with side effects like insomnia and weight gain. To our knowledge, total Dexamethasone omission has not been addressed previously. **Methods:** This is a prospective single arm phase II study designed to evaluate the efficacy of Olanzapine, Netupitant and Palonosetron in controlling nausea and vomiting induced by highly emetogenic chemotherapy. Eligible patients were women with histologic confirmed breast cancer, planned to start treatment with Doxorubicin and Cyclophosphamide. Exclusion criteria included use of opioids or antipsychotic medications, medical condition that could potentially cause vomiting or inability to take oral medications. Patients were assigned to take Olanzapine 5mg QD, days 1 – 5, Netupitant 300mg and Palonosetron 0.5mg on day one. No corticosteroid use was allowed. The null hypothesis considered that the scheme containing Olanzapine, Netupitant and Palonosetron could not effectively control nausea. Based on a previous phase III study with Olanzapine (Navari *et al.*), we set the control of nausea at 20% and the expected control rate at 40% for the present study. To reach 5% (two-sided) significance and 80% statistical power, we calculated that a minimum sample size of 50 patients was required, assuming a 5% dropout rate. We used the one-sample T-test of proportion to analyze the data, based on intent-to-treat (ITT) The primary endpoint was complete control of nausea in the first 5 days after chemotherapy administration. Secondary endpoints were complete emesis control (no emesis, no use of rescue medication) and complete control (no emesis, no rescue and no nausea) **Results:** Fifty patients were enrolled from January 2020 to December 2021. The median age was 47.6 years-old (range: 29 – 78 years) and 48 patients (96%) received chemotherapy with curative intent. For the primary endpoint, complete nausea control rate was 46% (IC 32 – 59%) and p < 0.0001. The emesis control rate was 68% (IC 55 – 80%) and overall control rate was 46% (IC 32 – 59%). One patient dropped out for dizziness and drowsiness following administration of Olanzapine. **Conclusions:** Omitting Dexamethasone for highly emetogenic chemotherapy is feasible and showed similar control of nausea and vomiting compared to standard four-drug protocol. This could be a potential prophylactic regimen of choice for patients who have a contraindication for Dexamethasone use. Clinical trial information: NCT04669132. Research Sponsor: None.

12105 **Poster Session**

Using the consolidated framework for implementation research to evaluate facilitators and barriers to early outpatient specialty palliative care in patients with advanced cancer. *First Author: Rachel E Rosenblum, Division of Hematology & Oncology, University of Pittsburgh Medical Center, Pittsburgh, PA*

Background: Prior studies have shown that integration of early outpatient specialty palliative care (OSPC) with oncologic care improves patient's symptom burden and quality of life. As a result, the American Society of Clinical Oncology (ASCO) recommends that OSPC be offered within 8 weeks of diagnosis of an advanced solid malignancy. Over the past decade, there has been an increase in the availability of OSPC services, particularly at National Cancer Institute (NCI)-designated cancer centers; however, the majority of OSPC referrals still occur late in the disease course. The aim of this study was to evaluate the facilitators and barriers to implementation of early OSPC. **Methods:** To assess the contextual determinants of early OSPC implementation, we developed a survey based on constructs from the Consolidated Framework for Implementation Research (CFIR), an implementation meta-framework. Using input from subject-matter experts, we tailored the survey to include a total of 18 relevant constructs from the 5 CFIR domains. The survey was distributed to the ambulatory palliative care (PC) clinical leader at NCI-designated cancer centers. The survey assessed each CFIR construct using a 5-point Likert Scale, where +2 represented the strongest facilitators, and -2 represented the strongest barriers. We inquired about respondent sociodemographics and OSPC clinic characteristics and used descriptive statistics to summarize responses to survey items. **Results:** Survey responses were collected between 12/15/21 and 1/18/22. Of the 63 NCI-designated cancer centers invited to participate, 40 (63%) completed the survey, while 3 (5%) did not due to not having an ambulatory program. All respondents were physicians. Half of the OSPC clinics were established for more than 10 years, and the majority (75%) provided care to more than 300 distinct outpatients annually. The most commonly agreed upon facilitators (Likert score = 1 or 2) to early OSPC included PC clinicians' awareness of the ASCO recommendation for early OSPC (100%), informal communication between PC and oncology clinicians (100%), PC clinicians' belief that OSPC improves the quality of oncology care (100%) and access to telemedicine (93%). The most commonly agreed upon barriers (Likert score = -1 or -2) included inadequate number of OSPC providers (73%) and lack of performance metric goals relating to early OSPC set by PC leadership (65%). **Conclusions:** Although OSPC clinics at NCI-designated cancer centers have grown over the last ten years, the utilization of early OSPC is impacted by the implementing institution's resource availability, interdepartmental communication, stakeholder beliefs, and leadership engagement. Future studies should compare the barriers and facilitators of early OSPC identified by PC clinicians and oncologists to inform implementation strategies. Research Sponsor: "Palliative Care Technological Extension and Assistance in the Community for Improved Healthcare Outcomes" - sponsored by McElhattan Foundation.

12106 **Poster Session**

Phase 2, randomized, double-blind trial of EC-18 versus placebo to mitigate the development and time course of oral mucositis from concomitant chemoradiation for head and neck cancer. *First Author: Christina Henson, University of Oklahoma Health Sciences Center, Oklahoma City, OK*

Background: Oral mucositis (OM) is a debilitating side effect of concomitant chemoradiotherapy (CRT) for head and neck cancer (HNC). EC-18 may effectively mitigate OM by minimizing the CRT-induced innate immune response. This Phase II, 2-stage trial evaluated safety, tolerability, and efficacy of EC-18 in reducing the duration, incidence, and trajectory of severe OM (SOM) in HNC patients. **Methods:** Patients (n = 105) with pathologically confirmed oral cavity, oropharynx, hypopharynx, or nasopharynx squamous cell cancers who received intensity-modulated radiation therapy (IMRT; with ≥ 55 Gy on ≥ 2 oral sites) and weekly or tri-weekly cisplatin were studied. In Stage 1, 24 patients were randomized (n = 6 per arm) to receive 500, 1000, or 2000 mg of EC-18, or placebo. Following independent Data Safety Monitoring Board review, 81 patients in Stage 2 received EC-18 2000 mg (n = 41) or placebo (n = 40) throughout CRT. WHO OM grade was assessed twice weekly during IMRT and then once weekly for up to 6 weeks post-IMRT. The primary efficacy endpoint was duration of SOM during the active and short-term follow-up (STFU) periods in the compliant per-protocol population (PP). Much of Stage 2 was conducted during peak periods of the COVID-19 pandemic which measurably impacted patient compliance relative to test medication dosing and planned radiation. Consequently, to assess efficacy most accurately, the PP population was analyzed (with at least 4 weeks of study drug dosing, minimum cumulative radiation of 55 Gy, 80% study drug compliance in the first 28 days of dosing, and without using not-allowed-therapy). **Results:** Patient demographics and baseline characteristics were balanced between groups. Adverse events (AEs) were comparable amongst cohorts without drug-related severe AEs. In the PP, the median duration of SOM from baseline through STFU was 0 day in the EC-18 group (n = 22) *v* 13.5 days in the placebo group (n = 20). SOM incidence through STFU (45.5% *v* 70%) and opioid use (time to onset: 32.3 *v* 26.0 days; and duration: 32.8 *v* 37.5 days) favored EC-18 *v* placebo. Results of the covariates analyses suggested that EC-18 favorably impacted SOM incidence in patients who experienced SOM treated with weekly low-dose cisplatin (n = 26; 37.5% *v* placebo 70.0%) and HPV+ tumors (n = 29; 35.3% *v* placebo 66.7%; Table). One-year long-term follow-up for tumor outcomes is ongoing. **Conclusions:** EC-18 safely mitigated the development and the time course of SOM in CRT-treated HNC patients. In addition, EC-18 may provide substantial benefits to subpopulations of HPV^+ HNC patients treated with low dose cisplatin. Clinical trial information: NCT03200340. Research Sponsor: None.

Incidence of SOM through STFU for the selected PP subgroups who experienced SOM.

PP Subgroups	EC-18	Placebo
All PP	45.5% (10/22)	70.0% (14/20)
Weekly Cisplatin	37.5% (6/16)	70.0% (7/10)
HPV^+	35.3% (6/17)*	66.7% (8/12)

*One unknown HPV status.

12107 **Poster Session**

Olanzapine with or without an NK-1 receptor antagonist for preventing chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic chemotherapy: A phase III randomized, double-blind, placebo-controlled trial (ALLIANCE A221602). *First Author: Rudolph M. Navari, Simon Williamson Clinic, Birmingham, AL*

Background: Chemotherapy-induced nausea and vomiting (CINV), a major adverse effect of cancer treatment, can attenuate life quality. Multiple international antiemetic guidelines have recommended a 4-drug regimen (corticosteroid, 5-HT3 receptor antagonist, NK-1 receptor antagonist, and the antipsychotic medication olanzapine) for decreasing highly emetogenic CINV. This raised a question regarding whether antiemetic therapy regimens for highly emetogenic chemotherapy could be de-intensified, decreasing cost and side effects from anti-emetogenic agents. **Methods:** Study A221602 was developed to compare two olanzapine-containing antiemetic regimens, one with the use of an NK-1 receptor antagonist (aprepitant or fosaprepitant) and one without. Patients (pts) received intravenous highly emetogenic chemotherapy as either 1) cisplatin, given on one day, at a dose of ≥ 70 mg/m2, with or without other chemotherapy agent(s) or 2) doxorubicin (60 mg/m2) plus cyclophosphamide (600 mg/m2) on one day. Pts in both arms received 1) a 5-HT_3 receptor antagonist (palonosetron 0.25 mg IV or ondansetron 8-16 mg IV or 16-24 mg PO,) on day one, 2) dexamethasone (12 mg PO, day one followed by 8 mg PO, days 2-4), and 3) olanzapine (10 mg/day PO, days 1 to 4). On Day 1, all agents were given prior to chemotherapy, with the exception that olanzapine could be taken prior to chemotherapy or at bedtime. Additionally, pts were randomized to receive an NK-1 receptor antagonist (fosaprepitant 150 mg IV or aprepitant 130 mg IV; 346 pts) or a matching placebo (344 pts). The primary objective was to compare the proportion of patients with no nausea for 5 days following receipt of their chemotherapy between the two study arms. **Results:** While there was no suggestion of outcome differences on day 1 between the two study arms, fewer pts (7.4%; upper limit of the 95% confidence interval was 13.5%) without NK-1 receptor antagonists were without nausea for the complete 5-day study period. **Conclusions:** Per the study design, created to exclude a 10% benefit for NK-1 receptor antagonists, the results did not provide sufficient evidence to reject the hypothesis that the 4-drug regimen was superior to the protocol 3-drug regimen (p=0.24). Support: UG1CA189823; Clinical trial information: NCT03578081. Research Sponsor: U.S. National Institutes of Health.

12109 **Poster Session**

A single-arm feasibility trial of memantine to prevent chemotherapy-related cognitive decline in patients with early breast cancer. *First Author: Zev Nakamura, University of North Carolina at Chapel Hill, Chapel Hill, NC*

Background: Up to 75% of patients with breast cancer report cognitive decline following chemotherapy. There is no standard of care prevention or treatment of cognitive problems in these patients. This trial (NCT04033419) examines the feasibility of using memantine to prevent cognitive decline during chemotherapy for breast cancer. **Methods:** We enrolled patients with stage I-III breast cancer scheduled to receive neo/adjuvant chemotherapy. Participants completed a cognitive battery (4 traditional neuropsychological measures and 3 computerized tests) and surveys of self-reported cognition (PROMIS Cognitive Function Short Form 8a) and other neuropsychiatric symptoms at pre-treatment (baseline) and 4 weeks after the last cycle of chemotherapy (post-assessment). Memantine (10 mg BID) was initiated within 1 week of starting chemotherapy and continued until the post-assessment. Adherence and adverse event (AE) monitoring occurred every 2-3 weeks during chemotherapy infusion visits. We used descriptive statistics to evaluate recruitment, retention, and tolerability, adherence, and acceptability of memantine. To evaluate objective cognition, we standardized individual measures using population-based data and averaged them to calculate composite scores of 1) global cognition; 2) attention, working memory, and executive function; and 3) learning and memory. Improvement or decline was defined as ≥ 0.5 SD change between the two assessments. For self-reported cognition, established cutpoints were used to define clinically meaningful change. **Results:** Of 154 eligible patients approached, 56 (36%) enrolled. Of 51 who completed the baseline assessment and started memantine, 44 (86%) completed the post-assessment; 2 remain active. Among evaluable participants, 92% reported taking ≥ 90% of scheduled doses. Only 36% self-reported cognitive decline, while no change was reported in 57% and improvement in 7%. Decline in objective cognitive domains was observed in 7 - 14% (see Table). There were 7 ≥ grade 3 AEs 2 were possibly related to memantine (diarrhea and hypokalemia). Only 3 participants expressed worry about memantine and only 2 felt that taking memantine disrupted their lives. **Conclusions:** Our findings suggest that memantine is a safe and feasible intervention for chemotherapy-related cognitive decline and may ameliorate cognitive loss. Randomized controlled trials are needed to determine its preliminary efficacy. Clinical trial information: NCT04033419. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

Pre- to post-chemotherapy cognitive changes in patients concurrently receiving memantine (N=44)

	Decline (%)	No Change (%)	Improve (%)
Global	7	59	34
AWE	14	52	34
LM	14	41	45
Self-Report	36	57	7

Randomized controlled trials are needed to determine its preliminary efficacy.

Abbreviations: AWE – attention, working memory, executive function; LM – learning and memory.

12110 **Poster Session**

Body weight (BW) response timing to anamorelin (ANAM) in advanced non–small cell lung cancer (NSCLC)–associated cachexia. *First Author: Richard J.E. Skipworth, Clinical Surgery, University of Edinburgh, Edinburgh, United Kingdom*

Background: BW loss and anorexia are key clinical manifestations of cancer cachexia, a multifactorial syndrome affecting around 80% of patients (pts) with advanced cancer. BW loss is associated with reduced tolerance and response to cancer therapy, and shorter survival. ANAM is a novel, oral selective ghrelin receptor agonist. In ROMANA 1 and 2 (NCT01387269, NCT01387282) studies in pts with NSCLC and cachexia, ANAM treatment significantly increased BW and improved anorexia symptoms and concerns compared with placebo (PBO), with rapid responses occurring at wk 3 and sustained at wk 6, 9, and 12. In this post-hoc analysis, we report the timing of BW responses to assess the effects of ANAM treatment at and beyond wk 3. **Methods:** In ROMANA 1 and 2, pts with advanced NSCLC and BMI <20 kg/m^2 or BW loss ≥5% in the past 6 mo received ANAM or PBO for 12 wk. BW responses were grouped on the basis of BW change from baseline (BW gain 0 to <5% or ≥5%, and BW loss); pts were classified according to the timing of first BW response as early responders (at wk 3), late responders (at wk 6, 9, or 12), and non-responders. Missing values were not imputed. Categorical variables are presented as number and percentages, with statistical comparisons performed using the chi-square test. **Results:** In total, 552 pts in the ANAM arm and 277 in PBO were included in the analysis for all time points; at wk 3/6/9/12, data were available for 534/520/461/412 pts in the ANAM arm and 270/262/229/206 in PBO. The non-cumulative rate of pts with BW gain ≥5% was significantly higher with ANAM compared with PBO at wk 3 (13 vs 6%, p=.0030), wk 6 (26 vs 8%, p<.0001), wk 9 (28 vs 9%, p<.0001), and wk 12 (31 vs 11%, p<.0001); conversely, the rate of BW loss was significantly lower with ANAM at all time points (p<.0001). There were no significant differences between ANAM and PBO in the rate of pts with BW gain 0 to <5% at wk 3, 6, 9, and 12 (p≥.0500). The timing of first occurrence of ≥5% BW gain response is shown in the table. The rates of early and late responders were significantly higher with ANAM compared with PBO, with 28% of ANAM-treated pts first responding beyond wk 3; a larger proportion of responses with ANAM were sustained over time. **Conclusions:** ANAM significantly increased the rates of ≥5% BW gain and reduced BW loss rates compared with PBO at all time points; the proportion of first responders at wk 3 and beyond wk 3 was higher with ANAM, with the most significant increase seen at wk 6. Continuing ANAM treatment beyond wk 3 results in a clinically significant benefit. Clinical trial information: NCT01387269, NCT01387282. Research Sponsor: Helsinn Healthcare SA.

First BW responses (≥5% BW gain from baseline).

Responder category	ANAM, n (%) N=552	PBO, n (%) N=277	p-value
Early responder (at wk 3)	71 (13)	17 (6)	.0030
Sustained response at wk 6, 9, and 12	41 (7)	7 (3)	.0044
Late responder (at wk 6, 9, or 12)	155 (28)	31 (11)	<.0001
Sustained response at wk 9 and 12	64 (12)	7 (3)	<.0001
At wk 6	92 (17)	13 (5)	<.0001
At wk 9	32 (6)	10 (4)	.1756
At wk 12	31 (6)	8 (3)	.0802
Non-responder	326 (59)	229 (83)	<.0001

12111 **Poster Session**

Intravenous amisulpride as rescue treatment of postoperative nausea and vomiting in patients undergoing oncologic surgical procedures. *First Author: Amber Elliott, Acacia Pharma, Amarillo, TX*

Background: Nausea and vomiting or retching after surgery can have significant adverse impacts, including increased length of stay, worse outcomes and patient dissatisfaction. Therefore, effective management remains a high priority. While more aggressive, multimodal prophylaxis has helped, options for treating those patients who fail are limited. Intravenous (IV) amisulpride has been shown to be safe and effective for the rescue treatment of Post-Operative Nausea and Vomiting (PONV) in a large, randomized, double-blind, placebo-controlled trial in a broad surgical population (Habib AS, Kranke P, Bergese SD, Chung F, et al. *Anesthesiology* 2019;130:203-212). We conducted a post-hoc analysis to investigate the safety and efficacy of amisulpride specifically in those patients undergoing oncologic surgery, predominantly excision of breast, gastrointestinal, or genitourinary malignancies. **Methods:** This subset analysis includes data from a randomized, double-blind, placebo-controlled, multicenter phase III trial of a single 10 mg dose of IV amisulpride as rescue treatment of PONV occurring in patients failing pre/peri-operative prophylaxis, generally with ondansetron and/or dexamethasone (Habib AS, Kranke P, Bergese SD, Chung F, et al. *Anesthesiology* 2019;130:203-212). The subset includes only those patients identified as undergoing surgery related to a specified malignancy or a mass considered likely to be malignant. The primary efficacy outcome was complete response (CR), defined as no emetic episodes (vomiting or retching) or administration of antiemetic rescue medication in the 24 hours after dosing. **Results:** In total, 465 patients were treated with either 10 mg amisulpride or placebo and 112 (56 in each group) underwent oncologic surgery. Of these, 43 (38%) underwent surgery for a pelvic tumor, 37 (33%) had breast or axillary surgery, 13 (12%) had colorectal, hepatic or pancreatic surgery and 19 (17%) underwent procedures for other malignancies, such as nephrectomy or thyroidectomy. The CR rate at 24 hours in the amisulpride group was 38%, compared to 23% with placebo. This was comparable with the success rates for the whole study population (42% vs 29%). The CR rate after 2 hours was 66% in the amisulpride group and 39% in the placebo group, also in line with the overall study results (70% vs 49%). Among those patients whose PONV occurred in the post-anesthesia care unit (PACU), the mean length of PACU stay from treatment to PACU discharge was 156 minutes in the amisulpride group and 230 minutes in the placebo group. Treatment-emergent adverse effects (TEAE) were comparable in nature and incidence between amisulpride and placebo. **Conclusions:** Amisulpride at 10 mg IV is safe and effective as rescue treatment for PONV in cancer patients undergoing surgery and is associated with a marked reduction in PACU length of stay. Research Sponsor: Acacia Pharma.

12112 **Poster Session**

Alleviating breathlessness in patients with cancer with dexamethasone (ABCD): A parallel-group, double-blind, randomized clinical trial (RCT). *First Author: David Hui, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Systemic corticosteroids are commonly prescribed for palliation of dyspnea in patients with cancer; however, evidence to support their use is limited. A small RCT suggested that dexamethasone may be efficacious. In this confirmatory RCT, we compared the effect of high dose dexamethasone and placebo on dyspnea in patients with cancer. **Methods:** This NCI-funded, multi-site, double-blind, parallel group RCT enrolled ambulatory patients with cancer, age ≥18, dyspnea ≥4/10 and randomly assigned them to receive dexamethasone 8 mg orally every 12 hours for 7 days followed by 4 mg orally every 12 hours for 7 days or matching placebo capsules. Permuted block randomization (block size = 6, 2:1) was conducted, stratified by baseline dyspnea and study site. Patients, research staff and clinicians were blinded. The primary outcome was change in average dyspnea intensity assessed with a 0-10 numeric rating scale (0 = none, 10 = worst) between baseline and day 7. Secondary outcomes included the Edmonton Symptom Assessment Scale (ESAS) and adverse effects (CTCAE v4.02). Intention-to-treat analysis was conducted with linear models to compare between groups. The planned sample size of 201 patients provided 80% power to detect a mean difference of 1.0 between treatment groups with a two-sided α of 5%, assuming a standard deviation of 2.0 and 15% attrition. (Clinicaltrials.gov NCT03367156). **Results:** Between 1/11/2017 and 4/23/2021, we enrolled 149 patients and 128 received the blinded study interventions (dexamethasone n = 85, placebo n = 43). Enrollment was terminated early by the Data Safety Monitoring Board when futility criterion was met in pre-planned interim analysis. The mean change in dyspnea NRS intensity between baseline and day 7 was -1.6 (95% CI -2, -1.2) in the dexamethasone group and -1.6 (95% CI -2.3, -0.9) in the placebo group, with no significant between-group difference (mean 0, 95% CI -0.8, 0.7; P = 0.91). Secondary analyses showed that the dexamethasone group had a significantly better ESAS appetite (mean difference -1.2, 95% CI -2.2, -0.1; P = 0.03) and well being (mean -1, 95% CI -1.8, -0.2; P = 0.02), and worse ESAS anxiety (mean 1.1, 95% CI 0.3, 1.9; P = 0.01) and depression (mean 0.9, 95% CI 0.1, 1.7; P = 0.02) compared to placebo. Similar magnitude of changes in dyspnea and ESAS symptoms were observed by day 14. Adverse effects were reported more frequently in the dexamethasone group (any grade): insomnia (38% v. 12%), neuropsychiatric symptoms (31% vs. 7%), infections (21% v. 12%), dyspepsia (26% v. 12%), edema (18% v. 9%), hiccups (12% v. 7%), flushing (9% v. 5%) and respiratory distress (6% v. 0%). More patients in the dexamethasone group required hospitalization within 30 d of last study medication (25% vs. 7%, P = 0.02). **Conclusions:** High dose dexamethasone did not improve dyspnea in patients with cancer more than placebo and was associated with more adverse events. Clinical trial information: NCT03367156. Research Sponsor: U.S. National Institutes of Health.

12113 **Poster Session**

Efficacy and safety of SER-109, an investigational microbiome therapeutic for recurrent *clostridioides difficile* infection: Data from ECOSPOR III, a phase 3 randomized trial. *First Author: Alla Paskovaty, Seres Therapeutics, Cambridge, MA*

Background: Patients with malignancies are at increased risk for recurrent *Clostridioides difficile* infection (rCDI) due to their immunosuppressed state and frequent exposure to antibiotics and chemotherapy. These factors disrupt the gut microbiome creating an environment conducive to *C. difficile* colonization. Patients with cancer have higher rates of rCDI and worse outcomes than those without malignancy. SER-109, an investigational microbiome therapeutic, was superior to placebo in reducing rCDI at 8 weeks compared with placebo (12% vs 40%, respectively) in ECOSPOR III, a Phase 3 randomized, double-blind trial of subjects with a history of rCDI [NEJM 2022; 386:220-9]. Here, we report secondary endpoints of rCDI rates at 4, 12 and 24 weeks. **Methods:** Adults with rCDI (≥3 episodes in 12 months) were screened at 56 US/Canadian sites. After standard-of-care antibiotics (vancomycin or fidaxomicin per investigator discretion), subjects were randomized 1:1 to SER-109 (4 capsules x 3 days) or matching placebo. The primary endpoint was rCDI (recurrent toxin + diarrhea requiring treatment) at 8 weeks; secondary endpoints included rCDI at 4, 12 and 24 weeks. Safety was evaluated through week 24. **Results:** 281 subjects were screened and 182 (intention-to-treat population; ITT) were randomized (59.9% female; mean age 65.5 years). The most common comorbidities were respiratory disease (36.3%) and cardiovascular disease (32.4%). A total of 28.6% and 18.1% had a history of immunocompromise and malignancy, respectively. Significantly fewer SER-109 vs. placebo treated subjects had rCDI posttreatment compared with placebo recipients at Weeks 4, 8, 12 and 24 (Table). The absolute risk reduction between placebo and SER-109 arms ranged from 22.1% to 28.3% across the 4 timepoints. The safety profile of SER-109 through week 24 was comparable to placebo. Most adverse events (AEs) were mild to moderate gastrointestinal occurrences. More placebo-treated vs SER-109-treated subjects experienced serious AEs through week 8, while comparable proportions of subjects in both arms reported serious AEs from 8 through 24 weeks. **Conclusions:** In this population of subjects with comorbidities, including malignancy and immunosuppression, SER-109 significantly reduced rCDI rates through week 24 with an observed safety profile comparable to placebo. Clinical trial information: NCT03183128. Research Sponsor: Seres Therapeutics.

Cumulative rCDI rates, relative risks, and rate differences at weeks 4, 8, 12 and 24.

Timepoint	SER-109 N=89	Placebo N=93	Relative Risk (95% CI)	Rate Difference
4 weeks, n (%)	10 (11.2)	31 (33.3)	0.35 (0.19-0.67)	-22.1
*8 weeks, n (%)	11 (12.4)	37 (39.8)	0.32 (0.18–0.58)	-27.4
12 weeks, n (%)	16 (18.0)	43 (46.2)	0.40 (0.24–0.65)	-28.3
24 weeks, n (%)	19 (21.3)	44 (47.3)	0.46 (0.30–0.73)	-26.0

*Week 8 was the primary efficacy endpoint. Weeks 4, 12 and 24 were secondary efficacy endpoints.

12114 **Poster Session**

Patient-reported hope, quality of life (QOL), symptom burden, and coping mechanisms in early phase clinical trial participants. *First Author: Debra Lundquist, Massachusetts General Hospital, Boston, MA*

Background: Early phase clinical trials (EP-CTs) investigate novel treatment options in oncology, with recent advances in personalized therapy leading to improved outcomes and offering hope to patients with cancer. However, little research has sought to understand associations of patient-reported hope with QOL, symptom burden, and coping mechanisms in EP-CT participants. **Methods:** We prospectively enrolled consecutive adults with cancer participating in EP-CTs at Massachusetts General Hospital from 04/2021-01/2022. Participants completed baseline surveys prior to treatment initiation that assessed hope (Herth Hope Index [HHI], higher scores indicate greater hope), QOL (Functional Assessment of Cancer Therapy-General), symptom burden (physical: Edmonton Symptom Assessment System [ESAS]; psychological: Patient Health Questionnaire-4 [PHQ4]), and coping mechanisms (Brief COPE). We used independent samples t-test to test for mean differences between groups and regression models to explore associations of hope with patient characteristics as well as patient-reported QOL, symptom burden, and coping mechanisms. **Results:** Of 92 eligible patients, we enrolled 85 (enrollment rate 92.4%, median age = 61.4 years [range 54.7-68.9]; 56.5% female, and 95.3% metastatic cancer). Most common cancer types were gastrointestinal (41.2%), breast (21.2%), lung (7.1%), and gynecologic (7.1%). Patients had an average HHI score of 28.2 (range 12.0-36.0), with 32.9% reporting high levels of hope. We found that married patients had higher mean hope score compared with non-married patients (28.9 versus 26.1, p = 0.024), those with children had higher mean hope scores than those without (28.9 versus 25.9, p = 0.013), and those who had received 3 or more lines of prior therapy compared with 1-2 (29.3 versus 27.2, p = 0.045) had higher hope scores. We also found associations of hope with patients' QOL (B = 0.24, p < 0.001), symptom burden (ESAS-physical: B = -0.13, p = 0.001; PHQ4-depression: B = -2.26 p = < 0.001; PHQ4-anxiety: B = -0.94, p = 0.008), and coping (self-blame [B = -1.39, p = 0.003]; acceptance [B = 1.23, p = 0.002], denial [B = -1.09, p = 0.009], support [B = 1.06, p = 0.002], active [B = 0.73. p = 0.034], disengage [B = -3.24, p < 0.001]). **Conclusions:** In this prospective cohort study, we demonstrated that a substantial proportion of EP-CT participants had high baseline hope, and we identified several patient factors associated with their hope scores. We also found novel associations of higher hope scores with better QOL, lower symptom burden, and more adaptive coping mechanisms. Collectively, our findings highlight the potential for patient-reported hope to represent a key factor to consider when seeking to improve outcomes in EP-CT participants. Research Sponsor: None.

12115 **Poster Session**

Implementation of electronic patient-reported outcomes in head and neck oncology at a comprehensive cancer center. *First Author: Nadine Jackson McCleary, Dana Farber Cancer Institute, Boston, MA*

Background: Monitoring electronic patient reported outcomes (ePROs) has demonstrated impact on quality of life and survival in oncology. Maintaining high response rates to ePRO measures is critical in routine care. We evaluate the routine care implementation of head and neck oncology (HNO)-focused ePROs and the impact of patient demographics and assignment method on response rate. **Methods:** Since October 2021, patients diagnosed with head and neck cancer (PHN) at Dana-Farber Cancer Institute (DFCI) have had the opportunity to respond to the EHR-integrated European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck Module (EORTC QLQ-H&N43) at clinic visits, not to exceed every 30 days. PHN are also prompted at 7 and 14 days postoperative, regardless of clinic visit. HNO clinicians selected EORTC QLQ- H&N43 because of its actionable scores and limited overlap with cross-cutting ePRO tools at DFCI. Reviewed by Patient and Family Advisory Council members, PHN can respond to the questionnaire in English or Spanish via any internet-enabled device or tablet provided in clinic. Tablet assignment rates are sent via automated report to the HNO clinic manager. **Results:** Between October 2021 and January 2022, PHN responded to 64% of questionnaires for eligible clinic visits (1618/2535). Post-operatively, 65% of PHN responded to EORTC QLQ- H&N43 at least once within 28 days of surgery. Prompted at 7 and 14 days, PHN responded to 44% (133/300) of all post-operative questionnaires. Overall, PHN responded on their own device 50% of the time and on tablets in clinic 50% of the time. Response rates significantly associated with race, primary language, and age at clinic, but not post-operatively due to low sample size. PHN with a primary language other than English, older PHN, and PHN with races other than white responded less frequently, with the exception of Asian PHN in clinic who had the highest response rates. Clinician champions, EHR-integration, and a timely feedback loop to clinic managers facilitated response rates. **Conclusions:** Successful implementation of HNO ePROs is aided by clinical engagement and availability of real-time response rate data. ePRO response rate in HNO was found to be associated with race, primary language, age, and assignment method. Further work to focus on improving disparities within response rates and linking automatic interventions to scores is needed. Research Sponsor: None.

Characteristic		Clinic Response Rate (%)	Post-operative Response Rate (%)
Race	White	65 (1447/2219)	46 (121/261)
P-value			
Clinic: <0.001			
Post-op: 0.19			
	Asian	67 (66/99)	36 (4/11)
	Black	48 (29/61)	17 (2/12)
	Other	49 (76/156)	38 (6/16)
Primary Language	English	66 (1545/2354)	46 (124/271)
P-value			
Clinic: <0.001			
Post-op: 0.25			
	Spanish	36 (23/64)	40 (4/10)
	Other	43 (50/117)	26 (5/19)
Age (yr)	<70	66 (1112/1697)	45 (105/231)
P-value			
Clinic: 0.01			
Post-op: 0.47			
	≥70	60 (506/838)	41 (28/69)

12116 **Poster Session**

Risk assessment model potency to detect patients most likely to benefit from thromboprophylaxis: An application of the TARGET-TP score. *First Author: Kate Burbury, Department of Haematology, Peter MacCallum Cancer Centre & Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Australia*

Background: Interventional trials applying risk models for targeted-thromboprophylaxis (TP) for ambulatory cancer patients have previously excluded low risk patients, preventing quantification of residual risk and unmet need. We compare potency and pragmatic application of risk models, to guide routine clinical utilisation. **Methods:** TARGET-TP, a three arm phase 3 randomized trial of TP, classified ambulatory lung and gastrointestinal cancer patients into high or low thromboembolism (TE) risk groups using an algorithm derived from fibrinogen and d-dimer levels. High risk patients (randomized arms) received enoxaparin or no TP. Low risk patients were enrolled as an observation arm. Risk model potency was assessed by comparing cumulative TE incidence at 180 days between the two arms not receiving enoxaparin. In this analysis, we also compared other risk models using published risk thresholds (Khorana Score (KS), PROTECHT, CONKO, CATS/MICA) using associations of predicted TE risk with observed TE events (cause specific Cox proportional hazards regression), sensitivity and specificity. **Results:** Among 328 patients, 200 (61%) were classified high TE risk using the TARGET-TP algorithm. Without TP, TE incidence was 23% among high risk and 8% low risk patients – compared to 8% in high risk enoxaparin treated patients. There was notable cohort migration, with individual patients reclassified between high- and low-risk across other risk. Up to 75% of TARGET-TP high risk patients were classified low risk by other models, and would not be considered for TP, potentially exposing substantive residual TE risk (75% low risk by CATS/MICA, 61% KS, 60% CONKO, 32% PROTECHT). Up to 57% of low risk patients were high risk by other models, potentially exposing unnecessarily to TP (57% high risk by PROTECHT, 27% KS, 26% CONKO, 5% CATS/MICA). Among 228 patients in TARGET-TP trial non-intervention arms: TE incidence and comparative risk (hazard ratio, HR) for high versus low TE risk were: TARGET-TP (23% high vs. 8% low, HR 3.33 [95%CI 1.58-6.99]), KS (17% vs. 13%, HR 1. 50 [95%CI 0.74-3.02]), PROTECHT (16% vs. 12%, HR 1.50 [95%CI 0.69-3.05]), CONKO (18% vs. 13%, HR 1.54 [95%CI 0.76-3.09]), CATS/MICA (26% vs. 12%, HR 2.72 [95%CI 1.26-5.86]). Sensitivity and specificity respectively: TARGET-TP 70%/61%, KS 39%/68%, PROTECHT 70%/37%, CONKO 39%/69%, CATS/MICA 27%/87%. **Conclusions:** Application of TE risk models demonstrated some ineffectual and if utilised to define TP eligibility, 4/5 would exclude patient cohorts with TE rates exceeding 10%. TARGET-TP was the only model to achieve both high sensitivity and specificity. This simple pragmatic model considers only d-dimer and fibrinogen, can be applied without complex calculations or nomograms, in real-time for any patient. Clinical trial information: ACTRN12618000811202. Research Sponsor: Peter MacCallum Cancer Foundation and Victorian Cancer Agency.

12117 **Poster Session**

Embedded outpatient palliative care for hematologic malignancies: Referral patterns and health care utilization. *First Author: Mazie Tsang, University of California San Francisco, San Francisco, CA*

Background: Patients with hematologic malignancies are less likely to receive outpatient palliative care (OPC) compared to patients with other cancer types. Little is known about the characteristics or health care utilization of patients with hematologic malignancies who are co-managed by OPC. In this study, we evaluated referral patterns and health care utilization of patients with hematologic malignancies who were seen in an embedded OPC clinic. **Methods:** We conducted a retrospective cohort study of patients who established care with an embedded OPC nurse practitioner from 3/2016 – 5/2020 at a quaternary academic medical center. We obtained information about patients' demographics, clinical characteristics, and reasons for referral to OPC from the electronic health record. Information about costs and health care utilization were provided by our finance team. For patients who were followed by OPC for at least 6 months, we used two-tailed t-tests to compare the number of hospitalizations and emergency department (ED) visits, as well as total costs, for the 6 months before and the 6 months after initiating OPC. This was approved by the UCSF IRB. **Results:** A total of 120 patients received OPC. Median age was 59 years (range 24-89), 48% were female, and 64% were Non-Hispanic White. Myeloma was the most common cancer (n = 50/120, 41.7%), followed by aggressive lymphoma (n = 21/120, 17.5%), and acute myeloid leukemia (n = 18/120, 15%). The primary reason for referral was for symptom management, such as pain (60%, n = 72/120), mood symptoms (12.5%, n = 15/120), and fatigue (7.5%, n = 9/120). Ten percent (n = 12/120) were referred for goals of care conversations prior to stem cell transplant (SCT). An advance directive was on file for 29% (n = 35/120) of patients, of which 34% (n = 12/35) were completed after OPC enrollment. Of the 38 patients who died, the median time from PC enrollment to death was 15.3 months, and 39% died on hospice. For the 65 patients who were followed by OPC for at least 6 months, the total number of inpatient hospitalizations, excluding SCT, went from 0.82 to 0.54 (p = 0.11) per person in the 6 months before compared to the 6 months after initiating OPC. ED visits went from 0.28 to 0.18 (p = 0.33). The total direct cost of inpatient hospitalizations, excluding SCT, decreased from $43,428 to $13,226 (p = 0.01), and the cost of ED visits went from $640 to $297 (p = 0.32) per person. **Conclusions:** There is an important role for embedded OPC for patients with hematologic malignancies, long before the end-of-life period, to manage symptoms and support decision-making. OPC is associated with a trend towards lower health care utilization and decreased hospitalization costs. Prospective studies are warranted to further explore the impact of OPC on symptoms and patient/caregiver experience, as well as to clarify how OPC impacts health care utilization. Research Sponsor: None.

12118 **Poster Session**

Efficacy of a nurse monitoring service at preventing disease- or therapy-related symptoms in patients receiving targeted therapy or immunotherapy. *First Author: Andrea Sbrana, Service of Pneumo-Oncology, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy*

Background: The safety profile of Targeted therapies (TT) and immunotherapy (IT) may be underestimated and negatively affect the clinical outcome. **Methods:** A nationwide, randomized, open-label trial (NCT04726020) conducted among 29 Italian centers involved two cohorts of 223 adult patients (pts) with a solid tumor, receiving TT (group B, 119 pts) or IT (group C, 104 pts). Pts were randomized to receive a weekly nurse monitoring phone call, together with an educational leaflet with some practical advice about toxicities (experimental arm), or only the educational leaflet (control arm). In the experimental arm, pts received their monitoring phone call before their treatment began, then every week for up to 16 weeks of treatment were completed. The primary objective was the evaluation of the difference in toxicities according to patient-reported outcome (PRO)-CTCAE. **Results:** Both arms were comparable in terms of pts' characteristics (e.g. site of primary tumor, line of treatment). The adherence to the project (that is the completion of every expected call) was 62.1% in group B and 66.9% in group C. In group B, in the experimental arm, we found a higher number of pts without pain (53.7 vs 39.9%, p = 0.047); a trend of lower fatigue (29.2 vs 18%, p = 0.067) was also observed. In group C, a higher number of pts did not report fatigue (29.1 vs 17.5%, p = 0.043), shortness of breath (61.4 vs 38.5%, p = 0.002) or dry skin (72 vs 52.3%, p = 0.004). More pts also referred to be without pain (51.6 vs 38.8%, p = 0.065) and pruritus (75.9 vs 64.5%, p = 0.088), even if these difference were not statistically significant. **Conclusions:** The use of PRO assessment through active nurse monitoring might lead to a better tolerance of TT and IT with possible implications on pts' quality of life and ultimately on treatment outcome. In particular, in the IT group, several symptoms were prevented from occurring, thus encouraging a major effort to implement such active monitoring in this population. Clinical trial information: NCT04726020. Research Sponsor: None.

12119 **Poster Session**

Suicide risk among patients with cancer in the United States, 2000-2016. *First Author: Xuesong Han, American Cancer Society, Atlanta, GA*

Background: Individuals diagnosed with cancer have elevated suicide risk in the US, although little is known about risk associated with state of residence, health insurance coverage, or time since diagnosis by cancer types. This study used a recent national dataset to examine a wide range of patients' sociodemographic and clinical factors that may be associated with suicide risks. **Methods:** We identified patients diagnosed with cancer from 43 population-based state cancer registries in 2000-2016 with follow-up through Dec 31, 2016. Standardized Mortality Ratios (SMR) and 95% confidence intervals (95CI) were calculated by state of residence, attained age group, sex, and race/ethnicity to compare suicide risks in the cohort vs. the general US population. Hazard Ratios (HR) and 95CI from multivariable Cox proportional hazard models were derived to identify cancer-specific risk factors of suicide among the cohort, controlling for competing risks from other causes of death. **Results:** Among 16,771,397 patients, 7,972,782 (47.5%) died during the study period, and 20,792 (0.3%) from suicide. The overall SMR for suicide was 1.26 (95CI = 1.24-1.28), decreasing from 1.67 (95CI 1.47-1.88) in 2000 to 1.16 (95CI 1.11-1.21) in 2016. Patients from Alaska, Colorado and Idaho, those aged 65-69 years (SMR = 1.44, 95CI = 1.39-1.50), Hispanic patients (SMR = 1.48, 95CI = 1.38-1.58), those uninsured (SMR = 1.66, 95CI = 1.53-1.80) or insured with Medicaid (SMR = 1.72, 95CI = 1.61-1.84) or ≤64 years of age with Medicare (SMR = 1.94, 95CI = 1.80-2.07) had the highest suicide risks compared to the general population. Moreover, the highest suicide risk occurred within two years of diagnosis (SMR [95CI] = 7.19 [6.97-7.41], 5.60 [5.35-5.84] and 4.18 [4.03-4.33] for ≤5 months, 6-11 months, and 12-23 months after cancer diagnosis, respectively). In the first two years following diagnosis, the risk of suicide was higher in patients diagnosed with distant-stage than early-stage diseases (HR = 1.29, 95CI = 1.21-1.37), and in patients with more cancer types with poor prognoses and high symptom burdens, such as cancers of oral cavity & pharynx, esophagus, stomach, brain, lung and pancreas (HRs ranged 1.23-2.10 vs. colorectal cancer, all $P \leq 0.001$). After two years, patients diagnosed with cancers subject to long-term quality of life impairment, such as cancers of oral cavity & pharynx, female breast, bladder, and leukemia (HRs ranged 1.17-1.54 vs. colorectal cancer, all $P \leq 0.01$), had higher suicide risks. **Conclusions:** Suicide risk among patients diagnosed with cancer decreased during the past two decades but remained elevated compared to the general population. Different geographic, racial/ethnic, socioeconomic, and clinical factors, some of which are modifiable, contribute to increased suicide risk among patients diagnosed with cancer. Tailored social and psych-oncological interventions are warranted for suicide prevention in this vulnerable population. Research Sponsor: None.

12120 **Poster Session**

Impact of cisplatin-induced hearing loss (CIHL) on patient-reported social and emotional functioning. *First Author: Victoria Sanchez, University of South Florida, Tampa, FL*

Background: Cisplatin is one of the most commonly used ototoxic drugs, but no study has quantified the handicap imposed by CIHL in U.S. adult-onset cancer survivors. Identification of survivors with high degrees of handicap and related risk factors is vital, as hearing loss (HL) in the general population is strongly related to adverse health outcomes, including cognitive decline, dementia, and poor mental health and social well-being. **Methods:** Eligible testicular cancer survivors (TCS) (age < 60 y at diagnosis, given first line cisplatin) completed comprehensive health surveys, including the validated 25-item Hearing Handicap Inventory for Adults (HHIA). HHIA quantifies emotional (13 items) and social difficulties (12 items) related to HL; for each scale (0-100%), based on their responses, TCS were grouped into 3 handicap levels: 0-16% (none/minimal), 17-42% (mild/moderate), and 43-100% (significant) following HHIA recommendations. A Spearman correlation evaluated the associations between increasing HL severity and HHIA group. The association between HL and reported cognitive dysfunction was evaluated by a logistic regression analysis adjusted for age, income, education, yrs since therapy, cisplatin dose, BMI, smoking, and hypertension, with results presented as OR[CI], p-value. **Results:** Among 213 TCS [median age at evaluation, 46 y (IQR: 38-52 y); median time since cisplatin completion, 10.6 y (IQR: 6.8-16.6 y)], CIHL was reported by 127 TCS (60%). Of TCS with CIHL, 31% reported some degree of related handicap (for total HHIA scale: 13% TCS and 18% TCS reporting mild/moderate and significant handicap, respectively). HL severity was significantly correlated with handicap level in all domains (social, $\rho = 0.85$, p < .001; emotional, $\rho = 0.72$, p < .001; and total, $\rho = 0.81$, p < .001). Cognitive dysfunction was more commonly reported by TCS with CIHL than TCS without (35% and 22%, p = .049). HL was a significant independent predictor of cognitive dysfunction, 2.20 [1.09-4.47], p = .028. Since many patients with HL in the general population report tinnitus (TINN), and TINN may suggest a worse HL phenotype, we additionally adjusted for TINN severity and found a significant independent association for TINN and cognitive dysfunction, 1.49 [1.05-2.11], p = 0.027. Despite these outcomes, only 10% of TCS with HL used hearing aids (n = 13). **Conclusions:** After cisplatin chemotherapy, 60% TCS report CIHL, and TCS with CIHL report poorer social and emotional function. One in 5 TCS with CIHL reported significant overall handicap. Despite these outcomes, the low prevalence of hearing aid use suggests a potential clinical intervention that could improve social and emotional well-being. If confirmed, the possible association between CIHL with TINN and cognitive dysfunction may be of particular interest, as the Lancet Commission on Dementia Prevention (2020) identified untreated HL as a key modifiable risk factor. Research Sponsor: National Cancer Institute.

12121 **Poster Session**

Machine learning model to predict mortality after discharge in hospitalized oncologic patients (pts) under active systemic therapy in the advanced setting: A multicenter cross-validation study. *First Author: Oriol Mirallas, Vall d'Hebron University Hospital and Institute of Oncology (VHIO), Barcelona, Spain*

Background: Prognostic factors for oncologic pts after surgery or curative systemic treatment have been described, including ECOG performance status, tumor staging and malnutrition. However, there is no solid evidence on which combination of variables best predicts mortality after hospitalization of metastatic cancer pts under active systemic treatment. **Methods:** Prospective multicentric study of pts hospitalized between 2020 and 2022 at the Oncology wards of Vall d'Hebron, Sant Pau and Mar Hospitals [PLANTOLOGY database] in Barcelona, Spain. Clinical factors such as ECOG, comorbidities, tumor characteristics, and laboratory results were collected at admission. Mental status (depression and anxiety) and QOL were assessed through the HADS and EORTC-QLQ30 questionnaires, respectively. Nutritional assessment was performed using the chair and hand grip tests. All variables were analyzed in uni- and multivariable regressions including a machine learning LASSO model to assess predictive discriminators of 30-day mortality after discharge. Missing data was imputed using Multivariate Imputation by Chained Equations. A bootstrap with 1000 iterations was used to validate the model and c-index. **Results:** Among 1,663 pts, 932 had advanced disease and were under oncologic treatment during the 6 months previous to urgent admission, our target population for model development and validation. Median age was 64 years, 51% had an ECOG > 1, median Charlson comorbidity index was 8 and 34% were under treatment in a clinical trial. The most frequent tumor types were lung (25%), colorectal (14%) and breast (12%) cancer. The most relevant factors associated with higher mortality at 30-day after discharge in LASSO model were high Charlson index, low neutrophil count, high LDH, poor ECOG status and progressive disease at admission (all p-values p < 0.05). The c-index corrected after bootstrap validation was 0.75. After adding the nutritional assessment, mental health status and QoL (subset of 606 with complete data), the predictive power of the model increased to a c-index corrected after bootstrap validation of 0.81. Our final prognostic model called the PRognostic Oncologic Plantology score (PROP) obtained a sensitivity of 0.75 and a specificity of 0.80 with an overall accuracy of 0.80. Only 10% of "low" PROP score pts (72% of the population) died within 30 days of discharge, as compared to 58% of early mortality in "high" PROP score pts. **Conclusions:** Our model, including clinical and analytical factors, predicts with accuracy the 30-day mortality of oncologic pts after discharge which is significantly improved with the addition of nutritional assessment and standardized questionnaires of QoL and mental status. The PROP score calculator will be built to help physicians adjust medical interventions for hospitalized cancer pts. Research Sponsor: None.

12122 **Poster Session**

Self-reported efficacy and usage of cannabis among patients with cancer within the Minnesota Cannabis Program. *First Author: Dylan M. Zylla, HealthPartners Cancer Research Center, Minneapolis, MN*

Background: Patients with cancer are increasingly using cannabis to alleviate symptoms of pain, nausea, insomnia, and appetite loss. Despite the increased popularity of cannabis, little is known about the patterns of use in the cancer population, efficacy in treating symptoms outside of small clinical studies, and out-of-pocket expenses. We assessed self-reported efficacy and patterns of cannabis use from patients with cancer registered with the Minnesota Cannabis Program (MCP). **Methods:** We conducted an anonymous survey from December 2021-January 2022 of 797 individuals with cancer-associated pain, nausea/vomiting and/or anorexia currently enrolled in the MCP who had purchased a cannabis related product in the preceding three months. The mailed survey included questions about cancer history, cannabis use, and changes in symptoms. We conducted a descriptive analysis to describe patterns of use. **Results:** 225 individuals responded to the survey after a single mailing for a 28% response rate. 70% reported using cannabis at least once prior to cancer diagnosis. Respondents had diverse cancer diagnoses (breast (24%), lung (14%), colorectal (10%), prostate (9%)) and were more often female (52%), married, (71%), white (95%), and retired (40%) with a median age of 62.0. Most respondents (46%) had stage IV disease with the remaining 34% stage 1-3 (20% unknown). Household income varied across respondents with 10% reporting annual income <$20,000, 39% between $50-100k, and 33% with incomes ≥100k. 88% purchased at least one product with THC:CBD (tetrahydrocannabinol/cannabidiol) composition >1. Respondents reported that oral products were preferred to vaporizers (81% vs 45%) and 75% reported at least daily use. 27% reported monthly average out of pocket expenses for cannabis of $100-200; with 31% spending ≥$200/mo. The Table outlines perceived change in symptoms amongst users. **Conclusions:** Patients with cancer in the MCP with recent cannabis purchases predominantly use high THC:CBD products delivered via oral or vaporizer route on daily basis. While out of pocket costs for these products can be significant, many respondents report significant improvements in cancer related symptoms. Research Sponsor: U.S. National Institutes of Health.

Patient responses to the question of "How much do you think cannabis has worsened or improved your..... (symptom)."

Symptom*, n (%)	Worsened quite a bit	Somewhat worsened	No change	Somewhat improved	Improved quite a bit	Do not have symptom
Pain	0	1 (0.5)	21 (10.2)	68 (33.2)	102 (49.8)	13 (6.3)
Anorexia	0	1 (0.5)	42 (20.4)	53 (25.7)	66 (32.0)	44 (21.4)
Insomnia	0	0	22 (10.6)	58 (28.0)	114 (55.1)	13 (6.3)
Stress/anxiety/depression	0	0	34 (16.4)	68 (32.9)	83 (40.1)	22 (10.6)
Digestive (nausea/vomiting, diarrhea, constipation)	0	2 (1.0)	49 (23.8)	52 (25.2)	51 (24.8)	52 (25.2)
Fatigue	0	8 (3.9)	92 (45.1)	65 (31.9)	16 (7.8)	23 (11.3)

12123 **Poster Session**

Increasing the use of olanzapine in patients receiving chemotherapy in a community oncology practice. *First Author: Bindu Rani Potugari, Saint Joseph Mercy Health System, Ann Arbor, MI*

Background: The addition of olanzapine to high emetic risk chemotherapy regimens substantially improves nausea and vomiting within 24 hours and is recommended in the guidelines of both the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN). However, the uptake of olanzapine has been low in national and institutional settings. The purpose of this project was to increase guideline-concordant prescribing of olanzapine in eligible patients in a community oncology practice. **Methods:** We developed a multiphase program to address the barriers to the use of olanzapine in a community oncology practice. Patients' medical records (N = 423) were reviewed to collect baseline data. Motivational interviewing with prescribing clinicians elicited barriers to prescribing, reinforced clinical guidelines, and elicited and reinforced language that suggested a willingness to change prescribing patterns. Chemotherapy protocols were subsequently updated to include olanzapine for high emetic chemotherapy regimens, and prescriber and nurse education was provided by our pharmacists regarding the most recent ASCO and NCCN guidelines. A fellow-led educational session was provided to the infusion nursing team and care managers. At the end of a seven-month period, prescribing information was identified through a system-generated report followed by a medical record review for validation (N = 136) and was shared monthly with prescribing clinicians. **Results:** At baseline, the use of olanzapine was zero. Multiple barriers were identified regarding the use of olanzapine during motivational interviewing with clinicians, including lack of knowledge of the guidelines, belief that most patients do not require olanzapine, concerns about sedation with the previously recommended dose of 10 mg, and order sets that did not include olanzapine. After the interventions, there was a statistically significant increase in the use of olanzapine from 0% to 56% (p-value < 0.001). **Conclusions:** A combination of motivational interviewing, prescriber and nurse information support, and changes to the pre-populated order sets for chemotherapy antiemetics was highly successful in improving the uptake of guideline-concordant prescribing of antiemetics. This model of quality improvement, including motivation interview, may support quality improvement efforts across oncology. Research Sponsor: None.

Monthly rate of olanzapine usage.

Month	Percentage usage
November 20 - April 21	0%
June 2021	18.18%
July 2021	11.11%
August 2021	66.67%
September 2021	89.29%
October 2021	84.38%
November 2021	85.71%

12124 **Poster Session**

Acupuncture for hot flashes in hormone receptor-positive breast cancer, a pooled analysis of individual patient data from parallel randomized trials. *First Author: Weidong Lu, Dana-Farber Cancer Institute, Boston, MA*

Background: Hot flashes are a common side effect of endocrine therapy in breast cancer patients (pts). In a coordinated multinational study, we evaluated the impact of acupuncture on hot flashes and related symptoms in hormone receptor-positive breast cancer pts undergoing adjuvant endocrine therapy in the USA, China, and South Korea. **Methods:** Parallel randomized trials were conducted at three sites: Dana-Farber Cancer Institute, USA; Jiangsu Hospital of Traditional Chinese Medicine, China; and Daegu Catholic University Medical Center, Republic of Korea, using the same inclusion/exclusion criteria, randomization, and measures. Breast cancer pts receiving adjuvant endocrine therapy and having ≥14 hot flashes per week were randomized equally to acupuncture (A) or usual care (UC); randomization was stratified by number of hot flashes per day (2-6 or 7+). Pts in arm A received a standardized acupuncture protocol twice per week for 10 weeks; pts in the UC arm received usual care. Symptoms were assessed at baseline and week 10. The primary endpoint was change in the Endocrine Symptom Subscale (ESS) of the Functional Assessment of Cancer Therapy-Endocrine Systems (FACT-ES). Secondary endpoints included changes in the FACT-Breast (FACT-B) and Daily Hot Flash Score (DHFS), a measure incorporating hot flash frequency and severity. Target enrollment was 160 pts (USA 80, China 40, Korea 40) providing 84% power to detect a clinically meaningful change in the ESS. Analyses were intention-to-treat. A pooled analysis of individual patient data was performed using linear models adjusted for site and baseline number of hot flashes. **Results:** Between Jan. 2019 and June 2021, 158 female pts with stage 0-III breast cancer were randomized from the USA (n=78), China (n=40), and South Korea (n=40). Median age was 48 years (range: 25 to 73). At baseline, pts reported similar numbers of hot flashes between study arms (6.2± 4.3 vs. 6.5± 3.8 per day). At week 10, pts in arm A reported statistically significant improvements in ESS score, FACT-B total score and DHFS compared with the UC arm (Table). The reduction in the DHFS from baseline in arm A was 53%. There were no serious adverse events. **Conclusions:** Acupuncture led to statistically and clinically meaningful improvements in hot flashes, endocrine symptoms, and breast cancer-specific quality of life in women undergoing adjuvant hormonal therapy for breast cancer in the USA, China and South Korea. Clinical trial information: NCT00797732, ChiCTR2100045888, KCT0003618. Research Sponsor: Comprehensive and Integrative Medicine Institute, South Korea.

Measurements	Time points	Acupuncture			Usual Care			p-value
		N	Mean	SD	N	Mean	SD	
FACT-ES endocrine symptom subscale (0-76)	Baseline	77	50.0	9.9	81	51.6	10.4	
	Changes at week 10	71	4.9	8.4	77	0.6	6.9	0.001
Daily Hot Flash Score	Baseline	77	10.0	7.6	81	10.7	7.9	
	Changes at week 10	71	-5.3	5.9	77	-1.8	5.5	0.0001
FACT-B total score (0-148)	Baseline	77	95.5	21.1	81	100.4	18.9	
	Changes at week 10	71	7.9	13.4	77	-0.2	10.3	0.0001

12125 **Poster Session**

Prevalence and perceptions of cannabis use among racially diverse patients with cancer pain: Results from a multi-site survey. *First Author: Brooke Worster, Thomas Jefferson University Hospital, Philadelphia, PA*

Background: While access to cannabis is prevalent among cancer patients[1], unknowns persist about real-time use, perceived effectiveness in cancer pain management and impact on other medication use, including opioids. Moreover, racial disparities in cancer pain management persist[2-3] with Black patients more likely to have undiagnosed pain.[4] Studies on the intersection of cannabis, opioids, race and cancer pain are needed. As part of an NCI-funded initiative, we assessed the perceived effectiveness of cannabis vs. opioids for pain control by race. **Methods:** A survey was created by three Mid-Atlantic, cancer centers to examine self-reported cannabis use and knowledge, barriers and perceptions about cannabis among cancer patients. All sites assessed common core questions and included additional questions assessing cannabis and opioid use. Patients were eligible to participate if they were treated for cancer within the prior year. Surveys were distributed both by mail and electronically via REDCap. Results are compared separately by site. **Results:** In all, 2,734 patients are included in this analysis. Rates of cannabis use since diagnosis ranged from 32-41% of respondents, with similar rates of use between gender and race. Patients under age 65 more frequently reported cannabis use. Across sites, only 7-8% of patients reported currently using opioids. A sizable number patients who use cannabis reported using cannabis instead of opioids to treat pain. Of those using cannabis, most felt that cannabis was better in managing their pain than opioids, with Black patients reporting this much more frequently than White patients across two sites (Site A 62.2% vs 43.2%, Site B 77.78 vs 48.96%, Site C 50.0% vs. 65.5%). The most common reasons patients reported using cannabis instead of opioids included the perception that: "cannabis is safer" (80-82%), "cannabis is less addictive" (70-73%), and "cannabis has fewer side effects" (68-74%). **Conclusions:** Cannabis is frequently used by cancer patients, with many reporting use instead of opioids for pain management. Of those using cannabis for pain management, a significant majority felt that it is more effective than opioids. Black patients report cannabis as more effective than opioids for pain control more frequently than other races. Given the ongoing under-treatment of cancer pain in Black patients, more data is needed to understand whether cannabis is an effective tool to reduce disparities in cancer pain management. Research Sponsor: U.S. National Institutes of Health.

	Site A (n = 1574)	Site B (n = 816)	Site C (n = 344)
Age (mean)	20-90 (64.62)	22-88 (60.52)	18-88 (58.45)
Female (%)	899 (58.5)	489 (59.93)	185(53.78)
Male (%)	633 (41.2)	325 (39.83)	159 (46.72)
White (%)	1201 (76.2)	716 (87.7)	315 (91.5)
Black (%)	289 (18.3)	81 (9.9)	22 (6.3)
Have you used cannabis at any time since your cancer diagnosis? (%)	Yes, < 65 yo = 43.0	Yes, < 65 yo = 47.9	Yes, < 65 yo = 53.4
	Yes, > 65 yo = 24.7	Yes, > 65 yo = 24.3	Yes, > 65 yo = 26.8

12126 **Poster Session**

Delayed versus immediate start of chemotherapy in asymptomatic patients with metastatic cancer: A systematic review and meta-analysis. *First Author: Simone Augustinus, Department of Surgery, Amsterdam Umc, University of Amsterdam, Cancer Center Amsterdam, Amsterdam, Netherlands*

Background: The number of asymptomatic patients diagnosed with metastatic cancer is increasing. This is mostly due to increased used of imaging, especially for screening and during follow-up. Traditionally, chemotherapy is started immediately in these patients, but some argue that withholding chemotherapy until symptoms occur may be beneficial for patients, especially in terms of quality of life. However, the impact on survival and quality of life is unknown. The aim of this study is to give an overview of delayed versus immediate chemotherapy in asymptomatic patients with metastatic cancer. **Methods:** We systematically searched PubMed, EMBASE (Ovid), and Cochrane for studies investigating the timing of start of chemotherapy in asymptomatic patients with metastatic cancer. Primary outcome was overall survival (OS). Secondary outcomes included quality of life (QOL) and toxicity. A meta-analysis was performed on OS, including all studies that compared direct versus delayed chemotherapy. Quality of life was described using the global health status derived from the EORTC-QLQ-C30 questionnaire evaluated in the studies. **Results:** Four randomized controlled trials and one retrospective study with overall 919 patients were included. The studies considered colorectal cancer (n = 3), ovarian cancer (n = 1), and gastric cancer (n = 1). The median OS varied from 11.9 to 25.7 months in the immediate treatment group versus 9.0 to 27.1 months in the delayed group. A pooled analysis demonstrated no significant differences in OS between the groups (pooled HR 1.05, 95% CI 0.90-1.22, p = 0.52). Quality of life was evaluated in three studies and suggested a better QOL in the delayed treatment group. In two studies including colorectal cancer patients the global health status in the immediate treatment group was lower at all time-points compared to the delayed treatment group, with no significant differences in any of the separate domains. In the study evaluating ovarian cancer patients, among others, the time median time spent in good global health score was lower in the immediate treatment group. Toxicity was compared between the two groups in one study, and this showed no significant differences. **Conclusions:** This systematic review with meta-analysis on timing of start of chemotherapy in asymptomatic patients with metastatic cancer suggests that a delayed start of chemotherapy, as compared to immediate start, does not result in worse OS, while it may better preserve QOL. Future randomized trials, with specific emphasis on quality adjusted life years are needed. Research Sponsor: None.

12127 **Poster Session**

Impact of an augmented intelligence-based tool upon the timeliness of referrals to palliative care and hospice in patients with advanced cancer in the real-world setting. *First Author: Ajeet Gajra, State University of New York Upstate Medical University, Syracuse, NY*

Background: Timely integration of palliative care (PC) and hospice management for patients with advanced cancer requires informed clinical decision-making and expectation-setting to help patients realize their end-of-life (EOL) goals. Longer stay with hospice is a quality indicator in oncology care that requires earlier referral to PC and hospice. We have previously demonstrated that an augmented intelligence (AI) tool used to predict 30-day mortality can assist with an increase in referrals to PC and hospice. In this secondary analysis, we report on the impact of the AI tool on the timeliness of referral to PC and hospice prior to death. However, calculating days with hospice across multiple hospice providers and geographies can be challenging. Thus, we used a real-world (RW) measure of 14 to 90 days prior to death as a surrogate for timeliness for hospice and 90 to 180 days prior to death for a PC referral. **Methods:** Medical records of patients at a large community-based hematology/oncology practice in the Pacific Northwest who experienced a mortality event pre-deployment (January 2017 to April 2018) or post-deployment (May 2018 to June 2021) of the AI tool were electronically reviewed for evidence of a PC or hospice referral. Patients were included if the referral was between 14 to 90 days of the mortality event for hospice care or between 90 to 180 days prior to death for PC. Outcomes for additional timepoints (1-3 days and 4-13 days and >90 days) will be provided at the final presentation. Data were analyzed using a statistical process control chart. **Results:** Of the patients who experienced a mortality event, the following percentages had been referred pre- and post-deployment of the AI tool: PC 7.1% pre- and 15.0% post-deployment; hospice 11.5% pre- and 32.1% post-deployment. A system shift (≥6 points in a row steadily increasing or decreasing) occurred early after deployment, in June 2018. The overall improvements were 111.0% in PC referrals and 179.1% in hospice referrals within the respective timeframes. **Conclusions:** Deployment of an AI tool at a hematology/oncology practice substantially increased the proportions of patients referred to PC 90-180 days prior to death and hospice between 14 -90 days prior to death, suggesting a favorable impact on timeliness of referrals. If confirmed in additional studies, the AI-based tool can be utilized to integrate PC early in the management of patients with advanced cancer. Research Sponsor: None.

Proportion of patients with a palliative care (PC) or hospice referral prior to death.

Referral type	Time frame	Pre-deployment (January 2017 to April 2018)	Post-deployment (May 2018 to June 2021)	Overall Improvement
PC	90 to 180 days before death	7.1%	15.0%	111.0%
Hospice	14 to 90 days before death	11.5%	32.1%	179.1%

12128 **Poster Session**

Major stressful events and risk of developing head/neck and pancreatic cancer. *First Author: Arthi Sridhar, The University of Texas Health Sciences Center at Houston, McGovern Medical School, Houston, TX*

Background: Major stressful life events have been shown to be associated with an increased risk of lung cancer, breast cancer and the development of various chronic illnesses. The stress response generated by our body results in a variety of physiological and metabolic changes which can affect the immune system, endocrine system and metabolism which has been shown to be associated with tumor progression. There is an indication that stress may need to be considered as a risk factor for malignancies. **Methods:** This is a matched case control study. The objective of this study was to determine if major stressful life events are associated with the incidence of head, neck, and pancreatic cancer (HNPC). Cases (CA) were HNPC patients diagnosed within the previous 12 months. Controls (CO) were patients without a prior history of malignancy and were matched with the cases by age and smoking status. Basic demographic data and medical information were collected from the patient's medical records. Data on major stressful life events were collected using the modified Holmes-Rahe stress scale, and the following variables: death of a spouse, death of a child/immediate family member, serious personal illness, divorce/separation, loss of a job, caring for ill family member, financial difficulties, relocation, stress at work, detention/incarceration and retirement. A total sample of 300 was needed (100 cases, 200 controls) to achieve at least 80% power to detect odds ratios (OR) of 2.00 or higher at 5% level of significance. **Results:** From January 2018 to August 2021, 278 patients were enrolled (CA = 77, CO = 201) matched for mean age (years) (CA = 63, CO = 64), median smoking exposure (years) (CA = 36, CO = 38). About 65% of patients in CA group and 49% of CO group were male and 54% and 46% of the CA and CO groups respectively were of white race. In a multivariable logistic regression analysis after controlling for potential confounding variables (including sex, age, race, education, marital status, smoking history), there was no difference in lifetime incidence of major stressful event between the cases and controls. However, patients with HNPC were significantly more likely to report a major stressful life event within past 5 years when compared to CO [OR = 2.59 (1.24, 5.44), p = 0.012]. **Conclusions:** Patients with head, neck and pancreatic cancers are significantly associated with having a major stressful life event within 5 years of their diagnosis. This study highlights the potential need to recognize stressful life events as risk factors for developing malignancies and consider incorporating early rehabilitative efforts for major life stressful events. Research Sponsor: None.

12129 **Poster Session**

Effects of a yoga intervention on distress indicators among diverse women with gynecologic, gastrointestinal, and thoracic cancers. *First Author: Grace Ann Hanvey, University of Florida, Gainesville, FL*

Background: Depression, anxiety, and fear of cancer recurrence (FCR) constitute prevalent psychological concerns necessitating further attention in developing supportive care interventions for women with gynecologic, gastrointestinal, and thoracic cancers. Recent evidence indicates that such concerns may be especially severe among underserved women of color and women affected by low-socioeconomic status (SES). The purpose of the present study is to evaluate the magnitude of changes in depression, anxiety, and FCR associated with a mindfulness-based yoga intervention among a diverse sample of women with these cancers. A second aim is to identify how changes in these concerns may differ across sociodemographic groups. **Methods:** Women with gynecologic (n=86), gastrointestinal (n=17), or thoracic (n=20) cancers were enrolled in a group-based 10-week yoga intervention utilizing mindfulness meditation, relaxation, and gentle yoga. Prior to and following intervention, participants were administered assessments, including the Beck Depression Inventory – Second Edition (BDI-II) to measure depression, the State-Trait Anxiety Inventory (STAI) to assess anxiety, and the Fear of Cancer Recurrence Inventory (FCRI) to evaluate aspects of FCR. Mixed-linear models evaluated change in outcomes from pre- to post-intervention, with conditional models assessing the effects of age, race/ethnicity, and SES on change. Analyses were conducted prior to trial completion due to approaching accrual period termination. **Results:** The sample demonstrated a mean age of 58.46 (SD=10.82) and mean SES score of 3.98 (SD=1.55) using a 1 to 7 composite scale. Twenty-six percent of participants were of racial and/or ethnic minority status (n=32). Significant declines in total depressive symptoms, somatic depressive symptoms, state anxiety, and psychological distress due to FCR were observed across the sample. Higher SES was associated with significantly greater reductions in total depressive symptoms and affective depressive symptoms, specifically. Women of color experienced significantly greater declines in somatic symptoms compared to non-Hispanic White women. **Conclusions:** This mindfulness-based yoga intervention was associated with significant reductions in depressive symptoms, state anxiety, and psychological distress related to FCR among women with gynecologic, gastrointestinal, and thoracic cancers. Higher SES and underserved race/ethnicity status moderated some of these effects. Future research should explore the efficacy of this intervention among diverse women in a randomized clinical trial context. Clinical trial information: NCT03385577. Research Sponsor: University of Florida Health Cancer Center.

12130 **Poster Session**

Can personality feedback improve the process of self-management in cancer? Results from a randomized controlled trial. *First Author: Laura M Perry, Northwestern University Feinberg School of Medicine, Chicago, IL*

Background: Although personality characteristics predict emotional and physical quality of life in cancer, personality assessments are rarely used to inform care. This study examined whether a personality feedback intervention improved three patient-reported outcomes underlying the process of cancer self-management: 1) self-awareness, 2) self-efficacy for managing symptoms, treatment/medication, and emotions, and 3) positive affect. **Methods:** A sample of 372 adults with a history of cancer participated in a single-session, pre-post randomized controlled trial via Qualtrics (Control n= 188, Intervention n= 184). The sample was recruited online through ResearchMatch.org and cancer social media sites. Participants completed a baseline survey of demographics, Big Five personality traits, and study outcomes using validated measures. Next, they were immediately randomized to receive either intervention or control materials, followed by a post-test of study outcomes. Intervention participants received a feedback report of their personality results and tailored self-management tips, while control participants received only a general description of the Big Five personality traits. Three general linear models tested between-group differences in changes from baseline to post-test on each outcome, while controlling for baseline scores and demographic and health characteristics. Significance thresholds for all coefficients across all three models were simultaneously adjusted for a false discovery rate of 15%. Intervention participants also responded to a 5-item acceptability scale. **Results:** Participants were mostly non-Latino/a White (91%), middle-to-older aged (M= 58.40, SD= 13.56), women (72%), and diagnosed with cancer an average of 6.06 years prior (SD= 3.91). Compared to controls, intervention participants experienced a greater increase on a composite measure of self-efficacy for illness self-management (d= 0.32, p= .002), as well as on the individual domain of self-efficacy for managing symptoms (d= 0.36, p< .001). Contrary to hypotheses, the intervention did not improve self-awareness or positive affect (ps ≥.132). Intervention participants rated the activity's acceptability a mean of 3.97 (SD= 0.68) on a scale from 1 to 5. **Conclusions:** This was the first study to demonstrate that a personality feedback intervention can improve self-efficacy in the context of managing a chronic illness. Findings call for follow-up studies to test whether these results translate into improved self-management behaviors and quality of life among individuals living with cancer. Clinical trial information: NCT04625439. Research Sponsor: None.

12131 **Poster Session**

Association between unmet needs and utilization of emergency services among cancer survivors in Canada. *First Author: Megan Delisle, University of Ottawa, Ottawa, ON, Canada*

Background: In 2016, the Canadian Partnership Against Cancer distributed surveys to over 40,000 cancer survivors to understand their experiences transitioning from primary cancer treatment to follow-up cancer care. Previously reported results of this survey identified that cancer survivors had high rates of unmet physical, emotional and practical needs. This study describes the association between these unmet needs and emergency services (ES) utilization within the first three years after cancer treatment. **Methods:** 13,319 respondents returned the survey (response rate 33%). Respondents in this study have non-metastatic breast, hematologic, colorectal, melanoma or prostate cancer. The association between self-reported unmet needs and ES utilization was assessed using multivariable logistic regression. High ES utilization was defined as accessing ES more than three times per year during the first three years after active cancer treatment. **Results:** 8,911 participants are included in this analysis; 80.5% reported at least one unmet practical, physical, and emotional need (n=7169, Table). A total of 3.9% (n=344) reported high ES utilization. Unmet needs were a significant predictor of high ES utilization (OR 1.75 95% CI 1.14-2.68 p=0.01). Other significant predictors of high ES utilization on the multivariable analysis included: not being able to identify a healthcare provider in charge of follow-up cancer care (OR 2.73 95% CI 1.32-5.65 p=0.01), high oncologist utilization (OR 3.08 95% CI 2.28-4.15 p<0.01), high primary care provider utilization (OR 2.3 95% CI 1.76-3.0 p<0.01), having a chronic condition (OR 1.6 95% CI 1.19-2.07 p<0.01), having colorectal cancer (OR 2.12 95% CI 1.31-3.44 p<0.01), being enrolled in a clinical trial (OR 1.54 95% CI 1.11-2.16 p=0.01), and rating follow-up cancer care coordination as fair or poor (OR 1.39 95% CI 1.03-1.86 p=0.03). **Conclusions:** Unmet needs are associated with high ES utilization in the first three years after cancer treatment. A better understanding of the reasons for this association is required to develop approaches to reduce potentially preventable ES utilization and improve perceived care needs among cancer survivors. Research Sponsor: None.

Differences in unmet needs among high and low ES utilizers.

	High ES Utilizers % (n)	Low ES Utilizers % (n)	P-value
Unmet Practical Needs	53.2% (183)	31.8% (2723)	<0.01
Unmet Emotional Needs	78.5% (270)	63.8% (5465)	<0.01
Unmet Physical Needs	71.5% (246)	60.5% (5180)	<0.01

12132 **Poster Session**

Sexual desire and satisfaction: Exploring gaps for the sexually inactive breast cancer survivor. *First Author: Hannah G. Peifer, Alpert Medical School of Brown University, Providence, RI*

Background: Sexual dysfunction is common among breast cancer survivors, but poorly characterized in sexually inactive women. We aim to better understand sexual desire in sexually inactive breast cancer survivors. **Methods:** We performed a cross-sectional survey of breast cancer survivors between 2014 and 2016. Women with a history of breast cancer were approached at a surveillance visit, offered enrollment, and signed consent. They completed the validated 19-question Female Sexual Function Index (FSFI) survey. The FSFI defines sexual inactivity as no sexual activity in the four weeks prior to survey completion. Fisher's exact test was used for categorical data analysis. Firth's bias-reduced logistic regression adjusted for age and menopausal status. **Results:** Of 585 respondents, 305 (53.1%) were age 40 to 59 and 241 (42.0%) were age 60 to 79 when surveyed. Four hundred and twenty-seven (73.0%) were post-menopausal and 285 (48.7%) were sexually inactive. Sexual inactivity was positively correlated with increasing age ($p < 0.001$) and not being in a current relationship ($p < 0.0001$). Four hundred and six (69.4%) respondents underwent lumpectomy and 179 (30.6%) underwent mastectomy with most having reconstruction, n = 129 (72.1%). Neither type of surgery or receipt of chemotherapy, endocrine therapy, or radiation were significantly different for sexually inactive and active respondents after controlling for age and menopausal status. 23.6% of sexually inactive respondents reported sexual desire half the time or more. 32.4% of sexually inactive respondents reported feeling sexual desire "a few times (less than half the time)" (versus 28.8% of sexually active respondents, $p = 0.005$) and 44% reported feeling sexual desire "almost never or never" (versus 8.0% of sexually active respondents, $p < 0.001$). 31.7% of sexually inactive respondents rated their degree of sexual desire as "low" (versus 25.0% of sexually active respondents, $p = 0.04$) and 40.9% rated it as "very low or none at all" (versus 7.0% of sexually active respondents, $p < 0.001$). 27.5% of sexually inactive respondents experienced moderately high sexual desire. Sexually inactive respondents were more likely to report being dissatisfied with their overall sexual life with 23.5% choosing the rating "moderately dissatisfied" (versus 8.8% of sexually active respondents, $p < 0.001$) and 28.1% choosing "very dissatisfied" (versus 5.8% of sexually active respondents, $p < 0.001$). **Conclusions:** Sexual inactivity is associated with lower rates of self-reported sexual desire and lower satisfaction with overall sexual life. However, nearly a quarter of sexually inactive respondents still reported significant sexual desire. This suggests patients classified as sexually inactive may not be content or indifferent to this lack of sexual activity or desire. Sexual inactivity in breast cancer survivors warrants intervention studies to improve sexual satisfaction. Research Sponsor: None.

12133 **Poster Session**

Assessing Egyptian oncology patients' perceptions of treatment goals: A multicenter study. *First Author: Manar Hamed, Oncology Center of Mansoura University (OCMU), Mansoura, Egypt*

Background: Management of metastatic solid malignancies is generally focused on prolonging life along with improvement of quality of life. Hence palliative intent treatment. The understanding of the disease nature and its treatment intent is variable among patients and it's unclear what are the main contributing factors. Our study across multiple cancer centers in Egypt evaluated patients' understanding of whether their treatment was for curative or palliative purposes and sought to identify factors associated with understanding of treatment intent. **Methods:** This was a survey based study of 489 consecutive patients with stage IV solid tumor malignancies at four different cancer centers in Egypt. Patients were given a questionnaire, during a routine visit. Requested information included primary site of malignancy, stage, duration of treatment, whether they think the treatment is curative, and whether they think the treatment will help them live longer and/or relieve cancer-related symptoms. Patients also provided basic demographic information such as age, gender, marital status, area of residence and education level. Their answers regarding cancer type, stage and length of treatment were compared with their medical records. **Results:** Median age was 53 with 67% females. Of the 489 patients, 48% finished at least middle school education. The primary malignancies consisted of 35% breast, 19% gastrointestinal/liver, 9% genitourinary, 9% lung, 8% ovarian/uterine, 11% others. 57% of patients had been on treatment for at least 6months. 45% of patients didn't know they had a malignancy. 69% could not identify their disease stage, and only 19% of patients knew their cancer is stage 4. Only 11% of patients knew their treatment was not curative while 35% thought it was, and 53% did not know. Only 29% of patients believed their treatment would help them live longer and 62% believed the treatment would alleviate their symptoms. Younger patients were more aware of the Disease Nature (DN), however were less aware of the treatment intent (TI), compared to patients older than 60yo (P value 0.02). Urban residents answered more accurate DN questions compared to rural residents (P value 0.01), but both had similar limited understanding to TI (P value 0.2). Education level was the most consistent factor showing difference with higher level of education correlated with better understanding of DN and TI (P value 0.01). **Conclusions:** In our study, only 11% of patients receiving treatment with palliative intent reported understanding the intent was not curative. Factors influencing perception of treatment goals are many and include those specific to patients (education level), their cancers, and providers (educational materials). Ongoing studies will focus on identifying factors most strongly associated with a patient's perceived TI with development of a knowledge score. Research Sponsor: None.

12134 **Poster Session**

The symbiosis of healthcare professionals and patients: Understanding the dynamics of long-term care relationships between healthcare professionals and patients in oncology. *First Author: Liam Il-Young Chung, Northwestern University Feinberg School of Medicine, Chicago, IL*

Background: Chronic diseases are a significant source of physical, emotional, mental, and social distress to not only patients but also their friends and family. Healthcare professionals (HCPs) also share in the burden as they strive to provide the best possible care. In particular, cancer patients face great burden as they grapple with the uncertainty of their futures. Given the respective difficulties associated with cancer treatment, fostering a collaborative environment in which patients, caregivers, and HCPs mutually encourage each other becomes necessary to improve the quality of life of everyone involved. This study aims to investigate factors that influence a healthy long-term care relationship between patients and HCPs. **Methods:** This study is a qualitative analysis of HCPs' experiences with patients and their caregivers at a large metropolitan academic medical center. This study analyzed reflective essays written by HCPs as part of the Pacemakers initiative at the medical center, which seeks to empower HCPs, patients, and caregivers in creative ways along the management journey. The essays focused on HCPs' participation in meaningful experiences with patients and caregivers such as patient/caregiver award ceremonies celebrating their resilience and hope. A total of 22 essays (N = 22) were thematically analyzed by two independent coders to produce meaning-making codes and themes (italicized). **Results:** The presence of *support networks* (n = 10) was very important for the patients and caregivers. Conveying *solidarity* (n = 21) was also central in helping patients experience companionship and fellowship in their community with their medical team, family, and friends. It was also noted that *little means much* (n = 10); small acts of kindness showing genuine interest led to meaningful interactions that provided encouragement for the patients. *Compassion* (n = 19) and *patient-centeredness* (n = 17) were important in fostering a receptive environment in which patients and caregivers felt heard. Celebrating and honoring the patients' *resilience* (n = 10) made patients feel recognized, and this process of celebration was also found to bolster a *renewed sense of purpose for the HCPs* (n = 11). **Conclusions:** The results of this study highlight the importance of supporting patients and their caregivers holistically. Understanding and meeting this need through creative encouragement empowers not only the patients and caregivers but also the HCPs. Trust is built and patients are strengthened to pursue their health to the best of their abilities as HCPs show their deep care for their struggles and resiliency. This sacred experience of entrusting one's life to another builds the best environment for healing and recovery. This study shares a glimpse of how to best support patients as well as HCPs in long-term care relationships. Research Sponsor: None.

12135 **Poster Session**

A comparative study of unmet information needs of patients with lymphoma and CLL: North America and Europe. *First Author: Olufunmilayo (Funmi) Bamigbola, Lymphoma Coalition, Mississauga, ON, Canada*

Background: Informed patients are consistently associated with better outcomes and overall patient experiences. However, there are still unknowns about the information needs of patients. This study uses the Lymphoma Coalition (LC) 2020 Global Patient Survey (GPS) on Lymphomas and CLL to describe the differences in the unmet information needs among patients with lymphoma and CLL in North America and Europe. **Methods:** Globally, 9,179 patients from 90+ countries took part in the LC 2020 GPS. The countries were grouped into regions, and the North American (NA) (n=1543) and European (EU) (n=4343) regions were used for this analysis (Table). The demographics of the regions were examined, and univariate, bivariate and multivariate analyses of questions relating to patients' information needs, were performed in IBM SPSS v27. **Results:** When compared, the regions differed significantly in patients' age distribution, lymphoma subtype, highest educational level completed, and area of residence. The top three areas of unmet information need for patients with lymphoma and CLL in both regions were: diagnosis and what it means, treatment options, and side effects from treatment. Compared to patients in the EU, patients in NA were 27% more likely to need more information about treatment options, 51% more likely to need more information about support for self-care, and 18% less likely to need more information about their diagnosis and what it means. These differences were statistically significant (Table). Patients from NA were 26% more likely to report that they had no informational needs compared to patients from EU (p=0.02) (Table). There was no significant difference between patients in both regions in their need for more information in the following areas: psychological support, support for their families, side effects from treatment and fertility (Table). **Conclusions:** Regardless of region, patients with lymphoma need more information about certain areas of their care than is currently provided. LC advocates for increased access to appropriate and adequate medical information for patients, and that this information be contextualized to the patient's needs. Research Sponsor: Pfizer Inc, AbbVie Corporation and Takeda Oncology.

Information needs of patients with lymphoma compared by regions.

Areas of informational needs	EU (%)	NA (%)	P-value	OR*· ** (95% CI)
Diagnosis and what it means	56%	51%	P=0.006	0.82 (0.71-0.95)
Treatment options	50%	61%	P=0.001	1.27 (1.01-1.46)
Support for self-care	14%	17%	P<0.001	1.51(1.24-1.84)
Psychological support/ counselling	26%	23%	P=0.27	1.10 (0.93-1.30)
Support for their family	12%	9%	P=0.06	1.26 (0.99-1.61)
Side effects from treatment	45%	38%	P=0.23	0.91 (0.79-1.06)
Fertility Have not needed more information	9% 11%	2% 16%	P=0.07 P=0.02	0.67 (0.43-1.04) 1.26 (1.03-1.55)

*Reference category is EU. **Adjusted for age, subtype, education, and area of residence.

12136 **Poster Session**

Vital best practices for antiracist patient engagement in AYA oncology research and advocacy: A Delphi study of BIPOC AYA experts. *First Author: Christabel K Cheung, 525 W. Redwood St., Baltimore, MD*

Background: In the thick of the ongoing global crises of the COVID-19 pandemic, uprisings against anti-Black racism and police brutality, and anti-Asian racism and violence, Black, indigenous, and people of color (BIPOC) adolescent and young adult (AYA) cancer patients may be particularly vulnerable and exploited. Whilst embroiled in sociopolitical complexity, BIPOC AYAs are increasingly called upon to contribute as patient advocates in AYA oncology research and advocacy. Researchers, clinicians, and advocates in AYA oncology must dismantle long-standing racism and create meaningful structural change. The purpose of this study is to derive vital best practices for implementing antiracist patient engagement in AYA oncology research and advocacy that are co-developed by BIPOC AYA cancer patients and oncology professionals. **Methods:** We utilized a modified Delphi technique with a panel of BIPOC AYA cancer patients (n = 32) to build consensus opinions on professional recommendations from a prior study (Cheung et al., 2021), and to generate antiracist best practices in patient engagement. The Delphi study was comprised of three consecutive and iterative survey rounds over the course of 8 months in 2021; participants were BIPOC AYAs diagnosed with cancer between ages 15-36 years. **Results:** Results detail best practices for the implementation of antiracist patient engagement across all research activities within the Patient-Centered Outcomes Research Institute's (PCORI) Framework for Patient Engagement. For example, BIPOC AYAs agreed with oncology professionals' high priority recommendation for including BIPOC AYAs at the highest levels of decision making in research topic selection. As such, a best practice is for researchers to ensure that such representatives not only hold BIPOC AYA identity, but also hold direct experience with the particular oncology diagnosis, issue, or other outcome of interest. Additionally, BIPOC AYAs concurred with oncology professionals' high priority for "transparency, honesty, and trust" as a core principle for best practices in patient engagement. They further explained that trustworthy relationships are especially important when collaborating with teens and young adults, who are developmentally just coming into their own. When describing successful experiences of inclusion, participants ranked "build collaborative relationships with BIPOC AYA communities and listen to patients not usually heard" and "recruit a diverse range of BIPOC patients and let them give actual input into the study" as the highest priority best practices. **Conclusions:** Findings from this study are instructional for AYA oncology researchers, clinicians, and advocates to prevent harmful tokenism and implement genuine antiracist inclusion to advance health equity. Future research should investigate best practices within unique clinical settings. Research Sponsor: University of Maryland School of Social Work, Competitive Innovative Research Award.

12137 **Poster Session**

Understanding barriers and facilitators to clinical trial participation among Black patients with multiple myeloma. *First Author: Claire Saxton, Cancer Support Community, Washington, DC*

Background: Currently, Black patients make up 20% of people living with multiple myeloma, yet they represent only 6% of participants in clinical trials.[1] The underrepresentation of Black patients in clinical trials can contribute to outcome disparities thereby negatively impacting health equity in cancer treatment and outcomes.[2] This project examined attitudes towards clinical trials among Black multiple myeloma patients and caregivers. Findings will inform the development of programs aimed at increasing clinical trial participation in this population. **Methods:** In 2021, the Cancer Support Community conducted an online survey to gain insights on barriers, facilitators, and perceptions of clinical trials among Black multiple myeloma patients and caregivers/ care partners. Survey questions were informed by insights from prior focus groups. 94 patients and 101 caregivers were surveyed. **Results:** Most participants were male (62%) and African American (90%). 5% identified as African Caribbean and 5% as Black and Hispanic. The average age was 46 years. Just over half (51%) currently or previously participated in clinical trials. Of those who chose not to participate in a trial, the most common reasons were fear of side effects (46%) and fear of receiving a placebo (38%). Another barrier to participation reported was discomfort with being randomly assigned to a treatment (56%). Participants reported a significant level of distrust in medical research and doctors, saying that it was "very or somewhat likely" that doctors provide treatment as part of an experiment without patient consent (41%) and that they might be used as a "guinea pig" (25%). Of note, 57% of respondents said COVID had changed their attitude towards participating in clinical trials. 14 of 16 factors mentioned in our focus groups were affirmed by more than half of respondents as facilitating participation in a clinical trial. The top factors were: Understanding potential side effects (66%) My health care team speaks to me about trials (65%) Compensation offered for transportation, childcare, or time off work (62%) My family/community support my decision (61%). **Conclusions:** These findings are consistent with previous research which found that cancer patients reported the biggest attitudinal barriers to clinical trial participation were fear of side effects, distrust in medical research, and random assignment to clinical trial groups.[3] Our study highlights that Blacks and African Americans living with multiple myeloma value multifactorial efforts to increase clinical trial participation: logistical and financial interventions, patient/provider communication, and culturally sensitive support and education programs. These programs can also work to improve health equity by reducing barriers to overall care and encouraging Blacks and African Americans living with multiple myeloma to be active members of their health care team. Research Sponsor: Amgen, bluebird bio, GlaxoSmithKline.

TPS12138 **Poster Session**

Take charge during treatment: A planned exercise protocol to evaluate disparities and cardiovascular outcomes in Black and White patients with breast cancer undergoing treatment. *First Author: Mary C Hidde, Medical College of Wisconsin, Milwaukee, WI*

Background: Cardiotoxicity is a significant challenge associated with common first-line breast cancer (BC) chemotherapy (CTx) treatments including anthracyclines (AC) and targeted therapies, such as anti-Her-2 therapy. For targeted therapies, cardiac complications typically resolve once treatment is completed or stopped. For ACs, treatment may lead to permanent long term cardiac damage, and elevated risk for major adverse cardiovascular events (MACE). Black/African American (B/AA) women are at higher risk for AC-based cardiotoxicity compared to Non-Hispanic White (NHW) women. To date, most efforts have targeted managing and defining mechanisms of large vessels and cardiac damage. However, impaired microvascular function, a powerful but clinically underused predictor of future MACE, may also be implicated. Extensive evidence shows that exercise interventions reduce systemic inflammation and possibly MACE. However, few cardio-oncology studies have utilized exercise to mitigate cardiotoxicity, and none have quantified microvascular endothelial function. A further gap in cardio-oncology research is a paucity of studies focused on understanding and addressing disparities. This research project aims to 1) test the feasibility and efficacy of an exercise intervention designed to mitigate the effects of CTx, Take Charge during Treatment (TCT) and 2) examine the influence of socio-ecological factors on endothelial function in response to an exercise intervention. **Methods:** B/AA (n=50) and NHW (n=50) women diagnosed with non-metastatic BC, scheduled to receive AC and/or anti-HER-2 therapy, will be recruited and randomized to participate in the TCT intervention or usual care (NCT05223322). TCT is a virtual exercise coaching program with weekly coaching sessions, six of which include supervised exercise. Assessments to assess socio-ecologic and vascular outcomes are presented in the Table. Assessments will be completed prior to treatment (T1), after treatment completion (18-24 weeks, T2), and 12-months post treatment (T3). Clinical trial information: NCT05223322. Research Sponsor: American Heart Association.

TCT outcome measures.

Construct	Measurement Tool
Exercise Capacity	Maximal oxygen consumption (VO_2peak)
Interpersonal Socioecological Factors	Perceived Discrimination Scale, Brief Resilience Scale, Interpersonal Support Evaluation List, Neighborhood Social Cohesion Scale
Neighborhood Socioecological Factors	Contemporary and historical redlining, Local segregation, Racial composition, Social vulnerability index, Residential mobility, Urbanicity/rurality, Air pollution Walkability, Density of vegetation, % Tree canopy and landcover, Pharmacy access
Cardiovascular Outcomes	Pulse wave velocity, Brachial artery flow mediated dilation (FMD), *Ex-vivo* microvascular function
Gene Expression and Cytokine Profiling	PBMC and EC RNAseq, Inflammatory cytokine panel

TPS12139 **Poster Session**

Episodic future thinking: A behavioral intervention to promote weight loss in breast cancer survivors. *First Author: Jasmine S Sukumar, The Ohio State University Comprehensive Cancer Center, Division of Medical Oncology, Columbus, OH*

Background: Obesity at diagnosis is associated with an increase in breast cancer (BC) specific mortality. Behavioral interventions targeting obesity-related health choices offer a scalable approach to improve patient engagement in the community. Episodic Future Thinking (EFT) is a novel remotely delivered behavioral intervention which engages the science of prospection where participants mentally simulate positive, detailed, and personal events that can occur in the future. EFT targets a key behavioral economic measure – Delay Discounting (DD). As DD rate rises, an individual devalues future outcomes to a greater degree and has a higher bias for immediate gratification. EFT can decrease DD in obese patients, leading to improved diet quality and weight loss. However, valuation of the future may impact cancer survivors differently. Herein, we propose the first randomized Phase II trial evaluating adherence and changes in DD and body weight with 12-week remotely delivered EFT vs control in overweight or obese BC survivors. **Methods:** Eligible patients have a history of DCIS or stage 1 to 3 BC, BMI > 25 kg/m^2, have completed surgery, radiation, and chemotherapy, and are motivated to lose weight. They are randomized 1:1 to a 12-week EFT intervention or control (Episodic Recent Thinking; ERT). ERT is a validated control in which patients imagine events in the recent past. Randomization will be stratified by baseline DD rate. There is an optional 12 week follow up period where patients can continue to receive EFT or ERT cues. DD will be measured at baseline and every 4 weeks for 24 weeks. The primary endpoint is adherence, measured by percentage of thrice daily smartphone prompts participants open and attend to during the 12-week trial. Secondary endpoints are changes in body weight and DD rate at 12 and 24 weeks and change in PROs (PROMIS scales), insulin resistance (HOMA-IR), hs-CRP, and diet quality (HEI 2015) at 12 weeks from baseline. With 20 subjects per arm, the study has 80% power to detect deviation of 14 points from a target adherence rate of 80% using a 1 sample t-test. The primary endpoint is evaluable for all subjects, regardless of drop-out. Secondary endpoints will be evaluated using a linear mixed effects model. Hypothesis tests and confidence intervals will be two-sided at 5% significance/95% confidence level. Since trial activation in November 2021, 9 of the planned 46 patients are enrolled. Accrual is closely integrated with the dedicated Ohio State University Comprehensive Cancer Center Survivorship Program. This work is supported by the Alliance Cancer Control Program Pilot Award (5UG1CA189823-08). Clinical trial information: NCT05012176. Research Sponsor: U.S. National Institutes of Health.

TPS12140 **Poster Session**

Targeting adiposity and inflammation with movement to improve prognosis in breast cancer survivors (the AIM trial): Rationale, design, and methods. *First Author: Christina Marie Dieli-Conwright, Dana-Farber Cancer Institute, Boston, MA*

Background: Obesity is considered a leading modifiable contributor to breast cancer mortality worldwide due to its association with increased recurrence and decreased overall survival rate. A central mechanism by which obesity stimulates cancer progression is through chronic, low-grade inflammation in adipose tissue. Exercise has shown potential in improving inflammation but has not been implemented with breast cancer survivors. Our hypothesis is that exercise designed to target chronic inflammation and associated sarcopenic obesity will improve prognosis in obese breast cancer survivors. **Methods:** The AIM trial is a prospective, three-armed, phase II randomized controlled trial investigating the effects of a 16-week supervised circuit aerobic and resistance exercise (CARE) program compared to a traditional aerobic and resistance exercise (TARE) program, and attention control (AC) group, on adipose tissue inflammation in 300 breast cancer survivors. Main inclusion criteria are histologically confirmed breast cancer stage 0-III, completion of chemotherapy and/or radiation, sedentary, centrally obese, and free from musculoskeletal disorders. The primary endpoint is adipose tissue inflammation as assessed by core biopsy and blood draw; secondary endpoint is sarcopenic obesity; and exploratory endpoints are physical fitness and function and patient reported outcomes. Participants randomized to the exercise groups participate in three weekly supervised exercise sessions for 16-weeks. Participants randomized to the attention control group are offered the CARE intervention after the 16-week period of observation. Discussion: This is the first randomized controlled trial examining the effects of exercise on adipose tissue inflammation in obese, breast cancer survivors. Results will contribute to a better understanding of exercise modality on adipose tissue inflammation that can potentially improve patient prognosis. Clinical trial information: NCT03091842. Research Sponsor: U.S. National Institutes of Health.

TPS12141 **Poster Session**

Preventive effect of goshajinkigan against peripheral neuropathy induced by paclitaxel-containing chemotherapy: An open-label, randomized, phase II study. *First Author: Naoki Nakamura, Department of Respiratory Medicine, Okayama University Hospital, Okayama, Japan*

Background: Paclitaxel is a taxane agent that has been used as a standard treatment for various malignancies. However, taxanes, such as paclitaxel, unfortunately cause a high frequency of chemotherapy-induced peripheral neuropathy (CIPN) as a result of axonal damage (All grade; 70%) (Clin Cancer Res.1996), CIPN worsens patients' QOL and then lead to poor treatment compliance. Furthermore, there is no evidence for the prevention of CIPN. Goshajinkigan (GJG) is one of the Kampo medicine and it is approved in Japan for the treatment of numbness and has been commonly used for diabetic peripheral neuropathy. In addition, a non-clinical study has also shown the preventive effect of GJG against CIPN induced by paclitaxel (Molecular pain. 2014). To investigate if GJG indeed has a preventive effect for severe CIPN in patients receiving chemotherapy including paclitaxel, we started a two-arm randomized trial of GJG vs physician's choice of treatment for patients. **Methods:** Patients have to meet the followings: pathologically diagnosed with malignant tumor (regardless of cancer type) and scheduled to receive ≥4 courses of chemotherapy including carboplatin and paclitaxel (paclitaxel ≥150mg/m^2 every 3-4 weeks) as initial chemotherapy; age ≥20yrs; Performance Status of 0 or 1. The primary endpoint is set as a proportion of ≥G2 CIPN by CTCAE ver.5.0 by the end of 4 courses of chemotherapy. With stratification by cancer type and age, patients will be randomized centrally to receive GJG at the same time as chemotherapy (A), or to receive the physician's choice of treatment for pts if ≥G2 CIPN occurs without prophylaxis (B). Assuming that the incidence of ≥G2 CIPN would be 50% without prophylaxis and 20% with GJG prophylaxis, and assuming an 80% completion rate of four paclitaxel courses, the required sample size is 66 patients (1-β: 0.75, α: 0.1). The secondary endpoint includes time to the onset of CIPN G2, incidence rate and severity of CIPN at the end of each course, relative dose intensity of paclitaxel, adverse events other than CIPN. Enrollment began in 2022, and will be complete by 2025. Clinical trial information: 061210047. Research Sponsor: None.

TPS12142 **Poster Session**

Prospective study of biomarkers predictive of radiation-induced bladder toxicity in patients treated with radiotherapy for localized prostate cancer: RABBIO (Radiotoxicity Bladder BIOmarkers). *First Author: Carole Helissey, Clinical Research Unit, Military Hospital Begin, Saint-Mandé, France*

Background: Despite improvements in irradiation techniques, pelvic radiotherapy is responsible for acute and late adverse events in the bladder, defined as radiation cystitis (CysR). The early symptoms of bladder lesions secondary to pelvic irradiation are likely to occur during treatment or after radiotherapy in approximately 50% of irradiated patients. Acute radiation-related injuries are the first step of the fibrosis process. Fibrosis causes loss of bladder function and has a significant impact on the quality of life of the patients.The pathophysiology of CysR is not well understood, in particular because of the risks of complications caused by accessing the bladder tissue after irradiation, thereby limiting our ability to investigate this process and develop treatments. The main objective of our study is to assess the correlation of biologic biomarkers with the intensity of acute CysR and the quality of life of patients, evaluated with the digital telemonitoring platform Cureety. **Methods:** Patients with intermediate-risk localized prostate cancer and eligible for localized radiotherapy will be included. Inflammatory biomarkers will be analyzed on urine and blood samples before the initiation of radiotherapy, at week 4, 12 and 48 of irradiation, by quantitative methods such as the Multiplex Luminex assay, cytometry in flow and enzyme-linked immunosorbent assay ELISA. We will also characterize the gut and urinary microbiota in stool and urine samples using 16S rRNA sequencing technology. This is in order to assess the impact of the fecal and urinary microbiota in acute CysR. Between sample collection visits, patients will answer various questionnaires relating to the symptoms of radiation cystitis (IPSS), adverse events and quality of life (FACT-P), using the digital telemonitoring platform Cureety. Upon receipt of the questionnaires, an artificial intelligence algorithm will process the information and classify the patients according to the severity of symptoms and adverse reactions reported in accordance with CTCAE / IPSS. This will ultimately allow us to correlate urinary, blood and fecal biomarker levels with the severity of acute CysR symptoms and the quality of life reported by the patients. Conclusion: This prospective study is the first to explore the overexpression of inflammatory proteins in fluid biopsies from patients with symptoms of acute CysR. In addition, the 1-year post-treatment follow-up will allow us to predict which patients are at risk for late CysR and to stratify these patients towards radioprotective treatment. The results of this study will allow us to develop strategies to limit radiation damage to the bladder and improve the quality of life of patients. Clinical trial information: 2021A0319635. Research Sponsor: None.

TPS12143 **Poster Session**

Telehealth cognitive-behavioral therapy for cancer-related cognitive impairment: A model for remote clinical trial participation. *First Author: Robert J. Ferguson, University of Pittsburgh, UPMC Hillman Cancer Center, Pittsburgh, PA*

Background: Cancer-related cognitive impairment (CRCI) can include persistent memory symptoms, and affects many cancer survivors. Memory and Attention Adaptation Training (MAAT) is an evidence-based cognitive behavioral therapy (CBT) that improves CRCI with demonstrated efficacy in telehealth delivery. MAAT consists of 8 weekly (45-minute) video visits. The aims of this study are to confirm MAAT telehealth efficacy in a phase III RCT (MAAT versus Supportive Therapy; ST) across large catchment areas of two comprehensive cancer centers. A secondary aim is to evaluate treatment-induced brain activation as assessed by functional MRI (fMRI) in a subset of participants. We present remote treatment and data capture methods of this open NCI-sponsored (R01CA244673) randomized clinical trial (NCT 04586530). These methods have high success in participant accrual despite COVID-19 pandemic conditions, and can be readily adopted to other clinical trials to enhance rural/underserved enrollment. **Methods:** We are enrolling 200 adult, stage I-III breast cancer survivors 1-5 years post-chemotherapy with cognitive complaints. Individuals with CNS disease, previous brain injury, dementia or psychiatric disorder are excluded. All study procedures are completed from the participant's home (except fMRI). Eligibility screening is a semi-structured phone interview followed by detailed informed consent online (Research Electronic Data Capture: REDCap) with staff phone guidance. Consented participants complete baseline brief phone-based neurocognitive assessment and validated patient-reported outcome measures (PROs) of cognition and quality of life via REDCap. Participants are randomized to MAAT or ST and assigned treating clinicians at respective cancer centers. All 8 visits are completed through secure telehealth platforms, followed by repeat phone/online assessment post-treatment and again at 6 months. Enrollment began in 3/2021. As of 1/2022 (9 months), 56 participants are enrolled (28% of the planned sample), 47 randomized (MAAT 24; ST 23), with 24 completing post-treatment assessments. If all assessments and treatment visits were in person, travel burden per participant is 968 miles/20.5 hours driven, and $542 (US 2021 Federal rate). Thus, study travel savings to date are $30,352. Participant feedback indicates telehealth makes participation possible, similar to previous MAAT research. The current RCT demonstrates utility, efficiency and cost-savings of telehealth and remote data capture technology in the conduct of cancer control research. Elements of methods described can also be adopted for cancer therapeutic trials. Comprehensive cancer centers, where most clinical trials are based, can enhance participation of remote and/or underserved populations that have higher rates of cancer, more disease burden and less opportunity for trial participation. Clinical trial information: NCT04586530. Research Sponsor: U.S. National Institutes of Health.

TPS12144 **Poster Session**

The RADIO trial: Randomized assessment of cisplatin dosing interval for ototoxicity with curative concurrent chemo-radiation for locally advanced head and neck squamous cell carcinoma. *First Author: Sara Kuruvilla, London Health Sciences Centre, London, ON, Canada*

Background: Patients with locally advanced squamous cell carcinoma of the head and neck (LASCCHN) receive curative chemoradiation (CRT) with Cisplatin, as a standard of care. A meta-analysis of 52 randomized trials comparing Low Dose (LD) and High Dose (HD) schedules demonstrated differing toxicity profiles but hearing effects were not rigorously studied. Hearing loss associated with HD Cisplatin can result in survivorship challenges. A local study suggested a protective effect for LD Cisplatin in relation to ototoxicity and pharmacogenomic markers, MATE1 and COMT, to be associated with risk for ototoxicity. We hypothesize that LD cisplatin is associated with reduced frequency of hearing loss when compared to the standard HD cisplatin in LASCCHN patients on CRT and that differences in MATE1/COMT can predict for cisplatin-related ototoxicity and be identified prior to treatment. Our goal is to develop an innovative personalized treatment pathway incorporating predictive pharmacogenomics markers to improve the tolerability and survivorship outcomes of curative CRT for LASCCHN. **Methods:** This is a prospective, open-label, randomized clinical trial. Following informed consent, eligible LASCCHN patients planned for primary CRT will be stratified by tumor p16 status and then randomized in 1:1 fashion to either concurrent LD Cisplatin (40mg/m2 every week) or HD cisplatin (100mg/m2 every 3 weeks). The primary outcome is to measure the change in incidence of CTCAE grade ≥2 hearing loss and hearing-related quality of life (QOL) at 1 year. As part of secondary and exploratory outcomes, differences in survival, loco-regional control, global QOL and other toxicities (e.g. nephrotoxicity, neurotoxicity) will be assessed. The relationship between MATE1 and COMT, as predictors for cisplatin-related ototoxicity will be evaluated. Cost-effectiveness analyses comparing the two regimens will be assessed. *Statistical plan:* Based on rates of CTCAE grade ≥2 hearing loss in an earlier study (Winquist et al., 2016), assuming a conservative rate of hearing loss, amongst treated patients, of 60% with HD cisplatin and 30% with LD cisplatin, a total sample size of 92 patients would achieve > 80% statistical power, (two-sided, alpha = 0.05 test of two proportions) to detect these differences. 100 patients would be targeted to accrual for an assumed 5% noncompliance rate. For hearing related QOL, a two-sided, alpha = 0.05, two-sample t-test with 50 patients per group would achieve > 80% statistical power to detect an effect size of 0.60 and > 95% power to detect an effect size of 0.75. All analyses will be based primarily on the intent-to-treat population. An arms-length data and safety monitoring committee (DSMC) will review safety data bi-annually. *Trial accrual status:* 60 participants have been accrued. Clinical trial information: NCT03649048. Research Sponsor: Academic Medical Organization of Southwestern Ontario, Medical Oncology Research Fund; Juravinski Cancer Center Foundation Grant.

TPS12145 **Poster Session**

A randomized phase III clinical trial of acupuncture for chemotherapy-induced peripheral neuropathy (CIPN) in cancer survivors. *First Author: Andee Dooley, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a common and debilitating side effect in cancer survivors that can last long after completion of neurotoxic chemotherapy. Patients with CIPN often experience neuropathy symptoms such as pain, tingling, numbness, paresthesia, and dysesthesia, which can lead to significant functional decline and diminished quality of life (QoL). Our prior study showed that more than half of breast cancer survivors who received taxane-based chemotherapy experienced persistent peripheral neuropathy symptoms for a mean duration of 5.6 years after completing chemotherapy. This outcome highlights the importance of developing effective CIPN treatments to improve cancer survivors' QoL. Identifying nonpharmacological approaches to reduce CIPN symptoms and improve cancer survivors' outcomes is urgently needed. Acupuncture is a widely used, minimally invasive Traditional Chinese Medicine technique that has shown promising evidence as an effective and safe treatment for CIPN. We hypothesize that acupuncture may reduce CIPN pain and improve overall CIPN symptoms in cancer survivors. **Methods:** We are conducting a two-arm, parallel randomized clinical trial comparing electroacupunture (EA) versus sham acupuncture (SA) in cancer survivors at Memorial Sloan Kettering Cancer Center, New York, NY. The EA arm includes a total of ten sessions of EA over eight weeks using a standardized, semi-fixed protocol developed by our group based on the previously published pilot study (NCT03183037). The SA arm includes a sham technique that uses a combination of non-acupuncture points and a non-insertion procedure in ten sessions over eight weeks. The primary outcome of this study is the Brief Pain Inventory-Short Form (BPI-SF) average pain item. The secondary outcomes are quantitative sensory testing measures and additional patient-reported outcomes that include the BPI-SF pain interference subscale, Neuropathic Pain Scale (NPS), Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx), CIPN-20, PROMIS Global Health Scale, and Patients' Global Impression of Change (PGIC). The primary end point is week 12 and the secondary end point is week 24; treatment effects are assessed at baseline and at weeks 4, 8, 12, 18, and 24. Eligibility criteria includes: 1) Moderate-to-severe CIPN pain, defined by a score of 4 or greater on a 0–10 numeric rating scale; 2) completion of neurotoxic chemotherapy at least three months prior to enrollment; and 3) no changes in anti-neuropathy medications within three months of enrollment. We have accrued 30 participants as of February 2022, with a total accrual target of 250 participants. Accrual completion is anticipated by December 2024. Funding resource: NIH R37 CA248563. Clinical trial information: NCT04917796. Research Sponsor: U.S. National Institutes of Health.

TPS12146 **Poster Session**

A randomized phase III clinical trial of yoga for chemotherapy-induced peripheral neuropathy treatment. *First Author: Katherine Han, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a common, painful, and debilitating side effect of many standard chemotherapy regimens. Patients with CIPN typically experience pain, paresthesia, and muscle weakness, and may exhibit significant functional decline and worsened quality of life. Our prior study showed more than half of breast cancer survivors experience persistent CIPN up to a mean duration of 5.6 years, which is associated with a doubled fall risk. Identifying nonpharmacological approaches to reduce CIPN symptoms and improve cancer survivors' outcomes is urgently needed. Yoga is a meditative movement therapy that that includes stretching, and flexibility and balance training. Our pilot study (NCT03292328) demonstrated that yoga reduced CIPN-related symptoms, and improved quality of life and functional reach scores compared to waitlist control. We hypothesize that yoga can reduce CIPN symptoms, improve function, and reduce the risk of falls. **Methods:** We are conducting a three-arm randomized education and usual care-controlled trial in cancer survivors with chronic CIPN pain at Memorial Sloan Kettering Cancer Center (MSK), New York, NY. Participants in the intervention arm will receive twice-weekly one-hour Hatha yoga classes virtually or in-person taught by MSK instructors, and practice yoga at home daily for eight weeks. Participants in the education control arm will receive one-hour virtual education classes twice per week taught by an MSK mind-body therapist for eight weeks. Participants in the usual care arm will continue their usual care for CIPN for eight weeks. The primary endpoint is the Brief Pain Inventory-Short Form (BPI-SF) average pain item at weeks 8 and 24. Secondary outcomes include the Neuropathic Pain Scale (NPS), Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx), Patient-Reported Outcomes Measurement Information System (PROMIS) Global Health outcome measure, Brief Fatigue Inventory (BFI), Insomnia Severity Index (ISI), Hospital Anxiety and Depression Scale (HADS), QLQ-CIPN-20, Functional Assessments, and quantitative sensory testing (QST) at weeks 0, 4, 8, 12, 18, and 24. Eligibility criteria included: 1) Moderate-to-severe CIPN pain, defined by a score of 4 or greater on a 0-10 numerical rating scale; 2) completion of neurotoxic chemotherapy at least three months prior; 3) no changes in anti-neuropathy medications within three months of enrollment; and 4) changes in balance and functionality. We have accrued five participants as of February 2022 with a total accrual target of 268 participants. We anticipate completing accrual in March 2025. Funding resource: NIH R01CA251470. Clinical trial information: NCT05121558. Research Sponsor: U.S. National Institutes of Health.

TPS12147 **Poster Session**

Immune-related adverse events and symptom burden in patients with melanoma receiving adjuvant immune checkpoint inhibitor. *First Author: Noha Abdel-Wahab, Assiut University Hospital, Faculty of Medicine, Assiut, Egypt*

Background: Adjuvant therapy with immune checkpoint inhibitors (ICIs) is approved for melanoma, but immune-related adverse events (irAEs) remain a challenge. Although acute toxicities are well defined, long-term AEs and impact on quality of life (QOL) are undetermined. Available data derived from clinical trials involve highly selected populations and do not reflect real world experience. Additionally, trials measure outcomes only at predetermined endpoints, and symptoms may vary throughout the course of therapy. Moreover, the pathogenesis of irAEs and symptoms remains poorly understood. We hypothesize that AEs and sustained inflammation induced by adjuvant ICIs increase symptom burden and negatively impact function and QOL in a subset of patients (pts), and elevated expression of pro-inflammatory cytokines and T cell signatures during therapy correlate with toxicity and symptom burden. Our preliminary data identified i) interleukin-6/Th-17 pathway as a possible mediator of irAEs, ii) immune reactivity and increases in inflammatory cytokines are associated with symptom burden in cancer survivors, and iii) prioritized 30 genetic markers conferring risk for irAEs in ICI-treated melanoma pts. **Methods:** This is a prospective longitudinal cohort study to evaluate potential toxicity/symptom burden and immune correlates in melanoma pts receiving adjuvant ICIs (NCT04990726). A total of 240 pts will be enrolled. Eligibility criteria: age ≥18 years (yrs), surgically resected stage II, III, or IV melanoma, initiating adjuvant nivolumab or pembrolizumab, no prior systemic therapy for melanoma, and no prior autoimmune diseases. Patients will be assessed at baseline (before ICI infusion) and every 3 months (mos) up to 2 yrs or until attrition or death. The primary endpoint is the incidence rate of any irAEs at 12 mos. Demographics, personal/family history, comorbidities, tumor history/stage, prior therapies, performance status, concurrent medications, and other factors that play a role in pts perceptions of disease are collected. At each visit, pts undergo a clinical evaluation to assess potential irAEs, new comorbidities, and tumor recurrence. Patient-reported outcomes of fatigue, depression, sleep disturbance, and QOL are collected at each visit to assess changes from baseline up to 2 yrs. In addition to standard methods of data collection at pre-specified times, we leverage mobile technology to capture symptoms and AEs in real time. Longitudinal blood samples will characterize pts immune signatures from baseline up to 2 yrs to evaluate their association with irAEs, symptom burden, and QOL, and to compare the genotype of pts with and without irAEs. To characterize the effect of adjuvant ICI on bone health, eligible pts are evaluated by whole body dual-energy X-ray absorptiometry at baseline and at 12 mos as an exploratory aim. The study is currently active, and 27 pts are enrolled. Clinical trial information: NCT04990726. Research Sponsor: U.S. National Institutes of Health, The University of Texas MD Anderson Cancer Center Institutional Research Grant, Division of Internal Medicine Developmental Funds, and Cancer Survivorship Seed fund.

TPS12148 **Poster Session**

Nurse AMIE: Addressing symptoms in rural patients with advanced cancer. *First Author: Cristina I. Truica, Penn State Health Milton S. Hershey Medical Center, Hershey, PA*

Background: Prior research has shown that monitoring symptoms in advanced cancer patients may provide a survival benefit. Monitoring is a labor-intensive process that requires nursing staff response and visiting a medical office. This may be more challenging in rural areas, given staffing challenges and distances traveled for care. Lower density of supportive care services has been documented in rural as compared to urban settings in Pennsylvania and West Virginia. We have developed a computer tablet-based supportive care program, called Nurse AMIE, and are investigating its use in symptom management among cancer survivors. Our hypothesis is that a tablet-based supportive care program can improve overall survival of advanced cancer patients in rural Pennsylvania and West Virginia. **Methods:** This randomized controlled trial will recruit 344 patients residing in a rural county or zip code (RUCC 4-9 or RUCA 4-10) in Pennsylvania or West Virginia, who receive treatment for stage III-IV cancer, are 18 years or older, ECOG 0-3, are fluent in written and spoken English, have sufficient vision/hearing to interact with a computer tablet and staff, and have a clinician-defined life expectancy of 6 months or more. Exclusion criteria: patients on active treatment or behavioral or supportive care trials, or with medical or psychiatric conditions that would impair ability to test study hypotheses. Patients will be randomized on a 1:1 basis to receive either Nurse AMIE or a binder with written supportive care materials. Intervention participants will be asked to log into Nurse AMIE daily, where they will interact with a nurse avatar and answer symptom questions (focusing on sleep, fatigue, pain, and distress). They will receive an empathic response to symptoms and be offered evidence based, guideline concordant self-care interventions to address symptoms (including exercise, nutrition, guided meditation, cognitive behavioral therapy videos, and soothing music). Once weekly, patients will answer 21 questions from the Pro-CTCAE survey. All symptom data will be loaded into a dashboard reviewed daily by study staff. Pain or distress scores of 7+ (out of 10) will be communicated to the care team through the EMR. The trial is powered to detect a 19% difference in overall survival at 2 years follow-up (based on Denis et al JAMA 2019). Secondary outcomes include incidence of chemotherapy toxicities, patient reported outcomes, and cost effectiveness. Enrollment is anticipated to start in March 2022. A community advisory board of 12 cancer patients and stakeholders meet on a quarterly basis to provide feedback on study activities (e.g., usability testing, adaptations, overall implementation) and ensure the project responds to the needs and preferences of rural cancer patients in Pennsylvania and West Virginia. NIH R01-CA254659. Clinical trial information: NCT05221606. Research Sponsor: U.S. National Institutes of Health.

TPS12149 **Poster Session**

Olanzapine versus fosaprepitant for prevention of chemotherapy induced nausea and vomiting in patients receiving carboplatin (AUC ≥ 4) containing chemotherapy regimen: A phase 3 randomized, double-blind, placebo-controlled trial. *First Author: Sneh Bhargave, Aiims, New Delhi, India*

Background: Chemotherapy-induced nausea and vomiting (CINV) is a common adverse effect affecting quality of life of patients of cancer undergoing chemotherapy. Carboplatin alone or in combination with various other chemotherapy drugs is one of the most commonly used drug in solid malignancies. It is categorised as a highly emetogenic drug in doses above AUC≥4 and multiple past studies revealed high CINV incidence. Current international antiemetic guidelines suggest NK1 receptor antagonist based triplet drugs as an effective regimen of CINV control in these patients. However, the nausea control rates are largely inadequate. Olanzapine, an atypical antipsychotic drug, is another drug that has shown significant activity in CINV control and is an integral part of current chemotherapy induced emesis and nausea prevention. However, robust comparative studies of olanzapine based triplets with NK1 based combination have been lacking. Hence we planned this study to compare efficacy of olanzapine containing triplet with NK1 receptor antagonist (fosaprepitant) based triplet drug combination in a phase 3 randomised study. **Methods:** This study is an investigator initiated phase 3 prospective randomised double blind placebo controlled trial comparing efficacy of olanzapine, 5HT3 receptor antagonist(ondansetron) and dexamethasone (experimental arm) against fosaprepitant, 5HT3 receptor antagonist(ondansetron) and dexamethasone (standard arm) for prevention of CINV among chemo-naïve patients (aged ≥18 years) receiving carboplatin (AUC ≥4) based chemotherapy regimen. Primary objective is to compare the number of patients with no nausea during overall periods (0-120 hours post-chemotherapy). Secondary objectives are to compare complete response (no emetic episodes and no use of rescue medication) in the acute(0-24 hr), delayed(25-120 hr),overall periods(0-120 hr) and to assess the frequency of rescue medication use. The other secondary objective includes assessment of adverse events in both the arms. Statistical Design: Planned accrual is total 214 patients including 10% drop out rate. It is a superiority design with an absolute improvement of 20% in the proportion of patients with no nausea from a baseline prevalence of 40% in the standard arm and two sided alpha of 5% as well as power of 80%. Conduct to date :Study activation : March 2021. Enrolment : 138 subjects. Clinical trial information: CTRI/2021/03/032165. Research Sponsor: None.

TPS12150 **Poster Session**

Optimizing supportive care for patients with metastatic lung cancer in the era of precision oncology. *First Author: Kelly Hsu, Massachusetts General Hospital, Boston, MA*

Background: Targeted therapy improves survival for patients with oncogene-driven non-small cell lung cancer (NSCLC). However, metastatic NSCLC remains incurable and patients often experience uncertainty about what to expect from their long and unpredictable illness trajectories. The aim of this trial is to pilot test a supportive care intervention that blends palliative care and survivorship for patients with metastatic oncogene-driven NSCLC. **Methods:** We will conduct a pilot randomized, controlled trial to evaluate the feasibility, acceptability and preliminary efficacy of a novel supportive care intervention for patients with metastatic oncogene-drive NSCLC. We will enroll 90 patients with a recent (within 6 months) diagnosis of metastatic NSCLC with a mutation in *EGFR*, *ALK*, *ROS1* or *RET* genes who are receiving targeted therapy. We will enroll the first ten patients in an open pilot and we will refine the intervention and study procedures based on pilot findings. We will randomize the remaining 80 patients 1:1 to the intervention or a usual care control. Participants randomized to the intervention arm will have four monthly visits with a palliative care clinician who has been trained to address the supportive care needs of patients with long illness trajectories. Sessions will cover 1) rapport building and baseline symptom and psychosocial assessment; 2) coping support and healthy lifestyle promotion; 3) cultivation of prognostic understanding; and 4) exploration of goals and values. Patients in both arms will complete surveys including secondary outcome measures at baseline, 12, and 20 weeks post-enrollment. The primary outcome of the study is feasibility of the palliative care intervention, defined as at least 60% enrollment among eligible patients and 75% completion of all four sessions and three surveys. We will also assess acceptability using measures of satisfaction and comfort with the intervention. We will evaluate the preliminary effects of this intervention on the following outcomes to inform a future large-scale efficacy trial: 1) distress related to prognostic uncertainty and 2) prognostic awareness (using the Prognostic Awareness Questionnaire: 34-item validated measure with items about likelihood of cure and impact of prognostic awareness on decisions, behaviors and mood); 3) confidence in chronic disease management using the Self-Efficacy of Management of Chronic Disease scale; and 4) documentation of discussions about goals and values in the medical record. We will analyze change within and between groups at 12 and 20 weeks using linear mixed models, controlling for baseline values and relevant demographic and clinical factors. Study accrual to the open pilot phase began in February 2022. Current enrollment: n = 0. Clinical trial information: NCT04900935. Research Sponsor: None.

TPS12151 **Poster Session**

Internet-delivered management of pain among cancer treatment survivors (IMPACTS WF-1901). *First Author: Megan Irby, Wake Forest School of Medicine, Clemmons, NC*

Background: Pain is a common symptom among cancer patients and often is inadequately treated. Treatment guidelines recommend patients have access to behavioral interventions that educate about pain and pain management. Pain coping skills training (PCST) accomplishes these goals through teaching cognitive and behavioral coping skills shown to reduce pain. When delivered in in-person, PCST can substantially improve chronic pain conditions. Yet, these interventions are underused due to myriad barriers (high costs, shortage of therapists, travel needs). There is a critical need for improved options to help reduce cancer-related pain and related impairment that should include evidence-based PCST interventions capable of overcoming access barriers. To address this need, we developed a web-based PCST program using a novel *expert systems* approach that retains critical features of in-person PCST in an automated program that requires no therapist. *PainTRAINER,* is an 8-week, interactive PCST program using tailoring algorithms, a knowledge database, and a virtual coach to guide development of essential skills for coping with chronic pain. **Methods:** With funding from the NIH HEAL Initiative, we have undertaken a randomized, prospective, comparative effectiveness trial through the Wake Forest NCI Community Oncology Research Program (NCORP) Research Base to determine the impact of *painTRAINER* on pain outcomes when compared to Enhanced Usual Care (EUC). Participants have a documented diagnosis of invasive cancer who are undergoing anticancer therapy or within 5 years of completing all cancer therapy. Participants must report cancer-related pain most days of the week of 4 or greater on the *PROMIS Pain Intensity Scale;* with pain of new onset or significantly exacerbated since cancer diagnosis. All participants receive usual care provided by their physician along with pain education materials. *PainTRAINER* arm participants have access to the *painTRAINER* program and a tutorial on how to use the program, and complete the *painTRAINER* modules on their own (1 session/week for 8 weeks). To enhance study access, patients without internet availability are provided a WiFi/cellular-enabled tablet during the intervention period. This trial examines short- and long-term outcomes measured immediately post-intervention and 3- and 6- months post-intervention. Primary outcomes are: pre- to post-intervention change in pain interference/severity. Secondary outcomes are: pain severity/interference at 3- and 6-month follow-up, opioid/analgesic use, health-related quality of life, and pain management self-efficacy. Qualitative interviews are conducted with a random sample of diverse participants who have completed the *painTRAINER,* and all who exit the study early, to subjectively assess experiences with pain and the clinical trial. Enrollment for this trial has begun (n = 36 of 456 patients enrolled) and is ongoing at 12 sites. Clinical trial information: NCT04462302. Research Sponsor: U.S. National Institutes of Health.

TPS12153 **Poster Session**

Use of the ORBIT model to refine and test a novel approach to exercise promotion for breast cancer survivors based on affect regulation. *First Author: Mary D. Chamberlin, Dartmouth-Hitchcock Medical Center, Lebanon, NH*

Background: Physical inactivity is a modifiable risk factor for breast cancer recurrence, but estimates suggest at least 50% of breast cancer survivors are insufficiently active. Guidelines specify all cancer survivors should avoid inactivity, and 90-minutes of moderate-vigorous physical activity (MVPA) per week is associated with clinically meaningful benefits (e.g., reduced cancer-related fatigue). Among the general population, how people feel during exercise (i.e., "affective response to exercise") predicts future exercise engagement. Past work shows prescribing affect-regulated exercise can increase MVPA among inactive adults; however, this strategy has yet to be tested with cancer survivors. The overarching goal of this trial-in-progress is to test the hypothesis that an affect-regulated exercise prescription (Affect-Rx) can promote clinically meaningful increases in MVPA among inactive breast cancer survivors. **Methods:** Design: The Obesity-Related Behavioral Intervention Trials (ORBIT) model was used to inform all choices about design and key research milestones for two sequential studies. Study 1 (Phase Ib) is a stakeholder-centered, single-arm pilot trial (NCT04903249). Study 2 (Phase IIa) is a randomized (2:1) proof-of-concept trial. In both studies, MVPA will be measured using waist-worn ActiGraph wGT3X-BT accelerometers for 10 days at baseline, 2-, 6- and 12-weeks follow-up. Participants also complete brief ecological momentary assessments (EMAs) of their feeling states (e.g., pain, fatigue) three times per day for the same 10-day data collection periods. Participants: >18 years or older, physically inactive, stage 0-III breast cancer survivors, with primary cancer-treatment completed within the last 5-years. Intervention: Both studies deliver the Affect-Rx prescription: Exercise at the highest pace that still feels good. The Control condition in Study 2 is a heart-rate regulated exercise prescription. Endpoints and Planned Analyses: The goal of Study 1 is to refine the study protocol for acceptability via participant interviews and objective indicators of acceptability (e.g., accelerometer wear-time). The primary milestone for Study 1 is a fixed protocol ready for testing in Study 2. The goal of Study 2 is to quantify the effect of Affect-Rx on MVPA at 12-weeks relative to Control. The primary milestone for Study 2 is clinically meaningful impact on MVPA operationalized as >50% participants completing 90-minutes of MVPA at the end of 12 weeks. The associations between daily variability in feeling states and MVPA will be analyzed using a mixed-effects, hierarchical regression modeling approach. Current Enrollment: Data collection for Study 1 are ongoing. To date, $N = 37$ women have enrolled in Study 1 and data collection is complete for $N = 13$ at week-12. We aim to collect complete data from at least $N = 20$ women in Study 1 and $N = 60$ women in Study 2. Clinical trial information: NCT04903249. Research Sponsor: U.S. National Institutes of Health, Other Government Agency.

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